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MELANOCYTIC TUMOUR PATHOLOGY

The complex management of atypical Spitz tumours

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Summary

In recent years, advances in molecular genetic characterisation have revealed that atypical Spitz tumours (ASTs) are basically heterogeneous diseases, although the clinical relevance of these findings is yet to be determined. Evidence of molecularly-defined diverse groups of lesions continues to accumulate; however, conflicting, confusing, and overlapping terminology has fostered ambiguity and lack of clarity in the field in general. The lack of fundamental diagnostic (morphological) unambiguous classification framework results in a number of challenges in the interpretation of the molecular genetic data. In this review, we discuss the main difficulties for pathologists and clinicians in the complex management of ASTs, with particular emphasis on the different genetic and biological features of recently-described entities, and offer our view of what could be medically reasonable to guide a rational approach in light of current data.

Key words: Atypical Spitz tumour; Spitz naevus; melanoma; FISH; sentinel lymph node.

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INTRODUCTION

Sixty years after the first description of atypical Spitz tumours (ASTs or so-called borderline lesions, histologically ambiguous spitzoid melanocytic neoplasms, or spitzoid melanocytic tumours of uncertain malignant potential, STUMP), there is still controversy about whether these elusive tumours should be viewed as benign melanocytic naevi or a group of melanomas with their own specific morphological and biological characteristics. Currently, there are three interpretations regarding the taxonomy of ASTs: (1) ASTs are actually naevi that have some features in common with melanoma, but are biologically benign; (2) ASTs are biological intermediates between naevi and conventional melanomas; and (3) ASTs represent a subset of melanomas with a better prognosis than conventional melanomas.

The common denominator of all these interpretations is that the vast majority of patients diagnosed with ASTs have an excellent survival rate. Since these lesions appear to be diverse from a morphological and genetic point of view, it seems reasonable to think that what we put under the umbrella of ASTs is essentially a group of heterogeneous tumours in which the better prognosis observed as compared to conventional melanomas is strictly related to the artefact of data dilution in clinical reported series. Basically, we include in the same cohorts a large proportion of morphologically atypical but biologically benign lesions, and a small group of true melanomas, the latter being the culprit of the rare fatal cases reported so far.

There are several methodological problems and interpretative dilemmas with which researchers are faced in their analyses. The first concerns the inclusion of biologically and genetically heterogeneous ASTs, as reflected by a diverse clinical behaviour and unpredictable lymph node status in morphologically overlapping ASTs. Furthermore, a subgroup of ASTs metastasises to the lymph nodes; however, most patients, even with massive lymph node localisation, do not metastasise to distant organs. Nevertheless, rare cases are associated with a clinical behaviour that is similar to conventional melanomas. It is evident that, morphologically, we cannot distinguish between lambs and wolves.

The implications of this heterogeneous behaviour can easily be summarised: there is a different attitude between expert clinicians, the significance of lymph node metastases is somewhat debated, and clinical approaches range from aggressive behaviour, such as that seen in patients with melanoma, to a minimalist management. Consequently, most of the series reported so far: (1) are retrospective cohorts; (2) are heterogeneous series regarding patient age and other inclusion criteria; (3) centralisation of the pathological diagnosis is rare; (4) the morphological diagnostic criteria used to define a lesion as AST are not standardised in different series; and (5) the low number of events hinders the identification of reliable morphological and molecular predictive biomarkers.

TERMINOLOGY

In the field of challenging spitzoid proliferations, a major drawback relates to terminology, which is far from standardised. The term ‘atypical Spitz naevus’ has been used to define a benign lesion with atypical histopathological features deviating from a stereotypical Spitz naevus, while the term AST has been associated with an atypical spitzoid lesion not fulfilling all criteria for melanoma definition, but considered to have a potential for detrimental outcome. Nevertheless, the two terms have been used interchangeably. According to the opinion of some investigators, most neoplasms claimed to be atypical Spitz naevi/tumours are *bona fide* melanomas, and only two categories should be considered: the Spitz naevus

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and melanoma.[1] Thus, it has been suggested that ASTs do not represent real clinical entities,[2] but this definition is pragmatically used to handle morphologically ambiguous lesions, ranging from Spitz naevi with some atypical features, melanomas that resemble Spitz naevi, or proliferations that harbour some, but not all, genetic features of conventional melanoma and, as such, do not carry the same metastatic potential.[2]

Following the emerging hypothesis that ASTs could be clinically indolent, low-grade melanomas, with a low metastatic potential,[2] more explicitly, the term 'spitzoid melanoma of childhood', or 'spitzoid melanoma, childhood type' has been introduced by Le Boit in cases of a spitzoid neoplasm featuring a multinodular growth pattern, thinning of the epidermis, deep mitoses, and cells with striking nuclear atypia in the deep part of the lesion, usually in the absence of Kamino bodies.[3]

CLINICOPATHOLOGICAL FEATURES

The true incidence of atypical Spitz tumours/naevi is not known, although values of 6–8% of the overall number of Spitz naevi have been reported.[2]

ASTs more commonly develop during the first two decades of life as medium to large (>7 mm in size), nodular, rarely ulcerated, hypopigmented or amelanotic cutaneous lesions (Fig. 1 and 2).[4,5] Dermoscopically, a reliable distinction between ASTs and spitzoid melanomas is not feasible[5] even if ASTs seem to be more regular in the arrangement of the dermoscopic parameters within the lesion. Ferrara *et al.* have recently described the most frequent dermoscopic characteristics of hypopigmented atypical spitzoid proliferations, which include: (1) homogeneous pink colour, which can be associated with a brownish hue or remnants of brown pigmentation; (2) dotted vascular pattern; (3) 'starburst' vascular pattern; (4) reticular depigmentation; (5) chrystalline (chrysalis-like) structures.[5] It should be underlined that none of these features is specific for AST and a clinical and dermoscopical diagnosis of spitzoid melanoma cannot be ruled out with certainty.

Histopathologically, ASTs pose unique diagnostic challenges as their cyto-architectural features are poorly standardised, and many characters overlap with those of melanoma (Fig. 3–9). Among them are cohesive cellular nodules (solid growth) with deep extension into the lower dermis or subcutaneous fat, asymmetry and lack of maturation, marked cytological atypia, and deep/marginal mitoses. Helpful clues for the differential diagnosis among Spitz naevus, AST and spitzoid melanoma are reported in Tables 1 and 2. It should be emphasised, however, that there are obviously exceptions to these criteria and we should be cautious to use any single criterion alone for the categorisation of a spitzoid proliferation. In complex cases, it is imperative to systematically weigh all parameters before expressing an opinion on the probable nature of the lesion under evaluation. Clear-cut histopathological criteria for AST identification are still lacking, possibly because of the large number of cyto-architectural variables under evaluation.[1,6–10] The wide range of possible combinations of such variables results in unacceptably high inter-observer divergence even among internationally recognised experts of the field.[11,12] In addition, in the absence of long-term follow-up information, suggested sets of criteria can offer only partially reliable indications.

MOLECULAR GENETICS

In recent years, it has been shown that ASTs are constituted of genetically diverse entities, including H-RAS mutant,[13] B-RAF^{V600E}/BAP-1 mutant,[14] and a likely still heterogeneous category of tumours with as yet undefined genetic abnormalities.[15,16]

Approximately 25% of Spitz naevi show an increase in the number of copies of chromosome 11p, where the *HRAS* gene is located, and 70% of amplified tumours harbour a *HRAS* mutation.[17,18] It has been demonstrated under the microscope that most *HRAS* mutated lesions are wedge-shaped spindle cell proliferations associated with marked desmoplasia.[13,18] Despite deep mitotic activity, *HRAS* mutated spitzoid lesions are associated with a benign clinical course.[13] Interestingly, *HRAS* mutation was detected in 20–27% of spitzoid tumours of uncertain malignant potential[15,19] while *HRAS* mutations were not found in spitzoid melanomas, thus indicating *HRAS* as a low sensitivity/high specificity marker of benign Spitz naevus.[15]

So far, opposing results have been gathered as to whether AST carry *BRAF* and *NRAS* mutations.[20–23] Most studies do not demonstrate high rates of BRAF mutations in Spitz naevi and AST,[15,23–27] although Fullen *et al.* reported rates of 25% in each of these groups.[20] More recently, two atypical cutaneous melanocytic tumours with spitzoid features were reported in which *NRAS* was both mutated and amplified.[28] Of note, two cases of *NRAS* mutated melanocytic BAP1

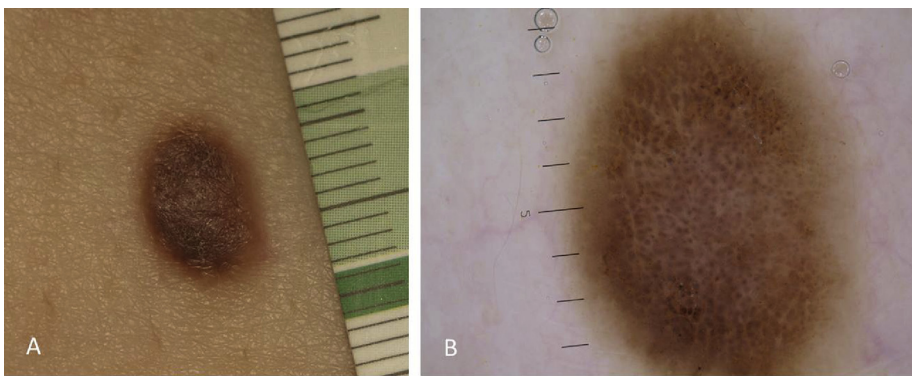

Fig. 1 Atypical Spitz tumour in a 43-year-old Caucasian woman. (A) Clinical examination: symmetrical brownish nodular lesion on lower arm. (B) Dermatoscopic examination: atypical inverted network with atypical globules.