Review paper

Atypical melanocytic lesions: a historical overview

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The distinction between atypical Spitz lesions, conventional melanocytic nevi including Spitz nevi, and malignant melanomas may be difficult in some cases or may even be impossible. The histological assessment of these lesions is necessary to ensure correct diagnosis and treatment. Nevertheless, pathologists may be subject to suboptimal concordance in the diagnosis of some atypical lesions. In literature, certain atypical lesions have been defined differently: the terms atypical and metastasising Spitz tumour, malignant Spitz nevus, borderline and intermediate melanocytic tumour, melanocytic tumour of uncertain malignant potential MELTUMP, and low-grade malignant melanoma have been introduced to designate this heterogeneous group of pathological entities and variants. This review focuses on some issues concerning the historical background, diagnostic state-of-the-art, evolution, and classification of these complicated lesions.

Key words: melanoma, Spitz nevus, Atypical Spitz tumour, Spitz nevus variants.

Introduction

In 1910, Darier and Civatte (Fig. 1, 2), two French dermatopathologists, described an unusual (Spitzoid) melanocytic tumour on the nose of an eight-month-old boy [1]. They were unsure whether it was a nevus or a malignant melanoma. The histological lesion was characterised by a cellular proliferation composed of fusiform nevic cells. At that time, the histologically distinctive features between "childhood melanomas" and melanomas in adults were also still undefined, so the only discriminating parameter was age. Endocrine influences were also claimed to highlight the age-related evolution of the lesion. In 1939, Pack and Anglem identified a particular type of melanocytic lesion in children up to puberty, in which the histological characteristics were different from the adult type [2]. They introduced the concept of "prepubertal melanoma". The main attitude was to describe all pigmented lesions in infancy and childhood that need to be removed before adult life, possibly avoiding the degeneration in a full malignant lesion. In 1948 Pack wrote: *our experience with now more than nine hundred cases of malignant melanomas has been that none of these melanotic tumours of infancy and childhood has metastasized to regional lymph nodes, although many of them have been labelled as malignant melanoma by extremely competent pathologists* [3]. Soon

Fig. 1. J. Darier (1910). From http://www.derm-vic.org/Research/Darier.html

Fig. 2. A. Civatte (1910). From http://www.dermvic.org/Research/Darier.html

after, Sophie Spitz contribution was aimed at identifying whether the lesions in childhood described as malignant melanoma could be distinguished from those occurring in adults.

This review focuses on some issues concerning the historical background, diagnostic state-of-the-art, evolution, and classification of these complicated lesions.

Historical background

Sophie Spitz (Fig. 3), born in 1910 in Nashiville, daughter of Jewish immigrants from Germany, received BD and MD degrees from Vanderbilt University in 1929 and 1932, respectively. After many activities in different institutions, she became Assistant Professor of Pathology at the Sloan-Kettering division of Cornell University. She died on August 11, 1956 from metastatic colon cancer.

In 1948, Sophie Spitz published an article in the American Journal of Pathology, entitled "Melanoma of Childhood" [4]. In this article, which challenged several prevailing concepts concerning the pathology of nevi and melanomas, she changed dramatically the criteria of diagnostic interpretation of some particular melanocytic lesions, so her paper became one of the most cited in the history of medicine. Spitz identified a particular group of melanocytic lesions designated as juvenile melanomas. Her major contribution to pathology was to recognise and to describe a separate category of melanocytic lesions that were previously diagnosed and treated as malignant melanomas. Thirteen cases histologically diagnosed as juvenile melanomas and occurring in children whose age ranged from 18 months to 12 years were compared with a group of melanomas occurring in young adults, 14 to 19 years of age, and with 50 cases of melanocytic nevi diagnosed in children. She described several histological features of these lesions, including: i) epidermal changes such as parakeratosis and acanthosis; ii) multinucleate or mononucleate giant cells with oval or round acidophilic cytoplasm; iii) large acidophilic spindle (pigmented) cells; iv) occasional mitotic figures; v) pigmentation mainly in the superficial part of the lesion; vi) inflammatory changes; and vii) oedema and vascular ectasia in the papillary dermis. In her seminal work, she proposed the concept that the presence of giant cells was the only characteristic that permitted a histological distinction from adult melanoma (Fig. 4). According to Spitz, all these features, except for the giant cells, met also the histological criteria for the diagnosis of malignant melanoma. At the time of her original report, Dr. Spitz was still convinced of the malignancy of the juvenile melanomas. She explained the usually benign clinical behaviour of these lesions by a hormonal-related effect. Unfortunately, Spitz's study included a 12-year-old girl with a fatal outcome. This case lent support to the notion that typical Spitz nevi were able to metastasise.

Fig. 3. Sophie Spitz 1910-1956 from https://en.wikipedia.org/wiki/Sophie_Spitz

In 1949, Arthur C. Allen, Spitz's husband and former co-worker, included juvenile melanomas in benign melanocytic lesions on the basis that they were considered to be a group of lesions occurring before puberty and did not show malignant behaviour [5]. In 1960, Allen re-evaluated the case of the 12-year-old girl and stated that the case lacked the histological diagnostic criteria of a juvenile melanoma [6]. In 1953, Allen and Spitz explained several histological characteristics to distinguish juvenile melanomas and adult malignant melanomas and noticed that childhood melanoma may exceptionally be able to metastasise [7]. The benign melanoma features were as follows: superficiality; association with compound nevus; oedema and telangiectasia; dyscohesion of spherical or spindle cells; large cells with

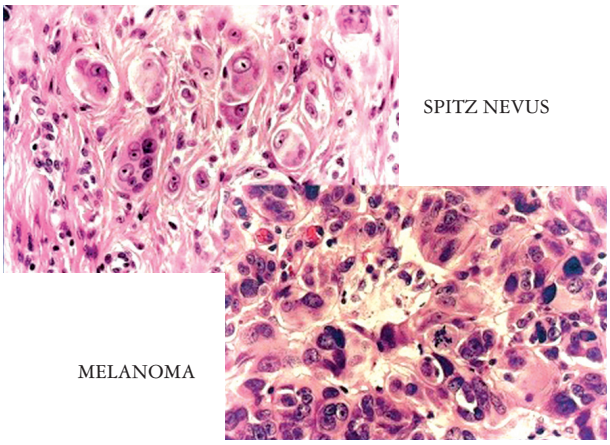

Fig. 4. J. Darier (A) and A. Civatte (B) 1910. From http://www.dermvic.org/Research/Darier.html

abundant, basophilic, myogenous-appearing cytoplasm; superficial giant cells; sharp demarcation; and sparse pigmentation. They distinguish rare malignant tumours of children from juvenile melanomas by the presence of cellular anaplasia and a cordlike pattern of invasion.

The evolution of Spitz's nevus terminology

In 1954, Mc Worther and Woolner proposed description of benign juvenile melanomas as spindle-cell and/or epithelioid-cell types, because these lesions can be composed of both types of cells in various proportions [8]. Moreover, they considered the cellular maturation and the superficiality of mitoses as two important criteria to distinguish benign lesions from malignant melanomas. In the same year, Elson B. Helwig proposed, for the first time, that these lesions be denominated as "spindle-cell nevi" [9]. According to Helwig's terminology, Kerner and Ackerman described 27 juvenile melanomas as "spindle cell nevi" and "epithelioid cell nevi" [10], emphasising that, based on their clinical evolution, these lesions *should be adequately treated by local surgical excision alone*. In 1967, the Pathology Committee of the Queensland Melanoma Project recommended the use of the name "Spitz naevus" instead of juvenile melanoma [11]. In 1971, Wayte exemplified the normalisation process of Spitz nevi into the category of benign melanocytic lesions [12]. He explained that *the spindle and epithelioid cell nevus is a variant of a compound nevus, and its life history doesn't differ from that of other nevi.*

But, since 1948, several publications appeared in the literature reporting child lesions that were originally diagnosed as juvenile melanoma or Spitz nevus but which metastasised [13, 14]. As noticed by Ackerman and Kernen in 1960, the histological descriptions and the photomicrographs of these cases supported the conclusion that the diagnoses were erroneous. Owing to the difficulties of differentiating Spitz nevus and melanoma, especially for lesions having unusual features, many different definitions and controversial hypotheses were considered during the subsequent period.

For example, in 1975 the concept of minimal deviation melanoma was introduced, mainly based on the feature of an expansile nodule confined to a widened papillary dermis [15]. This interesting concept is still used in the current classifications of cutaneous melanomas to describe the presence or absence of the radial growth phase and the vertical growth phase as determinant features for prognosis. In 1979, another morphological characteristic was described by Kamino as pink globules in the epidermis of Spitz nevi [16]. They were usually PAS-positive, diastase-resistant, and positive on trichrome staining. Unfortunately, they have been considered not fully specific because their presence does not rule out the diagnosis of malignant melanoma, but it makes it less likely. In effect, similar globules were noted in the epidermis of only 2% of malignant melanomas and 0.9% of ordinary melanocytic nevi. But, interestingly, the globules in malignant melanomas and ordinary melanocytic nevi are PAS and trichrome negative.

In 1983 the term "borderline minimal deviation melanoma, Spitz variant sub-type" to describe atypical Spitz lesions was introduced by Mahlauber *et al*. [17], and in 1989 an article entitled "Spindle Cell and Epithelioid Cell Nevi with Atypia and Metastasis (Malignant Spitz Nevus)" was published by Smith *et al*. [18]. In this study, 32 cases diagnosed histologically as malignant spindle and epithelioid nevi displayed high mitotic rate, with deep mitoses, lack of maturation, increased cellularity, pleomorphism, cellular dyscohesion, ulceration, and large size (> 1 cm). Only six were associated with lymph node metastases. After a follow-up of six years, only two cases had fatal outcome. Unfortunately, no punctual descriptions of differential diagnostic features between metastatic and non-metastatic or fatal and non-fatal cases were available. Now, this study suggests a better prognosis for melanomas histologically resembling Spitz nevi.

Spitzoid lesions: clinical and histopathological features

The distinction between Spitz tumours, atypical Spitzoid lesions and Spitzoid melanomas clinically and histologically remains difficult, and the accurate prediction of biological behaviour of these tumours, even after sentinel lymph node biopsy, is often impossible. Immunohistochemistry, genetic analysis, and mutation analysis have contributed to a better understanding the biology of these tumours in order

to improve the accuracy of the diagnosis. In Table I the main histopathologic features on Spitz nevi, atypical Spitz tumours, and Spitzoid melanomas are summarised.

Atypical Spitz tumour

The atypical Spitz tumours (AST) are borderline lesions with clinical and histological features significantly deviated from classic Spitz nevus, frequently overlapping with those of melanoma [19]. These tumours are usually compound lesions predominantly consisting of epithelioid cells. There may be histologic features of Spitz nevus, but the lesions are larger, asymmetric, and not circumscribed as classic Spitz nevi. They have cytological atypia, nuclear pleomorphism, and aberrant sheet-like growth with a dense and compact cellularity. The mitotic activity is often present in the deep dermis and the maturation with dermal descent is lacking. The presence of mitoses near the base of the lesion is a significant feature to distinguish lesions with unfavourable clinical behaviour from those with favourable behaviour [20]. Ulceration, extension into the deep dermis or upper subcutis, and bulbous or expansile and pushing borders at the base of the lesion can also be seen. Because many of these histologic features are observed in melanomas, proper classification of these lesions can be exceedingly difficult.

Pigmented spindle cell nevus

Pigmented spindle cell nevi (PSCN) are circumscribed lesions with epidermal hyperplasia, and they form flat-topped, heavily pigmented papules. The cells form moderate to large sized nests along the dermal epidermal junction where the spindle cells can be arranged in a vertically oriented or 'raining down' fashion, a whirling pattern, or less commonly they are oriented parallel to the epidermal surface. There is granular melanin pigment within the cytoplasm of nevus cells and in adjacent keratinocytes. Typically, the pigment is present within the scales of the stratum corneum and within dermal melanophages [21].

Spitzoid dysplastic nevus

This lesion combines the cytomorphologic features of Spitz nevi with altered architectural patterning and Clark's dysplastic nevi. According to Ko *et al*., these lesions occurred in adults, mostly in females, and were located on the trunk and lower extremities [22]. Spitzoid dysplastic nevi are junctional or compound and are composed of variable proportions of spindled and epithelioid Spitzoid-appearing melanocytes. They are disposed in irregular nests on the sides and tips of often hyperplastic rete ridges along the dermal-epidermal junction, with extensive bridging of nests between rete ridges in a horizontal or plaque-like pattern. The junctional component extends laterally beyond the dermal component in compound lesions. Foci of small cluster and single-unit melanocytes can be found in the epidermis within the centre of the lesion. At variance of melanomas, Spitzoid dysplastic nevi lack melanocyte involvement of suprapapillary plates, and therefore no junctional confluence and/or pagetoid spread are usually observed [23].

Spitzoid melanoma

Spitzoid melanoma can arise "de novo" or within a pre-existing nevus. It displays the following characteristics: it is rare under the age of 20 years; the head and extremities are common sites; 1-cm or more nodular lesions that can be crusted and ulcerated; pagetoid scattering and dyscohesion of melanocytes within nests; epidermal atrophy with consumption; lymphoplasmacytic infiltrates, disruption of dermal structures; high-grade cytological atypia with nuclear pleomorphism; no maturation; mitotic activity in deep aspects vs. more than six MFs /sqmm or three MFs x HPF; necrosis and angiolymphatic and perineural spread. Features of a Spitz nevus or its variants can be present and may cause diagnostic difficulties. When present, nests in the junctional component are larger and more irregular and are concomitant with areas of single-unit melanocytes with pagetoid spread. Spitzoid melanomas are often associated with epidermal atrophy, resulting from consumption

Table I. Histopathologic features of Spitz nevus, atypical Spitz tumor and Spitzoid melanoma.

Features	Spitz nevus	Atypical Spitz tumor	Spitzoid melanoma
Size	< 1 cm	Often > 1 cm	> 1 cm
Symmetry	Symmetric	Often asymmetric	Asymmetric
Cytologic atypia	Uncommon	Variably present	Common
Maturation	Common	Uncommon, variable	Uncommon or absent
Mitotic activity	Uncommon superficial	Common, superficial and deep	Common, superficial and deep
Ulceration	Rare	Variable, uncommon	Common
Kamino bodies	Frequent	Variable	Less common

of the epidermis, rather than epidermal hyperplasia, commonly seen in Spitz nevi. The invasive dermal component demonstrates similar features of ASTs because it can form large nodules of compact, sheet-like growth, resulting from high cellularity, which may compress or disrupt surrounding adnexal and vascular structures of the dermis. The cells exhibit cytological atypia, which is often high grade, and includes prominent nuclear pleomorphism. There is no maturation of the Spitzoid melanocytes with descent into the dermis, and mitotic activity is conspicuous, also in deep aspects of the lesion. An inflammatory response is often present with lymphocytes and plasma cells, which can be associated with regression and melanosis [24].

Special techniques

Immunohistochemistry

A panel of immunohistochemical markers can be used to define Spitz nevi or their variants and melanomas. The mitotic rate is one of the most important factors in determining the biological potential. Ki-67 (MIB-1), a proliferation index, may be used to differentiate melanoma from benign Spitzoid lesions. In Spitz nevi and AST, Ki-67 stains the junctional and papillary dermal parts of a given lesion, whereas in melanoma is more diffuse [25]. In a study, Ki-67 positive indexes were 10% in ASTs compared to 0.53% in ordinary nevi, 5.04% in convectional Spitz nevi, and 36.83% in melanomas [26]. However, even if a high proliferative index is a cause of concern, a low ki-67 does not exclude the diagnosis of melanoma. In Spitz nevi a stratification pattern of HMB-45 staining with a decreasing gradient from the junctional and superficial dermis to the base of the lesion was demonstrated [27]. Accordingly, in Spitzoid melanoma there is greater HMB-45 expression in the deep dermal component than in Spitz nevi. Therefore, the use of HMB-45 staining may be suitable for distinguishing Spitz nevi or ASTs and melanomas, but, again, negative staining does not exclude the diagnosis of melanoma. On the other hand, S-100 protein has a diffuse pattern of positivity in all types of lesions [28]. Moreover, Spitz tumours exhibit lower rates of p53 and bcl-2, compared to melanomas [29]. Interestingly, there is controversy regarding the expression of p16 in Spitzoid lesions. Although some studies find a difference in p16 expression between Spitz nevus, ASTs, and melanomas, others do not. Recent data correlate p16 expression with abnormalities at 9p21 locus, with p16 expression retained in ASTs with heterozygous loss of 9p21, whereas lost in all ASTs or melanomas with homozygous loss of 9p21.

Table II summarises the expression of immunochemical markers in the differential diagnosis of Spitzoid melanocytic lesions.

Molecular studies

In contrast to Spitz nevi, which tend to have a normal karyotype, AST and melanomas typically contain genotypic abnormalities. In this context, BRAF/NRAS and FISH analyses may provide important information for the biological characterisation of these lesions.

BRAF

BRAF (v-raf murine sarcoma viral oncogene homolog B1) mutations may be found in approximately 50% of conventional melanomas, 80% of ordinary nevi [30], and a small subset of Spitzoid melanomas [31]. The majority of conventional Spitz nevi do not contain BRAF mutations [30]. Some studies have examined BRAF mutations in ASTs, and only one study reported evidence of BRAF mutations in ASTs [32]. Recently, the availability of BRAF- and NRAS-specific antibodies made it possible to perform pertinent immunohistochemical analyses in these lesions.

FISH

FISH represents a well-established ancillary diagnostic test for a subset of problematic melanocytic lesions. The composition of probe sets for analysing Spitzoid lesions may prove to be different from those used in the analysis of conventional nevi and melanomas. In their study, Gerami *et al*. identified

Table II. Expression of immunochemical markers in the differential Spitzoid melanocytic lesions

Antigen	Spitz nevus	Atypical Spitz tumor	Spitzoid melanoma
Ki-67	< 5% junctional and papillary dermis	5-25% junctional and papillary dermis	> 10% diffuse
HMB-45	Superficial expression, less intense with depth	Data not clear	Expression persists deeply
p-53 mutant	Low	Data not clear	High late event
S-100	+/– diffuse	Data not clear	+/– dermal patchy

a panel of FISH probes applicable in the diagnosis of melanoma. A combination of four probes targeting 6q23, 6p25, 6 centromere, and 11q13 correctly classified melanoma with 86.7% sensitivity and 95.4% specificity when compared with various nevi, including Spitz nevi. The study included 27 lesions with ambiguous morphology, 24 of which were Spitzoid lesions difficult to classify. Among this group of 24 difficult lesions, FISH probes identified six lesions that later metastasised, although further biological details relating to the Spitzoid cases were not carried out.

Therefore, a limited panel of FISH probes may provide useful diagnostic information in cases that could not be classified reliably by histopathology [33]. The same group of authors concluded that molecular abnormalities in melanoma were heterogeneous and that the sensitivity of this probe set varied in relation with subtypes of melanoma [34]. For example, Gaiser *et al*., utilising an identical FISH probe set, reported a sensitivity of 60% a specificity of 50% in discriminating melanomas from nevi, based on a series of patients with histologically ambiguous lesions and long-term clinical follow-up. Therefore, according to these authors, this probe set did not achieve sufficient sensitivity and specificity to be clinically useful in this setting [35].

Conclusions

The contribution of Sophie Spitz was to recognise and to describe a separate category of melanocytic lesions previously diagnosed and treated as malignant melanomas. Nevertheless, some tumours displaying some classic morphological features of the Spitz nevus are associated with worrisome atypical characteristics. Thus, there is an urgent need to identify more accurate histological and/or biological features that could be useful in the differential diagnosis between Spitz nevi, ASTs, and Spitz-like or Spitzoid melanomas. A practical approach to the diagnosis of these difficult lesions may derived by admitting a unifying concept for Spitzoid melanomas and ASTs, comprehensively described by a putative diagnosis of "low-grade melanoma". However, this viewpoint needs further confirmation. Integrating molecular and histopathological analyses may improve our understanding and our ability to dissect the spectrum of Spitzoid lesions. Nevertheless, the consistently different intragroup prognoses of these problematic lesions implies the need for intensive pathological workups and the organisation of multi-centric studies.

The authors declare no conflict of interest.

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