Junctional Spitz Tumor (Nevus) of the Upper Lip

Evangelia P. Piperi · Konstantinos I. Tosios ·
Alexandra Sklavounou · Eric Stich ·
Ioannis G. Koutlas

Received: 5 October 2013 / Accepted: 24 November 2013 / Published online: 29 November 2013
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Abstract Spitz tumor (nevus) is a rare, melanocytic lesion that primarily affects children and adolescents. The lesion may share many clinical and histological similarities with malignant melanoma and careful microscopic examination is required to render the proper diagnosis. Complete excision with close follow-up is considered the appropriate treatment. Despite the common presentation of Spitz nevi on the facial skin, lip involvement has only rarely been described in the English language literature. In the present study, a case of Spitz tumor located on the vermilion border of the upper lip in a 16-year old female patient is reported.

Keywords Lip · Melanoma · Spitz tumor ·
Vermilion border

Introduction

Spitz tumor, also called Spitz nevus or spindle and epithelioid cell nevus, is an uncommon melanocytic lesion that represents the “benign” or “less aggressive” end in a group of melanocytic neoplasms termed spitzoid melanocytic lesions/proliferations; this group encompasses benign

Spitz tumors without appreciable abnormality or Spitz nevi, Spitz tumors with one or more atypical features (atypical Spitz tumors), including those with indeterminate biological potential; and malignant melanomas [1, 2]. The a priori characterization of all spitzoid melanocytic lesions/proliferations as benign is not always possible, thus replacement of the term nevi with “tumor” [1] or use of the term “Melanocytic Tumor of Uncertain Malignant Potential” or “MELTUMP” [3, 4] have been proposed. In fact, in many cases diagnosis and management of these lesions may turn into a real challenge [5, 6].

Spitz tumor is most frequently encountered in children and adolescents (57–79 %), although about 15 % of cases occur in patients older than 40 years of age [7, 8]. The lesion represents <1 % of all melanocytic nevi in childhood [9] and 1–2 % of surgically excised melanocytic lesions [6]. Spitz tumor has been reported to show a slight female preponderance [7, 8], but this may be attributed to a higher rate of surgical removal in women due to cosmetic reasons. It typically presents on the head and neck area, especially in children [7, 8], the lower extremities and the trunk as a solitary, rapidly growing, pink, red or brown dome-shaped, firm cutaneous nodule or papule, with a size less than 1 cm in the majority of cases [7, 8, 10].

Due to its clinical characteristics, the differential diagnosis commonly includes non-melanocytic skin lesions such as pyogenic granuloma, hemangioma or dermatofibroma [7, 11]. Spitz tumor can be rarely congenital [12] or it may arise either de novo or in association with a pre-existing melanocytic nevus [13]. Flat pigmented lesions are not unusual, while multiple lesions, either grouped or disseminated, may also be seen [6, 8]. Spitz tumors are usually asymptomatic and tend to remain static after the initial phase of rapid growth, although localized pruritus and bleeding have been reported [13].

E. P. Piperi (✉) · K. I. Tosios · A. Sklavounou
Department of Oral Pathology and Medicine, Dental School,
National and Kapodistrian University of Athens, Thivon 2,
Goudi, 11527 Athens, Greece
e-mail: liapiperi@dent.uoa.gr

E. Stich
Private Practice, Minneapolis, MN, USA

I. G. Koutlas
Division of Oral and Maxillofacial Pathology, University of
Minnesota, Minneapolis, MN, USA

Microscopically, the typical Spitz nevus is characterized by a proliferation of spindle and/or epithelioid cells with a junctional, intradermal or most commonly compound distribution [6–9, 11, 14, 15]. Neoplastic cells are large with abundant eosinophilic cytoplasm and feature enlarged vesicular nuclei with slight pleomorphism and prominent, occasionally multiple, nucleoli. Multinucleated giant cells may also be found [6–9, 11, 13, 14]. Melanocytes are organized into well-demarcated nests that tend to show a vertical orientation to the epidermis, while focal pagetoid melanocytosis limited to the central part of the epidermis is not uncommon [6–9, 11, 14, 15]. Separations of nests from the surrounding tissues, described as clefs, are also observed. The dermal component shows zonation and gradual maturation towards the deeper portions, with dispersion of the cells along collagen fibers. Symmetrical epithelial hyperplasia, including hyperkeratosis, hypergranulosis, acanthosis, elongation and thickening of the rete ridges and occasionally pseudo-epitheliomatous hyperplasia [16] are observed. Large, confluent, PAS-diastase positive eosinophilic globules of basement membrane material (Kamino bodies) along the dermo-epidermal junction are also common but they may also be found in some dysplastic or halo nevi and in 12–26 % of malignant melanomas [2, 8]. The stroma may be hyalinized and edematous with some degree of telangiectasia in the superficial dermis. Many histologic variants of the typical Spitz tumor including desmoplastic, angiomatoid or halo-Spitz tumor, pagetoid, plexiform, tubular, myxoid, polypoid, and Reed nevus have also been described while Spitz tumor may also be a part of a combined nevus [15].

Despite the common presentation of Spitz nevi on the facial skin, lip involvement has rarely been described in the English language literature [17]. In this study, we report a case of Spitz tumor on the vermillion border of the upper lip in a 16-year old female patient. To our knowledge, this is the second documented case of a Spitz nevus located on the lip.

Case Report

A 16-year-old Caucasian female presented for evaluation of an asymptomatic pigmented lesion of 2 months duration, located on the right side of the upper lip. The medical history of the patient was insignificant. Clinically, a solitary, brown and oval-shaped 0.3 × 0.2 cm macule with well-defined borders was observed on the upper lip vermillion (Fig. 1). Intraoral mucosa was normal while no regional lymphadenopathy was evident on palpation. A clinical diagnosis of melanocytic nevus or melanotic macule was rendered and an excisional biopsy under local anesthesia was performed.

Fig. 1 A flat and oval-shaped melanotic macule on the vermillion border of the upper lip

Grossly, a white and centrally brown mucosal fragment measuring 0.3 cm in greatest dimension was observed. Microscopic examination of multiple 5 µm thick formalin-fixed and paraffin-embedded tissue sections stained with hematoxylin-eosin revealed a mucosal fragment surfaced by orthokeratinized stratified squamous epithelium, showing some degree of acanthosis and bulging of the rete pegs (Fig. 2). In the central part of the specimen a sharply circumscribed and small-diameter proliferation of spindle- to epithelioid-shaped melanocytes was seen (Fig. 2). The melanocytes were observed individually in the lower to middle levels of the epithelium (pagetoid melanocytosis) and the upper reticular lamina propria (Fig. 3), or arranged in a single junctional nest (Fig. 4). The nest was composed of spindle-shaped melanocytes oriented vertically to the mucosal surface (Fig. 4). Focal separation of the nest's cells from the adjacent keratinocytes due to junctional vacuolar myxoid change, in a pattern reminiscent of cleft formation was also observed (Fig. 4). The melanocytes were large, with abundant eosinophilic cytoplasm, large vesicular nuclei and prominent nucleoli, while rare cells were featuring hyperchromatic, dark-staining nuclei. Most melanocytes showed fine and evenly distributed melanin granules (Fig. 4). Cellular and nuclear pleomorphism was limited. The number of mitoses was <1 per HPF and no atypical mitoses were identified. The subepithelial fibrous connective tissue showed an apparent mild perivascular chronic inflammatory infiltrate, while no Kamino bodies were observed.

Fig. 2 Mucosal fragment surfaced by orthokeratinized stratified squamous epithelium, showing a sharply circumscribed and small-diameter proliferation of spindle- to epithelioid-shaped melanocytes (*box*). Notice acanthosis and bulging of the rete pegs (hematoxylin and eosin stain, original magnification $\times 20$)

Fig. 3 Spindle- and epithelioid-shaped melanocytes in the lower level of the epithelium (*arrowheads*) and the upper reticular lamina propria (*arrow*), respectively (hematoxylin and eosin stain, original magnification $\times 100$)

Fig. 4 Spindle-shaped melanocytes arranged in a junctional nest. Note their vertical arrangement to the mucosal surface, focal separation of the nest's cells from the adjacent keratinocytes in a pattern reminiscent of cleft formation (*arrows*), and melanin pigmentation (hematoxylin and eosin stain, original magnification $\times 100$)

A diagnosis of a predominantly junctional and partially pigmented Spitz tumor was rendered. Due to the uninvolved margins and lack of significant atypia the lesion was

categorized as low-risk (score = 1), according to the grading system for risk of metastasis proposed by Spatz et al. [18]. The patient was placed on close follow-up and 3 years after the excision there has been no recurrence.

Discussion

A review of the English language literature revealed one previous report describing a macule on the upper labial mucosa adjacent to the vermilion border of the lip, in a 24 year-old male patient [17]. Another case [19] is considered not properly documented, since the photomicrographs of the lesion are not representative of a Spitz nevus. It is presumed that some additional cases may have been grouped in large case series of head and neck lesions [17]. In addition, there is a report of a lip lesion in a 9-year old girl that was erroneously diagnosed as Spitz nevus, and was re-diagnosed as a melanoma after regional lymph node metastases 2 years later [20].

Both lip lesions were of the junctional type, pigmented, and without significant epithelial hyperplasia. As has been shown, the histopathological subtype of a nevus may be related to the anatomic site of location, its evolutionary stage and the age of the patient [3]. In this regard, the predominance of the junctional component in these two cases may be attributed to the fact that both lesions were removed soon after their appearance, as they were located on an easily discernible region. Melanin pigmentation in the form of fine and evenly distributed granules, as seen in our patient, may be present in $<10\%$ of Spitz tumors [2, 5] and is more common in flat lesions of the junctional type [3] as well as in lesions with a predominance of spindle cells [6]. Its limited distribution though in the present case could not support the diagnosis of a “classic” pigmented spindle cell nevus [3], while lack of prominent proliferation of epithelioid melanocytes along the dermoepidermal junction with extensive pagetoid spread did not support the diagnosis of an extremely rare pagetoid Spitz nevus [21]. Kamino bodies were not identified but their presence is not diagnostic of a Spitz nevus, since they may also be found, as already mentioned, in common nevi and malignant melanomas [2, 8]. Finally, the lack of significant lentiginous proliferation, bridging or confluence of junctional nests, lateral extension of the junctional component, and in particular the absence of parallel arrangement of the spindle cells to the surface do not support a diagnosis of a melanocytic lesion with features of both Clark's/dysplastic and Spitz nevus, also called “Spark's” nevus [22].

The diagnosis of Spitz tumor can sometimes be problematic, since an atypical Spitz tumor may share many clinical and histological similarities with a malignant melanoma that resembles a Spitz tumor (“spitzoid”

melanoma) [3, 11–16]. Several sets of, even contrasting, criteria describing specific architectural, cytological and proliferational characteristics have been proposed and although not solid, they may help differentiate Spitz tumor from malignant melanoma and enhance diagnosis [1, 2, 5, 6, 8, 9, 11, 15, 18]. Small size of the lesion, sharp lateral demarcation of an intraepidermal component, symmetric epidermal hyperplasia, presence of clefts surrounding intraepithelial nests, low mitotic activity and absence of mitoses at the bottom, progressive dermal maturation, large and confluent Kamino bodies, regular distribution of melanin, focal pagetoid spread at the lower epidermis and patchy inflammatory infiltrate are more in favor of a Spitz tumor as opposed to the presence of ulceration, large size, lack of symmetry, loss of nesting pattern, prominent epithelioid morphology of tumor cells, nuclear pleomorphism and hyperchromasia, pagetoid growth at the lateral aspects/upper layers of the lesion, deep, atypical mitoses, lack of maturation and band-like lymphoid infiltration, which are considered alarming features reminiscent of malignant melanoma and should prompt a further evaluation [3, 11, 13–16]. Clinical features, such as an older age, location of the tumor on sites less commonly involved by Spitz tumor, asymmetry and lack of well-defined borders, pigmentation, history of recent changes in a longstanding stable lesion and a family history of melanoma should, also, be considered carefully [1, 15].

Several ancillary techniques have been used in trying to distinguish between these two lesions, including immunohistochemistry and molecular methods, but no reliable marker currently exist. A variety of antibodies including melanocytic specific markers, cell-cycle regulators, proliferative activity markers, membrane receptors, and cell-matrix transition proteins have been applied in order to facilitate the differentiation of Spitz tumor from melanoma [1, 5, 9, 23]. Combination of two or more antibodies may be of help in the differential diagnosis as has been suggested by Kapur et al. [24], who found that an immunohistochemical profile of high p21, low Ki-67 index and weak fatty acid synthetase expression was more in favor of Spitz tumor over melanoma. In another study, the application of the Bayes rule (MIB-1 proliferation index [PI]) in a given melanocytic lesion, in order to estimate its predictive probability in diagnosis, indicated that a PI >10 % is in favor of the diagnosis of melanoma in comparison to a PI <2 % in Spitz tumor [25].

Comparative genomic hybridization (CGH) and fluorescence in situ hybridization (FISH) have identified a subset of Spitz tumors with amplifications in chromosome 11p and alterations in the HRAS gene, while loss of heterozygosity of chromosome 9p and hotspot activating mutations in the BRAF, NRAS, or HRAS genes have also been reported [1, 5, 11]. Additionally, alterations targeting

11, 6, and 9 chromosomes have been described in atypical spitz tumors with a propensity for aggressive behaviour [26], while recently Requena et al. [27] reported that a FISH assay—designed to detect the copy number of the *RREB1* (6p25), *MYB* (6q23) and *CCND1* (11q13) genes and of centromere 6 (Cep 6) can distinguish Spitz nevus from spitzoid melanoma, with a sensitivity of 87.5 % and a specificity of 100 %. Nevertheless, the diagnostic application of the above findings in differentiating Spitz tumor from Spitzoid melanomas should be further evaluated.

Recommendations for the management of Spitz nevi vary and are not evidence-based [28], while treatment planning may be affected by the age of the patient and the anatomic constraints [5, 6, 29]. Complete surgical excision facilitates the microscopic examination of the entire lesion and diminishes the risk of recurrence, while in cases with positive surgical margins a re-excision should be carried out [1, 5, 8, 15, 28, 29]. In atypical cases a more aggressive surgical management with wider margins and long-term follow up is strongly advised [6, 28, 29], although atypical Spitz tumors seem to behave more like a Spitz nevus than a malignant melanoma [30]. Recurrences are estimated to occur in a time period of approximately 1 year and most of them are attributed to incomplete resection [5, 7, 29]. The biologic significance of the nodal aggregates of melanocytes found in sentinel lymph nodes of atypical Spitz nevi is not clear [29–31]. In general, prognosis of completely excised lesions is usually good and fatal outcome in typical cases is extremely rare [1].

In the present case, a case of junctional Spitz tumor of the upper lip vermilion is presented. The lesion was excised completely but despite the absence of atypical features, the patient was put in a long-term follow-up, as there is a lack of knowledge on the biological behavior of Spitz lip lesions.

Acknowledgments We thank Dr. Raymond L. Barnhill, M.D., M.Sc., Professor of Pathology, Co-Director of Dermatopathology, Department of Pathology and Laboratory Medicine, University of California, Los Angeles, USA for his consultation in the present case.

Conflict of interest None.

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