CASE REPORT

Tuberous Sclerosis with Severe Cutaneous Manifestation and Multiples Facial Angiofibromas

Natália Galvão Garcia¹ · Marina Lara de Carli² · Denise Tostes Oliveira¹ · Cléverson Teixeira Soares³ · Noé Vital Ribeiro Júnior² · Felipe Fornias Sperandio² · João Adolfo Costa Hanemann²

Received: 21 March 2016 / Accepted: 27 April 2016 / Published online: 2 May 2016
© Springer Science+Business Media New York 2016

Abstract Tuberous sclerosis is an extremely variable disease that can affect virtually any organ in the body. The most common findings are cutaneous manifestations, that are critical features in helping to establish diagnosis. We present a case of young man with diagnosis of tuberous sclerosis presenting multiple shagreen patches around the trunk, in the neck and genital region; large plaques with uneven surfaces on the right side of the lower back; and multiple papular lesions in his face, particularly around the nasolabial region, eyebrows and forehead. Considering that tuberous sclerosis is a disease with a highly variable clinical presentation, thus dentists and doctors should be aware of the different manifestations that may be found.

Keywords Tuberous sclerosis · Critical features · Cutaneous manifestations

Introduction

Tuberous sclerosis is an extremely variable disease that can affect virtually any organ in the body [1]. The main findings are cutaneous manifestations, that are critical features

in helping to establish diagnosis [2, 3]. The most common cutaneous manifestations are: hypopigmented maculas, shagreen patches, periungueal fibromas, forehead fibrous plaques, and facial angiofibromas, one of the most prevalent that appear in 80 to 90 % of patients [4]. Nearly 100 % of individuals affected with tuberous sclerosis have some of these cutaneous manifestations that are easily detectable on physical examination, and may range from mild to severe [1]. We present a case of young man with diagnosis of tuberous sclerosis presenting a variety of severe cutaneous lesions and multiples facial angiofibromas, affecting almost the whole face.

Case Report

A 22-year-old man with diagnosis of tuberous sclerosis had been treated for epilepsy since childhood. The patient presented severe neurological impairment and could not communicate by oral language. His daily medication included Lamotrigine, Phenobarbital and Clonazepam.

On intraoral examination were observed gingival hyperplasia and teeth with destroyed crowns and residual roots (Fig. 1a) that were removed because the patient suffered toothache, and it was unfeasible to perform more complex dental treatment. The extractions were performed under sedation and general anesthetic in hospital.

On physical examination, multiple shagreen patches were located around the trunk, and in the neck and genital region (Fig. 1c). Large plaques with uneven surfaces were observed on the right side of the lower back; according to the patient's mother these caused great discomfort, and his hands presented longitudinal depressions in the nails (Fig. 1b). Also were observed multiple papular lesions in his face, particularly around the nasolabial region

✉ Natália Galvão Garcia
natgalvao@hotmail.com

¹ Department of Stomatology, Area of Pathology, Bauru School of Dentistry, University of São Paulo, Al. Dr. Octávio Pinheiro Brisolla, 9-75, Bauru, São Paulo 17012-901, Brazil

² Department of Clinic and Surgery, Area Stomatology, Alfenas Federal University, Alfenas, Minas Gerais, Brazil

³ Department of Pathology, Lauro de Souza Lima Institute, Bauru, São Paulo, Brazil

Fig. 1 Clinical manifestations: **a** on intraoral examination teeth with destroyed crowns and residual roots were observed; **b** the hands presented longitudinal depressions in the fingernails; **c** on physical

examination large plaques with lumpy surfaces were noted on the right side in lower back region and multiple shagreen patches around the trunk and neck

Fig. 2 Clinical manifestations in face: **a, b** the patient also presented multiple papular lesions in his face, particularly around the nasolabial region, eyebrows and forehead

(Fig. 2a, b), eyebrows and forehead. The larger lesion, located at the tip of his nose, was removed.

Microscopically, the lesion was well circumscribed (Fig. 3a), presenting spindle cells with an oval to fusiform nucleus and a scanty amount of lightly eosinophilic cytoplasm, numerous small to medium-sized vessels distributed rather uniformly in a stroma consisting primarily of fine collagen fibers (Fig. 3b).

Immunohistochemistry analysis showed that some tumor cells were positive for CD34 (Fig. 4a) and D2-40 (Fig. 4b). Intense reactivity for CD34 (Fig. 4a) and CD31 (Fig. 4c) was also observed in the walls of small blood vessels. The tumor cells showed negative expression for smooth muscle actin (SMA) (Fig. 4d), desmin (Fig. 4e), S100 (Fig. 4f) and AE1/AE3 (Fig. 4g). Masson's Trichrome showed intense reactivity of collagen fibers (Fig. 4h). The lesion was histopathologically diagnosed as angiofibroma.

Discussion

Tuberous sclerosis is an autosomal dominant neurocutaneous syndrome with variable clinical expression. It most often affects the skin and central nervous system [5]. In the present study, the patient had severe neurological impairment and unable to communicate by oral language.

Oral manifestations are also commonly observed in patients with tuberous sclerosis, mainly dental enamel pitting, gingival fibromas and gingival hyperplasia [6]. However, in this case no dental enamel pitting could be observed, because the tooth crowns were destroyed. Moreover, we observed gingival hyperplasia, but this may not have been due to true tuberous sclerosis, and could have resulted from the poor oral hygiene.

Among the main cutaneous manifestations, the most common are hypopigmented maculas, shagreen patches,

periungueal fibromas, forehead fibrous plaques and facial angiofibromas [4].

Hypopigmented/achromic macules, found in 90 to 98 % of patients, are white lesions classically rounded at one end and tapered at the other or polygonal in shape and are enhanced by examination with a Wood lamp [6]. These macules frequently present within the first few years of life, tend to increase in number and size throughout life, but are less prominent in adults, as they become more pigmented, and may even disappear [5, 7]. Therefore, in the present case was not observed hypochromic macules, probably because of the patient being adult. Furthermore, the presence of several skin lesions may mask hypopigmented macules.

Shagreen patches are fibrotic plaque with irregular margins and raised, grayish-green or light brown roughened surfaces (“orange-peel”), generally appearing in the lumbosacral area. They are present in approximately 20–54 % of patients and are rare during infancy, tending to increase in size and number with age [1, 5, 6]. In this case, the patient had large plaques with lumpy surfaces on the right side of the lower back, causing great discomfort. He also had several minor shagreen patches located around the trunk, neck and genital region.

Periungueal fibromas are skin-colored or reddish nodules adjacent to or underneath the nails, present in approximately 15–20 % of patients [6]. In some cases, there is only a longitudinal depression in the nail, corresponding to the fibroma still in the nail matrix or to the remnant of the tumor, after being excised by the patient himself [5]. The patient here described presented only longitudinal depressions in the fingernails.

Forehead fibrous plaques are skin-colored or brown lesions observed in about 25 % of patients that may occur on other parts of the face or scalp. These lesions can often be similar to angiofibromas [1]. Due to the presence of multiple and large papular lesions in the face, mostly

Fig. 3 Histopathology analysis: **a** the lesion was well circumscribed; (Hematoxylin and eosin; $\times 50$); **b** spindle cells with oval to fusiform nucleus and a scanty amount of lightly eosinophilic cytoplasm,

numerous small to medium-sized vessels distributed rather uniformly in a stroma consisting primarily of fine collagen fibers (Hematoxylin and eosin; $\times 200$)

Fig. 4 Immunohistochemistry analysis: **a** some tumor cells and walls of small blood vessels were positive for CD34; **b** some tumor cells and lymphatic vessels were positive for D2-40; **c** intense reactivity for CD31 was observed in walls of small blood vessels. **d** negative expression for smooth muscle actin (SMA); **e** negative expression for

desmin; **f** negative expression for S100; **g** negative expression for AE1/AE3; **h** Masson's Trichrome showed intense reactivity of collagen fibers. (Immunohistochemistry: CD34; D2-40; CD31; SMA; Desmin; S100; AE1/AE3 and Masson; $\times 200$)

angiofibromas, in the case of this patient, we have not identified a lesion that was precisely a forehead fibrous plaque.

The presence of facial angiofibromas is a major criterion and is a pathognomonic sign of tuberous sclerosis, appearing in 80 to 90 % of patients [8]. They are popular lesions that primarily affect the nasolabial folds, cheeks and chin, bilaterally and symmetrically or unilaterally and mosaic [5]. The patient here described presented multiple lesions bilaterally around the nasolabial region affecting almost the entire face.

Microscopically, angiofibromas are typically well circumscribed and may or may not have a fibrous pseudocapsule. The main proliferating element is a spindle cell with a cytologically bland, oval to fusiform nucleus and a scanty amount of lightly eosinophilic cytoplasm with ill-defined margins. Atypical mitotic figures and necrosis are absent. The vascular component consists of numerous small to medium-sized vessels distributed rather uniformly throughout the process. Perivascular hyaline fibrosis is present to some degree in all tumors. The stroma consists primarily of fine collagen fibers. Additional stromal elements may include scattered thick bundles of eosinophilic collagen, a myxoid and edematous stromal matrix, and hypocellular bands of collagen separating lesional tissue [9]. In the present case, the lesion was well circumscribed, presented tumor cells with oval or fusiform nuclei and numerous small to medium-sized vessels distributed rather uniformly in a stroma consisting primarily of fine collagen fibers.

The immunophenotype showed negative expression for muscle-specific, smooth muscle actin and desmin and positive expression for CD34 in one third of the tumors [9]. Perez et al. [10], evaluating the presence of myofibroblasts in angiofibromas, reported that the tumor cells were negative for smooth muscle actin; and connective tissue was positive for Masson's Trichrome [10]. So they claimed they did not observe any presence of myofibroblasts. In the immunohistochemistry analysis of this case, some tumor cells were positive for CD34 and D2-40 and were negative for smooth muscle actin (SMA), desmin, S100 and AE1/AE3. Positive expression for CD34 and CD31 was also observed in the walls of small blood vessels. The Masson's Trichrome showed intense reactivity of collagen fibers. Therefore, in this case, also was not observed the presence of myofibroblasts.

Tuberous sclerosis is a disease with a highly variable clinical presentation, thus dentists and doctors should be aware of the different manifestations that may be found.

Compliance with Ethical Standards

Conflict of interest None declared.

References

1. Northrup H, Krueger DA, International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. *Pediatr Neurol.* 2013;49(4):243–54.

2. Wataya-Kaneda M, Yano K, Hosokawa K, Yoshikawa K. A case of tuberous sclerosis with a giant angiofibroma. *J Dermatol*. 1997;24(2):132–4.
3. Schwartz RA, Fernández G, Kotulska K, Jóźwiak S. Tuberous sclerosis complex: advances in diagnosis, genetics, and management. *J Am Acad Dermatol*. 2007;57(2):189–202.
4. Camprubí M, Balaguer A, Azon Masoliver A, Jiménez-Feijoo R, Escribano Subias J. Unilateral facial angiofibromas; a review of the literature. *Pediatr Dermatol*. 2006;23(3):303–5.
5. Rodrigues DA, Gomes CM, Costa IM. Tuberous sclerosis complex. *An Bras Dermatol*. 2012;87(2):184–96.
6. Rabito MJ, Kaye AD. Tuberous sclerosis complex: perioperative considerations. *Ochsner J*. 2014;14(2):229–39.
7. Teng JM, Cowen EW, Wataya-Kaneda M, Gosnell ES, Witman PM, Hebert AA, Mlynarczyk G, Soltani K, Darling TN. Dermatologic and dental aspects of the 2012 international tuberous sclerosis complex consensus statements. *JAMA Dermatol*. 2014;150(10):1095–101.
8. Silvestre JF, Bañuls J, Ramón R, Guijarro J, Botella R, Betlloch I. Unilateral multiple facial angiofibromas: a mosaic form of tuberous sclerosis. *J Am Acad Dermatol*. 2000;43(1 Pt 1):127–9.
9. Laskin WB. Cellular Angiofibroma. In: Fletcher CDM, Unni KK, Mertens FD, editors. *World health organization classification of tumours. Pathology and genetics of tumours of soft tissue and bone*. Lyon: IARC Press; 2002. p. 73–4.
10. Perez EG, Paranaíba LR, Bonan PR, Orsi Júnior JM, Oliveira AM, Martelli Júnior H. Tuberous sclerosis: evaluation of myofibroblasts in cutaneous angiofibromas—case report. *An Bras Dermatol*. 2010;85(1):84–8.