JOURNAL OF BIOLOGICAL REGULATORS & HOMEOSTATIC AGENTS
Volume 30, No. 2 (Supplement 2), April - June, 2016
Global Dermatology

CONTENTS

F. Fama', A. Ieni, G. Tchernev, A.A. Chokoeva, G.K. Maximov, U.Wollina, T. Lotti, J.W. Patterson, M. Fioranelli, M.G. Roccia, C. Guarneri and M. Gioffre'-Florio. Pilomatrixoma of the breast in a patient with type 1 myotonic dystrophy: successful surgical approach 1

G.K. Maximov, K.G. Maximov, A.A. Chokoeva, T. Lotti, U. Wollina, J.W. Patterson, C. Guarneri, C. Tana, M. Fioranelli, M.G. Roccia, N. Kanazawa and G. Tchernev. 5-hydroxytryptamine and lyme disease. Opportunity for a novel therapy to reduce the cerebellar tremor? 7

D.J. Klug, M.D. Darling, J.R. Kaley, G. Tchernev, A.A. Chokoeva, U. Wollina, T. Lotti, M.Fioranelli, M.G. Roccia, G.K. Maximov, A.L. Gagnon and J.W. Patterson. Isolated CMV infection causing perianal and sacral ulceration in a patient with aids 13

A.M. Stowman, M.M. Griffin, W.A. Kanner, G. Tchernev, A.A. Chokoeva, U. Wollina, T. Lotti, M. Fioranelli, M.G. Roccia, G.K. Maximov and J.W. Patterson. Coexistent trichilemmoma and trichoblastoma without associated nevus sebaceous 17

O. Ramos, G. Tchernev, A.A. Chokoeva, U. Wollina, G. K. Maximov, J.W. Patterson, M. Fioranelli, M.G. Roccia, J. Ananiev and T. Lotti. Biofibre hair implant – impact on the quality of life 21

G. Tchernev, M. Sheta, M. Rahoui, A.A. Chokoeva, U. Wollina, G.K. Maximov, J.W. Patterson, M. Fioranelli, M.G. Roccia, J. Ananiev and T. Lotti. Biofibre hair implant: what is new, what is true? 27

F. Fama', A. Sindoni, G. Tchernev, A.A. Chokoeva, U. Wollina, T. Lotti, G.K. Maximov, J.W. Patterson, M. Fioranelli, M.G. Roccia, A. Ieni, A. Cascio, M. Gioffre'-Florio and C. Guarneri. Uncommon clinical presentation of Kimura's disease as bilateral retroauricular masses in a young Malian male: successful surgical approach 35

A.L. Gagnon, S. Daniel, K. Greer, J.W. Patterson, G. Tchernev, A.A. Chokoeva, U.Wollina, T. Lotti, M. Fioranelli, M.G. Roccia, C. Guarneri and N. Aguilera. Langerhans cell sarcoma: an unusual microscopic presentation 39

C. Tana, G. Tchernev, A.A. Chokoeva, U. Wollina, T. Lotti, M. Fioranelli, M.G. Roccia, G.K. Maximov and M. Silingardi. Pulmonary and abdominal sarcoidosis, the great imitators on imaging 45

N. Kanazawa, G. Tchernev, A.A. Chokoeva, G.K. Maximov, U. Wollina, T. Lotti, J.W. Patterson, C. Guarneri, C. Tana and F. Furukawa. Interstitial granulomatous dermatitis demonstrating small, discrete skin-colored papules 49

A. Goldman, U. Wollina, G. Tchernev, A.A. Chokoeva and T. Lotti. Medium-sized congenital melanocytic nevus of the forehead, glabella and temple – surgical treatment and long-term follow-up 53

A.A. Chokoeva, M. Fioranelli, M.G. Roccia, T. Lotti, U. Wollina and G. Tchernev. Giant congenital melanocytic nevus in a Bulgarian newborn 57

Aa. Chokoeva, M. Fioranelli, Mg. Roccia, T. Lotti, U. Wollina and G. Tchernev. Multifocal infantile progressive hemangiomatosis with ocular involvement: unique presentation in a Bulgarian newborn 61

PILOMATRIXOMA OF THE BREAST IN A PATIENT WITH TYPE 1 MYOTONIC DYSTROPHY: SUCCESSFUL SURGICAL APPROACH

F. FAMA'[1], A. IENI[1], G. TCHERNEV[2], A.A. CHOKOEVA[3,4], G.K. MAXIMOV[5], U.WOLLINA[6], T. LOTTI[7], J.W. PATTERSON[8], M. FIORANELLI[9], M.G. ROCCIA[10], C. GUARNERI[11] and M. GIOFFRE'-FLORIO[1]

[1]Department of Human Pathology; University Hospital of Messina, Messina, Italy; [2]Medical Institute of Ministry of Interior (MVR-Sofia), Department of Dermatology, Venereology and Dermatologic Surgery, Sofia, Bulgaria; [3]Onkoderma"- Policlinic for Dermatology and Dermatologic Surgery, Sofia, Bulgaria; [4]Department of Dermatology and Venereology, Medical University of Plovdiv, Medical Faculty, Plovdiv, Bulgaria; [5]Department "Medicinal Information and Non-Interventional studies", Bulgarian Drug Agency, Sofia, Bulgaria; [6]Department of Dermatology and Allergology, Academic Teaching Hospital Dresden-Friedrichstadt, Dresden, Germany; [7]Department of Dermatology, University of Rome "G. Marconi" Rome, Italy; [8]University of Virginia Health System, Department of Pathology, Charlottesville, VA USA; [9]History Department, G. Marconi University, Rome, Italy; [10]University B.I.S. Group of Institutions, Punjab Technical University, Punjab, India; [11]Department of Clinical and Experimental Medicine, Unit of Dermatology University Hospital of Messina, Messina, Italy

Malherbe's calcifying epithelioma is an uncommon cutaneous tumour that originates from the matrix cells of hair follicle. It was initially described by Malherbe as a benign calcifying epithelioma. Several ultra-structural and electron-microscopic studies later demonstrated its origin from matrix cells and the term pilomatrixoma was introduced. The treatment of this tumour remains mainly surgical. Malignant cases with post-surgical recurrences have been described in literature and recurrences have been related to an incomplete surgical treatment or tumour aggressiveness. We present the case of 31-year-old female patient with pilomatrixoma of the breast, which was very similar to fibroadenoma, in terms of size and other clinical features. We successfully treated this patient surgically, and the aesthetic results were good, despite the proximity of the tumour to the areola-nipple complex. Fifteen months later, the patient is doing well, free of any clinical local recurrence.

Malherbe's calcifying epithelioma is an uncommon cutaneous tumour that originates from the matrix cells of hair follicle (1). It was first described by Malherbe as a benign calcifying epithelioma; Several ultrastructural studies later demonstrated its origin from the matrix cells and the term pilomatrixoma (PMX) was introduced (1).

This tumour occurs as solitary or multiple lesions located on the neck, face and upper trunk, isolated or as a hallmark of type 1 myotonic dystrophy (Steinert's disease) or of Gardner syndrome (2-5). The tumour size is generally small, measuring between 0.5 and 2 cm in diameter, although lesions greater than 2 cm have been described. The most frequently involved

Key words: Malherbe epithelioma, pilomatrixoma, breast, myotonic dystrophy

Mailing address:
Fausto Fama', PhD, MD,
Complesso MITO - Residenza Ginestre F/2,
98151 Messina, Italy
Tel.: +390902212406
Fax: +390902212801
e-mail: famafausto@yahoo.it

0393-974X (2016)

decades are the 1st and 2nd, though it has occurred, with somewhat lower incidence, in the 5th and 6th decades (5, 6). Kazakov et al. demonstrated that recurrent activating mutations on the β-catenin gene [CTNNB1 or catenin (cadherin-associated protein), beta 1, 88kDa] induced tumorigenesis for cutaneous adnexal tumours by means of activation of the Wnt signalling pathway (7). The treatment of this tumour remains mainly surgical. Malignant cases with post-surgical recurrences have been described in literature and recurrences were related to an incomplete surgical treatment or tumour aggressiveness (8-12).

Case report

A 31-year-old woman presented to our Surgical Department complained a longstanding breast nodule, which recently enlarged. Significantly, her medical history included a twenty-year history of type 1 myotonic dystrophy.

The physical examination revealed a superficial palpable and painless breast lump, approximately 20 mm in diameter, localised in the upper-outer quadrant of the left breast. No axillary lymphadenopathy, nipple discharge and/or systemic symptoms were found. Breast ultrasound scan confirmed a well-circumscribed hypoechoic inhomogeneous roundish nodule (18.2 mm in its largest diameter) without either intralesional vascularization signals at colour Doppler or regional lymph node enlargement (Fig. 1a). Standard mammograms showed a dense breast structure and highlighted a round uneven high-density lesion (Fig. 1b). As per protocol, a fine-needle aspiration cytology (FNAC) procedure was performed by means of a 26-gauge needle, with

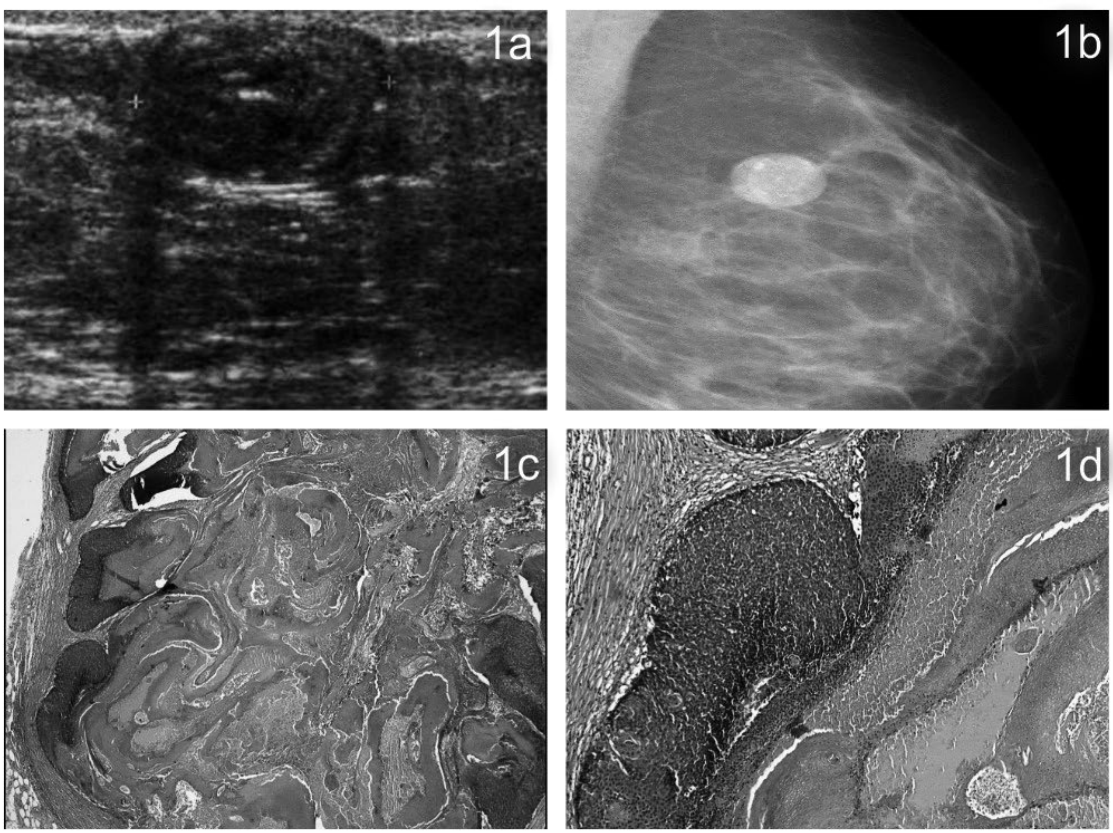

Fig. 1. ***a)****: Ultrasound scan: hypoechoic roundish inhomogeneous nodule of 18.2 x 15.1 mm;* ***b)****: Standard mammography: mediolateral oblique view;* ***c)****: Histological examination showed a subcutaneous nodular lesion, partly cystic, delimited by a uniform basaloid elements with central keratin debris, calcifications and occasionally multinucleate giant cells (inset);* ***d)****: Inside the acellular material shadow cells were encountered. The diagnosis of pilomatrixoma was made.*

a negative result for neoplastic findings. Routine laboratory investigations were within normal limits. The patient underwent surgery and a lumpectomy was performed.

Histological examination showed a subcutaneous nodular lesion, partly cystic, delimited by uniform basaloid elements with central keratin debris, calcifications and occasional multinucleate giant cells (Fig. 1c, d). Inside the acellular material ghost cells were encountered (Fig. 1c, d). The diagnosis of PMX was made. Fifteen months later, the patient doing well, free of any clinical local recurrence.

DISCUSSION

PMX is an uncommon neoplasia with an incidence of 1/800-1000 cutaneous tumours and about 20 new reports per year (13, 14). It commonly presents as a solitary lesion, affecting predominantly young women, especially in the first two decades of life. In only 5% of cases, lesions are multifocal (14, 15). Clinical diagnosis may be often difficult with a high rate of misdiagnosis (8) (i.e. sebaceous cysts, haematomas, dermatofibrosarcomas, calcified epidermal cysts or squamous cell carcinomas), particularly when suspected lesions are located on the face or neck (16, 17).

Despite the benign biological behaviour of the majority of cases, recently some aggressive lesions presenting with multiple local recurrences or distant and visceral metastases have been reported (9-11).

The tumour presents as a slow growing subcutaneous mass, dark or pink in colour, showing well-defined borders and, frequently, breast localisation, particularly in men (18-21). In these cases, because of the small volume of the breast, it may mimic male breast carcinoma (22-25). In regards to these concerns, Nori et al. report a case with a cluster of pleomorphic irregular microcalcifications in mammograms simulating female breast cancer (21).

FNAC has been widely accepted as a fundamental approach in the preoperative diagnostic investigation for years, although incompletely discovered cytological features may lead to a mistaken diagnosis.

The presence of the entire spectrum of PMX cytological characteristics, such as basaloid cells, calcium deposits, naked nuclei, shadow (ghost) cells and giant cells with an inflammatory background, allows a reliable histopathological diagnosis. However, all of these characteristics can be clearly detected in about 40% of the cases only.

The differential diagnosis includes benign or malignant breast lesions as well as calcifying skin lesions (e.g. seborrheic keratosis and inclusion cysts), fibrocystic changes (typical ductal hyperplasia, adenosis, apocrine metaplasia), lobular neoplasias, papillomas, calcified fibroadenomas, fat necrosis, and invasive ductal carcinoma, signified by nodular opacities with pleomorphic calcifications on mammographic examination (26).

Literature data suggest careful ultrasound evaluation, using high frequency probes, in order to separate pilomatricomas into five different patterns (type 1 or full calcified, type 2 or partially calcified, type 3 or complex lesion, type 4 or pseudocystic lesion, type 5 or pseudotumoral) (10, 27). On the contrary, colour-power Doppler and second generation contrast media seem to not provide significant advantages in terms of non-invasive diagnosis.

Molecular studies on Malherbe's epithelioma show that recurrent activating mutations in the β-catenin gene (CTNNB1) induce pilomatrixoma tumorigenesis through activation of the Wnt signalling pathway, as usually occurs in molecular mechanisms regulating hair follicle development (7, 28, 29). Thus, the disease seems to rely on what is suspected to be the inappropriate activation of signalling pathways that regulate hair follicle morphogenesis.

A better understanding of these phenomena at the molecular level needs to be found in the study of these signalling molecules and their related pathways (30). The FNAB was useless and inadequate in our case. An ultrasound-guided core needle biopsy should be obatined (21, 31-33). The first line treatment is the wide and complete surgical excision, which has a low probability of recurrence.

In our report, the lesion was very similar to fibroadenoma in terms of size and other clinical features. We successfully treated this patient and the

aesthetic results were good, despite the proximity of the tumour to the areola-nipple complex.

REFERENCES

1. Forbis R Jr, Helwig EB. Pilomatrixoma (calcifying epithelioma). Arch Dermatol 1961; 83:606-18.
2. Berberian BJ, Colonna TM, Battaglia M, Sulica VI. Multiple pilomatricomas in association with myotonic dystrophy and a family history of melanoma. J Am Acad Dermatol 1997; 37(2Pt1):268-9.
3. Sherrod QJ, Chiu MW, Gutierrez M. Multiple pilomatricomas: cutaneous marker for myotonic dystrophy. Dermatol Online J 2008; 14(7):22.
4. Pujol RM, Casanova JM, Egido R, Pujol J, de Moragas JM. Multiple familial pilomatricomas: a cutaneous marker for Gardner syndrome? Pediatr Dermatol 1995; 12(4):331-5.
5. Pirouzmanesh A, Reinisch JF, Gonzalez-Gomez I, Smith EM, Meara JG. Pilomatrixoma: a review of 346 cases. Plast Reconstr Surg 2003; 112(7):1784-9.
6. Darwish AH, Al-Jalahema EK, Dhiman AK, Al-Khalifa KA. Clinicopathological study of pilomatricoma. Saudi Med J 2001; 22(3):268-71.
7. Kazakov DV, Sima R, Vanecek T, Kutzner H, Palmedo G, Kacerovska D, Grossmann P, Michal M. Mutations in exon 3 of the CTNNB1 gene (beta-catenin gene) in cutaneous adnexal tumors. Am J Dermatopathol 2009; 31(3):248-55.
8. Solivetti FM, Elia F, Drusco A, Panetta C, Amantea A, Di Carlo A. Epithelioma of Malherbe: new ultrasound patterns. J Exp Clin Cancer Res 2010; 29:42.
9. Herrmann JL, Allan A, Trapp KM, Morgan MB. Pilomatrix carcinoma: 13 new cases and review of the literature with emphasis on predictors of metastasis. J Am Acad Dermatol 2014; 71(1):38-43.e2.
10. Mikhaeel NG, Spittle MF. Malignant pilomatrixoma with multiple local recurrences and distant metastases: a case report and review of the literature. Clin Oncol (R Coll Radiol) 2001; 13(5):386-9.
11. Niedermeyer HP, Peris K, Höfler H. Pilomatrix carcinoma with multiple visceral metastases. Report of a case. Cancer 1996; 77(7):1311-4.
12. Bremnes RM, Kvamme JM, Stalsberg H, Jacobsen EA. Pilomatrix carcinoma with multiple metastases: report of a case and review of the literature. Eur J Cancer 1999; 35(3):433-7.
13. Harbon S, Choisnard S, Carbillet JP, Agache P, Laurent R, Ricbourg B. Malherbe's calcified epithelioma. Review of 80 cases. Ann Chir Plast Esthet 1990; 35(4):277-82.
14. Guinot-Moya R, Valmaseda-Castellon E, Berini-Aytes L, Gay-Escoda C. Pilomatrixoma. Review of 205 cases. Med Oral Patol Oral Cir Bucal 2011; 16(4):e552-5.
15. Sari A, Yavuzer R, Isik I, Latifoglu O, Ataoglu O. Atypical presentation of pilomatricoma: a case report. Dermatol Surg 2002; 28(7):603-5.
16. Abdeldayem M, Mekhail P, Farag M, Shehata G, Al Sheikh M, Izzidien A, Naguib N. Patient profile and outcome of pilomatrixoma in district general hospital in United kingdom. J Cutan Aesthet Surg 2013; 6(2):107-10.
17. Duflo S, Nicollas R, Roman S, Magalon G, Triglia JM. Pilomatrixoma of the head and neck in children: a study of 38 cases and a review of the literature. Arch Otolaryngol Head Neck Surg 1998; 124(11):1239-42.
18. Reynaud P, Orliaguet T, Robin YM, Buono JP, Darcha C, Suzanne F, Déchelotte P. Mammary pilomatrixoma clinically mimicking carcinoma. Ann Pathol 1997; 17(3):213-4.
19. Imperiale A, Calabrese M, Monetti F, Zandrino F. Calcified pilomatrixoma of the breast: mammographic and sonographic findings. Eur Radiol 2001; 11(12):2465-7.
20. Rousselot C, Tourasse C, Samimi M, Degand P, Dénier JF, Michenet P. Breast pilomatrixoma manifested as microcalcifications on mammography: report of two cases. J Radiol 2007; 88(7-8 Pt 1):978-80.
21. Nori J, Abdulcadir D, Giannotti E, Calabrese M. Pilomatrixoma of the breast, a rare lesion simulating breast cancer: a case report. J Radiol Case Rep 2013; 7(10):43-50.
22. Gilles R, Guinebretière JM, Gallay X, Vanel D. Pilomatrixoma mimicking male breast carcinoma on mammography. AJR Am J Roentgenol 1993; 160(4):895.
23. Hamilton A, Young GI, Davis RI. Pilomatrixoma mimicking breast carcinoma. Br J Dermatol 1987; 116(4):585-6.
24. Ismail W, Pain S, al-Okati D, al Sewan M. Giant

pilomatricoma simulating carcinoma of the male breast. Int J Clin Pract 2000; 54(1):55-6.
25. Becker TS, Moreira MA, Lima LA, de Oliveira EL, Freitas-Júnior R. Pilomatrixoma mimicking breast cancer in man. Breast J 2010; 16(1):89-91.
26. Ieni A, Todaro P, Bonanno AM, Catalano F, Catalano A, Tuccari G. Limits of fine-needle aspiration cytology in diagnosing pilomatrixoma: a series of 25 cases with clinico-pathologic correlations. Indian J Dermatol 2012; 57(2):152-5.
27. Garioni E, Danesino GM, Madonia L. Pilomatricoma: Sonographic features. J Ultrasound 2008; 11(2):76-8.
28. Millar SE. Committing to a hairy fate: epigenetic regulation of hair follicle stem cells. Cell Stem Cell 2011; 9(3):183-4.
29. Kranjčec I, Roganović J, Jonjić N. Pilomatrixoma: A Benign Appendageal Tumor not Uncommon in Children. Acta Dermatovenerol Croat 2015; 23(4):308-9.
30. Millar SE. Molecular mechanisms regulating hair follicle development. J Invest Dermatol 2002; 118(2):216-25.
31. Ma KF, Tsui MS, Chan SK. Fine needle aspiration diagnosis of pilomatrixoma. A monomorphic population of basaloid cells with squamous differentiation not to be mistaken for carcinoma. Acta Cytol 1991; 35(5):570-4.
32. Gómez-Aracil V, Azua J, San Pedro C, Romero J. Fine needle aspiration cytologic findings in four cases of pilomatrixoma (calcifying epithelioma of Malherbe). Acta Cytol 1990; 34(6):842-6.
33. Nigam JS, Singh S. Fine-needle aspiration cytology of pilomatrixoma: A short series of three cases. Cytojournal 2014; 11:30.

5-HYDROXYTRYPTAMINE AND LYME DISEASE. OPPORTUNITY FOR A NOVEL THERAPY TO REDUCE THE CEREBELLAR TREMOR?

G.K. MAXIMOV[1], K.G. MAXIMOV[2], A.A. CHOKOEVA[3,4], T. LOTTI[5], U. WOLLINA[6], J.W. PATTERSON[7], C. GUARNERI[8], C. TANA[9], M. FIORANELLI[10], M.G. ROCCIA[11], N.KANAZAWA[12] and G. TCHERNEV[13]

[1]Department "Medicinal Information and Non-interventional studies", Bulgarian Drug Agency, Sofia, Bulgaria; [2]Neuromed Center for Neurology and Neurosurgery, Military Medical Academy, Sofia, Bulgaria; [3]"Onkoderma"- Policlinic for Dermatology and Dermatologic Surgery, Sofia, Bulgaria; [4]Department of Dermatology and Venereology, Medical University of Plovdiv, Medical Faculty, Plovdiv, Bulgaria; [5]Department of Dermatology, University of Rome "G. Marconi" Rome, Italy; [6]Department of Dermatology and Allergology, Academic Teaching Hospital Dresden-Friedrichstadt, Dresden, Germany; [7]University of Virginia Health System, Department of Pathology, Charlottesville, VA USA; [8]Department of Clinical and Experimental Medicine, Section of Dermatology, University Hospital of Messina, Messina, Italy; [9]Internal Medicine Unit, Guastalla Hospital, AUSL Reggio Emilia, Reggio Emilia, Italy; [10]History Department, G.Marconi University, Rome, Italy; [11]University B.I.S. Group of Institutions, Punjab Technical University, Punjab, India, [12]Department of Dermatology, Wakayama Medical University, Wakayama, Japan, [13]Medical Institute of Ministry of Interior (MVR-Sofia), Department of Dermatology, Venereology and Dermatologic Surgery, Sofia, Bulgaria

Lyme boreliosis is caused by the spirochete Borrelia burdorferi, which is transmitted by ticks. A 59 year-old woman developed pyrexia, strong headaches, ataxia, dysarthria and tremor of the limbs after a tick bite. She was unable to work and eat on her own. She was hospitalized three times and diagnosed with cerebellar intention tremor, cerebellar ataxia, dysarthria, bilateral horizontal gaze paralysis and a central lesion of the left facial nerve. There were no pyramidal, sensory or psychiatric disturbances. The brain MRI showed multifocal leucoencephalopathy with many hyperintense areas in both hemispheres, as well as in the left superior pedunculus cerebellaris. Diagnosis was confirmed by serologic examination. Treatment with cephtriaxone, doxycycline, methylprednisolone, cephixime and ciprofloxacine was administered without effect on the tremor, ataxia and horizontal gaze paralysis. Treatment was then administered with 5-hydroxytriptamine (5-HT) in increased doses. The result of the three-month treatment with 5-HT was a gradual diminution of the tremor and the ataxia and an increase in the ability to eat, walk and work independently.

Key words: Lyme borreliosis, treatment, tremor, ataxia, 5-hydroxitriptamine

Mailing address:
Prof Dr Georgi Tchernev PhD,
Medical Institute of Minitry of Interior (MVR-Sofia),
Department of Dermatology, Venereology and Dermatologic Surgery,
General Skobelev Nr 79, 1606 Sofia, Bulgaria
Tel.: +359885588424
e-mail: georgi_tchernev@yahoo.de

0393-974X (2016)

Lyme disease or Lyme borreliosis is caused by the spirochete *Borrelia burgdorferi* and transmitted by ticks of the *Ixodes ricinus* complex. It is a multisystemic illness that primarily affects the skin (stage 1, localized infection, erythema migrans) (1). After several days or weeks, the spirochete may spread to many different sites (stage 2, disseminate infection) (1). Possible manifestations may include meningitis, subtle encephalitic signs, cranial neuritis (including bilateral focal palsy), motor or sensory radiculopathy, peripheral neuropathy, mononeuritis multiplex or cerebellar ataxia, alone or in various combinations (1). During this stage migratory musculoskeletal pain, chronic cardiomyopathy and atrioventricular nodal block are common. Months or years later (usually after a period of latent infection) arthritis, chronic encephalopathy, polyneuropathy or acrodermatitis may develop (stage 3, persistent infection) (1). Lyme disease is now the most common vector-borne infection in the United States and Europe (1).

Serotonin (5-hydroxytryptamine, 5-HT), a biogenic amine synthesized from the amino acid tryptophan, regulates several vital processes in the body (2). The enzyme tryptophan hydroxylase converts tryptophan to 5-hydroxytryptophan and the enzyme amino acid decarboxylase converts 5-hydroxytryptophan to 5-hydroxytryptamine (5-HT, Serotonin) (3, 4). The key enzyme involved in the metabolism of 5-HT is MAO, preferentially MAO A (2, 3, 4). The major sites of serotoninergic neurons are the upper pons and the midbrain, specifically the raphe nuclei and to a lesser extent, the caudal locus ceruleus, the postrema area and the interpeduncular area (5). The raphe nuclei form a more or less continuous collection or cell groups close to the midline throughout the brainstem (5, 6). They have been subdivided into a rostral group (rostral raphe nucleus and median nuclei) (5, 7) and a caudal group. The caudal raphe nuclei (raphe magnus, raphe obscurus, raphe pallidus and a cluster of neurons in the lateral reticular formation of the myelencephalon) project caudally to the spinal cord, where 5-HT is involved in pain perception, visceral regulation and motor control (7). Midbrain nuclei (particularly the dorsal raphe nucleus and the median raphe nucleus) innervate the cortical and limbic areas and are likely to modulate cognitive, affective and neuroendocrine functions (8). Projections of a single typical serotoninergic neuron can reach distant brain areas that are in charge of various functions (7). 5-HT receptors, subtypes of which are widely present in cortical areas, amygdala, hippocampus, substantia nigra, caudate and putamen, may regulate the firing rate of dopamine-containing cells and the release of dopamine at axonal terminals (4). The modulation of the brain dopamine function provides the opportunity for the development of a novel therapeutic approach to reduce the tremor in parkinsonian patients (9-19). On the other hand, both the cranial and caudal serotonergic raphe groups project abundantly to the cerebellum which is the site of the cerebellar tremor (5, 7).

The aim of this study is to elucidate the possible efficacy of serotonin on the cerebellar tremor and ataxia in a patient with Lyme disease.

Case report:

A tick (Ixodes spp.) bit a 59-year-old woman. The tick was removed in its entirety. She did not remember having skin changes (erythema chronicum migrans) after the bite. The patient's temperature rose as high as 40^{o}C during the next month with strong headaches, ataxia and tremor of upper and lower limbs. She was hospitalized and diagnosed with static (vestibular) and locomotor (cerebellar) ataxia, muscle hypotonia, expressed intention tremor, dysarthria, bilateral horizontal gaze paralysis, bilateral lesion of the paramedian pontine reticular formation and a muscular lesion of the left facial nerve. She had no signs of encephalitis. The psychic state was normal. The physical examination showed normal blood pressure of 130/80. The brain MRI showed multifocal leucoencephalopathy with many hyperintense areas in both hemispheres, as well as in the left superior pedunculus cerebellaris. The hematologic tests showed nonsignificant leukocytosis with neutrophilia. Serologic examination for anti-*Borrelia burgdorferi* antibodies (ELISA) showed increased IgM antibodies. Treatment with Cephtriaxone 2 mg/day i.v. and methylprednisolone 40 mg i.v. for 10

days was prescribed. After this period, Doxycycline 10 mg/day was administered orally for 20 days. There was no improvement in the condition of the patient. A new hospitalization in a second hospital took place in 2011. Treatment at that time included Cephtriaxone 2g/day i.v. and Methylprednisolone 250 mg/day i.v. (in descending doses) for 10 days. The new serological examination did not show the presence of the specific IgM and IgG antibodies for *Borrelia burgdorferi*. The second (control) brain MRI was identical to the first one. The only improvement was in the neurological examination with regard to the facial paralysis. During a third hospitalization (in a third hospital) in 2012, therapy included a two-week course of Ciprofloxacin 1 g/day (oral administration) and Methylprednisolone 500 mg/day i.v. (descending dose), followed by Cefixime 400 mg/day (oral administration) for 10 days. Serological tests for *Borrelia burgdorferi*-related IgG showed borderline results (21, 44 U/ml) but IgM was negative. No IgG or IgM-specific antibodies for *Borrelia burgdorferi* were found in the serum. No changes in neurologic symptoms were observed. The patient's main complaints during this period were insomnia and tremor, which was the main reason that the patient was not able to move and/or eat independently and she lost 24 kg.

In 2013 we administered a new therapy to the patient for the tremor. 5-hydroxytryptophan (50 mg and 100 mg tablets), which is a direct precursor of 5-HT. During the first 10 days, the daily dose was 100 mg. During the next 15 days, the daily dose was increased to 200 mg, followed by five days of therapy with 300 mg. During the second month, the oral daily dose decreased to 200 mg for 10 days, followed by 100 mg for 20 days. In the third month the daily dose was 100 mg/day during the first 15 days. After this period, we continued the therapy with 50 mg/day. The result of this three-month course of treatment was a gradual diminution of the tremor and the ataxia. As a result, the patient had the ability to walk on her own with the support of a walker and to eat independently. These activities were not possible before the treatment with 5-hydroxytryptophan. This treatment had no effect on the bilateral horizontal gaze paralysis.

DISCUSSION

5-hydroxytryptophan (5-HTP) is the direct precursor to the important neurotransmitter serotonin (5-hydroxytriptamine, 5-HT). 5-HTP easily crosses the blood-brain barrier and is the major determinant in raising the brain serotonin levels (20). Serotonin-selective re-uptake inhibitors (SSRIs) drugs do not enhance serotonin production. Unlike SSRIs, 5-HTP has few known undesired side effects (21, 22).

The main role of the central 5-HT system is to regulate the behavioral inhibitory system, but it is also implicated in the regulation of food intake, circadian rhythms, temperature, sleep, anxiety, aggression and impulsivity (7). 5-HT is also a regulator of the smooth muscles in the cardiovascular system and the gastrointestinal tract and an enhancer of platelet aggregation (4).

5-HT-containing nerve terminals make synaptic contacts with the corticotrophin-releasing hormone (CRH)-containing cells in the hypothalamus, with direct and indirect 5-HT agonists, all of which increase adrenocorticotropic hormone (ACTH), beta-endorphin and cortisol release (23). Another pituitary hormone that is partially regulated through 5-HT neurons is prolactin (23). There is extensive pharmacological and neuroanatomical evidence that the 5-HT-containing neurons regulate the hypothalamic-pituitary-adrenal (HPA) axis in rats (24). The pituitary-adrenal response to a 5-HT agonist (e.g. the release of cortisol, prolactin and beta-endorphin) is commonly used as a marker to assess the functional state of the 5-HT system in humans (23).

At cellular level, seven types of 5-HT receptors are now recognized, 5-HT_1 through to 5-HT_7 with numerous subtypes totaling 14 distinct receptors (5, 11, 12, 25-28). Each of them have specific localization and effector pathways (7).

The largest family of 5-HT receptors is the 5-HT_1, with five 5-HT receptor subtypes (4, 7, 29). The 5-HT_1A receptor is found in the raphe nuclei of the brainstem, where it functions as an inhibitory somatodendritic autoreceptor on cell bodies of serotonergic neurons (4). The 5-HT_{1D} also functions as an autoreceptor, but at the axon terminal,

inhibiting 5-HT release (4). 5-HT_{1D} and 5-HT_{1E} receptor subtypes have a high density in cortical areas, caudate and putamen (23, 30).

Enhanced aggressive behavior in mice lacking the 5-HT_{1B} receptor was found (29, 30). Altered amounts of brain serotonin and norepinephrine in mice lacking MAO A also provoked aggressive behavior (30). The 5-HT_{2C} receptor is regulated by RNA ending, a post-transcriptional event that alters expression of the genetic code at the level of RNA (4). The 5-HT_{2C} receptor has been implicated in behavior and susceptibility to seizure (4). The 5-HT_3 receptor is unique, being the only monoamine neurotransmitter receptor that is known to function as a ligand-operated ion channel (4).

All of the cloned 5-HT receptors are expressed in the brain, often in overlapping domains (4). Although patterns are defined, it is likely that multiple 5-HT receptors subtypes with similar or opposing actions are expressed in individual neurons, leading to a tremendous diversity of actions (4).

The excessive rise of serotonin levels increases the receptor activation and can cause serotonin intoxication: receptors in the basal ganglia may produce akathisia and agitation, the receptors in the limbic system may cause an initial increase in anxiety, the receptors in the cranial blood vessels may cause headache, etc. (5). The most dangerous intoxications include Serotonin syndrome and Call-Fleming syndrome (8).

Although 5-HT is implicated in the regulation of a number of physiological processes and their malfunctions, the exact sites and modes of its action are still being defined (4).As with the catecholamines, serotonin is synthesized in the axonal terminal. In contrast to the catecholamines, the availability of tryptophan is the rate-limiting function, and the enzyme tryptophan hydroxylase is not rate-limiting (5). Therefore, dietary variations in tryptophan can measurably affect serotonin levels in the brain (5). Once synthesized, serotonin is packaged into the presynaptic terminal by the plasma membrane transporter (5). The promotor of the transporter gene contains a polymorphism that creates a twofold variation in levels of anxiety (5).

The serotonergic system exerts its action by modulating various other transmitter systems and by integrating and connecting other spatially distinct systems (7). The physiological consequences of 5-HT release vary with the brain area and the neuronal element involved, as well as with the population of 5-HT receptor subtypes expressed (30). The serotonergic system mediates many different functions within the nervous system. Functionally, serotonin functions as a neurotransmitter, neuromodulator, as a hormone, as a mitogen (4, 8) and as an autoreceptor, but on axon terminal inhibiting 5-HT release (4).

Although the cerebellum constitutes only 10% of the total volume of the brain, it contains more than half its neurons (8). Cerebellar neurons receive input from numerous serotonin-containing neurons of raphe nuclei. Lesions of the dentate nucleus or its pathways result in intention tremor, which is a severe, coarse tremor that is present at rest and is intensified during activity. Lesions of the vestibulocerebellum produce hypotonia and dysarthria. All these symptoms were present in the patient. A lesion on the pons containing the nuclei of cranial nerves VI and VII explains the paralysis of the conjugate gaze and the facial palsy. Insomnia of the patient was only partially influenced after the serotonin treatment. However, it may be that serotonin is only one of the sleep-promoting factors, which also include melatonin, sleep inducing peptide, muramil peptides, vasoactive intestinal peptide, interferon-alpha 2, interleukin-1, tumor necrosis factor, etc. (8).

5-HTP can be used in daily doses up to 900 mg and the common side effect is gastrointestinal intolerance.

The various manifestations of Lyme disease can usually be treated successfully with antibiotics. The response to treatment is best in the early stages of the disease. For early Lyme disease doxycycline 100 mg bid for 14-day course of therapy is a first choice and amoxicillin, cefuroxime axetil and erythromicin or its congeners are second-, third- and fourth- choice alternatives, respectively (1). In contrast to second- or third- generation cephalosporin antibiotics, first generation cephalosporins, such as cephalexin, are not effective (1). Patients with neurologic involvement are most commonly treated with 2 g

qd cephtriaxone IV as first choice and with 2 g q8h cephotaxime and Na penicillin G 5 million U q6h as second and third choice alternatives, respectively (1).

CONCLUSION

The role of serotonin might be of particular interest in patients with cerebellar tremor. Taking into account the intractability of this type of tremor, serotonin use is justified when clinically indicated. Our results concerning the efficacy of 5-HT on cerebellar tremor and ataxia seem promising.

For the first time it is found that 5-HT may reduce cerebellar tremor and ataxia in patients with Lyme disease. Potential adverse effects are rare and largely dose-related. Further treatment studies are necessary to test the therapeutic role of 5-HT on cerebellar tremor.

REFERENCES

1. Steere AC. Lyme Borreliosis. Harrison's principles of internal medicine. McGraw Hill, New York 2012; 1:(173)1401-6.
2. Cooper JR, Bloom FE, Roth RH. The biochemical basis of neuropharmacology, ed.7, Oxford University Press New York 1996; 355.
3. Senders-Bush E, Mayer SE. 5-hydroxytryptophan (serotonin) receptor agonists and antagonists. In: Brunton LL, Laszo JS and Parker KL eds. Goodman & Gilman's. The pharmacological basis of therapeutics, 11th ed., McGraw-Hill, New York. 2006; 11:297-315.
4. Descarries L, Audet MA, Dowcet G, Garcia S, Oleskevich S, Seguela P, Soghomonian JJ, Watkins KC. Morphology of central serotonin neurons. Brief review of quantified aspects of their distribution and ultra-structural relationships. Ann NY Acad Sci 1990; 600:81-92.
5. Hecimovic H, Santos J, Gilliam F, Kanner AM. Neuroanatomical and neurobiological bases of psychiatric disorders. In: Effinger A, Kanner AM. eds. Psychiatric issues in epilepsy, 2nd ed., Lippincott Williams & Wilkins, Philadelphia 2007; 93-118.
6. Jenner P, Sheehy M, Marsden CD. Noradienaline and 5-hydroxytryptamin modulation of brain dopamine function: implications for the treatment of Parkinson's disease. Br J Clin Pharmacol 1983; 15:277-89.
7. Sawada M, Nagatsu T, Ito K, Iizuka R, Kondo T, Narabayashi H. Triptophan activity in the brain of controls and Parkinsonian patients. J Neural Transmission 1985; 62(1-2):107-15.
8. Palacios JM, Waeber C, Hoyer D, Mengod G. Distribution of serotonin receptors. Ann NY Acad Sci 1990; 600:36-52.
9. Barnes NM, Sharp TA. A review of central 5-HT receptors and their function. Neuropharmacol 1999; 38 (8):1083-152.
10. Carta M, Carlsson T, Kirik D, Bjorklund A. Dopamine released from 5-HT terminals is the cause of L-dopa-induced dyskinesia in Parkinsonian rats. Brain 2007; 130(7):1819-33.
11. Fox SH, Chuang R, Brotchie JM. Serotonin and Parkinson's disease on movement, mood and madness. Movement disorders 2009; 24 (9):1255-66.
12. Nicholson SL, Brotchie JM. 5-hydroxytriptamine (5HT, serotonin) and Parkinson's disease – opportunities for novel therapeutics to reduce the problems of levodopa therapy. Eur J Neural 2002; 9:31-6.
13. Aviles-Olmos I, Martinez-Fernandes R, Foltynie T. L-dopa-induced dyskinesias in Parkinson's disease. European Neurological Journal 2010; 2:2.
14. Carta M, Carlsson T, Munoz A, Kirik D, Bjorklund A. Role of serotonin neurons in the induction, of levodopa and Graft-induced dyskinesias in Parkinsons's disease. Movement Disorders 2010; 25(1):174-9.
15. Hinz M, Stein A, Uncini T. Amino acid management of Parkinson's disease: a case study. Int J Gen Med 2011; 4:165-74.
16. Birdsall TC. 5-hydroxytryptophan: a clinically-effective serotonin precursor. Altern Med Rev 1998; 3:271-89.
17. Sano I. L-5 hydroxytryptophan (L-5-HTP) therapy. Folia Psychiatr Neurol Jpn 1972; 26(1):7-17.
18. Van Praag H. Management of depression with serotonin precursors. Biol. Psychiatry 1981; 16 (3):291-310.
19. Den Boer JA, Slaap BR, Bosker FJ. Biological aspects of anxiety disorders and depression. In: Montgomery SA and den Boer J A. "SSRIs in depression and anxiety" 2nd ed., John Wiley & Sons, Chichester 2001; 24-86.
20. Fuller RW. Serotonin receptors and neuroendocrine

responses. Neuropsychopharmacol 1990; 3(5-6):495-502.
21. Murphy DL. Neuropsychiatric disorders and the multiple human brain serotonin receptor subtypes and subsystems. Neuropsychopharmacol 1990; 3(5-6):457-71.
22. Hoyer D, Clarke DE, Fozard JR, Hartig PR, Martin GR, Mylecharane EJ, Saxena PR, Humphrey PP. International Unia of Pharmacology classification of receptors for 5-hydroxytryptamine (serotonin). Pharmacol Rev 1994; 46(2):157-203.
23. Hoyer D, Martin G. 5-HT receptor classification and nomenclature: towards a harmonization with the human genome. Neuropharmacol 1997; 36(4-5):419-28.
24. Bonasera SJ, Tecoff LH. Mouse models of serotonin receptors function: toward a genetic dissection of serotonin systems. Pharmacol Ther 2000; 88(2):133-42.
25. Azmitia EC, Gannon PJ, Kheck NM, Whitaker-Azmitia PM. Cellular localization of the 5-HT1 A receptor in primate brain neurons and glial cells. Neuropsychopharmacol 1996; 14(1):35-46.
26. Gross C, Zhuang X, Stark K, Ramboz S, Ooosting R, Kirby L, Santarelli L, Beck S, Hen R. Serotonin 1A receptor acts during development to establish normal anxiety-like behavior in the adult. Nature 2002; 416(6879):396-400.
27. Saudou F, Amara DA, Dierich A LeMeur M, Ramboz S, Segu L, Buhot MC, Hen R. Enhanced aggressive behavior in mice lacking 5-HT 1B receptor. Science 1994; 265(5180):1875-8.
28. Cases O, Seif I, Grimsby J, et al. Agresive behavior and altered amounts of brain serotonin and norepinephrine in mice lacking MAOA. Science 1995; 268(5218):1763-6.
29. Burns CM, Chu H, Rueter SM, Hutchinson LK, Canton H, Sanders-Bush E, Emeson RB. Regulation of serotonin-2C receptor G-protein coupling by RNA editing. Nature 1997; 387(6630):303-8.
30. Tecott LH, Sun LM, Akana SF, Strack AM, Lowenstein DH, Dallman MF, Julius D. Eating disorder and epilepsy in mice lacking 5-HT2c serotonin receptors. Nature 1995; 374(6522):542-6.

ISOLATED CMV INFECTION CAUSING PERIANAL AND SACRAL ULCERATION IN A PATIENT WITH AIDS

D.J. KLUG[1], M.D. DARLING[2], J.R. KALEY[2], G. TCHERNEV[3], A.A. CHOKOEVA[4,5], U. WOLLINA[6], T. LOTTI[7], M.FIORANELLI[8], M.G. ROCCIA[9], G.K. MAXIMOV[10], A.L. GAGNON[11] and J.W. PATTERSON[2]

[1]University of Nebraska Medical Center College of Medicine, Omaha, Nebraska; [2]Departments of Pathology, University of Virginia Health System, Charlottesville, Virginia; [3]Medical Institute of Ministry of Interior (MVR-Sofia), Department of Dermatology, Venereology and Dermatologic Surgery, Sofia, Bulgaria; [4]"Onkoderma"- Policlinic for Dermatology and Dermatologic Surgery, Sofia, Bulgaria; [5]Department of Dermatology and Venereology, Medical University of Plovdiv, Medical Faculty, Plovdiv, Bulgaria; [6]Department of Dermatology and Allergology, Academic Teaching Hospital Dresden-Friedrichstadt, Dresden, Germany; [7]Department of Dermatology, University of Rome "G. Marconi" Rome, Italy; [8]History Department, G. Marconi University, Rome, Italy; [9]University B.I.S. Group of Institutions, Punjab Technical University, Punjab, India; [10]Department "Medicinal Information and Non-Interventional Studies", Bulgarian Drug Agency, Sofia, Bulgaria; [11]Department of dermatology, University of Virginia Health System, Charlottesville, Virginia

Cytomegalovirus (CMV) is a DNA virus estimated to infect 70-90% of the world's population, producing minimal symptoms in immunocompetent hosts. In the immunocompromised host, CMV infection can be potentially fatal, producing systemic or localized forms. We report the case of a 52-year-old female with acquired immunodeficiency virus (AIDS) who presented multiple sacral and perineal ulcers clinically and histopathologically consistent with CMV ulcerations. We discuss the patient's clinical presentation and histologic findings to remind physicians to consider CMV as a cause for cutaneous and systemic infection in the immunocompromised host.

Cytomegalovirus (CMV) is a DNA virus from the herpesviridae family that is estimated to infect 70-90% of the world's population (1). In the majority of immunocompetent hosts, CMV infection produces minimal symptoms (1). In the immunocompromised host, infections can be potentially fatal and manifest in either a systemic or localized form. In the localized, ulcerative form of infection, CMV is almost always found to co-infect with other herpesviridae viruses, making it difficult to establish whether CMV is involved in the pathologic formation of lesions or simply a bystander (1). Here we report a case of isolated CMV ulcerations in a patient with AIDS.

Case report

A 52-year-old female with a history of acquired

Key words: Cytomegalovirus, AIDS, ulcers, immunodeficiency

Mailing address:
James W. Patterson, MD,
Department of Pathology,
University of Virginia Health System,
1215 Lee Street, Box 800214,
Charlottesville, VA 22908 USA
e-mail: jwp9e@virginia.edu

0393-974X (2016)

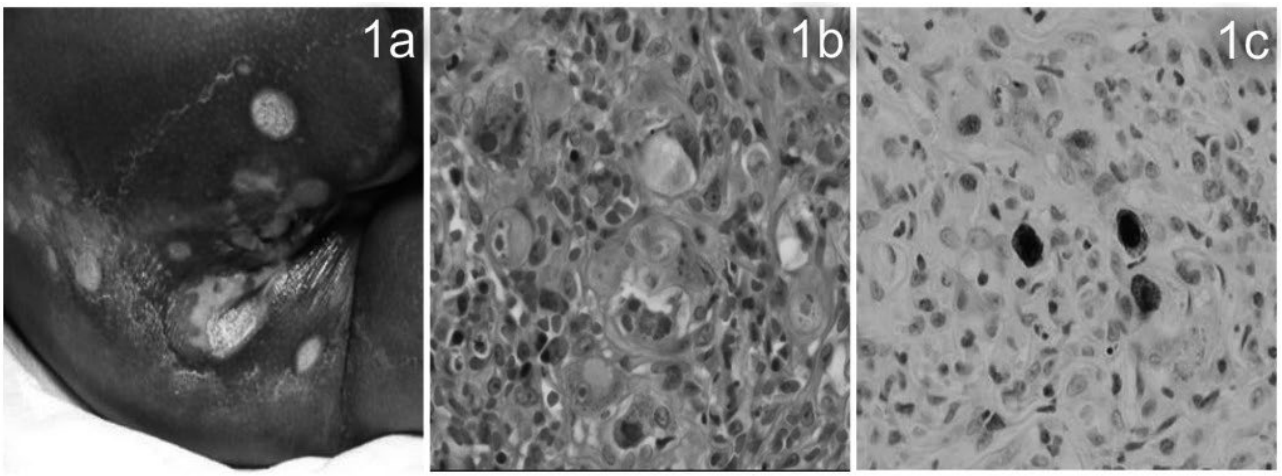

Fig. 1. ***a)****: Clinical manifestation of the perianal and sacral ulceration;* ***b)****: Histopathological findings (hematoxylin-eosin, original magnification x400) showing endothelial cells with large, eosinophilic intranuclear viral inclusions;* ***c)****: Histopathological findings (CMV antigen immunohistochemical stain, original magnification x400) highlighting CMV-positive endothelial cells.*

immune deficiency syndrome (AIDS) and a recent CD4 count of 0 (normal range 400-1500 µl) presented to the hospital with fever, altered mental status and sacral and perianal ulcerations. Computerized tomography scans showed intracranial hemorrhage and a possible demyelinating process. A lumbar puncture indicated pleocytosis.

Blood, urine and cerebrospinal fluid cultures were negative. Assays for cryptococcal antigen, Haemophilus influenza B antigen, Neisseria meningitidis antigen, Streptococcal B antigen, toxoplasma, syphilis IgG and Quantiferon Gold were negative. The patient was noncompliant with HAART therapy. Dermatology was consulted for the sacral and perianal ulcerations. On physical examination, the patient had multiple punched out ulcerations, some with scalloped borders and fibrinous indurated base, scattered around the anus. Most were superficial, but there was one larger ulcer in the right gluteal cleft that measured approximately 3-4mm in depth (Fig. 1a).

A punch biopsy of the larger ulcer on the right gluteal cleft was performed and histopathologic examination revealed an ulcerated epidermis with large eosinophilic intranuclear viral inclusions concentrated within endothelial cells of adjacent vessels, morphologically consistent with cytomegalovirus (CMV) infection (Fig. 1b). Positive staining of these inclusions with CMV antigen immunohistochemistry (IHC) was confirmatory (Fig. 1c), notably, the cells failed to stain for HSV1 and HSV2.

DISCUSSION

Cytomegalovirus is closely related to HSV-1 and HSV-2, Epstein-Barr virus (EBV), and human herpesvirus -6, -7, and -8 (2). The natural history of a CMV infection includes primary infection, followed by latent infection or reinfection (2). Transmission is thought to occur through bodily secretions in both immunocompromised and immunocompetent individuals (2, 3). As immunocompetent individuals are often unaware of their seroconversion in the absence of clinical signs, a majority of postnatal infections are not detected immediately (3, 4), however, CMV may also present overt symptoms resembling EBV mononucleosis, manifested as febrile illness, tonsillitis, pharyngitis, lymphadenopathy, and arthralgia (2).

In the immunocompromised host, CMV infection tends to be more severe and potentially fatal, with mortality in disseminated disease ranging between 80 and 90% (2, 5). In HIV-infected individuals, reactivation of a latent intracellular virus is believed to be the major source of infection (5). CMV may

also act as a cofactor in hastening the progression to AIDS (2). In skin, CMV has been reported to manifest as generalized macular and papular eruptions or as localized, ulcerative lesions (5).

The ulcerative lesions associated with CMV occur when the CD4+ T-lymphocyte count is below 50 cells/mm (3, 4). In the majority of CMV cases, the ulcers are located on the genital and perineal region and occur as a polymicrobial infection with HSV -1, -2, or VZV (3). These infections alone could account for the ulcerations, making it difficult to establish whether CMV has a pathogenetic role in the formation of these lesions or is simply a bystander (1).

Microscopically, biopsies of CMV lesions may show intranuclear inclusions surrounded by halos, often within endothelial cells, as was found in this case (2). It was speculated that in severely immunocompromised patients, CMV could be activated from a latent state causing a viremia that may evolve into cutaneous vasculitis (5). This may lead to localized vascular damage and ulceration (5).

We believe this case is an example of CMV acting as the primary cause of the perianal ulcerations in this severely immunocompromised individual. Establishment of a pathologic role for CMV can be complicated not only by coexistent infection with other herpesviruses, but also by the concurrent administration of antiviral and antibiotic therapy, resulting in decreased likelihood of bacterial or viral isolation (2). This case and similar cases have the potential to be dismissed as other herpetic infections if further investigation of the cause is not undertaken. It is important to keep CMV in the differential diagnosis of persistent ulcerative lesions in immunocompromised patients, because detection of CMV in these lesions has been noted to precede systemic infection, with severe consequences and rapid decline (3).

Our patient was also found to have a CMV viral load of 393,000 IU/mL. She was started on IV ganciclovir for management of the CMV ulcers as well as possible CMV-induced meningoencephalitis and retinitis. Her perianal ulcers responded well to ganciclovir, but unfortunately, the patient ultimately died from complications of atypical mycobacterial pulmonary infection and fungemia.

REFERENCES

1. Dauden E, Fernandez-Buezo G, Frago J, et al. Mucocutaneous presence of cytomegalovirus associated with human immunodeficiency. Arch Dermatol 2001; 137:443-8.
2. Drago F, Aragone MG, Lugani C, et al. Cytomegalovirus infection in normal and immunocompromised humans. A review. Dermatology 2000; 200:189-95.
3. Guo RF, Gebreab FH, Tang EH, Piao Z, Lee SS, Perez ML. Cutaneous ulcer as Leading symptom of systemic cytomegalovirus infection. Case Rep Infect Dis 2015; 2015:723962.
4. Nico MMS, Cymbalista NC, Hurtado YCP, et al. Perianal cytomegalovirus ulcer in an HIV infected patient: case report and review of literature. J Dermatol 2000; 27: 99-105.
5. Pariser, RJ. Histologically specific skin lesions in disseminated cytomegalovirus infection. JAAD 1983; 9: 937-9.

COEXISTENT TRICHILEMMOMA AND TRICHOBLASTOMA WITHOUT ASSOCIATED NEVUS SEBACEUS

A.M. STOWMAN[1] , M.M. GRIFFIN[2], W.A. KANNER[2,3], G. TCHERNEV[4], A.A. CHOKOEVA[5,6], U. WOLLINA[7], T. LOTTI[8], M. FIORANELLI[9], M.G. ROCCIA[10], G.K. MAXIMOV[11] and J.W. PATTERSON[1]

[1]Department of Pathology, Division of Dermatopathology, University of Virginia Health System, Charlottesville, Virginia; [2]University of South Carolina School of Medicine Greenville, Greenville, South Carolina; [3]Pathology Consultants, Greenville, South Carolina; [4]Medical Institute of Ministry of Interior (MVR-Sofia), Department of Dermatology, Venereology and Dermatologic Surgery, Sofia, Bulgaria; [5]"Onkoderma"- Policlinic for Dermatology and Dermatologic Surgery, Sofia, Bulgaria; [6]Department of Dermatology and Venereology, Medical University of Plovdiv, Medical Faculty, Plovdiv, Bulgaria; [7]Department of Dermatology and Allergology, Academic Teaching Hospital Dresden-Friedrichstadt, Dresden, Germany; [8]Department of Dermatology, University of Rome "G. Marconi" Rome, Italy; [9]History Department, G. Marconi University, Rome, Italy; [10]University B.I.S. Group of Institutions, Punjab Technical University, Punjab, India; [11]Department "Medicinal Information and Non-Interventional Studies", Bulgarian Drug Agency, Sofia, Bulgaria

Trichilemmoma and trichoblastoma are benign adnexal neoplasms derived from the hair follicle unit. While trichilemmomas are closely associated with the epidermis, trichoblastomas are found within the dermis and subcutaneous tissue. Both tumors have been reported to arise within nevus sebaceus of Jadassohn (NSJ). We present a 42-year-old white male with a 5 mm crusted, erythematous papule on the right occipital scalp that had been present for years. A shave biopsy was performed and read as trichilemmoma involving the biopsy base. The patient returned for follow-up 2 months later with recurrence of a crusted papule, measuring 9 mm in greatest diameter at the site of the previous biopsy. The lesion was excised for complete histologic evaluation, diagnosed as trichilemmoma with verrucoid features and associated basaloid proliferation with adnexal differentiation, again involving the biopsy base. The lesion recurred 2 months later in the form of an 8 mm multilobulated pink nodule. It was again excised and diagnosed as trichoblastoma with overlying trichilemmoma. The significance of this finding is that coexistent lesions do not necessarily necessitate a preexisting nevus sebaceous. Rather, this finding supports the notion of a common stem cell capable of differentiating toward the various portions of the hair follicle unit and adnexal structures. The idea is that any portion of the skin adnexal structure may develop out of a pluripotential germ cell and develop into a tumor.

Trichilemmoma and trichoblastoma are benign adnexal neoplasms derived from the hair follicle unit (1). Trichilemmoma appears to be derived from the follicular infundibulum but also shows differentiation

Key words: coexistent lesions, trichoblastoma, trichilemmoma, surgery, shave

Mailing address:
James W. Patterson, MD,
Department of Pathology,
University of Virginia Health System,
1215 Lee Street,
Box 800214 Charlottesville, VA 22908 USA
e-mail: jwp9e@virginia.edu

0393-974X (2016)

toward the outer root sheath epithelium, whereas trichoblastoma is composed of follicular germinative cells (1, 2). While trichilemmomas are closely associated with the epidermis, trichoblastomas are found within the dermis and subcutaneous tissue. Both tumors have been reported to arise within nevus sebaceus of Jadassohn (NSJ) (1, 2). Multiple trichilemmomas are seen in Cowden's syndrome (2). The concurrence of trichilemmoma and trichoblastoma outside the setting of a nevus sebaceus has not been reported.

Case report

A 42-year-old white male presented with a 5 mm crusted, erythematous papule on the right occipital scalp that had been present for years. The clinical impression was trichilemmoma. A shave biopsy was performed and read as trichilemmoma, involving the biopsy base. The patient returned for follow-up 2 months later with recurrence of a crusted papule, measuring 9 mm in greatest diameter, at the site of the previous biopsy. The lesion was excised for complete histologic evaluation, diagnosed as trichilemmoma with verrucoid features and associated basaloid proliferation with adnexal differentiation, again involving the biopsy base. The lesion recurred 2 months later as an 8 mm multilobulated pink nodule. It was again excised and diagnosed as trichoblastoma with overlying trichilemmoma.

Histologically, the findings were similar in all specimens (Fig. 1, 2). They included a polypoid lesion with markedly acanthotic epithelium, mild papillomatosis, hyperkeratosis with areas of parakeratosis, and focal scale-crust formation. Within the lobulated epithelium comprising the superficial tumor, there were foci of pilar keratinization and areas of clear cell change. Peripheral palisading was also noted, but significant cytologic atypia was not appreciated. These findings are considered typical for trichilemmoma. Underlying this tumor, within the mid-dermis and extending into the subcutaneous adipose tissue, was a well-circumscribed, unencapsulated proliferation composed of islands of basaloid cells. Cytologically, the cells had ovoid nuclei with vesicular chromatin and scant amounts of basophilic cytoplasm. Scattered mitotic figures and apoptotic bodies were seen. Central areas of eosinophilic squamoid cells reminiscent of hair follicle differentiation were also identified.

Occasional papillary mesenchymal bodies were present. The intervening stroma was moderately cellular with a mixed inflammatory infiltrate. These are features associated with trichoblastoma. The excisional specimens also showed prior biopsy site changes and dermal scar.

DISCUSSION

As pointed out previously, the concurrence of trichilemmoma and trichoblastoma can be seen in the setting of NSJ (1, 2). Outside of this scenario, however, the two lesions have never been reported together. The significance of this finding is that coexistent lesions do not necessarily necessitate a preexisting nevus sebaceous. Rather, this finding supports the notion of a common stem cell capable of differentiating toward the various portions of the hair follicle unit and adnexal structures (3). This pluripotentiality hypothesis has been made and given a number of proposed names including: "complex neoplasm of the primary epithelial germ", "complex adnexal tumor of the skin" or "mixed tumor of the folliculosebaceous-apocrine complex" (3, 4, 5).

The idea is that any portion of the skin adnexal structure may develop out of a pluripotential germ cell and develop into a tumor (4). A common example is that of coincident syringoma and cylindroma (4). Other associations appearing in case reports include: syringocystadenoma papilliferum (SCAP), apocrine hidrocystoma and clear cell syringoma; proliferating pilar tumor (PPT) and SCAP; PPT and tubulopapillary hidradenoma (TPH); SCAP and TPH (3, 6, 7).

Interestingly, the lesion described here was biopsied, it recurred and then recurred a second time. Although malignant change was not observed, local recurrence following biopsy and excision was seen, a feature not typically described in cases of isolated trichoblastoma or trichilemmoma (8).

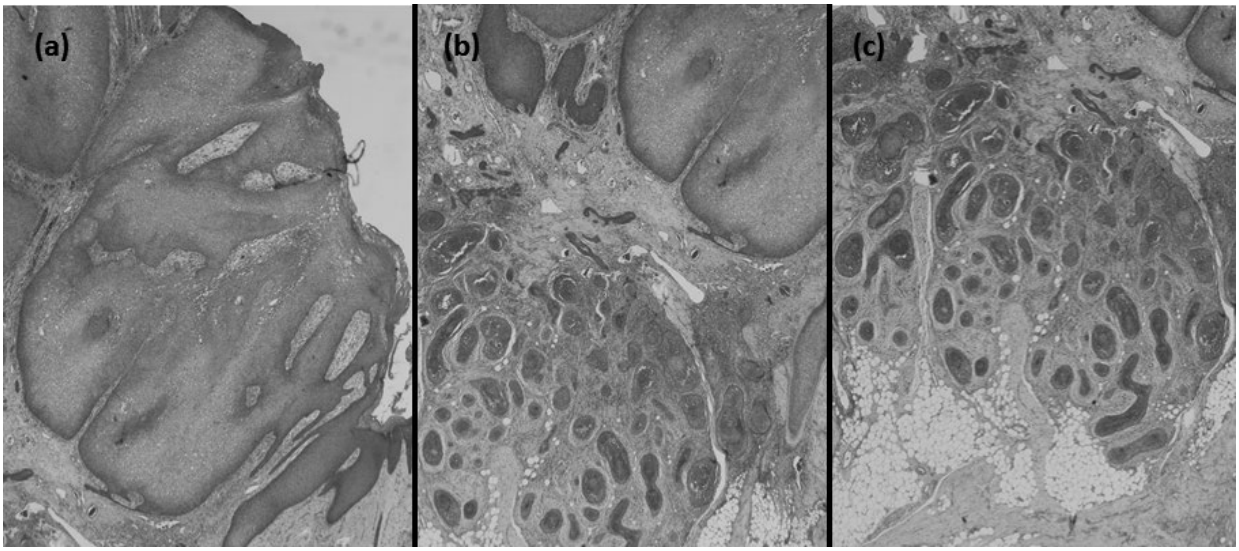

Fig. 1. **a, b, c):** *Histopathologicsal findings: Polypoid acanthotic squamous epithelium with some clear cell change with underlying well-circumscribed nodular dermal basaloid proliferation (H&E,2x).*

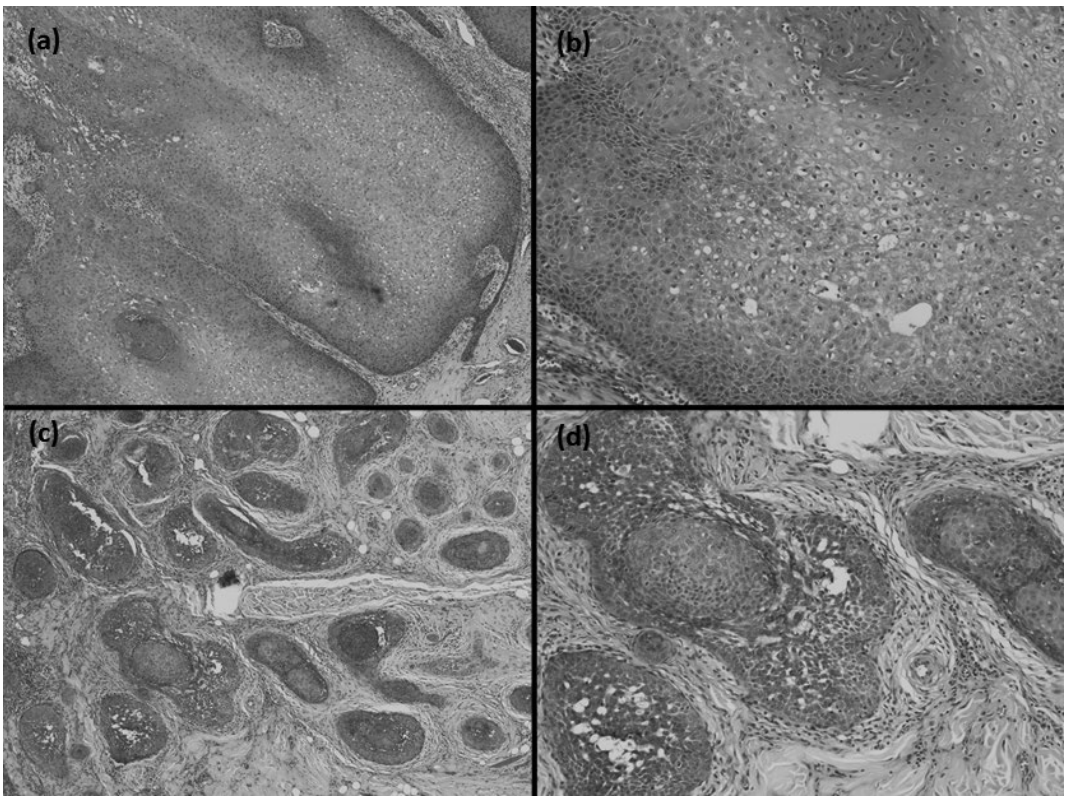

Fig. 2. **a, b, c, d)**: *Acanthotic squamous epithelial tongues showing clear cell change and focal pilar keratinization. Peripheral palisading is noted of the basilar cell layer (a-4x), b-10x). The discrete dermal islands are composed of uniform basaloid cells. Suggestion of hair follicle differentiation is seen and papillary mesenchymal bodies are identified (c-4x, d-10x) (H&E).*

REFERENCES

1. Idriss MH, Elston DM. Secondary neoplasms associated with nevus sebaceus of Jadassohn: a study of 707 cases. J Am Acad Dermatol 2014; 70(2):332-37.
2. Cribier B, Scrivener Y, Grosshans E. Tumors arising in nevus sebaceus: a study of 596 cases. J Am Acad Dermatol 2000; 42(2):263-8.
3. London V, Saadat P, Vadmal MS. Complex adnexal tumours of the skin: a report of three cases and review of the literature. J Clin Pathol 2012; 65:819-22.
4. Rodriguez-Diaz E, Armijo M. Mixed tumors with follicular differentiation: complex neoplasms of the primary epithelial germ. Int J Dermatol 1995; 34(11):782-5.
5. Kazakov DV, Belousova IE, Bisceglia M, et al. Apocrine mixed tumor of the skin ("mixed tumor of the folliculosebaceous-apocrine complex"). Spectrum of differentiations and metaplastic changes in the epithelial, myoepithelial, and stromal components based on a histopathologic study of 244 cases. J Am Acad Dermatol 2007; 57(3):467-83.
6. Lin WL, Lin WC, Kuo TT, Chen CH, Hong HS. An unusual complex cutaneous adnexal tumor composed of syringocystadenoma papilliferum, apocrine hidrocystoma, and clear cell syringoma. Dermatol Surg 2007; 33:876-9.
7. Hsu PJ, Liu HC, Huang CJ. Mixed tubulopapillary hidradenoma and syringocystadenoma papilliferum occurring as a verrucous tumor. J Cutan Pathol 2003; 30:206-10.
8. Zeller KA, Billmire DF. Trichoblastoma: management of a rare skin lesion. J Ped Surg 2012; 47:250-2.

BIOFIBRE HAIR IMPLANT – IMPACT ON THE QUALITY OF LIFE

O. RAMOS[1], G. TCHERNEV[2], A.A. CHOKOEVA[3,4], U. WOLLINA[5], G. K. MAXIMOV[6], J. W. PATTERSON[7], M. FIORANELLI[8], M.G. ROCCIA[9], J. ANANIEV[10] and T. LOTTI[11]

[1]Clinica Dermatologica Tavizon y Torres, Coyoacan, Distrito Federal, Mexico; [2]Medical Institute of Ministry of Interior (MVR), Department of Dermatology, Venereology and Dermatologic Surgery, Sofia, Bulgaria; [3]"Onkoderma"-Policlinic for Dermatology and Dermatologic Surgery, Sofia, Bulgaria; [4]Department of Dermatology and Venereology, Medical University of Plovdiv, Medical faculty, Plovdiv, Bulgaria; [5]Department of Dermatology and Allergology, Academic Teaching Hospital Dresden-Friedrichstadt, Dresden, Germany; [6]Department "Medicinal Information and Non-interventional studies", Bulgarian Drug Agency, Sofia, Bulgaria; [7]University of Virginia Health System, Department of Pathology, Charlottesville, VA USA; [8]History Department, G. Marconi University, Rome, Italy; [9]University B.I.S. Group of Institutions, Punjab Technical University, Punjab, India; [10]Department of General and Clinical Pathology, Forensic Medicine and Deontology, Trakia University, Armeiska str.11, Stara Zagora, Bulgaria; [11]Department of Dermatology, University of Rome "G. Marconi" Rome, Italy

Body image refers to how we feel about our bodies. It does not refer to what we actually look like, but rather to our perceptions, opinions and ways of thinking about our appearance. How we feel about our appearance is part of our body image and self-image. The hair is a significant part of this image. The problem of alopecia affects both sexes and all ages with significant sequelae. Along with androgenetic alopecia, there are forms of alopecia of various origins: traumatic, surgical, pharmacological and others. Polyamide artificial hair implant (Biofibre®) is one of the current techniques used to treat this problem.

It is recognized worldwide that a favourable perception of one's appearance can enhance self-confidence. The hair significantly contributes to this perception. For example, the problem of alopecia affects both sexes and all ages with significant sequelae (1). Along with androgenetic alopecia, there are forms of alopecia of various origins: traumatic, surgical, pharmacological and others (1). Polyamide artificial hair implant (Biofibre®) is one of the techniques available today to treat this problem.

Biofibre® hair implant success depends on three decisive factors: high quality of the fiber, correct implant techniques and choice of a suitable patient (1). This hair restoration procedure is performed in cases connected to lack of a donor (2), in the setting of an atrophic or cicatricial scalp (3), when patients refuse invasive techniques and for patients with burn sequelae (4). In all these cases, fiber can be used as a reconstructive or cosmetic hair restoration treatment solution to allow the patient to promptly recover the expected aesthetic result with significant improvements of self-esteem and social

Key words: polyamide artificial hair implant, alopecia, treatment

Mailing address:
Prof. Dr. Torello Lotti MD, MD (Hon),
Professor & Chair of Dermatology,
University of Rome " G.Marconi",
Rome, Italy
Tel.: +393286214588 - Fax: +390637725647
e-mail: professor@torellolotti.it

0393-974X (2016)

life. Biofibre® is suitable both for male and for female patients from 18-years-of-age onwards. This technique can be used alone or in combination with other hair restoration techniques (5, 6).

Suitable fibre

The modern hair implant (Biofibre®) is the result of more than 20 years of investigation and experience in biocompatibility materials and is approved as an implantable hair prosthetic medical device. Thanks to its safety features, this fiber allows creation of a keratin sheath, which, by protecting the pseudo-infundibula from external contamination, reduces possible cutaneous irritation (7). If necessary, the anchoring system enables the fiber to be pulled out without residual adverse effects; this reversibility is an additional important safety feature (8). Biofibre® is very similar to natural hair: soft, flexible, fine and resistant. These characteristics enable rapid cicatrization, trauma-free skin following implantation, and a long-lasting aesthetic result. The mechanical strength of this hair implant fiber is 3 times greater than that of natural hair and allows the best preservation over time. It is available in 13 colors, which, if properly mixed, satisfies most patients' demands. Length ranges from 15 to 45 cm and it is also produced in different shapes: straight, curly and wavy. It can be washed and dried like natural hair. It can't be bleached or permanent-waved. To increase hair density in the crown area it is now available as new high-density fibers (MHD®); this allows three times more volume, reducing the quantity of hair needed to reach the expected result and therefore minimizing the need for additional procedures (8).

Patient selection

Patient selection is very important to assess suitability both from a physical and psychological point of view. The clinical history of the patient, a general physical examination, assessment of scalp conditions and a physiological profile are necessary. The suitable patient for implant must be in good health, have a healthy scalp and be able to follow the rules described in the post-implant protocol, which provides for periodic medical checkups and cleaning of the scalp. Also the expectations of the patient have to be considered. A pre-implant protocol, entailing a sensitization test of 100 fibers, is carried out one month prior to the implantation sessions to limit the risk of possible subjective reactions (9).

The following conditions are considered unsuitable for this treatment: seborrhea, eczematous or proliferative diseases, chronic skin inflammation, anxiety, depression, hypomanic states, chronic metabolic diseases, allergy, immunodeficiency, and working activities where hygiene cannot be guaranteed and maintained.

Pre implantation laboratory blood tests are required. Patients must be informed that about 10% of their implanted hair will be lost each year (10); this is very important, both to assure that the patient is prepared for this normal circumstance and to not adversely affect their confidence in the procedure. Patients should also be informed that the Biofibre® hair implant requires good hygiene and care, that permanent or other aggressive treatments cannot be performed, and that certain specific products have to be used periodically. Periodic medical checkups must be performed and patients need to follow this requirement. The first such checkup occurs 4 weeks after the test implant, or sooner if any problem occurs. Standard follow-up is about every 3 months, but the frequency may have to be customized. In any event, if problems arise, the patient must promptly inform the implant physician in order to reach an appropriate resolution.

Implant

One week before the implant, the patient should avoid ingestion of salicylic acid derivatives. One day before implant, smoking and alcohol are to be avoided, and the patient should start taking a systemic broad-spectrum antibiotic; these instructions should also be followed in the days following the implant. In order to achieve the best aesthetic result, two or more colors of Biofibre® hair are mixed. Since not all areas of the scalp are equally suitable for the implant, implantation should be avoided in areas such as the temples, lower forehead, or sideburns.

Surgical cleaning with betadine is performed before preoperative marking. Local anesthesia is then given.

Biofibre® hairs are implanted one by one in a 45° radius, leaving between each implant a space of 2 mm following the natural pattern of the hair. The implantation is performed by an adjustable implanter or with the new automatic implant machine (11). Both devices fit a special stainless steel hooked needle of 0.25 mm thickness to minimize tissue trauma. The fibers are implanted at the *galea capitis* level, and in one h, about 600 fibers are implanted. To conclude the procedure, the implanted area is cleansed and disinfected with betadine, avoiding any traction on the fibers that might produce unwanted hair loss. An ice pack is applied for 5-10 min and if necessary, an analgesic may be administered (10).

After the hair implant, the patient receives systemic antibiotic therapy for a week, sometimes together with antihistamines and an anti-inflammatory or topical antifungal lotion (depending upon the climate). The first shampoo can be performed after 3-4 d with gentle motions. The hair should not be cut for 2 weeks after implant to avoid risk of infection. A follow-up implant session can be performed after 3-4 weeks. The elapsing time between the two sessions allows a gradual change of image and better psychological acceptance both by the patient and by other people.

Histological and clinical study

Three years after implantation, Biofibre hair is surrounded by hyperplastic epidermis (pseudo -infundibulum) at the level of the papillary dermis and in the uppermost part of the reticular dermis. Inside the pseudo-infundibula, a compact keratin layer adheres perfectly to the implanted fibers. In the middle and deep reticular dermis, the fibers are surrounded by a focally granulomatous chronic infiltrate of limited extent. In the deepest dermis and hypodermis, the fibers are surrounded by fibroplasia, and no inflammatory infiltrate is observed (12).

Among the 133 patients treated with Biofibre® hair implants, the results were considered satisfactory in 96.2% by both physicians and patients in terms of coverage of the area of alopecia and resemblance to natural hair color and texture. Dissatisfaction among the remaining 3.8% of patients was linked to failure of the tolerance test or improper follow up. Of those patients, 2.1% had fibers removed without any residual difficulty (13).

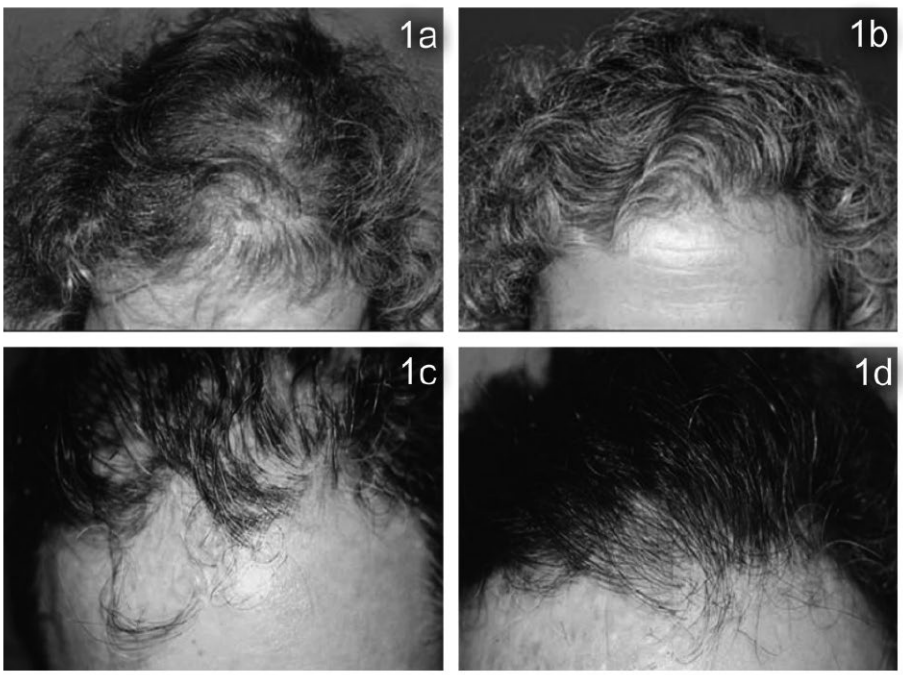

Fig. 1. ***a, b)****: Implant of 2000 Biofibre wave in women in two sessions*; ***c, d)****: Implant of 1500 Biofibre to correct scars in 2 sessions.*

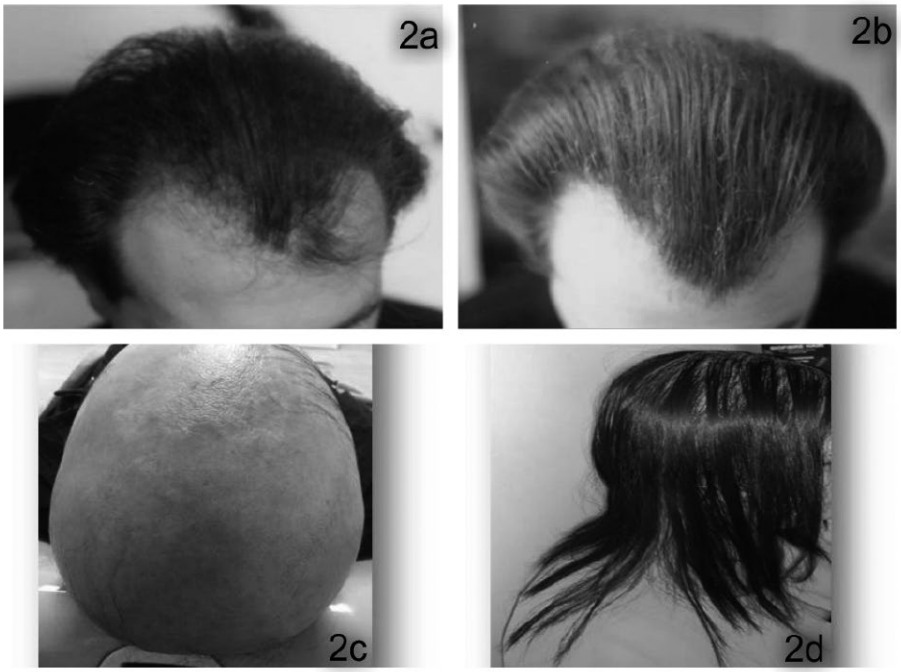

Fig. 2. ***a, b):*** *Implant of 1000 Biofibre in young man in one session;* ***c, d)****: Implant of 15000 Biofibre long size in a patient with total alopecia in 16 sessions.*

DISCUSSION

Biofibre® hair implants, performed both for reconstructive and cosmetic hair restoration, result in significant improvements in self-esteem and social life (Fig. 1a-d).

Experience has shown that more women suffer from baldness or hair thinning. The social problem in the majority of those cases represents major trauma for female patients, sometimes with severe psychological complications (14, 15). Biofibre® hair implants can be considered a valid option for these cases since they ensure immediate aesthetic results and increased quantity of hair in a short period. Patient can have implant results closely resembling his/her own natural hair, as the hair implant fibers are available in many colors and different lengths and shapes; this can have an immediate, beneficial psychological impact (Fig. 2a-d).

Another important issue to consider is related to total alopecia. Although total alopecia cannot be considered a major indication for Biofibre® hair implants because of the large number of hairs required and the consequent major difficulties of post-procedural management, several such cases were treated with this method in the past year (16-18). Although the clinical results were on average not as good as for other standard applications of this technique, there was nevertheless, enormous benefit in selected cases. The use of Biofibre® hair density (MHD®) in the crown area allows a significant reduction in the quantity of hair needed to achieve an acceptable result and allows less intense after-care procedures. Additional investigations of this treatment and selection of an ideal protocol for total alopecia are the subject of ongoing investigation.

In addition to the these applications, it is important to consider the psychological benefit for all those people who suffer from baldness or who simply want to improve their self-image with a minor surgical technique that can produce immediate results without hospitalization.

CONCLUSION

Biofibre® hair implants should be considered part of the armamentarium to be used in hair restoration treatment, especially because of the high

quality of cosmetic results and prompt psychological benefits. A low-impact and rapid procedure that can be performed on suitable patients with automatic or manual devices. The fibers that are used are available in 13 colors, in straight, undulated or curly shapes and three different lengths to satisfy all patient requirements. This implantation technique is suitable for treatment of many different types of alopecia in male and female patients from 18 years onwards, as it ensures immediate results and rapid return to a normal social life. It can be used alone or in combination with other hair restoration techniques. Additional applications will be the subject of investigation in the coming years.

REFERENCES

1. Perez Rangel R. Cabello Inorganico Biocompatible. Dermatologia Cosmética, Texto Académico, I° edicion 2011, presentacion February 2012 in 8th WCOCD.
2. Brady G. Cases without Hope - Innovative Solutions in Difficult Cases. International Society of Hair Restoration Surgery, 13th Annual Meeting, Sydney, Australia, August 24-28, 2005.
3. Santiago M, Perez Rangel R, D'ugo A, et al. Artificial hair fiber restoration in the treatment of scalp scars. Derm Surg 2007; 33(1):35-44
4. Rahoui M. Biofibre et Cicatrice de Brulure du cuir Chevelu. 6° Congres National Algérienne de Chirurgie Esthétique, 28-29 Avril 2016, Alger, Algérie.
5. Perez Rangel R. How and when to combine the different methods for baldness. 8th World Congress of Cosmetic Dermatology, Cancun, Mexico, February 2012.
6. Carreno N. Lo Nuevo Implante Capilar. Ix Curso Internacional De Dermatologia Quirurgica, Lima, Peru, 21-23 Agosto, 2015.
7. Fanti PA. Comparison between cases with and without clinically evident inflammatory complications in patients subjected to artificial hair implantation. Department of Dermatology, Laboratory of Dermatologic Histopathology, University of Bologna, Italy, April 11th, 1994.
8. D'Ugo A, Santiago M, Chaker C, Perez Rangel R, Saad Eddin U, Ramponi V. Safety of Biofibre® CE 0373/TGA artificial hair implants: importance of the scalp anchoring system. International Society of Hair Restoration Surgery, 10th Annual Meeting, Chicago, USA, October 9-13, 2002.
9. Espinoza W. Nuevas tendencia en calvicie: Biofibre implante de fibras biocompatibles, Peruderm , Lima, Peru, 1-3 October 2015.
10. D'Ugo A. Follow-up study of 503 patients three years after surgical implantation of artificial fibers on the the scalp. 4th Congress of the European Academy of Dermatology and Venereology (EADV), Brussels, Belgium, October 10-15, 1995.
11. Donici D. Biofibre hair implant a modern baldness solution. Imcas 18th International Congress, 28-31 January 2016, Paris, France.
12. Gonzalez M. Biofibre hair replacement. ASAPS 35th Anniversary Meeting, Las Vegas, NV, USA, April 27-May 3, 2002.
13. Sheta M, Muntean D. Biofibre Hair Implant: the Evolution of Artificial Hair. 1st Anti-Aging Medicine European Congress, Paris, France 11-12 October 2013.
14. Fanti PA, Pistorale T, D'Urso C, Misciali C, Tosti A. Histological study on 5 cases of patients who underwent artificial hair implantation without complications. 35th Annual Meeting American academy of Dermatology, New Orleans, 01-03 Feb 1995.
15. Serdev N, D' Erme A, Hercogova J, Zarrab Z, Chokoeva AA, Tchernev G, Wollina U, Lotti T. Polyamide hair implant (Biofibre®): evaluation of efficacy and safety in a group of 133 patients. J Biol Regul Homeost Agents 2015; 29(1S):103-9.
16. Al-Noori B. Biofibre Hair Implant. Annual Congress of the Palestinian Society of Dermatology and Venereology, Ramallah, Palestine, 16-17 of April 2015.
17. Rahoui M. Artificial hair implant Biofibre in 2 cases of alopecia totalis and experimental test in eyebrows. 17th IMCAS Annual Congress, Paris, France, 29 Jan 01 Feb 2015.
18. Santiago M. Extreme artificial hair implant: Biofibre® treatment of total alopecia. International Society of Hair Restoration Surgery, 10th Annual Meeting, Chicago, USA, October 9-13, 2002.

BIOFIBRE HAIR IMPLANT: WHAT IS NEW, WHAT IS TRUE?

G. TCHERNEV[1], M. SHETA[2], M. RAHOUI[3], A.A. CHOKOEVA[4,5], U. WOLLINA[6], G.K. MAXIMOV[7], J.W. PATTERSON[8], M. FIORANELLI[9], M.G. ROCCIA[10], J. ANANIEV[11] and T. LOTTI[12]

[1]Medical Institute of Ministry of Interior (MVR-Sofia), Department of Dermatology, Venereology and Dermatologic Surgery, Sofia, Bulgaria; [2]Al Mansour Dermatologic Clinic, Kuwait City, Kuwait; [3]Clinique Cheveux et Lifting, Tunis, Tunisia; [4]"Onkoderma"- Policlinic for Dermatology and Dermatologic Surgery, Sofia, Bulgaria; [5]Department of Dermatology and Venereology, Medical University of Plovdiv, Medical faculty, Plovdiv, Bulgaria; [6]Department of Dermatology and Allergology, Academic Teaching Hospital Dresden-Friedrichstadt, Dresden, Germany; [7]Department "Medicinal Information and Non-interventional studies", Bulgarian Drug Agency, Sofia, Bulgaria; [8]University of Virginia Health System, Department of Pathology, Charlottesville, VA USA; [9]History Department, G. Marconi University, Rome, Italy; [10]University B.I.S. Group of Institutions, Punjab Technical University, Punjab, India; [11]Department of General and Clinical Pathology, Forensic Medicine and Deontology, Trakia University, Armeiska str.11, Stara Zagora, Bulgaria; [12]Department of Dermatology, University of Rome "G. Marconi" Rome, Italy

Ensuring the safety of hair implant fibers is essential. At the same time, good aesthetic quality and durability should also be considered in order to maintain expected result over the years. The main features required are biocompatibility, resistance to traction, absence of capillarity, resistance to physical-chemical stress, and low tissue trauma, in addition to good aesthetics. Biofibre® medical hair prosthetic fibers meet all the biocompatibility and safety requirements established by international standards for medical devices. They are available in 13 colors, with different lengths (15, 30 or 45 cm) and various shapes (straight, wavy, curly and afro). Biofibre® hair implants are indicated for diffuse hair loss or hair thinning in cases where an immediate aesthetic result is required, when patients request minor surgery without hospitalization, both for male and female patients, in combination with other hair restoration techniques to improve the final aesthetic result, to correct scars or scalp burns and in cases of poor donor areas. Biofibre® Hair Implant is in fact a minor surgery technique, performed under local anesthesia by either a manual implanter or an automatic machine which enables an immediate aesthetic result and the desired quantity of hair without pain or hospitalization. Clinical and histological studies have demonstrated that Biofibre® hair Implants are safe and well tolerated by patients and can be totally reversible if the need arises. This technique requires good after-care, periodical check-ups and yearly implant re-touches to maintain the best cosmetic result.

Key words: biofibre, hair implants, alopecia, treatment

Mailing address:
Prof. Dr. Torello Lotti MD, MD (Hon),
Professor & Chair of Dermatology,
University of Rome "G.Marconi",
Rome, Italy
Tel.: +393286214588 - Fax: +390637725647
e-mail: professor@torellolotti.it

0393-974X (2016)

In the USA, as early as 1900 there were patents for artificial hair implant instruments (1). Around the '70s this technique spread from Japan to the US and Brazil. Unfortunately, in the beginning there were unqualified operators, who more often than not were not physicians; the materials were unsuitable, there was a lack of any kind of formal medical protocols and an absence of meaningful patient information or proper after-care instructions. This inevitably led to unacceptable complications in treatment with the result that in the USA, FDA restrictions were applied for the implantation of human hair and artificial fibers made of modacrylic, polyacrylic, polyesther, etc., which were used at that time (2, 3).

In the '90s, research institutes and medical staff began to select biomaterials and develop medical protocols that allowed this technique to become safer and more reliable. In 1995, the hair implant technique was recognized as a medical procedure that could only be performed by trained physicians in a suitable environment. CE, TGA and other markings placed on devices and their registration among the various Ministries for Health, guaranteed safety for the patient and its suitable application. Polyamide Italian fibers Biofibre®, CE and TGA approved, possess all the safety requirements (5). The approval of this methodology was a great advantage for patients since it legally prevents the procedure from being performed by unqualified people (Fig. 1-4).

Materials

Ensuring the safety of hair implant fibers is essential. At the same time, good aesthetic quality and durability must also be considered in order to maintain the expected results over time. The main features required are biocompatibility, resistance to traction, absence of capillarity, resistance to physical-chemical stress, low tissue trauma and good aesthetic qualities. Biofibre® medical hair prosthetic fibers meet all the biocompatibility and safety requirements established by international standards for medical devices. They are available in 13 colors, with different lengths (15, 30 or 45 cm) and in various shapes (straight, wavy, curly and afro). It is also available in the new high-density version that allows each implant to have three hairs. This fibre is used for the crown area only, while for the front hairline the single Biofibre® is recommended.

Indications

Biofibre® hair implants are indicated in the case of diffused hair loss or hair thinning, when an immediate aesthetic result is required, when the patient requests minor surgery without hospitalization, for both male and female patients and in combination with other hair restoration techniques, to improve final aesthetic results or to correct scars or scalp burns (6) and in the case of poor donor areas (7, 8). Biofibre® is not indicated in patients with diabetes mellitus, hepatitis, autoimmune diseases, scalp diseases, alopecia that is not stabilized, lack of personal hygiene or employment in dusty or dirty environments. These implants are not indicated in the temple area, low frontal scalp or in any scalp areas with thin tissue (such as the sideburns). A preliminary screening of the patient, including blood testing, is essential before proceeding with an implant test.

Medical protocol

A correct hair implant procedure requires a combination of safe fibers, suitable implant instruments, trained doctors, careful patient selection, and proper after-care (9).

The selection of suitable patients is important. A preliminary visit with tolerance testing allows the exclusion not only of those patients who are sensitive to the fibre but also those who have contraindicating skin conditions. The tolerance implant test is performed with 100 fibers and results are evaluated after 4 weeks.

The implant technique is based on small hooking needles that go out to the implanter and hook the fiber's root, placing it under the scalp at galea level. The procedure is performed under local anaesthesia and in 600 fibers are implanted 1 h. A small quantity of local anesthesia is recommended initially, with repeat administration in case of need.

The average implant is about 1000 fibers per session, respecting the appropriate distance between each fiber (2 mm) and correct inclination of the implant (45°). When performed by an automatic hair implant device, this process minimizes implant

Fig. 1. *Reversible knot of Biofibre® after extraction. To remain embedded in the scalp, allowing prompt scalp healing.*

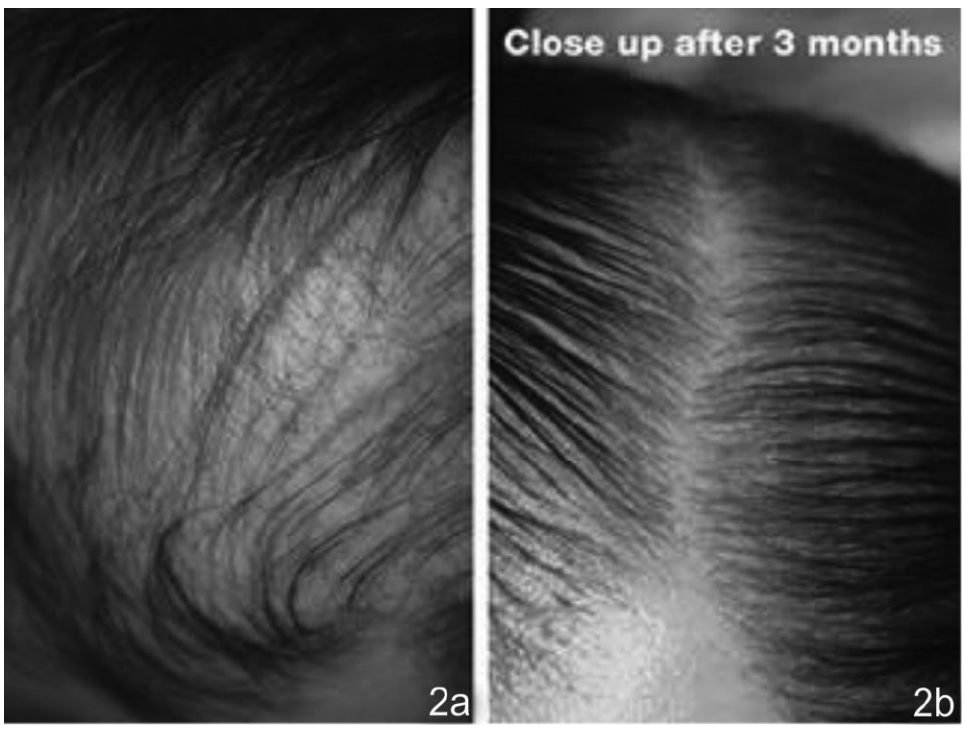

Fig. 2. ***a, b****): Before and after implant close-up after 3 months.*

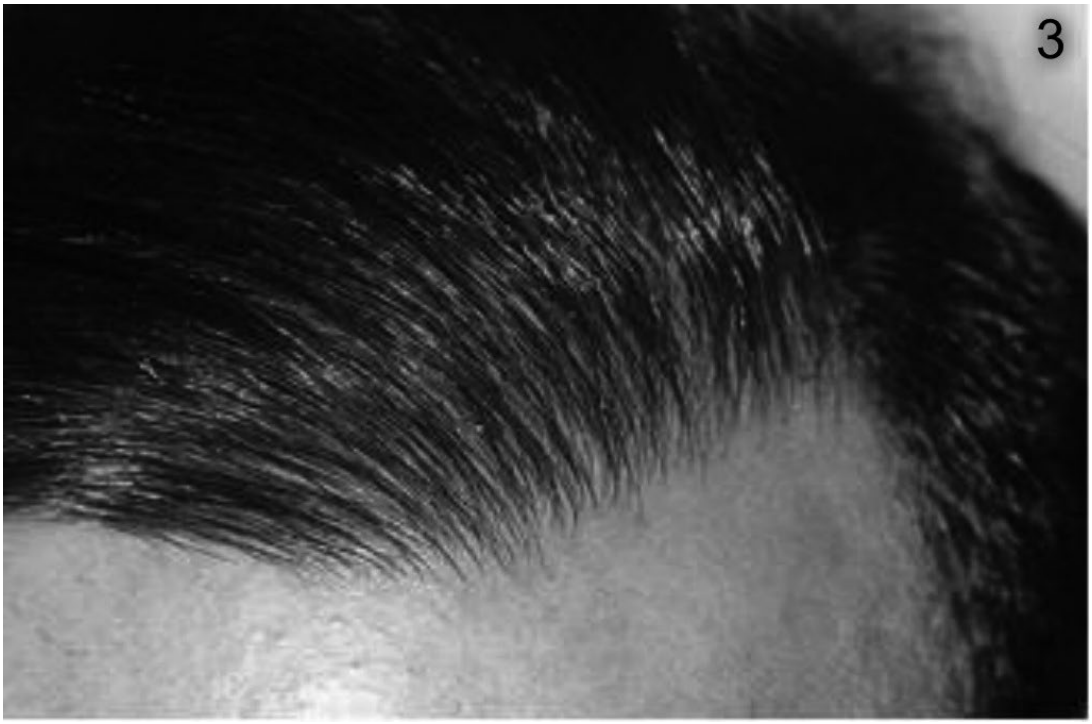

Fig. 3. *Biofibre® implant in front line patient.*

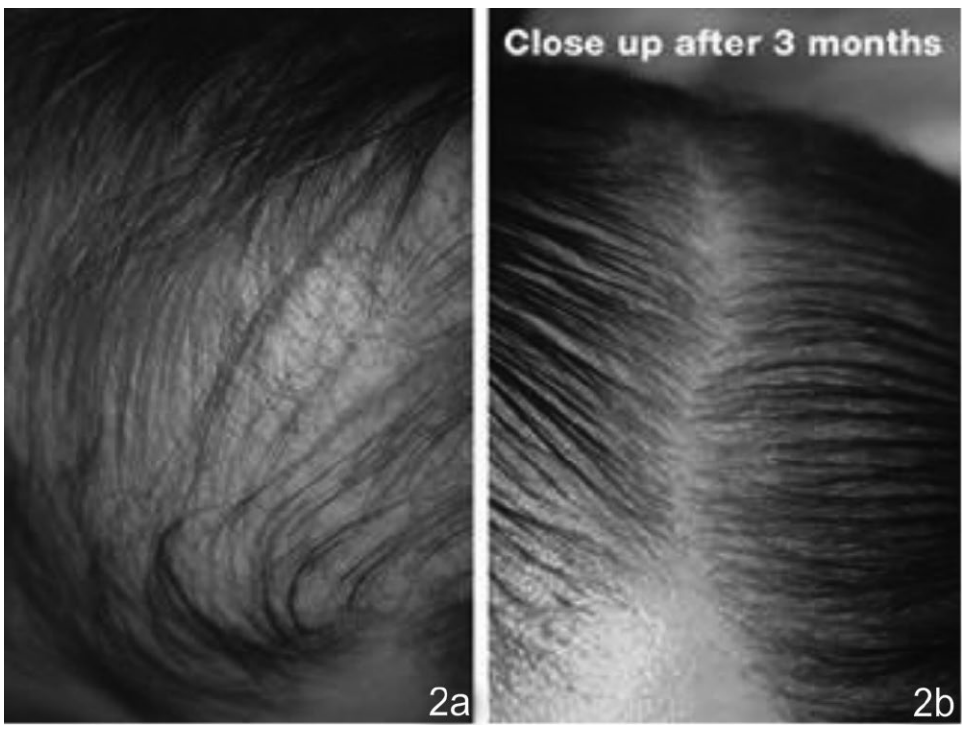

Fig. 4. *Right implant deepness of Biofibre®.*

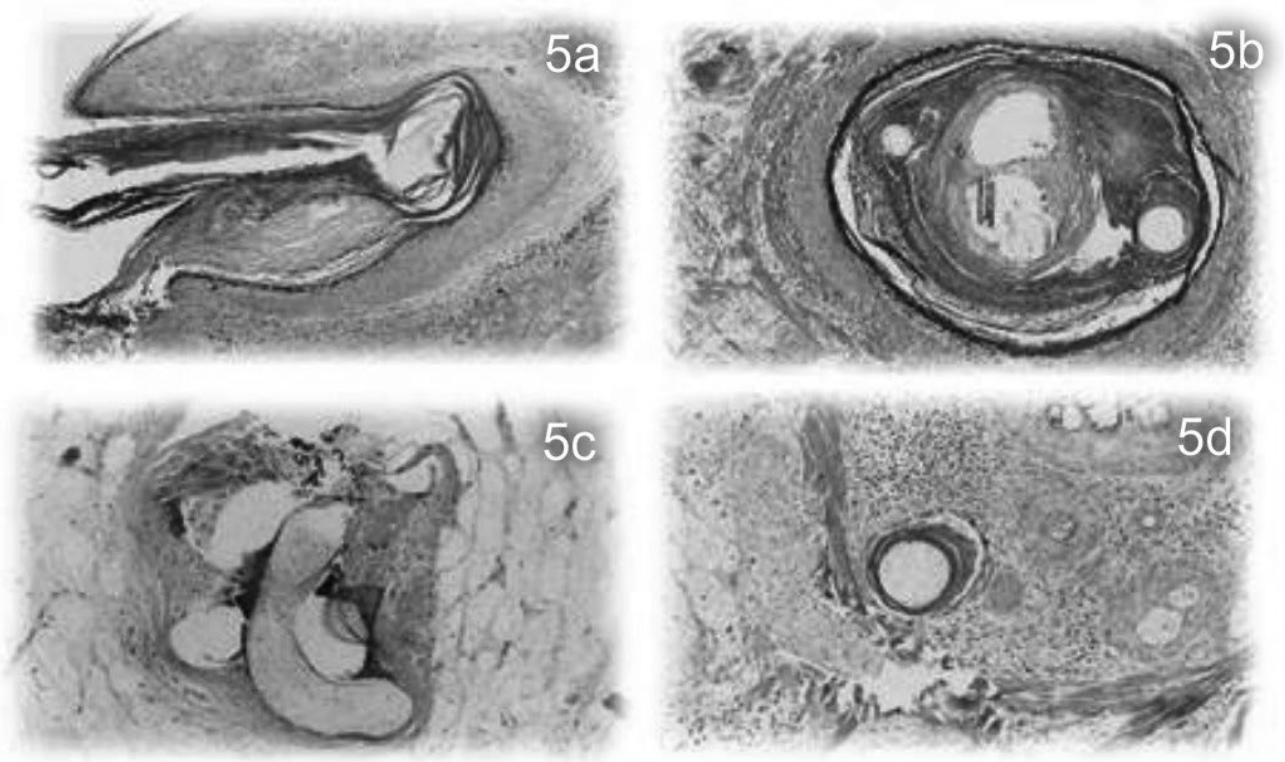

Fig. 5. **a, b, c, d**): *Within the pseudo-infundibula a compact keratin layer adheres closely to the fibers. In the middle and deep reticular dermis, the fibers are surrounded by a small amount of focally granulomatous chronic infiltrate. In the deepest dermis and hypodermis, the fibers are surrounded by fibroplasia and no inflammatory infiltrate is noted. Courtesy of Dr. Pier Alessandro Fanti, Laboratory of Dermatologic Histopathology, University of Bologna, Italy.*

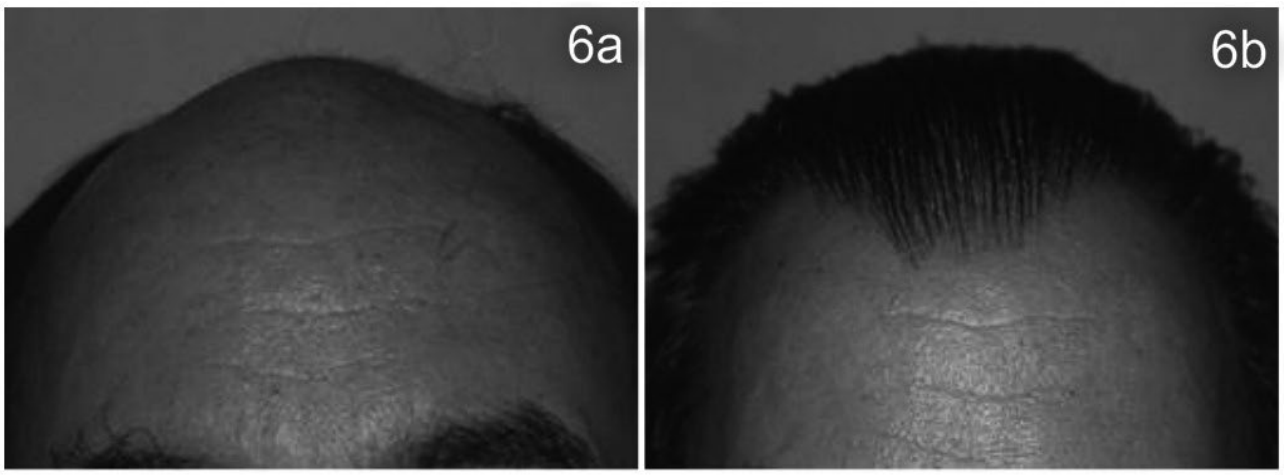

Fig. 6. ***a, b)****: Implant of 7000 Biofibre®; patient previously had a wig.*

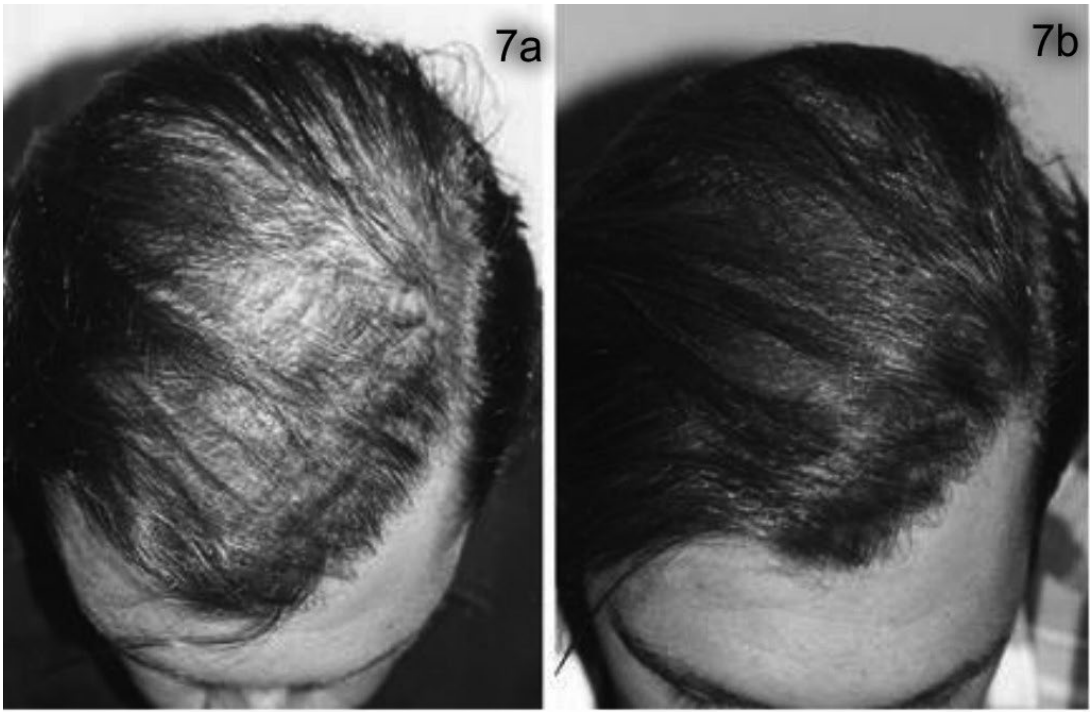

Fig. 7. ***a, b****): Young male patient with 2000 Biofibre®.*

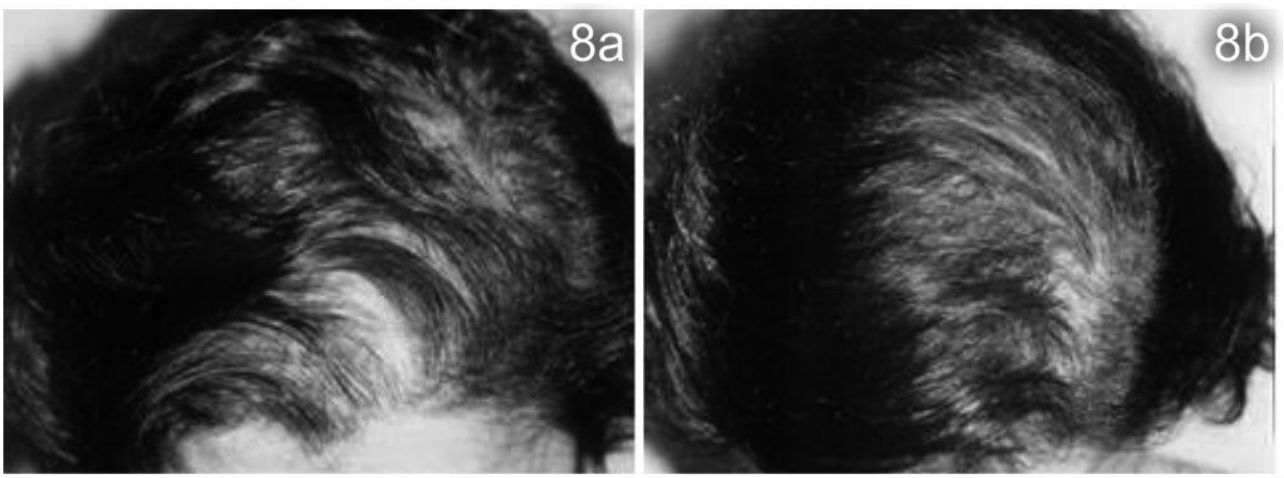

Fig. 8. ***a, b****): Female patient with just 500 Biofibre®.*

trauma and hastens cicatrization and implant procedure by allowing a higher degree of fixation (10). Immediate post-implant care requires that the patient alternately use Betadine and saline spray and wash with ketaconazole shampoo. Systemic antibiotic coverage is recommended for one week after the implant (11), with allowance for adjustments in the specifics of therapy depending upon local circumstances.

Maintenance of scalp hygiene and periodic medical check-ups are required to keep the expected aesthetic results. Follow-up is very important in order to check the patient's scalp and prevent possible complications, such as infection or inflammation.

Biofibre after-care protocol consists of regular follow up, proper scalp hygiene, use of suitable products and avoidance of dangerous products or treatments such as hair bleaching, permanent waving, thermal shocks and hair curlers.

The various behaviors that can lead to problems with the implant procedure include lack of patient hygiene or lack of asepsis during the procedure, excessive density and quantity of implanted fibers in one session, personal fiber intolerance, incorrect choice of implant area and failure in after-care. Most of these problems can be solved with appropriate therapies and change of habits. When the problem is recurrent or cannot be easily resolved with appropriate antibiotics and or corticosteroid therapy, it may be necessary to proceed with fiber removal. The reversible knot of Biofibre does not allow the fiber to fall out from the implant area, but it can be pulled out entirely with appropriate traction. This ability to remove the implant contributes to the overall safety of the procedure, since, once removed, the scalp is healed after several days (7, 13).

Clinical and histological studies

The implant technique was validated with clinical studies and scientific research from the 1990s onwards (14, 15, 16). Difference in the results achieved during the year represent a constant improvement of the technique and related protocols. Over the last 3 years we have treated 133 patients with good immediate results (Fig. 5-8) (12, 17, 18). There were 95 men and 38 women. The most represented age group was between 30 and 60. These patients underwent implants of up to 6000 fibers (average of 5-6 implants in three months). The fiber loss was no more than 10% per year in 91.4% of the cases, 15% in 7.8% of the cases, and 20% in 0.8% of the cases. 96.2% of patients stated that they were satisfied with the results of the implant while 3.8% were not satisfied. As for post-implantation tolerability and complications, 90.3% of the patients recorded no difficulties after surgery. Of the remainder, 5.9% developed mild infection and 3.8% presented with inflammatory changes (mainly from the use of improper chemical substances). Resolution of these infectious and inflammatory issues occurred in 97.9% of the cases within an average of 15 days with the use of systemic antibiotics and/or local corticosteroid therapy. In 2.1% of the cases, it was necessary to remove the fibers, which was accomplished without leaving any lasting scar.

Histological studies after 3 years on Biofibre® (9, 10) have shown that fiber appears surrounded by a keratin layer, hindering bacterial penetration. Thin diameter and proper distances between the fibers reduced the occurrence of rejection phenomena. One infundibulum comprised of Malpighian epithelium, quite similar to the cutaneous one, forms around the implanted fiber. We can consider it as the basis for adequate fiber anchorage. A moderate, controlled inflammatory infiltrate can be noticed. In the middle and deep reticular dermis, the fiber is in contact with collagen. In the hypodermis no inflammatory infiltrate is noticed.

Using the Biofibre Implant offers high hair density within a very short time, with natural-appearing aesthetic results and the accompanying psychological and physical wellness of the patient. The implant is a simple and virtually painless outpatient procedure, which is safe for the patients because it uses biocompatible material. The use of this technique allows the patient to lead an active lifestyle even soon after the implant procedure. The artificial hair does not age, i.e. it will not turn whiter.

One disadvantage of this technique is that the "hair" will not grow, requiring patients to have suitable hygiene of the scalp and proper after-care. Patients with unbalanced diabetes, hepatitis, autoimmune diseases, scalp diseases, or unstable alopecia should not be implanted. In addition, as previously mentioned, some scalp area should not be implanted (temples, low areas of the forehead, along the sideburns). Additionally, small yearly implant sessions are needed to maintain the results.

CONCLUSION

Biofibre Hair Implant is a minor surgery technique, performed under local anaesthesia by a manual implanter or automatic machine, which enables an immediate aesthetic result and the desired quantity of hair without pain or hospitalization. It

can be considered an efficient surgical technique for male and female patients in cases of androgenetic alopecia, hair thinning and to cover scars. Clinical and histological studies demonstrated that Biofibre hair Implant is safe and well tolerated by patients and is totally reversible if needed. This technique requires good after-care, periodic check-ups and yearly implant re-touches to maintain the best aesthetic result. It can be used alone or in combination with other hair restoration techniques [FUE, (Follicular Unit extraction) etc.].

REFERENCES

1. Fukuta K, Narita I, Jodo T. A new procedure of cosmetic prosthetic surgery. Jpn J Plast Reconstr Surg 1976; 19:613.
2. Food and Drug Administration: Listing of banned devices, prosthetic hair fibers. Code of federal regulations 21:895.101.
3. Universal Medical Device Nomenclature System, Prostheses, Hair. Universal Medical Device Code 16611.
4. Directive 93/42/EEC of the Council, 14th of June 1993, concerning Medical Services.
5. Careno N. Injerto de pelo: qué hacer cuando no hay pelo donante? Jornadas Universitarias de la Asociacion de Dermatologia de Chile, Santiago, Chile, 23 of June 2015.
6. Santiago M, Perez Rangel R, D'ugo A, et al. Artificial Hair Fiber Restoration in the Treatment of Scalp Scars. Derm Surg 2007; 33(1):35-44.
7. D'ugo A, Santiago M, Chaker C, Perez Rangel R, Saad Eddin U, Ramponi V. Safety of Biofibre® CE 0373/TGA artificial hair implants: importance of the scalp anchoring system, International Society of Hair Restoration Surgery. 10th Annual Meeting, Chicago, USA, October 9-13, 2002 poster presentation.
8. Perez Rangel R. Cabello Inorganico Biocompatible. Dermatologia Cosmética, Texto Académico, I° edicion 2011, presentacion February 2012 in 8th WCOCD.
9. Fanti PA, Pistorale T, D'Urso C, Misciali C, Tosti A. Histological study on 5 cases of patients who underwent artificial hair implantation without complications. XXXII Annual Meeting, American Society of Dermatopathology, New Orleans, February 01-03, 1995.
10. Santiago M. Estudo histológico de couro cabeludo implantado com fibras artificiais de poliamida, XXXV Congreso Brasileiro de Cirurgia Plástica. Goiânia, November 1-4 1998.
11. D'Ugo A. Protocolo para una óptima implantación de fibras protésicas en cuero cabelludo. X Congreso Internacional de Medicina Estética, Buenos Aires, March 24-26, 1995.
12. Serdev N, D Erme AM, Hercogova J, Zarrab Z, Chokoeva AA, Tchernev G, Wollina U, Lotti T. Polyamide hair implant (Biofibre®): evaluation of efficacy and safety in a group of 133 patients. J Biol Regul Homeost Agents 2015; 29(S1):103-9.
13. Donici D. Biofibre hair implant a modern baldness solution. Imcas 18th International Congress, 28-31 January 2016, Paris, France.
14. Zhilina NV, Igytyan GG, Antonova LE. Clinical anlyses of the results of treatment of alopecia with the Biofibre® implant methodology, Annals of Plastic Reconstr Aethetic Surg 2000; 1:34-36.
15. Palmieri B, Griselli G, D'ugo A, Palmieri G, Salti G. Evaluation of polyamide synthetic hair. A long-term clinical study. Panminerva Med 2000; 42(1):49-53.
16. Sheta M. Modern Artificial Hair Implant. FACE congress, London, UK, 20-22 June 2014.
17. Giovannini M. Securidad y Eficacia de Biofibre implante capilar. VII Jornadas AMECLM, Madrid, Espana, 23 -25 October, 2014.
18. Serdev N. Biofibre implantation-Biofibre Hair Implant: 12-year experience. CCRExpo, London, UK, 10-11 October 2014.

UNCOMMON CLINICAL PRESENTATION OF KIMURA'S DISEASE AS BILATERAL RETROAURICULAR MASSES IN A YOUNG MALIAN MALE: SUCCESSFUL SURGICAL APPROACH

F. FAMA'[1], A. SINDONI[2], G. TCHERNEV[3], A.A. CHOKOEVA[4,5], U. WOLLINA[6], T. LOTTI[7], G.K. MAXIMOV[8], J.W. PATTERSON[9], M. FIORANELLI[10], M.G. ROCCIA[11], A. IENI[1], A. CASCIO[1], M. GIOFFRE'-FLORIO[1] and C. GUARNERI1[2]

[1]Department of Human Pathology, University Hospital of Messina, Messina, Italy; [2]Department of Biomedical and Dental Sciences and of Morphological and Functional Images, University Hospital of Messina, Messina, Italy; [3]Medical Institute of Ministry of Interior (MVR-Sofia), Department of Dermatology, Venereology and Dermatologic Surgery, Sofia, Bulgaria; [4]"Onkoderma"- Policlinic for Dermatology and Dermatologic Surgery, Sofia, Bulgaria; [5]Department of Dermatology and Venereology, Medical University of Plovdiv, Medical Faculty, Plovdiv, Bulgaria; [6]Department of Dermatology and Allergology, Academic Teaching Hospital Dresden-Friedrichstadt, Dresden, Germany; [7]Department of Dermatology, University of Rome "G. Marconi" Rome, Italy; [8]Department "Medicinal Information and Non-Interventional Studies", Bulgarian Drug Agency, Sofia, Bulgaria; [9]University of Virginia Health System, Department of Pathology, Charlottesville, VA USA; [10]History Department, G.Marconi University, Rome, Italy; [11]University B.I.S. Group of Institutions, Punjab Technical University, Punjab, India; [12]Department of Clinical and Experimental Medicine - Section of Dermatology, University Hospital of Messina, Messina, Italy

We present a case of a 27 year-old Malian male referred to our hospital for two large, painless retroauricolar masses that had appeared two years earlier. Bilateral cervical painless lymphadenopathy was present at physical examination, without any other systemic symptoms. His history was relevant for bilateral Kimura's disease lesions resected 5 years earlier in the same locations. Lymphocytosis and a mild hypereosinophilia were found in routine blood tests, together with increased total IgE levels. After surgery, histology showed lymphoid infiltrates with reactive prominent germinal centres containing eosinophils, suggesting relapse of Kimura's disease, in the context of nonencapsulated fibrous proliferation with discontinuous collagen fibers, consistent with keloid. Three months after removal of retroauricular masses, abnormal laboratory findings reverted to normal. To the best our knowledge, this is the first case in literature of bilateral keloid lesions developed after surgery for Kimura Disease and harbouring its histopathologic features. Clinicians should be aware of these unusual reactive phenomena and their possible simulators.

Key words: keloid, Kimura disease, neck, retroauricular, non-Asian

Mailing address:
Fausto Fama', PhD, MD,
Complesso MITO, Residenza Ginestre F/2,
98151 Messina, Italy
Tel.: +390902212406 - Fax: +390902212801
e-mail: famafausto@yahoo.it

0393-974X (2016)

The condition now known as Kimura's disease (KD) was first described in China by Kim and Szeto in 1937, then re-named, on the basis of studies by Kimura *et al.* in 1948, as "abnormal granuloma with proliferation of lymphoid tissue" (1, 2). In 1959, Iizuka *et al* presented a clinical case in which the eponym "Kimura disease" was used for the first time (3). KD is a rare, benign and chronic lymphoproliferative inflammatory disease of unknown etiology and typically seen in young Asian men in the second or third decade of life (4, 5). Painless lesions, regional lymphadenopathy, hypereosinophilia and elevation of serum immunoglobulin E (IgE) levels are the characteristic clinical features of KD (6).

We present a case of bilateral retroauricular masses with histopathological features suggesting relapse of Kimura's disease, successfully excised after preoperative intralesional corticosteroid injection treatment.

Case report

A 27 year-old Malian male complained of two large, almost symmetrical, painless and hard-elastic masses situated over the mastoid areas bilaterally (Fig. 1a, b). The lesions, covered by smooth and shiny skin, had firm consistency and measured 9 and 8 cm in their greatest diameters on the right and left side, respectively. They were described as having developed and gradually enlarged over the previous 2 years, with no constitutional symptoms and no lesions located anywhere else in the body. The patient's history indicated a bilateral excision, carried out in the country of origin five years previously for retroauricular masses, which resulted in a final diagnosis of Kimura's disease. Physical examination revealed bilateral cervical painless lymphadenopathy. Blood tests and urine routine examinations were normal apart from lymphocytosis (48%, normal values 20-35%) and mild hypereosinophilia (8%, n.v. up to 5%). Tuberculin skin test, treponemal and non treponemal tests for syphilis and HIV serology were negative, whereas the immunoglobulin quantification revealed increased total serum IgE levels (660 IU/mL; n.v. <250 IU/ml). A chest X-ray showed no abnormalities. Additionally, contrast-enhanced, computed tomography and magnetic resonance were not helpful. Under local anaesthesia, a punch biopsy (1.5 cm in its largest diameter) on the right-sided lesion was performed and histopathologic findings showed a hyperkeratotic, stratified epidermis with a normal basal cell distribution and a rare basal cell vacuolar alteration. The underlying dermis was characterized by the presence of large, glassy, eosinophilic, focally discontinuous and haphazardly arranged collagen complexes (keloidal collagen) associated with a patchy myxoid extracellular matrix (Figure 1c), resembling a keloid.

The patient underwent wide excision of both lesions which was performed after preoperative intralesional corticosteroid (triamcinolone acetonide) treatment. Post surgical histopathology (haematoxylin-eosin routine stain) confirmed the earlier biopsy findings. Additionally, areas of infiltration by lymphocytes and eosinophils were present and a moderate perivascular chronic inflammatory infiltrate was also noticed (Figure 1d), suggesting a relapse of the KD excised five years earlier. At a three-month follow-up visit, blood test and urine exams showed no abnormalities. An Eighteen-month follow-up visit demonstrated no evidence of recurrences with good cosmetic and functional results.

DISCUSSION

KD is a rare chronic inflammatory and immune-mediated disorder with unclear aetiology-pathogenesis, characterized by a slowly progressive clinical course that waxes and wanes over time, but with no malignant potential (7). Most commonly seen in young Asian males (second-third decade of life), with only sporadic cases reported in the rest of the world, KD usually presents as painless unilateral masses of the head and neck with lymph node and salivary gland involvement, the periauricular area being the favored site of development (7, 8, 9). If untreated, these swellings tend to slowly enlarge, sometimes leading to disfigurement (8, 9). Eosinophilia and elevated serum IgE are also common findings (7). Bilateral masses in the course of KD have been rarely described (9). Since the first report by Kennedy *et al*. in 1992, no more than 10

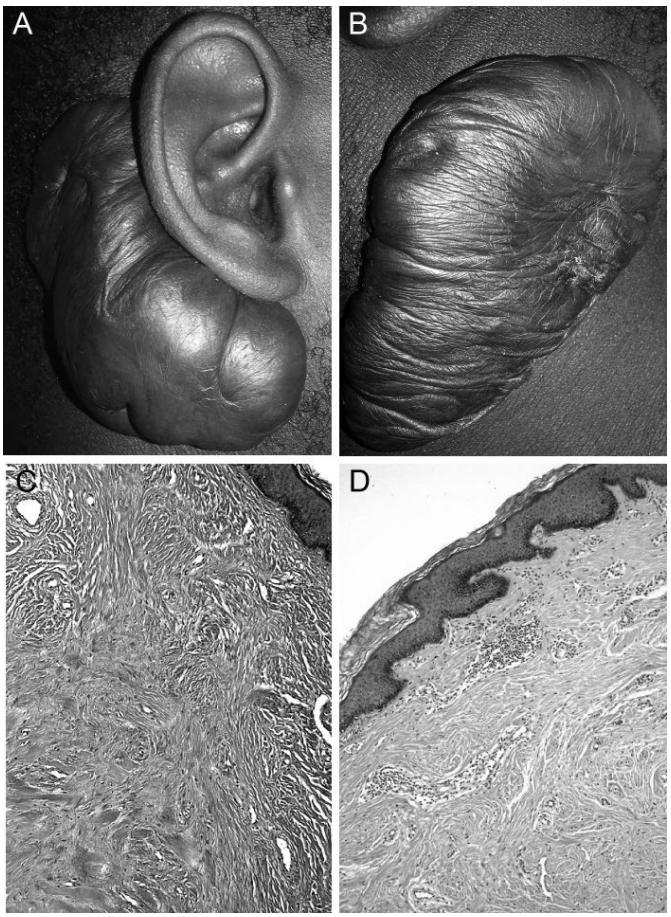

Fig. 1. a)*: Clinical presentation. Right-side retroauricular painless mass;* ***b)****: Left-side retroauricular painless mass;* ***c)****: Nonencapsulated fibrous proliferation with discontinuous collagen fibres;* ***d):*** *Evidence of a moderate perivascular chronic inflammatory infiltrate (D) (Haematoxylin-Eosin stain, original magnification ×200).*

cases have been found in medical literature (10). On the contrary, keloids represent an overgrowth of collagenous tissue following a surgical or traumatic skin injury and are characterized by the presence of thick, hyalinized collagen bundles or "keloidal collagen" with unusual large, dense, wide, glassy, eosinophilic and focally fragmented complexes arranged haphazardly and overlying hyperkeratotic, hyperplastic epidermis. The pathogenesis of keloidal scar is complex, and involves both genetic and environmental factors (11).

This case presented many of the salient features of recurrent KD. The patient was a young male who had developed KD 5 years earlier. He had lesions in typical locations with associated bilateral cervical lymphadenopathy, which followed a chronic course with progressive growth over time. At the time of the diagnosis, he had elevated IgE levels with mild hypereosinophilia. Histopathological features suggested KD relapse, as there were areas of lymphoid infiltrates with reactive germinal centres and eosinophilic infiltrates into the interfollicular zones. Abnormal laboratory findings were not present 3 months after surgery. All these data support the diagnosis of a KD relapse.

The diagnosis of KD can be difficult because clinicians and pathologists are relatively unfamiliar with this disease in Western countries (10). Apart from the anamnestic data and the characteristic laboratory findings, several conditions have to be clinically considered in differential diagnosis, including angiolymphoid hyperplasia with eosinophilia, cutaneous tuberculosis (in particular, scrofuloderma), Sjogren syndrome with parotid

involvement, Hodgkin's disease, Kaposi's sarcoma, nodal metastasis, Warthin's tumour and low grade angiosarcoma (7, 12). In some ethnic groups Keloids are also often considered because they show significant clinical similarities to KD, representing a reactive inflammatory process with indolent clinical course with (at times) the same localization, slow growth, and benign prognosis (13). Surgery is the mainstay of treatment, although regional or systemic corticosteroid treatment, cytotoxic treatment and radiation have also been used (12, 13).

In summary, KD is a chronic condition that mostly occurs in young Asian males, although patients of any ethnicity can be affected, having head and neck masses as a cutaneous hallmark. Bilateral involvement is rare.

To the best our knowledge, this is the first case in the literature of bilateral keloidal lesions developing after surgery for KD and harbouring histopathologic features of KD. Clinicians should be aware of these unusual reactive phenomena and of their possible simulators.

REFERENCES

1. Kim HT, Szeto C. Eosinophilic hyperplastic lymphogranuloma. Comparison with Mikulicz's disease. Chin Med J 1937; 23:699.
2. Kimura T, Yoshimura S, Ishikawa E. On the unusual granulation combined with hyperplastic changes of lymphatic tissues. Trans Soc Pathol Jpn 1948; 37: 179.
3. Iizuka S. Eosinophilic lymphadenitis and granulomatosis: Kimura's disease. Nihon Univ Med J 1959; 18 900.
4. Park SW, Kim HJ, Sung KJ, Lee JH, Park IS. Kimura disease: CT and MR imaging findings. AJNR Am J Neuroradiol 2012; 33:784.
5. Choi WJ, Hur J, Ko JY, Yeo KY, Kim JS, Yu HJ. An unusual clinical presentation of Kimura's disease occurring on the buttock of a five-year-old boy. Ann Dermatol 2010; 22:57.
6. Chung YG, Jee WH, Kang YK, et al. Kimura's disease involving a long bone. Skeletal Radiol 2010; 39:495.
7. Chen H, Thompson LD, Aguilera NS, Abbondanzo SL. Kimura disease: a clinicopathologic study of 21 cases. Am J Surg Pathol 2004; 28:505.
8. Abuel-Haija M, Hurford MT. Kimura disease. Arch Pathol Lab Med 2007; 131:650.
9. Kar IB, Sethi AK. Kimura's Disease: Report of a Case & Review of Literature. J Maxillofac Oral Surg 2013; 12:109.
10. Kennedy SM, Pitts JF, Lee WR, Gibbons DC. Bilateral Kimura's disease of the eyelids. Br J Ophthalmol 1992; 76:755.
11. Jumper N, Paus R, Bayat A. Functional histopathology of keloid disease. Histol Histopathol 2015; 30:1033.
12. Ortak T, Tekin F, Aksoy E, Kerem M, Uraloglu M, Sensoz O. Kimura disease: a brief clinical report. Eur J Plast Surg 2008; 31:253.
13. Yeh SW, Lee WR, Hu CH, Tsai HH. Kimura's disease mimicking an earlobe keloid. Clin Exp Dermatol 2010; 35:e97.

LANGERHANS CELL SARCOMA: AN UNUSUAL MICROSCOPIC PRESENTATION

A.L. GAGNON[1], S. DANIEL[2], K. GREER[1], J.W. PATTERSON[2], G. TCHERNEV[3], A.A. CHOKOEVA[4,5], U.WOLLINA[6], T. LOTTI[7], M. FIORANELLI[8], M.G. ROCCIA[9], C. GUARNERI[10] and N. AGUILERA[11]

[1]Department of Dermatology, University of Virginia Health System, Charlottesville, Virginia, USA; [2]Departments of Pathology and Dermatology, University of Virginia Health System, Charlottesville, Virginia, USA; [3]Medical Institute of Ministry of Interior (MVR-Sofia), Department of Dermatology, Venereology and Dermatologic Surgery, Sofia, Bulgaria; [4]"Onkoderma"- Policlinic for Dermatology and Dermatologic Surgery, Sofia, Bulgaria; [5]Department of Dermatology and Venereology, Medical University of Plovdiv, Medical Faculty, Plovdiv, Bulgaria; [6]Department of Dermatology and Allergology, Academic Teaching Hospital Dresden-Friedrichstadt, Dresden, Germany; [7]Department of Dermatology, University of Rome "G. Marconi" Rome, Italy; [8]History Department, G. Marconi University, Rome, Italy; [9]University B.I.S. Group of Institutions, Punjab Technical University, Punjab, India; [10]Department of Clinical and Experimental Medicine, Unit of Dermatology University Hospital of Messina, Messina, Italy; [11]Department of Pathology, University of Virginia Health System, Charlottesville, Virginia, USA

A 70-year-old Caucasian male presented to our clinic for a pruritic eruption progressing over several months. He complained of fatigue with a 20-pound weight loss over the past year. On presentation, the patient had browny-yellow to violaceous, purpuric, macular and papular lesions on the legs, arms, lower abdomen and back. Initial biopsy showed an angiocentric infiltrate with a suggestion of intraluminal proliferation; CD31 and Fli-1 positivity suggested either reactive angioendotheliomatosis or an unusual intravascular histiocytosis. Further excisional biopsies demonstrated perivascular collections of cells with ample cytoplasm, prominent nuclear pleomorphism and mitotic activity. The nuclei demonstrated nuclear folding, grooves and indentations. The atypical cells were S100, CD1a and CD56 positive with immunohistochemistry. A diagnosis of Langerhans cell sarcoma (LCS) was made. LCS is a rare, aggressive malignancy that can involve multiple organs including the skin, lymph nodes, lung, bone marrow, spleen, heart, and brain. The skin and lymph nodes are commonly involved, and the cutaneous presentation varies greatly. Immunohistochemistry characteristically shows CD1a and S100 positivity. CD56 expression is uncommon and often portends a poor prognosis. There is no established treatment of LCS due to its rarity. Surgery, radiation, and chemotherapy have been used with varied outcomes. Our patient was treated with prednisone with improvement of cutaneous disease. He did not develop systemic involvement, but died 1.5 years later from complications associated with heart failure. Langerhans cell sarcoma should be considered when faced with an unusual angiocentric infiltrate in which initial immunohistochemical staining results may be misleading.

key words: Langerhans cell sarcoma, angiocentric infiltrate

Mailing address:
James W. Patterson, MD,
Department of Pathology,
University of Virginia Health System,
1215 Lee Street, Box 800214,
Charlottesville, VA 22908 USA
e-mail: jwp9e@virginia.edu

0393-974X (2016)

Neoplasms of Langerhans cells have been classified into benign Langerhans cell histiocytosis and malignant Langerhans cell sarcoma by the World Health Organization in 2001 (1). Langerhans cell sarcoma (LCS) is a rare malignancy characterized by multi-organ involvement and an aggressive clinical course (1).To date, approximately 32 cases (including our case) of LCS have been reported (2, 3, 4, 5). Of the cases reported, only 15 presented with cutaneous findings, either alone or in combination with systemic involvement and the presentation varied greatly among patients (4). We report a case of Langerhans cell sarcoma with an unusual cutaneous presentation.

Case report

A 70-year-old Caucasian male with past medical history of coronary artery disease, hypertension, diabetes mellitus, and chronic tobacco abuse presented to our clinic for a pruritic dermatitis that had progressed over several months. The eruption began on the patient's legs and was described by his primary care physician as non-blanching macules. These eventually spread to involve his lower abdomen, back, and upper extremities. He complained of severe fatigue with a 20-pound unintentional weight loss over the past year. Recently, he had a normal chest radiograph and colonoscopy.

On physical examination, the patient had a brown-yellow to violaceous, purpuric, macular and papular eruption becoming confluent on the legs, arms, lower abdomen, and back. Overlying ichthyosis of his bilateral lower extremities was noted (Fig. 1a, b). Our initial clinical differential diagnosis included a lichenoid reaction and a form of pigmented purpuric dermatosis.

Histologic findings

The patient had two initial biopsies demonstrating what appeared to be an angiocentric infiltrate of macrophages and lymphocytes with erythrocyte extravasation (Fig.2 a). Histopathologically, a granulomatous dermatitis or angioendotheliomatosis was considered, which did not correlate with the clinical findings.

Due to the clinicopathologic discrepancy, multiple immunohistochemical studies were performed (Fig. 2b). The perivascular cells were largely negative for CD68 and CD123. Some of the cells stained positively for S100. The cells were markedly positive for CD31 and Fli-1 but negative for other vascular markers (Factor VIII, Ulex, and CD34). The accompanying lymphocytic inflammation was found to be negative for T-cell receptor or Immunoglobulin gene rearrangements. The staining patterns and the clinical presentation, again, did not correlate and so a subsequent set of biopsies was taken including a biopsy from an area of more recent clinical involvement.

These excisional biopsies demonstrated similar perivascular collections of cells with ample cytoplasm. However, these cells displayed more prominent nuclear pleomorphism and mitotic activity. The nuclei demonstrated nuclear folding, grooves and indentations. Once again, these cells were positive for CD31 and Fli-1 and were largely negative for CD207 (Langerin), CD68 and CD123. The largest, most atypical cells were positive for S100 positive as well as CD45RO, CD43, CD5 and CD4. An immature T-cell lymphoma was considered but these large cells failed to stain for CD2, CD3, CD7, CD8, and TdT. Due to the partial S100 positivity and the cytology, a CD1a stain was performed which diffusely stained the large atypical perivascular cells (Fig. 2c). Given these staining patterns, a diagnosis of Langerhans cell sarcoma was made. CD56 expression was present, which is rare in LCS but when positive may indicate a poor prognosis.

The previous two biopsies were retrospectively examined and similar nuclear cytology was seen, though with significantly less nuclear pleomorphism and mitotic activity. However, close re-inspection did reveal cells with enlarged and atypical folded nuclei in these previous two biopsies that had previously gone unnoticed.

Clinical course

We obtained laboratory studies including a complete blood count, comprehensive metabolic panel, ESR, LDH, and hepatitis panel. All test results were normal except the findings of leukopenia,

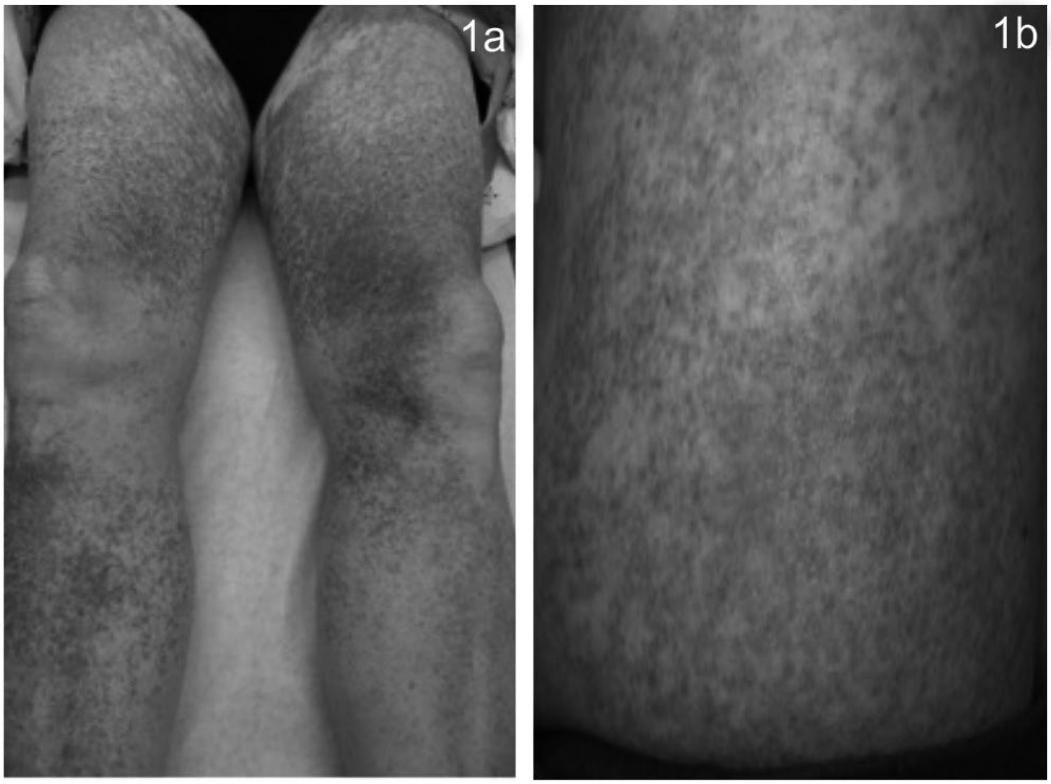

Fig. 1. ***a)****: Clinical presentation of patient with a brown-yellow to violaceous, purpuric, macular and papular eruption becoming confluent on the legs;* ***b):*** *Similar cutaneous involvement of the arms, lower abdomen, and back.*

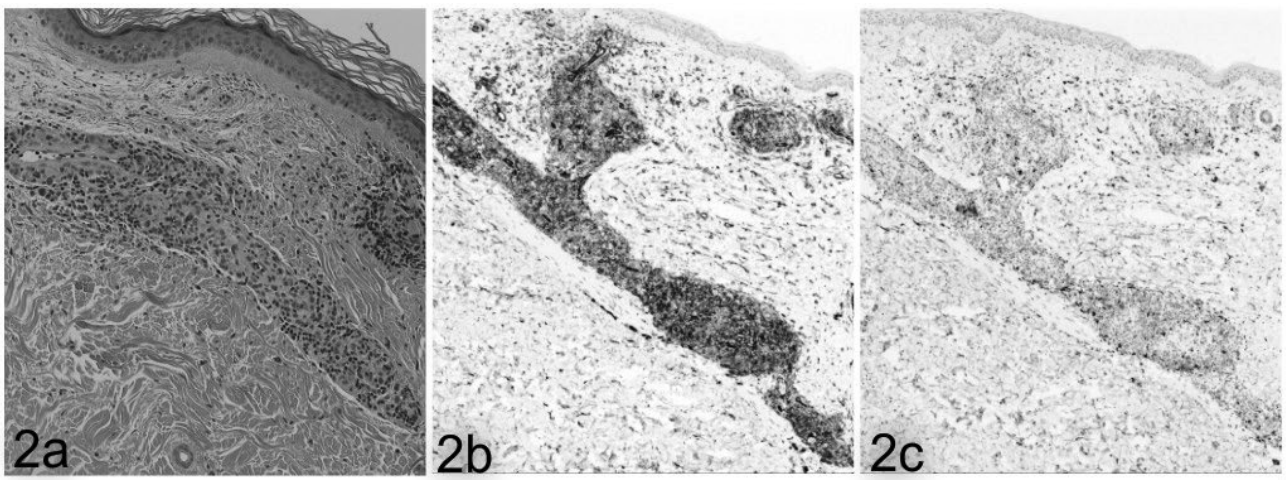

Fig. 2. ***a)****: Initial biopsy showing angiocentric infiltrate of macrophages and lymphocytes with erythrocyte extravasation;* ***b)****: Immunohistochemical studies were performed showing a) perivascular cells markedly positive for CD31. (Immunoperoxidase, CD31). b) These perivascular cells were largely negative for CD68. (Immunoperoxidase, CD68). c) The largest, most atypical cells were positive for S100. (Immunoperoxidase, S100). D) Perivascular cells negative for Ulex. (Immunoperoxidase, Ulex);* ***c):*** *Excisional biopsies demonstrated collections of cells with ample cytoplasm, more prominent nuclear pleomorphism, and mitotic activity. The nuclei demonstrated nuclear folding, grooves and indentations. Due to the partial S100 positivity and the cytology, a CD1a stain was performed which diffusely stained the large atypical perivascular cells. (Immunoperoxidase, CD1a).*

anemia, and an elevated ESR: WBC 3,490 k/uL, hemoglobin 13.9 g/dL, hematocrit 39.2%, ESR 43. A BRAF mutation analysis was performed with skin biopsy and was negative.

After diagnosing LCS, the patient was sent to our malignant hematology clinic for further evaluation. A computerized tomography (CT) scan of the abdomen did not show visceral disease. A bone marrow biopsy showed normal trilineage hematopoiesis. Our patient was treated with prednisone with improvement of cutaneous disease, but subsequent relapse with cutaneous lesions on the face after discontinuation. He was again reinitiated on prednisone. He did not develop systemic involvement, but died 1.5 years later from complications associated with heart failure.

DISCUSSION

Langerhans cells are antigen presenting dendritic cells present in the suprabasal epithelium of the skin and mucous membranes (5, 6). Langerhans cells are positive for CD1a and S100, and contain characteristic intracytoplasmic organelles known as Birbeck granules (4).

Neoplasms of Langerhans cells are classified into—benign Langerhans cell histiocytosis and malignant Langerhans cell sarcoma (LCS) (4, 7). While Langerhans cell histiocytosis follows an indolent chronic course, Langerhans cell sarcoma is characterized by an aggressive clinical behavior with high 5-year mortality rates (4, 8). LCS was first recognized by Wood and colleagues in 1984 as "malignant histiocytosis X" to describe a rapidly fatal mass with tumor infiltration of multiple organs (9). Histiocytic cell proliferations have been variably defined in the past but were recently classified by the International Lymphoma Study Group based on morphologic, ultrastructural and immunohistochemical properties.

Tumors of histiocytes and dendritic cells are classified into four groups: 1) histiocytic sarcoma, 2) Langerhans cell tumor (cytologically typical and Langerhans cell sarcoma (cytologically malignant), 3) interdigitating dendritic cell tumor/sarcoma and 4) follicular dendritic cell tumor/sarcoma (3, 10). LCS can involve multiple organs including the skin, lymph nodes, lung, bone marrow, spleen, heart, and brain. The skin and lymph nodes are most commonly involved (11, 12). Unlike Langerhans cell histiocytosis, which typically occurs in childhood and adolescence, LCS usually occurs in third to fourth decade (12, 13, 14). It can occur at any age, and the majority of patients die within 2 years of diagnosis (15, 16).

Valentin-Nogueras recently reported a case of LCS and reviewed 30 previously reported cases of Langerhans sarcoma in literature. They found that 15 patients presented with skin lesions, either alone or in combination with systemic involvement, and of these, five patients had only skin involvement (4). The cutaneous findings of these patients included nodules, ulcerated nodules, tumors, ulcerated erythematous plaques, ulcerated tumors, and soft tissue masses. The case reported by Valentin-Nogueras was the only one to describe purpuric macules, which were also seen in our patient's case (4).

There is no established treatment for LCS due to the small number of cases (2, 3). Surgery, radiation, chemotherapy and combinations of these have been used in the past, with varied outcomes (3, 5). Chen et al (2013) reported a case of Langerhans Cell Sarcoma arising from Chronic Lymphocytic Lymphoma. Clonality study with FISH analysis showed the two entities were clonally related and BRAF V600E mutation was detected for the first time in LCS (8). The finding has spurred interest in using the monoclonal antibody vemurafenib that targets BRAF V600E mutant (8). Currently, the Food and Drug Administration have approved Vemurafenib for therapy of BRAF V600E mutant metastatic melanoma (6).

Unfortunately, due to its aggressive nature, the overall survival rate of LCS is less than 50% (4, 7, 17).

CONCLUSION

In conclusion, we report a case of LCS presenting with a cutaneous eruption of purpuric macular and papular lesions and usual histologic findings of an angiocentric infiltrate with initially misleading immunohistochemical staining. If feasible, we recommend re-biopsy and additional immunohistochemical workup when

clinicopathologic discrepancy is encountered.

ACKNOWLEDGEMENTS

Joel Pinczewski, MD, PhD, first suspected the diagnosis of Langerhans cell sarcoma microscopically and made substantial efforts to establish the diagnosis in this case.

REFERENCES

1. Ferringer T, Banks PM, Metcalf JS. Langerhans cell sarcoma. Am J Dermatopathol 2006; 28(1):36-9.
2. Sumida K, Yoshidomi Y, Koga H, et al. Leukemic transformation of Langerhans cell sarcoma. Int J Hematol 2008; 87(5):527-31.
3. Tani M, Ishii N, Kumagai M, Ban M, Sasase A, Mishima Y. Malignant langerhans cell tumour. Br J Dermatol 1992; 126(4):398-403.
4. Valentin-Nogueras SM, Seijo-Montes R, Montalvan-Miro E, Sanchez JL. Langerhans cell sarcoma: A case report. J Cutan Pathol 2013; 40(7):670-5.
5. Wang C, Chen Y, Gao C, Yin J, Li H. Multifocal langerhans cell sarcoma involving epidermis: A case report and review. Diagn Pathol 2012; 7(99):1596-99.
6. Chakraborty R, Hampton OA, Shen X, et al. Mutually exclusive recurrent somatic mutations in MAP2K1 and BRAF support a central role for ERK activation in LCH pathogenesis. Blood 2014; 124(19):3007-15.
7. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2011; 364(26):2507-16.
8. Chen W, Jaffe R, Zhang L, et al. Langerhans cell sarcoma arising from chronic lymphocytic Lymphoma/Small lymphocytic leukemia: Lineage analysis and BRAF V600E mutation study. N Am J Med Sci 2013; 5(6):386-91.
9. Wood C, Wood GS, Deneau DG, Oseroff A, Beckstead JH, Malin J. Malignant histiocytosis X. report of a rapidly fatal case in an elderly man. Cancer 1984; 54(2):347-52.
10. Howard JE, Dwivedi RC, Masterson L, Jani P. Langerhans cell sarcoma: a systematic review. Cancer Treat Rev 2015; 41(4):320-31.
11. Kawase T, Hamazaki M, Ogura M, et al. CD56/NCAM-positive Langerhans cell sarcoma: a clinicopathologic study of 4 cases. Int J Hematol 2005; 81(4):323-9.
12. Kairouz S, Hashash J, Kabbara W, McHayleh W, Tabbara IA. Dendritic cell neoplasms: An overview. Am J Hematol 2007; 82(10):924-8.
13. Lauritzen AF, Ralfkiaer E. Histiocytic sarcomas. Leuk Lymphoma 1995; 18(1-2):73-80.
14. Pileri SA, Grogan TM, Harris NL, et al. Tumours of histiocytes and accessory dendritic cells: An immunohistochemical approach to classification from the international lymphoma study group based on 61 cases. Histopathology 2002; 41(1):1-29.
15. Li Y, Li B, Tian XY, Li Z. Unusual cutaneous langerhans cell sarcoma without extracutaneous involvement. Diagn Pathol 2013; 8(20):1596-20.
16. Subbiah V, Subbiah IM. Killing two birds with one stone: BRAF V600E inhibitor therapy for hairy cell leukemia and Langerhans/dendritic cell sarcoma. Ann Hematol 2013; 92(8):1149(013):1681-9.
17. Zhao G, Luo M, Wu ZY, et al. Langerhans cell sarcoma involving gallbladder and peritoneal lymph nodes: A case report. Int J Surg Pathol 2009; 17(4):347-53.

PULMONARY AND ABDOMINAL SARCOIDOSIS, THE GREAT IMITATORS ON IMAGING?

C. TANA[1], G. TCHERNEV[2], A.A. CHOKOEVA[3,4], U. WOLLINA[5], T. LOTTI[6], M. FIORANELLI[7], M.G. ROCCIA[8], G.K. MAXIMOV[9] and M. SILINGARDI[10]

[1]Internal Medicine Unit, Guastalla Hospital, AUSL Reggio Emilia, Italy; [2]Medical Institute of Ministry of Interior (MVR-Sofia), Department of Dermatology, Venereology and Dermatologic Surgery, Sofia, Bulgaria; [3]"Onkoderma"-Policlinic for Dermatology and Dermatologic Surgery, Sofia, Bulgaria; [4]Department of Dermatology and Venereology, Medical University of Plovdiv, Medical Faculty, Plovdiv, Bulgaria; [5]Department of Dermatology and Allergology, Academic Teaching Hospital Dresden-Friedrichstadt, Dresden, Germany; [6]Department of Dermatology, University of Rome "G. Marconi" Rome, Italy; [7]History Department, G. Marconi University, Rome, Italy; [8]University B.I.S. Group of Institutions, Punjab Technical University, Punjab, India; [9]Department "Medicinal Information and Non-Interventional Studies", Bulgarian Drug Agency, Sofia, Bulgaria; [10]Department of Pathology, University of Virginia Health System, Charlottesville, Virginia, USA

Sarcoidosis is an insidious disorder that virtually affects every body organ. Lungs are the site most often affected (in up to 90 % of patients) followed by intra thoracic more often than peripheral lymph nodes and other sites can be involved in different percentages. The evaluation of pulmonary sarcoidosis is best performed with high-resolution computed tomography (HRCT), as traditional chest X-ray has a low resolution and can be negative or give non-significant results. Disorders such as interstitial lung diseases (ILDs), tuberculosis, lung cancer and lymphangitis carcinomatosis can manifest with similar radiological findings that can deceive clinics and radiologists. The need of a clear distinction between these conditions is important not only for diagnostic purposes but also because treatment differs significantly in different conditions. However, conventional Ultrasound (US) can be negative if small lesions are present and false negative images can result if US is not followed by a contrast-imaging technique. Contrast enhanced computed tomography (CECT) and magnetic resonance imaging (CEMRI) are preferred to detect single or multiple masses, which appear hypodense and hypointense after contrast agent administration, respectively. We think that a correct algorithm should include a thorough clinical and radiological evaluation, a definite biopsy of affected tissues revealing classical non-caseating granulomas and a certain exclusion of conditions that can give similar clinical/histophatological patterns before considering the diagnosis of sarcoidosis. Only in these cases, a diagnosis of sarcoidosis can be sufficiently achieved before starting an appropriate treatment.

Sarcoidosis is an insidious disorder that virtually affects every body organ. The term sarcoidosis was coined by Caesar Boeck from the fusion of the greek words *σαρκ* (sarc) and *ουδ* (oid), meaning a flesh-like condition (1). The key feature of this uncommon disorder is the granuloma, a non-necrotizing lesion that tend to become chronic in absence of an appropriate treatment (1, 2). Lungs are the sites most

Key words: sarcoidosis, CECT, CEMRI,Utrasound, Imitators

Mailing address:
Claudio Tana M.D,
Internal Medicine Unit ,
Guastalla Hospital,
AUSL Reggio Emilia,
Reggio Emilia (RE) Italy
e-mail: claudio.tana@yahoo.it

0393-974X (2016)

often affected (in up to 90 % of patients), followed by intra thoracic more often than peripheral lymph nodes (2, 3) and other sites such as skin, heart (4), eyes (5), liver, spleen (6), gastrointestinal, genitourinary districts (7), neuroendocrine and nervous system (both central and peripheral) (8) can be involved in different percentages. The mainstay of treatment is characterized by corticosteroids as first-line therapy, followed by immunosuppressive agents if the first are ineffective. Diagnosis can be very difficult because a) a clinical suspicion sometimes is not present without symptoms of lung involvement; b) several other conditions can easily mimic sarcoidosis and c) imaging findings are often not specific due to non-specific macroscopic appearance of these lesions (9, 10, 11). The evaluation of pulmonary sarcoidosis is best performed with HRCT, because traditional chest X-ray has a low resolution and can be negative or give non-significant results. Four classes of disease can be found with HRCT (12):

1. Bilateral hilar lymphadenopathy (Stage I).
2. Bilateral hilar lymphadenopathy with lung infiltrates (Stage II)
3. Parenchymal infiltrates in absence of hilar lymphadenopathy (Stage III).
4. Advanced disease and complications such as lung fibrosis, emphysema, bullae, cavitations and hilar retraction (Stage IV), which have the worse prognosis.

Disorders such as ILDs, tuberculosis, lung cancer and lymphangitis carcinomatosis can manifest with similar radiological findings that can deceive clinics and radiologists. The need of a clear distinction between these conditions is important not only for diagnostic purposes, but also because treatment differ significantly in the various conditions. Risk of misdiagnosis is high also with hepatosplenic sarcoidosis (10, 13, 14) which can manifest with diffuse (most often homogeneous) hepatosplenomegaly in absence of prominent lesions or with hypo, iso and hyperechoic avascular lesions on B-mode and color Doppler US. Lymph node enlargement can be found in up to 76 % of cases (15). However, conventional ultrasound can be negative if small lesions are present, and false negative images can result if US is not followed by a contrast-imaging technique.

CECT and CEMRI are preferred to detect single or multiple masses that appear hypodense and hypointense after contrast agent administration, respectively (16, 17). In addition, contrast-enhanced ultrasound (CEUS) can reveal sarcoid nodules despite a negative conventional ultrasound, and this technique is more advantageous than CECT and CEMRI because it does not use nephrotoxic contrast agents and there is no risk of radiation exposure (18). In this regard, CEUS has great potential in the evaluation of hepatosplenic sarcoidosis, but there is need of large controlled trials (evidence is obtained mostly from case series) that aim to compare CEUS findings with those of CECT and CEMRI before considering CEUS as an alternative second-line imaging technique (19).

Diseases such as lymphoma, hepatocellular carcinoma and abdominal tuberculosis can give similar findings on imaging and can generate a great diagnostic confusion, also because sometimes these disorders coexist (20, 21, 22). Although techniques such as CECT and CEMRI can reveal lung dysfunction, organ and lymph node enlargement and/or hepatosplenic prominent sarcoid lesions, these findings are not specific if isolated and in absence of a high clinical suspicion. For these reasons, the histopathological evaluation of affected organ and tissues is mandatory every time there is the suspect of sarcoidosis (23, 24) as both clinical and imaging findings can overlap with those of most common disorders and differential diagnosis is broad and insidious (25, 26, 27).

We think that a correct algorithm should include a through clinical and radiological evaluation, a definite biopsy of affected tissues revealing classical noncaseating granulomas and a certain exclusion of conditions that can give similar clinical/histophatological patterns (28, 29, 30) before considering the diagnosis of sarcoidosis. Only in these cases, a diagnosis of sarcoidosis can be achieved before starting an appropriate treatment.

REFERENCES

1. Grutters JC, Drent M, Van den Bosch JMM. Sarcoidosis. Eur Respir Mon 2009; 46:126-154.
2. Morgenthau AS, Teirstein AS. Sarcoidosis of the upper and lower airways. Expert Rev Respir Med 2011; 5(6):823-33.
3. Soto-Gomez N, Peters JI, Nambiar AM. Am Fam Physician. 2016; 93(10):840-8.
4. Kandolin R, Lehtonen J, Kupari M. Cardiac sarcoidosis. J Intern Med 2016; doi:10.1111/joim.12498.
5. Pasadhika S, Rosenbaum JT. Ocular Sarcoidosis. Clin Chest Med. 2015; 36(4):669-83.
6. Valeyre D, Prasse A, Nunes H, Uzunhan Y, Brillet PY, Müller-Quernheim J. Sarcoidosis. Lancet 2014; 29; 383(9923):1155-67.
7. Vardhanabhuti V, Venkatanarasimha N, Bhatnagar G, Maviki M, Iyengar S, Adams WM, Suresh P. Extra-pulmonary manifestations of sarcoidosis. Clin Radiol 2012; 67(3):263-76.
8. Tana C, Wegener S, Borys E, Pambuccian S, Tchernev G, Tana M, Giamberardino MA, Silingardi M. Challenges in the diagnosis and treatment of neurosarcoidosis. Ann Med 2015; 47(7):576-91.
9. Chokoeva AA, Tchernev G, Tana C, Ananiev J, Wollina U. Sarcoid-like pattern in a patient with tuberculosis. J Biol Regul Homeost Agents 2014; 28(4):783-8.
10. Tana C, Iannetti G, Mezzetti A, Schiavone C. Splenic sarcoidosis remains a diagnostic challenge. J Clin Ultrasound 2014; 42(3):156.
11. Tchernev G, Tana C, Schiavone C, Cardoso JC, Ananiev J, Wollina U. Sarcoidosis vs. Sarcoid-like reactions: The Two Sides of the same Coin? Wien Med Wochenschr 2014; 164(13-14):247-59.
12. Statement on sarcoidosis. Joint statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. Am J Respir Crit Care Med 1999; 160(2):736-55.
13. Bauones S, Le Corroller T, Durieux O, Guenoun D, Del Grande J, Pirro N, Champsaur P. Splenic sarcoidosis mimicking neoplastic disease. J Clin Ultrasound 2014; 42(1):38-41.
14. Tana C, Iannetti G, D'Alessandro P, Tana M, Mezzetti A, Schiavone C. Pitfalls of contrast-enhanced ultrasound (CEUS) in the diagnosis of splenic sarcoidosis. J Ultrasound 2013; 16(2):75-80.
15. Folz SJ, Johnson CD, Swensen SJ. Abdominal manifestations of sarcoidosis in CT studies. J Comput Assist Tomogr 1995; 19:573-579.
16. Warshauer DM, Lee JK. Imaging manifestations of abdominal sarcoidosis. AJR Am J Roentgenol 2004; 182(1):15-28.
17. Kessler A, Mitchell DG, Israel HL, Goldberg BB. Hepatic and splenic sarcoidosis: ultrasound and MR imaging. Abdom Imaging 1993; 18(2):159-63.
18. Tana C, Dietrich CF, Schiavone C. Hepatosplenic sarcoidosis: contrast-enhanced ultrasound findings and implications for clinical practice. Biomed Res Int 2014; 2014:926203.
19. Tana C, Silingardi M, Dietrich CF. New trends in ultrasound of hepatosplenic sarcoidosis. Z Gastroenterol 2015; 53(4):283-4.
20. London J, Grados A, Fermé C, et al. Sarcoidosis occurring after lymphoma: report of 14 patients and review of the literature. Medicine (Baltimore) 2014; 93(21):e121.
21. Chalayer É, Bachy E, Occelli P, et al. Sarcoidosis and lymphoma: a comparative study. QJM 2015; 108(11):871-8.
22. Agrawal R, Kee AR, Ang L, et al. Tuberculosis or sarcoidosis: Opposite ends of the same disease spectrum? Tuberculosis (Edinb) 2016; 98:21-6.
23. Shorr AF, Torrington KG, Hnatiuk OW. Endobronchial biopsy for sarcoidosis: a prospective study. Chest 2001; 120(1):109-14.
24. Ma Y, Gal A, Koss MN. The pathology of pulmonary sarcoidosis: update. Semin Diagn Pathol 2007; 24(3):150-61.
25. Govender P, Berman JS. The Diagnosis of Sarcoidosis. Clin Chest Med. 2015; 36(4):585-602.
26. Palmucci S, Torrisi SE, Caltabiano DC, et al. Clinical and radiological features of extra-pulmonary sarcoidosis: a pictorial essay. Insights Imaging 2016; (epub ahead of print).
27. Soto-Gomez N, Peters JI, Nambiar AM. Diagnosis and Management of Sarcoidosis. Am Fam Physician

2016; 93(10):840-8.
28. Judson MA, Costabel U, Drent M, et al. The WASOG Sarcoidosis Organ Assessment Instrument: An update of a previous clinical tool. Sarcoidosis Vasc Diffuse Lung Dis 2014; 31(1):19-27.
29. Wessendorf TE, Bonella F, Costabel U. Diagnosis of Sarcoidosis. Clin Rev Allergy Immunol 2015; 49(1):54-62.
30. Chokoeva AA, Tchernev G, Tana M, Tana C. Exclusion criteria for sarcoidosis: A novel approach for an ancient disease? Eur J Intern Med 2014; 25(10):e120.

INTERSTITIAL GRANULOMATOUS DERMATITIS DEMONSTRATING SMALL, DISCRETE SKIN-COLORED PAPULES

N. KANAZAWA[1], G. TCHERNEV[2], A.A. CHOKOEVA[3,4], G.K. MAXIMOV[5], U.WOLLINA[6], T. LOTTI[7], J.W. PATTERSON[8], C. GUARNERI[9], C. TANA[10] and F. FURUKAWA[1]

[1]Department of Dermatology, Wakayama Medical University, Wakayama, Japan; [2]Medical Institute of Ministry of Interior (MVR-Sofia), Department of Dermatology, Venereology and Dermatologic Surgery, Sofia, Bulgaria; [3]"Onkoderma"- Policlinic for Dermatology and Dermatologic Surgery, Sofia, Bulgaria; [4]Department of Dermatology and Venereology, Medical University of Plovdiv, Medical Faculty, Plovdiv, Bulgaria; [5]Department "Medicinal Information and Non-Interventional studies", Bulgarian Drug Agency, Sofia, Bulgaria; [6]Department of Dermatology and Allergology, Academic Teaching Hospital Dresden-Friedrichstadt, Dresden, Germany; [7]Department of Dermatology, University of Rome "G. Marconi" Rome, Italy; [8]University of Virginia Health System, Department of Pathology, Charlottesville, VA USA; [9]Department of Clinical and Experimental Medicine, Unit of Dermatology University Hospital of Messina, Messina, Italy; [10]Internal Medicine Unit, Guastalla Hospital, AUSL Reggio Emilia, Italy

We report the case of a 67-year-old female with a rare variant of interstitial granulomatous dermatitis showing multiple skin-colored papules. Clinically, numerous skin-colored or reddish papules were distributed on her back and posterior thighs with itchy scaly erythema on the upper back. After topical steroid application, skin-colored papules still remained after the disappearance of itchy scaly erythema. Histopathologically, perivascular and interstitial infiltration of lymphocytes and histiocytes with occasional multinucleated giant cells were observed in the superficial and mid reticular dermis, accompanied by mild mucin deposition. Interstitial granulomatous dermatitis is similar to interstitial granuloma annulare, but can be differentiated from it by lesser degrees of collagen degeneration with mucin deposition and frequent association with arthritis or rheumatic diseases. As previously reported, multiple asymptomatic skin-colored papules are considered a rare but distinct variant of interstitial granulomatous dermatitis. Although no apparent underlying disorder has developed in the presented case, careful follow-up needs to be continued.

Interstitial granulomatous dermatitis (IGD) is a distinct entity, which was histopathologically defined by Ackerman in 1993 (1). However, histological differentiation of IGD from the interstitial type granuloma annulare is not always easy. Since more than half of the IGD cases are reportedly accompanied by arthritis or rheumatic disorders, clinical differentiation should also be important (2). Although erythematous papules and plaques are typically observed, skin-colored multiple papules are considered to represent a distinct variant of IGD.

Case report

A 67-year-old Japanese female had a 3-year

Key words: interstitial granulomatous dermatitis, interstitial granuloma annulare, diagnosis, treatment

Mailing address:
Dr. Nobuo Kanazawa,
Department of Dermatology, Wakayama Medical University,
Kimiidera 811-1, Wakayama 641-0012, Japan
Tel.: +81-73-441-0661 - Fax: +81-73-448-1908
e-mail: nkanazaw@wakayama-med.ac.jp

0393-974X (2016)

history of multiple small asymptomatic papules on the upper back. Although topical steroid ointment was effective, skin lesions had recurred and gradually extended to the lower back and posterior thighs after discontinuation of the treatment. As she additionally noticed itching on her back, she was consulted in the outpatient clinic of the Dermatological Department of Wakayama Medical University. On physical examination, multiple skin-colored or reddish small papules of around 1-2 mm diameter were widely distributed in the upper and lower back and posterior thighs with focal accumulation in some areas. Scaly and erythematous changes were also observed in the upper back (Fig. 1a). She had experienced no apparent internal disorders, although her mother and grandmother suffered from diabetes mellitus and her mother suffered from type C hepatitis.

Although an underlying metabolic abnormality was suspected, no abnormalities were detected in the levels of glucose, hemoglobin A1c, hepatic transaminases, creatinine, uric acid, free thyroid hormones, thyroid stimulating hormone, cortisol, immunoglobulins or complement in her serum. Blood cell counts were within normal limits. Anti-nuclear antibody (ANA) of homogenous-pattern was weakly positive at a titer of 1:80. Although the serum level of total cholesterol was slightly elevated at 225 mg/dl, the triglyceride level was within normal range. Scaly and erythematous changes immediately improved through application of a topical corticosteroid with emollient, but the papular lesions remained. Histological assessment of a papule revealed intact epidermis and perivascular and interstitial infiltration of lymphocytes and histiocytes with occasional multinucleated giant cells in the superficial and mid-reticular dermis (Fig. 2a, b). Multiple empty spaces around swollen degenerative collagen bundles, associated with surrounding lymphohistiocytic infiltration, represented the "floating sign" (Fig. 2b). With alcian blue staining, a moderate degree of mucin deposition was observed around the infiltrating cells in the superficial and mid reticular dermis (Fig. 2c). Chest roentgenogram and ophthalmologic examination revealed no significant abnormalities. Based upon these observations, the diagnosis of interstitial granulomatous dermatitis

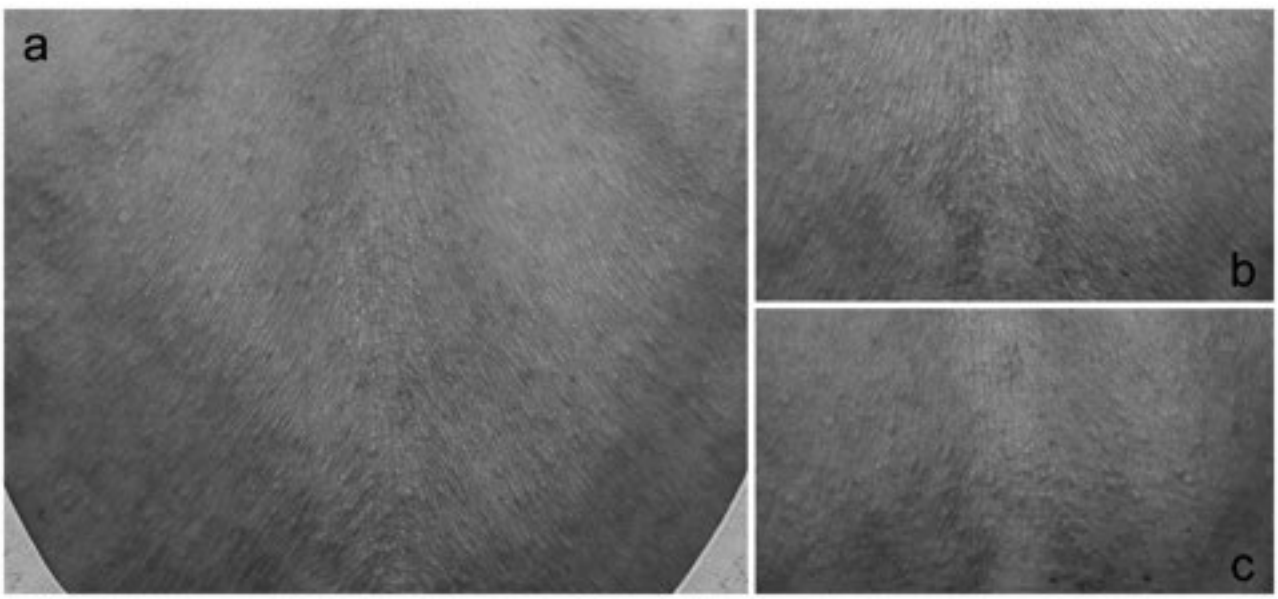

Fig. 1. ***a)****: Pictures of the patient's back skin. Multiple skin-colored or reddish small papules of around 1-2 mm diameter were widely distributed on her back with focal accumulation in some areas;* ***b, c)****: Scaly and erythematous changes were also observed. (Repeated disappearance and appearance of skin-colored small papules occurred on her back, despite continuous topical steroid application*

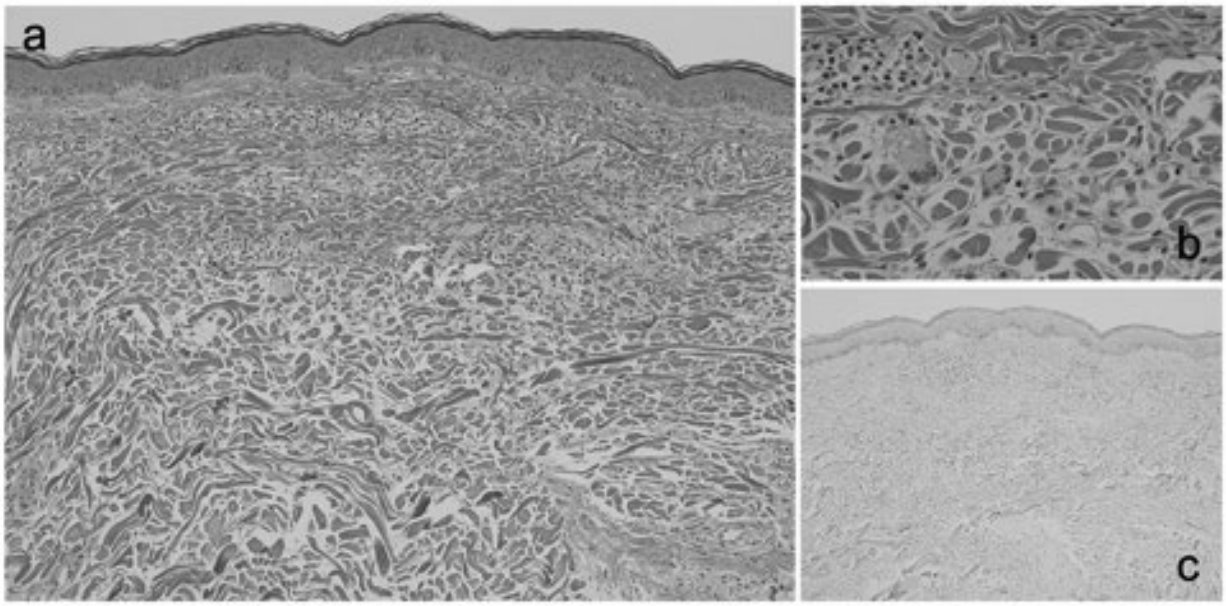

Fig. 2. *a): Histological images from biopsy of a skin-colored papule on the patient's back. Hematoxylin and eosin stain. Original magnification x100; b): Hematoxylin and eosin stain. Original magnification x400; c): Alcian blue stain. Original magnification x100.*

was made, although any detectable underlying internal disease was absent. Topical application of a very strong class corticosteroid ointment was effective for the established papular lesions, though papules repeatedly appeared and disappeared asymptomatically despite continuous application of the topical steroid (Fig. 1b, c).

DISCUSSION

Typically, granuloma annulare (GA) is characterized clinically by skin-colored infiltrating annular lesion and histologically by palisading granulomas surrounding degenerated collagen. However, the concept of GA includes other variants without these typical characteristics, including papular, subcutaneous, erythematous, perforating and generalized types in the clinical classification and interstitial and epithelioid/sarcoidal types in the histological classification (3).

Histologically, interstitial type GA does not show clear-cut palisading but instead displays histiocytic infiltration among collagen bundles with milder mucin deposition, and is considered an earlier change of GA.

IGD, sometimes called as IGD with arthritis or Ackerman syndrome, is a disease that was histopathologically defined by Ackerman in 1993 (1). Interstitial infiltration of histiocytes among collagen bundles without palisading is characteristic.

Histological differentiation of IGD from the interstitial type GA can be difficult, although less collagen degeneration and less mucin deposition are related to IGD. Another related entity, called palisading neutrophilic granulomatous dermatitis (PNGD), was proposed by Chu et al in 1994 (4) to include Churg-Strauss granuloma, cutaneous extravascular necrotizing granuloma, rheumatoid papules, superficial ulcerating rheumatoid necrobiosis and IGD with arthritis. PNGD was originally defined to include IGD, however, typical PNGD, which is characterized by infiltration of neutrophils with nuclear dust, can usually be differentiated from IGD, which is typically accompanied by infiltration of only a small number of neutrophils and/or eosinophils (2). According to a summary of 53 IGD cases reported up to 2010, after exclusion of PNGD, Churg-Strauss syndrome and histiocytic Sweet syndrome, three times more female than male patients were affected and the average age at disease onset was 52 years (2). The most common clinical phenotype presented as

multiple papules and plaques ranging in color from skin-colored to erythematous (70-90%); multiple skin-colored papules represented a rare presentation.

In most cases, eruptions were distributed symmetrically over the lateral sides of the trunk and the inner surfaces of the proximal extremities. Eruptions were usually asymptomatic, but were occasionally accompanied by burning and/or itching. More than half of the cases showed joint symptoms or signs such as arthralgia and/or arthritis. Furthermore, serum ANA level was slightly or moderately elevated in about half of the cases. Twenty to 30% of the patients developed rheumatic diseases such as rheumatoid arthritis, seronegative nonerosive polyarthritis and systemic lupus erythematosus, while 6% developed hematological diseases such as hemolytic anemia, leukopenia and cryoglobulinemia. Underlying internal malignancy was also reported in about 9%. On histology, the "floating sign" was frequently observed; this represents histiocytic rosette formation surrounding empty spaces adjacent to focally degenerated collagen. In contrast, multinucleated giant cells were rarely observed.

The picture of multiple discrete skin-colored papules presented in our case looks quite similar to that reported by Proni et al.(2). In that report two women, aged 32 and 56 years showed asymptomatic, skin-colored, symmetrical small papules on the trunk and extremities. The younger patient suffered from arthralgias, fibromyalgia, hypergammaglobulinemia and leukopenia, while the older patient had manifested HLAS-B27^{+} spondyloarthritis since childhood with high serum ANA titer (x640). On biopsy, abundant mucin deposition was observed in the younger patient but was absent in the older individual. Topical corticosteroid was effective in the younger patient but the eruption had appeared 7 years before diagnosis and recurred during a 2-year follow-up period. In the older patient, the eruption had appeared 2 years before diagnosis and disappeared within 4 months after administration of etanercept. In our case, no apparent underlying disorder had developed 4 years after disease onset. However, eruptions have repeatedly appeared despite continuous topical corticosteroid application, and careful follow-up is still necessary.

In conclusion, this is a case of 67-year-old female with a rare variant of IGD showing multiple skin-colored papules. Multiple small, asymptomatic, skin-colored papules seems to be a rare but distinct variant of IGD. Further accumulation of similar cases with careful histological observation and clinical follow-up is needed.

REFERENCES

1. Ackerman AB. Histologic diagnosis of inflammatory skin diseases: interstitial granulomatous arthritis. Clues to Diagnosis in Dermatology 1993; 3:309-12.
2. Peroni A, Colato C, Schena D, Gisondi P, Girolomoni G. Interstitial granulomatous dermatitis: a distinct entity with characteristic histological and clinical pattern. Br J Dermatol 2012; 166:775-83.
3. Mizuno K. Granuloma annulare, not limited to annular lesion with palisading granuloma, but showing a variety of clinicopathological presentations which cannot be considered as a single entity. Jap J Dermatol 2015; 125:2067-71.
4. Chu P, Connolly MK, LeBoit PE. The histopathologic spectrum of palisading neutrophilic and granulomatous dermatitis in patients with collagen vascular disease. Arch Dermatol 1994; 130:1278-83.

MEDIUM-SIZED CONGENITAL MELANOCYTIC NEVUS OF THE FOREHEAD, GLABELLA AND TEMPLE – SURGICAL TREATMENT AND LONG-TERM FOLLOW-UP

A. GOLDMAN[1], U. WOLLINA[2], G. TCHERNEV[3], A.A. CHOKOEVA[4,5] AND T. LOTTI[6]

[1]Clinica Goldman, Porto Alegre/RS, Brazil; [2]Department of Dermatology and Allergology, Academic Teaching Hospital Dresden-Friedrichstadt, Dresden, Germany; [3]Medical Institute of Ministry of Interior (MVR-Sofia), Department of Dermatology, Venereology and Dermatologic Surgery, Sofia, Bulgaria; [4]"Onkoderma"- Policlinic for Dermatology and Dermatologic Surgery, Sofia, Bulgaria; [5]Department of Dermatology and Venereology, Medical University of Plovdiv, Medical Faculty, Plovdiv, Bulgaria; [6]Department of Dermatology, University of Rome "G. Marconi" Rome, Italy

Congenital melanocytic nevi can be stigmatising for the patient. Larger nevi bear an increased risk for melanoma development. Large congenital melanocytic nevi may be a symptom of neurocutaneous melanosis. We report on a 5-year-old boy with an extensive hair-bearing facial congenital melanocytic nevus, covering forehead, glabella and temple region associated with unilateral brow and blepharoptosis. The lesion was excised en bloc. The resulting defect had been closed by full thickness skin graft. Healing was unremarkable and long-term follow-up over 13 years demonstrated a satisfying esthetic and functional outcome. There was no evidence of melanoma development. Surgery is an option for disfiguring larger congenital melanocytic nevi as long as esthetics and function can be preserved. Long-term follow-up is recommended due to the increased risk of melanoma.

Congenital melanocytic nevi (CMN) are defined as nevi present on skin surface at the time of birth. CMN occur in 1-3% of newborns and in about 3% with multiplicity (1, 2). Etiology of CMN development is not fully understood (2). Melanocytic nevus cells in general derive from the neural crest. It has been suggested that CMN may originate from somatic stem cells in the bulge area of hair follicles, from transformed nerve sheath stem cells or migrating embryonic stem cells (2). There are experimental data suggesting that large postnatal CMN host a subpopulation of clonogenic and tumorigenic nevus cells capable of self-renewal and interaction with keratinocytes (3).

They can be classified by size. CMN size categories include: small (<1.5 cm); medium (M1: 1.5-10 cm, M2: >10-20 cm); large (L1: >20-30 cm, L2: >30-40 cm); and giant (G1: >40-60 cm, G2: >60 cm). Other parameters are the number of satellite nevi in the first year of life, anatomic localization, color heterogeneity, surface rugousity, presence of hypertrichosis and dermal or subcutaneous nodules (4).

We report on a patient with a medium-sized CMN of the face, surgical treatment and long-term follow-up.

Case report

In this report, we present a long-term follow-up

Key words: congenital melanocytic nevi, melanoma, surgery, transplantation

Mailing address:
Prof. Dr. Uwe Wollina,
Department of Dermatology and Allergology,
Academic Teaching Hospital Dresden-Friedrichstadt,
Friedrichstrasse 41,
01067 Dresden, Germany
e-mail: wollina-uw@khdf.de

0393-974X (2016)

of a surgical resection of a congenital melanocytic nevus (CMN). A 5-year-old male patient presented an extensive hairy congenital melanocytic nevus of the forehead, temporal and glabellar region. There was a unilateral brow and associated blepharoptosis (Fig. 1a). There was no family history of any similar lesion. The neurological examination was normal and there were no associated anomalies.

The physical examination revealed an extensive pigmented hairy patch which covered all skin surface of the forehead, right temporal area and glabella. Clinical evaluation demonstrated no other associated congenital anomalies. X-ray, ultrasonography and other imagine analysis were normal.

The patient underwent surgery. The tumor, measuring approximately 15 cm x 5 cm, was removed surgically in a single block (Fig. 1b, c). A primary skin grafting was carried out, with the full thickness

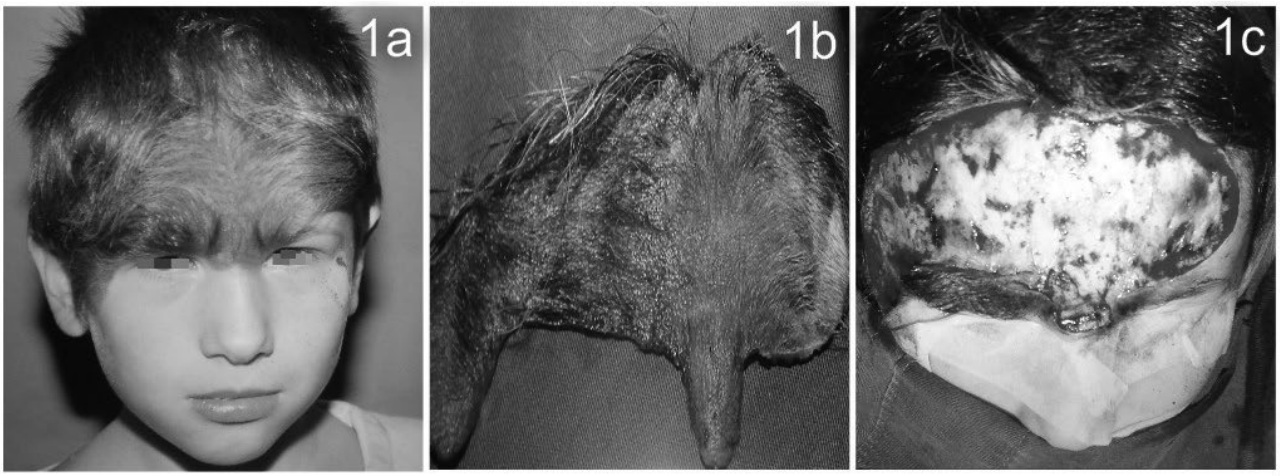

Fig. 1. ***a)****: Extensive hairy congenital melanocytic nevus in a 5-year-old boy. Unilateral brow ptosis and blepharoptosis on the right side.* ***b)****: Surgical treatment. En bloc-resection of the congenital melanocytic nevus.* ***c)****: The resected facial defect.*

Fig. 2. ***a)****: - Follow-up 5 years after the surgical procedure.* ***b)****: Follow up after another 3 years with satisfying esthetic and functional result.*

skin graft being taken from the lower abdomen. Histopathological examination demonstrated a congenital melanocytic nevus. No evidence of a malignant transformation was observed. The esthetic and functional results were satisfactory (Fig. 2a).
The 13 year' follow-up of the transplant did not show any problems. The patient is currently 25-years-old with no evidence of pigmented skin alterations or melanoma development (Fig. 2b).

DISCUSSION

Congenital melanocytic nevi (CMN) of the face bear psychological and functional problems and a possible cancer risk (5). Whereas smaller CMN do not pose a significant risk for melanoma development, the risk reaches about 0.7% to 5% in those with GMN larger than 20 cm in diameter (6, 7, 8, 9). Mutations that have been observed in cutaneous melanomas can be observed in CMN as well (8, 9). In a study NRAS Q61 mutations affected about 80% to 95% of giant and large CMN and 62.5% to 70% of smaller CMN. BRAF mutation were identified in 5% of large and 11.4% of giant CMN and up to 30% in smaller CMN (10, 11). Melanoma development can be cutaneous or extra cutaneous (10). Patients with large CMN should be investigated by magnetic resonance imaging of the brain to exclude neurocutaneous melanosis (7). A periodic total body skin examination is recommended for patients with large GMN even after complete excision of the nevus (7). The development of melanoma within a large CMN is a rare event; survival is comparable to superficial spreading melanoma without CMN (12). Melanoma development has also been reported on medium-sized CMN (13).

The treatment is surgical and the goal is to obtain optimal esthetic results (8). For large CMN of the face excision with transplantation, use of dermal templates, defect closure by flaps, serial sections, and the use of (osmotic) tissue expanders is possible (8, 14, 15, 16, 17, 18). Curettage is an option mainly for extra facial lesions (19).

We report on a medium-sized CMN per definition, although it covered a large area of the face. Due to the hairy appearance, it was stigmatizing for the patient when he was a student. En bloc-excision was performed and the defect was covered by a full thickness skin graft. Neither evidence of any recurrence nor development of melanoma was noted. The patient is still satisfied with the outcome after 13 years of follow-up (Fig. 3b).

Our case was also remarkable due to the associated unilateral brow and blepharoptosis. We could identify only one other case from India. It was a 16-year-old girl with neurocutaneous melanosis and tuberous sclerosis complex (20). In contrast to this, our patient had no indication of neurocutaneous melanosis nor tuberous sclerosis complex.

CONCLUSION

Patients with large to giant congenital melanocytic nevi bear an increased risk of melanoma development during their life. Therefore, there is a need of life-long dermatological follow-up. Since these nevi can easily be stigmatizing, especially when located on the face, surgical removal is an option. The major goal is to reduce the nevus cell burden while ensuring good functional and esthetic results in the long term.

REFERENCES

1. Kanada KN, Merin MR, Munden A, Friedlander SF. A prospective study of cutaneous findings in newborns in the United States: correlation with race, ethnicity, and gestational status using updated classification and nomenclature. J Pediatr 2012; 161(2):240-5.
2. El-Moneim AA, El-Dawela RE. Survey of skin disorders in newborns: clinical observation in an Egyptian medical centre nursery. East Mediterr Health J 2012; 18(1):49-55.
3. Charbel C, Fontaine RH, Kadlub N, et al. Clonogenic cell subpopulations maintain congenital melanocytic nevi. J Invest Dermatol 2015; 135(3)824-33.
4. Krengel S, Scope A, Dusza SW, Vonthein R, Marghoob AA. New recommendations for the categorization of cutaneous features of congenital melanocytic nevi. J Am Acad Dermatol 2013; 68(3):441-51.
5. Captier G. The congenital melanocytic nevi of

the face in child: What's new? Rev Stomatol Chir Maxillofac Chir Orale 2015; 116(4):187-99.
6. Krengel S, Hauschild A, Schäfer T. Melanoma risk in congenital melanocytic naevi: a systematic review. Br J Dermatol 2006; 155(1):1-8.
7. Price HN, Schaffer JV. Congenital melanocytic nevi - when to worry and how to treat: Facts and controversies. Clin Dermatol 2010; 28(3):293-302.
8. Arad E, Zuker RM. The shifting paradigm in the management of giant congenital melanocytic nevi: review and clinical applications. Plast Reconstr Surg 2014; 133(2):367-76.
9. Yun SJ, Kwon OS, Han JH, et al. Clinical characteristics and risk of melanoma development from giant congenital melanocytic naevi in Korea: a nationwide retrospective study. Br J Dermatol 2012; 166(1):115-23.
10. Salgado CM, Basu D, Nikiforova M, Bauer BS, Johnson D, Rundell V, Grunwaldt LJ, Reyes-Múgica M. BRAF mutations are also associated with neurocutaneous melanocytosis and large/giant congenital melanocytic nevi. Pediatr Dev Pathol 2015; 18(1):1-9.
11. Charbel C, Fontaine RH, Malouf GG, et al. NRAS mutation is the sole recurrent somatic mutation in large congenital melanocytic nevi. J Invest Dermatol 2014; 134(4):1067-74.
12. Turkeltaub AE, Pezzi TA, Pezzi CM, Dao H Jr. Characteristics, treatment, and survival of invasive malignant melanoma (MM) in giant pigmented nevi (GPN) in adults: 976 cases from the National Cancer Data Base (NCDB). J Am Acad Dermatol 2016; 74(6): 1128-34.
13. Kiyohara T, Takata M, Itoh H, Kawami K, Ido H, Ishida H, Kumakiri M. Malignant melanoma arising from an NRAS-mutated medium-sized congenital melanocytic nevus. J Dermatol 2012; 39(12):1034-5.
14. Venugopal PR. Giant congenital melanocytic nevi of face - primary excision with reconstruction using self-filling osmotic expanders. Indian J Surg 2015; 77(S3):1201-4.
15. Tønseth KA, Filip C, Hermann R, Vindenes H, Høgevold HE. Extraordinary large giant congenital melanocytic nevus treated with Integra dermal regeneration template. Plast Reconstr Surg Glob Open 2015; 3(7):e469.
16. Hassanein AH, Rogers GF, Greene AK. Management of challenging congenital melanocytic nevi: outcomes study of serial excision. J Pediatr Surg 2015; 50(4):613-6.
17. Zaal LH, van der Horst CM. Results of the early use of tissue expansion for giant congenital melanocytic naevi on the scalp and face. J Plast Reconstr Aesthet Surg 2009; 62(2):216-20.
18. Chokoeva AA, Tchernev G, Trayanova E, Patterson JW, Lotti T, Wollina U. Giant congenital melanocytic nevus localized in the axillary area: serial excisions as optimal treatment option. J Biol Regul Homeost Agents 2015; 29(1S):123-8.
19. Gatibelza ME, Denis D, Bardot J, Casanova D, Degardin N. Current place of curettage in the management of giant congenital nevi: report of 29 patients. Ann Chir Plast Esthet 2013; 58(3):228-34.
20. Rai S, Kalakoti P, Syed MA, Thacker PJ, Jain R, Kalra G. An unusual case of congenital melanocytic nevus presenting as neurocutaneous melanoma coexisting with tuberous sclerosis complex: A case report. J Med Case Rep 2011; 5:267.

GIANT CONGENITAL MELANOCYTIC NEVUS IN A BULGARIAN NEWBORN

A.A. CHOKOEVA[1,2], M. FIORANELLI[3], M.G. ROCCIA[4], T. LOTTI[5]
U. WOLLINA[6] and G. TCHERNEV[7]

[1]"Onkoderma"- Policlinic for Dermatology and Dermatologic Surgery, Sofia, Bulgaria; [2]Department of Dermatology and Venereology, Medical University of Plovdiv, Medical Faculty, Plovdiv, Bulgaria; [3]History Department, G. Marconi University, Rome, Italy; [4]University B.I.S. Group of Institutions, Punjab Technical University, Punjab, India; [5]Department of Dermatology, University of Rome "G. Marconi" Rome, Italy; [6]Department of Dermatology and Allergology, Academic Teaching Hospital Dresden-Friedrichstadt, Dresden, Germany; [7]Medical Institute of Ministry of Interior (MVR-Sofia), Department of Dermatology, Venereology and Dermatologic Surgery, Sofia, Bulgaria

Giant congenital melanocytic nevus (GCMN) is a rare disorder affecting 1 in 200,000–500,000 live births. Central nervous system defects such as spina bifida, meningocele, Dandy Walker malformation may accompany it and thus cause significant morbidity. Despite the related risk for malignant transformation, GCMNs may be associated with neurocutaneous melanosis, a rare syndrome in which a giant CMN or multiple smaller CMNs are accompanied by melanocytic deposition in the brain and the spinal cord. We present a case of a 5-day-old newborn with giant congenital melanocytic nevus on his back, as we discuss the diagnostic and treatment approach.

Congenital melanocytic nevi (CMN) are benign proliferations that may be associated with various consequences depending on their size (1). Giant congenital melanocytic nevus (GCMN) is a rare disorder affecting 1 in 200,000-500,000 live births (2). It is regarded as giant CMN when it involves more than 20 cm in greatest dimension or >9 cm in the scalp or more than 6 cm in the trunk (as in the present case) (3). In about 82% of cases, the disease is axially distributed (2). Central nervous system (CNS) defects such as spina bifida, meningocele, Dandy Walker malformation may accompany it and thus cause significant morbidity (4). Furthermore, invasive malignant melanoma (MM) could arise in CMN in adults, with overall survival rate similar to that in superficial spreading melanoma (5). Clinicians should be aware of the continued risk of MM in adults with GCMN with low threshold for biopsy (5).

We focus the readers' attention on a case of a newborn with GCMN on the back, as we discuss the diagnostic and treatment approach.

Case report

A 5-day-old, otherwise healthy male newborn, born from first normally proceeded pregnancy and healthy parents, consulted with a dermatologist because of a giant pigmented lesion located on his back. The lesion presented at the time of birth, as few smaller satellite lesions were noticed later. No family

Key words: congenital melanocytic nevi, giant form, diagnosis, treatment

Mailing address:
Prof. Georgi Tchernev,
Medical Institute of Ministry of Interior (MVR),
Department of Dermatology, Venereology and Dermatologic Surgery,
General Skobelev blvd. 79, 1606 Sofia, Bulgaria
Tel.: 00359 885 588424
e-mail: georgi_tchernev@yahoo.de

0393-974X (2016)

history for dermatologic diseases was reported, neither other abnormalities related to the pregnancy and the delivery.

Within the dermatologic examination, a giant melanocytic nevus was observed, covering almost the whole skin on the back (Fig. 1a). The lesion was dark brown to black, with irregular borders and pigmentation on the peripheral areas, without elevation from the surrounding tissue, as no nodular areas were detected on palpation (Fig. 1b). No other abnormalities were established within the conducted laboratory blood tests and neonatology screening.

DISCUSSION

Congenital melanocytic nevi represent abnormal collections of melanocytes that arise in different locations (6). Melanoblasts begin to develop from 5 weeks gestation and later migrate from the neural crest to various locations, including the skin, mucosa, eyes and meninges (6). Dysregulation of this process leads to aberrant growth, resulting in occurrence of melanocytic nevi (6). The giant variant of CMNs is the rarest among them with an incidence of approximately 1 in 200.000, predominantly female (6). The typical clinical manifestation of CMNs present as hyperpigmented, initially flat lesions that change their appearance with age and growing process (6). As a child grows, CMNs can undergo color variegation, hypertrichosis, nodular formation, and ulceration (6). They most commonly occur on the trunk, followed by the extremities and head and neck region (1, 2). Smaller satellite nevi can often be seen at other locations dispersed across the body (6). Lesions may be also associated with pruritus or ulceration (6).

Congenital melanocytic nevi are classified according to their size: small nevi with a diameter of less than 1.5 cm and medium nevi with diameters between 1.5 and 19.9 cm (2). They are defined as giant if they exceed 20 cm at their greatest diameter and occupy 2% or more of the total body surface area or are predicted to reach 20 cm by adulthood (2).

Despite the related risk for malignant transformation, GCMNs may be associated with neurocutaneous melanosis, a rare syndrome in which a giant CMN or multiple smaller CMNs are accompanied by melanocytic deposition in the brain and the spinal cord (8). Risk factors for neurocutaneous melanosis are midline nevi and the presence of more than 20 satellite nevi (6, 8). Symptoms include hydrocephalus, seizures, developmental delay and cranial nerve palsy (6). Prognosis is poor in symptomatic patients, with death usually occurring within 2 to 3 years of diagnosis (9). Congenital melanocytic nevi can also undergo malignant conversion and although the frequency varies widely throughout the literature, most report a 1% to 5% transformation rate (10, 11).The lifetime risk for malignant melanoma in a

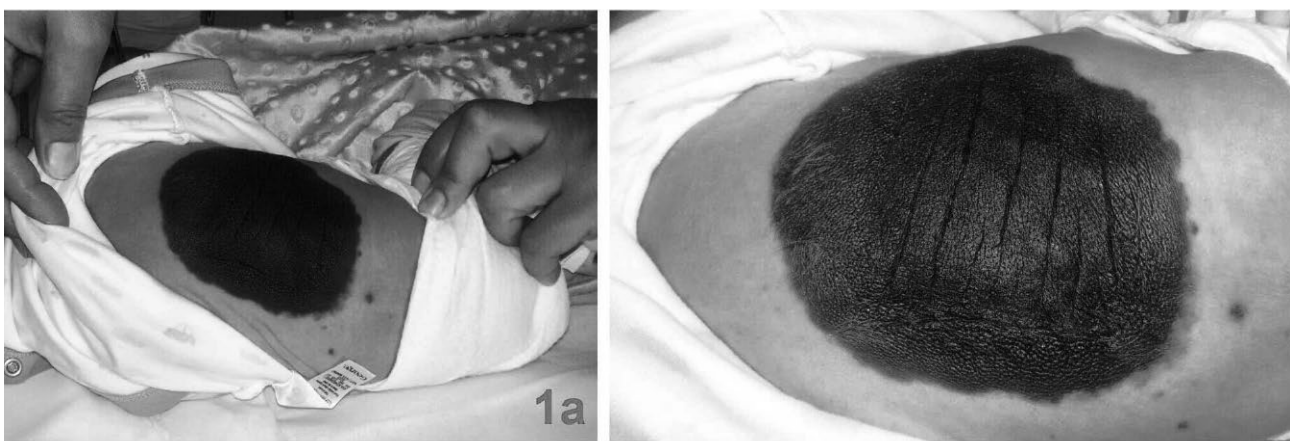

Fig. 1. ***a****): Clinical manifestation of a giant congenital melanocytic nevus on the back of a 5-day-old newborn;* ***b****): The lesion was dark brownish to black colored, with irregular borders and pigmentation on the peripheral areas, without elevation from the surrounding tissue, as no nodular areas were detected on palpation.*

patient with a CMN is approximately 6.3%, or a 17-fold increase compared with the general population (6). Risk factors for malignant transformation include 3 or more nevi, nevi greater than 20 cm in diameter and a younger age of onset (12). Although these considerations require a mandatory screening, no uniform screening programs are yet available. The recommended initial examination should include mandatory neurological screening with CT and MRI, PET scan, with further performance of confocal microscopy (if possible) instead of only dermatoscopy. LDH and S-100 should also be evaluated as a part of the initial screening, especially in patients with GCMN.

As malignancy rates increase with age, many surgeons stress the importance of early and complete excision (6). The most important types of treatment used for CMNs are serial excision, tissue expansion, and skin grafting (6). Serial excisions are performed when the lesion can be excised in two 3-5 stages. Approximately 6 months between excisions should be allowed so that tissues have ample time to recover (6). Serial excision has a low complication profile and offers patients time for psychosocial adjustment due to the gradual correction of the nevus (6). If additional surgical procedures (more than 3) are anticipated, tissue expansion may be also a choice. Expansion typically occurs over a course of 3 to 6 months (6).

Total surgical excision followed by Integra and split-thickness skin grafting has been described in the treatment of giant CMNs (13). Schiestl et al. reported high take rates and excellent functional and cosmetic outcomes using this method on nevi covering up to 12% of the total body surface area (13). Disadvantages of this technique are its high cost and susceptibility to infection before biointegration of the template (13).

In our case, we have decided to perform 3 serial excisions in 6 months intervals, in order to provide enough repair and recover time. We consider this technique as an optimal prevention and curative option regarding associated risks for further transformation on one hand and the aesthetic results on the other hand and to avoid the psycho-emotional negative impact on patients in elderly age. The choice of the type of therapy is subjective and should be made based on the physician's experience, patient's age and general condition, size and location of the nevus. Mandatory screening is recommended in all patients with giant forms of CMN.

REFERENCES

1. Guégan S, Kadlub N, Picard A, et al. Varying proliferative and clonogenic potential in NRAS-mutated congenital melanocytic nevi according to size. Exp Dermatol 2016; doi: 10.1111/exd.13073 [Epub ahead of print].
2. Bhagwat PV, Tophakhane RS, Shashikumar BM, Noronha TM, Naidu V. Giant congenital melanocytic nevus (bathing trunk nevus) associated with lipoma and neurofibroma: Report of two cases. Indian J Dermatol Venereol Leprol 2009; 75:495-8.
3. Imchen S, Ghosh S, Dayal S, Marwah N, Jindal N, Sangal S. Giant congenital melanocytic nevus with developmental dysplasia of bilateral hip: A rare association. Indian J Dermatol 2013; 58:475-7.
4. Ansarin H, Soltani-Arabshahi R, Mehregan D, Shayanfar N, Soltanzadeh P. Giant congenital melanocytic nevus with neurofibroma-like changes and spina bifida occulta. Int J Dermatol 2006; 45:1347-50.
5. Turkeltaub AE, Pezzi TA, Pezzi CM, Dao H Jr. Characteristics, treatment, and survival of invasive malignant melanoma (MM) in giant pigmented nevi (GPN) in adults: 976 cases from the National Cancer Data Base (NCDB). J Am Acad Dermatol 2016; 74(6):1128-34.
6. Marano AA, Feintisch AM, Datiashvili R. Giant Congenital Melanocytic Nevus of the Buttock. Eplasty 2015; 15:ic31. eCollection 2015.
7. Bittencourt FV, Marghoob AA, Kopf AW, et al. Large congenital melanocytic nevi and the risk for development of malignant melanoma and neurocutaneous melanocytosis. Pediatrics 2000; 106(4):736-41.
8. Araújo C, Resende C, Pardal F, Brito C. Giant congenital melanocytic nevi and neurocutaneous melanosis. Case Rep Med 2015; 2015:545603.
9. Agero AL, Benvenuto-Andrade C, Dusza SW, et al. Asymptomatic neurocutaneous melanocytosis in

patients with large congenital melanocytic nevi: a study of cases from an Internet-based registry. J Am Acad Dermatol 2005; 53(6):959-65.
10. Marghoob AA, Schoenbach SP, Kopf AW, et al. Large congenital melanocytic nevi and the risk for the development of malignant melanoma. A prospective study. Arch Dermatol 1996; 132(2):170-5.
11. Ruiz-Maldonado R, Tamayo L, Laterza AM, et al. Giant pigmented nevi: clinical, histopathologic, and therapeutic considerations. J Pediatr 1992; 120(6):906-11.
12. Arneja JS, Gosain AK. Giant congenital melanocytic nevi. Plast Reconstr Surg 2007; 120(2):26e-40e.
13. Schiestl C, Stiefel D, Meuli M. Giant naevus, giant excision, eleg(i)ant closure? Reconstructive surgery with Integra Artificial Skin to treat giant congenital melanocytic naevi in children. J Plast Reconstr Aesthet Surg 2010; 63(4):610-5.

MULTIFOCAL INFANTILE PROGRESSIVE HEMANGIOMATOSIS WITH OCULAR INVOLVEMENT: UNIQUE PRESENTATION IN A BULGARIAN NEWBORN

AA. CHOKOEVA[1,2], M.FIORANELLI[3], MG. ROCCIA[4], T.LOTTI[5] U.WOLLINA[6] and G. TCHERNEV[7]

[1]"Onkoderma"- Policlinic for Dermatology and Dermatologic Surgery, Sofia, Bulgaria; [2]Department of Dermatology and Venereology, Medical University of Plovdiv, Medical Faculty, Plovdiv, Bulgaria; [3]History Department, G.Marconi University, Rome, Italy; [4]University B.I.S. Group of Institutions, Punjab Technical University, Punjab, India; [5]Department of Dermatology, University of Rome "G. Marconi" Rome, Italy; [6]Department of Dermatology and Allergology, Academic Teaching Hospital Dresden-Friedrichstadt, Dresden, Germany; [7]Medical Institute of Ministry of Interior (MVR-Sofia), Department of Dermatology, Venereology and Dermatologic Surgery, Sofia, Bulgaria

Vascular disorders are considered a common finding among infants and in general, hemangioma is the most common. Diffuse neonatal hemangiomatosis is a rare and frequently fatal variant of them. We describe a case of a 2-months-old infant with multiple cutaneous hemangiomatosis and ocular involvement. To the best of our knowledge, this is the first reported case. We focus on the different treatment modalities and current diagnostic approaches.

Vascular disorders are considered a common finding among infants and in general, hemangioma is the most common (1). Diffused neonatal hemangiomatosis is a rare and frequently fatal variant of them (1, 2). Diagnosis of cutaneous hemangioma limited to the skin, usually shows a benign course in most cases, with a complete involution of the clinical symptoms without treatment (3). In contrast to this excellent prognosis, if visceral involvement is present, the morbidity and mortality rate increases (3). A high incidence of complications, presenting in multiple organ involvement is often associated with the presence of five or more cutaneous hemangiomas (2).

We present a case of a 2-month-old male infant, with diffuse cutaneous hemangiomatosis and ocular involvement and we discuss the current therapeutic options.

Case report

A 2-month-old male infant presented to the dermatology clinic with multiple skin lesions, which were present since birth (Fig. 1a, b, c). The patient was born pre-term from a first pregnancy, which proceeded normally without complications during delivery. According to the mother's data, the lesions were initially small, but gradually doubled in within 2 months. No family history for dermatologic disease was reported.

Multiple hemangiomatous nodules and papules were established within the clinical examination, covering almost the whole body surface of the patient,

Key words: multifocal hemangiomatosis, systemic involvement, treatment

Mailing address:
PProf. Georgi Tchernev,
Medical Institute of Ministry of Interior (MVR),
Department of Dermatology, Venereology and Dermatologic Surgery,
General Skobelev blvd. 79, 1606 Sofia, Bulgaria
Tel: 00359 885 588424
e-mail: georgi_tchernev@yahoo.de

0393-974X (2016)

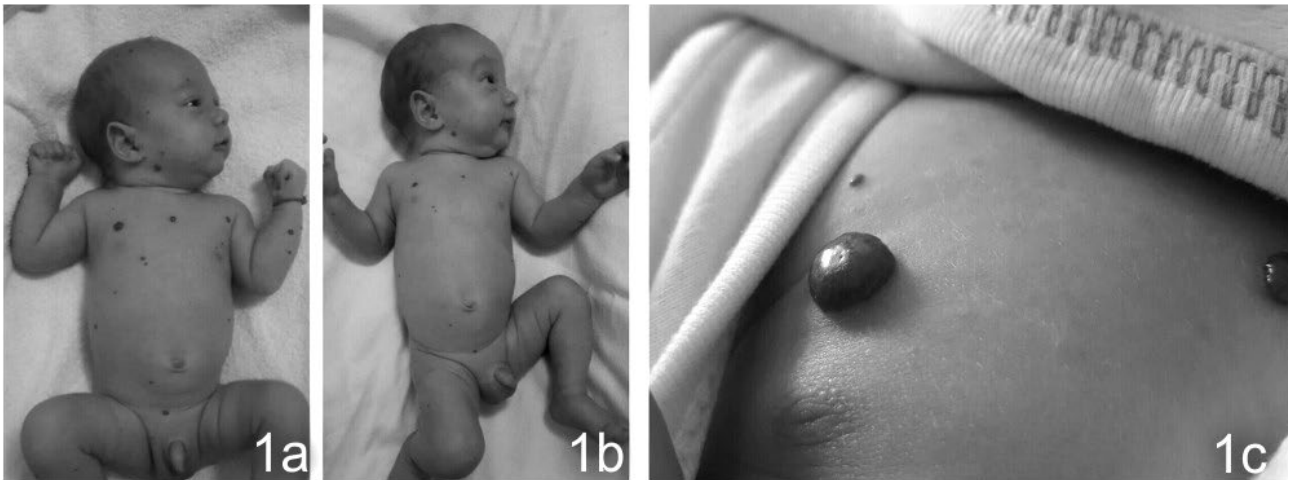

Fig. 1. ***a, b, c****): Clinical manifestation of a diffuse progressive hemangiomatosis on a 2-months old infant, with multiple cutaneous hemangiomas and ocular involvement.*

measuring approximately 0.5-2 cm in diameter. Some of the lesions were presented as small red papules, predominantly on the trunk and extremities, while some had a nodular appearance, affecting the upper part of the body. Ocular involvement was also established with hemangiomatous tumor in the left eye. No abnormalities in the complete blood count were detected in laboratory tests.

DISCUSSION

Hemangioma is the most common vascular tumor of infancy, with an incidence varying between 1 and 12% with predominant affection of the female gender (3). The prognosis is good, as 15% of the cutaneous lesions involute spontaneously by the age of 5, 75% by age 7 and 90% by age 9 (3). Multiple cutaneous hemangiomas is usually associated with the presence of hemangiomas in inner organs (1). The term "diffuse neonatal hemangiomatosis" has been used to describe multifocal vascular lesions affecting the skin and viscera in infants (4). In 2012, Glick ZR, et al. established the term "multifocal infantile hemangioma-with or without extracutaneous disease" instead of "diffuse neonatal hemangiomatosis" (4). Although rare, multifocal hemangiomatosis with systemic involvement is potentially fatal (2). According to data from a research by Schupp CJ, et al., pre-term infants (p=0.02) and patients with a high number of cutaneous hemangiomas (p=0.02) are at higher risk of organ involvement (5). Liver is the most commonly involved internal organ, followed by lungs, brain and intestine, with complications such as high output cardiac failure, coagulopathy and hepatomegaly, which generally develop between 1 and 16 weeks of age (3). The reported mortality without treatment is 81%, while it could decrease to 29% if treatment is performed (3, 4). Indications for active treatment include severe or recurrent hemorrhage unresponsive to treatment, threatening ulceration in areas where serious complications might ensue, interference with vital structures, pedunculated hemangiomas and significant disfigurement (3).

Different therapeutic options have been reported with variable degrees of success. Systemic or intralesional corticosteroids, interferon-alpha, and their combination were among the most common recommendations in the past (1, 2). Nonselective β-blocker propranolol is used today as a first-line treatment of infantile hemangioma (3). In cases of failure with corticosteroids, cyclophosphamide has also given satisfactory results in the involution of the cutaneous lesions and in the systemic involvement in case of diffuse cutaneous hemangiomatosis, associated with the presence of hemangiomas in the liver and kidneys, as well as in the tracheobronchial tree in a 3-months-old infant (6).

Although single therapy with the flashlamp pulsed dye laser was effective for cutaneous hemangiomas, the systemic involvement remains stable, as does the risk of complications (7). Recent studies demonstrate superior efficacy of propranolol over steroids, vincristine, and laser treatment (3, 8). The effectiveness of this medicine presents in reduction in size of the tumor, as a result of vasoconstriction due to decreased nitric oxide release, downregulation of vascular growth factors, and induction of apoptosis (3, 8, 9).

In the presented case, a systemic therapy with propranolol was planned at a later stage. This case study indicates that to the best of our knowledge, diffuse cutaneous hemangiomatosis is frequently associated with systemic involvement. This is the first reported case of multifocal cutaneous hemagiomatosis with ocular involvement. Further monitoring of the patient is still needed, as additional organ involvement at a later stage cannot be excluded.

REFERENCES

1. Stratte EG, Tope WD, Johnson CL, Swanson NA. Multimodal management of diffuse neonatal hemangiomatosis. J Am Acad Dermatol 1996; 34(2 Pt 2):337-42.
2. Dotan M, Lorber A. Congestive heart failure with diffuse neonatal hemangiomatosis. Case report and literature review. Acta Paediatr 2013; 102(5):e232-8.
3. Nip SY, Hon KL, Leung WK, Leung AK, Choi PC. Neonatal Abdominal Hemangiomatosis: Propranolol beyond Infantile Hemangioma. Case Rep Pediatr 2016; 2016:9803975.
4. Glick ZR, Frieden IJ, Garzon MC, Mully TW, Drolet BA. Diffuse neonatal hemangiomatosis: an evidence-based review of case reports in the literature. J Am Acad Dermatol 2012; 67(5):898-903.
5. Schupp CJ, Holland-Cunz S, Schenk JP, Weisser H, Grimm D, Günther P. Multiple hemangiomas and hemangiomatosis--risk factors and outcome over an eight year period. Eur J Pediatr Surg 2010; 20(6):379-81.
6. Vlahovic A1, Simic R, Djokic D, Ceran C. Diffuse neonatal hemangiomatosis treatment with cyclophosphamide: a case report. J Pediatr Hematol Oncol 2009; 31(11):858-60.
7. Endo H, Kawada A, Aragane Y, Yamashita Y, Isogai R, Yudate T, Tezuka T. The successful treatment of diffuse neonatal hemangiomatosis with flashlamp pulsed dye laser. Pediatr Dermatol 2001; 18(2):146-8.
8. Lou Y, Peng WJ, Cao Y, Cao DS, Xie J, Li HH. The effectiveness of propranolol in treating infantile haemangiomas: a meta-analysis including 35 studies. British Journal of Clinical Pharmacology 2014; 78(1):44-57.
9. Hon KLE, Burd A, Chu WC, Lee V, Li CK. Propranolol for infantile hemangiomas: strawberry matters? Indian Journal of Pediatrics 2012; 79(1):130-131.