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EXPERT REVIEWS

Lack of significance of sentinel lymph node biopsy for the prognosis and management of the atypical Spitz tumor of uncertain biologic potential

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Evaluation of: Ludgate MW, Fullen DR, Lee J *et al.* The atypical spitz tumor of uncertain biologic potential. A series of 67 patients from a single institution. *Cancer* 115, 631–641 (2009).

Most Spitzoid melanocytic lesions can be identified histologically as either a benign Spitz nevus or malignant Spitzoid melanoma. However, a rare intermediate subset of Spitzoid proliferation exists that has overlapping histological features of both entities. Such equivocal lesions, which can be designated atypical Spitzoid tumors (ASTs) of uncertain biologic potential, are difficult to manage due to this unclear potency. Although patients with AST generally have a good prognosis, rarely these tumors can metastasize and become fatal. Consequently it has been suggested that all ASTs should be treated as melanomas, with a wide excision and a sentinel lymph node biopsy (SLNB). Although SLNB may still be utilized to improve prognosis, it is now recognized that it does not improve outcome in patients with melanomas. We review a recent paper by Ludgate *et al.*, which studied a cohort of 67 patients with ASTs. Results from this paper suggest that ASTs do not behave like conventional melanomas and, in particular, positive SLNB is not associated with an adverse outcome. This important finding questions the use of SLNB in the management of ASTs.

Keywords: ambiguous Spitzoid tumor • atypical Spitz tumor • melanoma • sentinel lymph node biopsy • Spitz nevus • Spitzoid melanoma • Spitzoid tumor of uncertain malignant potential • Spitz tumor • STUMP

Spitz nevus & Spitzoid tumors

The Spitz nevus is a benign, usually acquired, melanocytic tumor that is characteristically composed of spindle or epithelioid melanocytes, or a mixture of these two cell types [1,2]. Clinically, Spitz nevi are dome shaped lesions with a smooth surface and are typically pink or tan, but may also be brown or black. They are usually less than 1 cm in diameter and often appear to be vascular lesions and, hence, can be mistaken for pyogenic granulomas. These nevi may occur anywhere on the body, but the face and extremities are most frequently involved. Criteria to discriminate Spitz nevi from the major differential diagnosis of cutaneous malignant melanoma were first published in 1947 by Sophie Spitz [3]. In this paper she suggested that these lesions were a juvenile variant of cutaneous melanoma with an excellent prognosis. In subsequent studies it was suggested that 'juvenile melanoma' was a benign tumor. There is still disagreement between dermatopathologists concerning which exact criteria define the entity of Spitz nevus, and how these differ from those used in the diagnosis of 'common' cutaneous melanomas (i.e., melanoma without Spitzoid features) 60 years later [1]. Numerous histological features have been described that may be present or absent in classic Spitz nevi, but these are often subjective and nonspecific and, as a consequence, diagnosis requires the interpretation of a constellation of criteria [2]. The relative importance placed upon these features also varies considerably between pathologists. The lack of diagnostic clarity is greater still in tumors that deviate

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from the classical Spitz nevus and show features more commonly associated with the main differential diagnosis, malignant melanoma. The terms 'atypical Spitz tumor', 'atypical Spitz nevus', 'ambiguous Spitzoid tumor' and 'Spitzoid tumor of uncertain malignant potential' are used for the classification of lesions that are neither classic Spitz nevus nor common melanoma (i.e., non-Spitzoid cutaneous melanoma). In this paper we will refer to these lesions hereafter as atypical Spitz tumors (ASTs). There is a great deal of uncertainty about their propensity for causing metastasis and death, although generally the prognosis is good. The entity of Spitzoid melanoma implies a tumor with a combination of features of classical Spitz nevus and common melanoma. As with all Spitzoid tumors there are no accepted criteria for their diagnosis, but it is expected that such lesions will behave in a malignant fashion.

Methods & results

In a retrospective study, Ludgate and colleagues followed up a group of 67 patients with AST. The Breslow depth ranged from 0.3 to 8 mm, with a mean of 2.4 mm [4]. A total of 57 patients, with tumors thicker than 1 mm or with thin tumors and adverse features (ulceration, a high mitotic range and young age), underwent a sentinel lymph node biopsy (SLNB). A total of 27 patients (47%) had a positive SLNB. The only significant difference between the positive and negative SLNB groups was age, with SLNB positive patients being younger ($p = 0.013$). At follow-up all 27 patients with a positive SLNB were alive and disease free (median follow up 43.8 months), as were all the patients with a negative SLNB (median follow-up 28.6 months).

Ten patients were treated by wide local excision without SLNB. One of these patients, in whom the primary tumor was of sufficient depth for SLNB counseling to be offered, developed a recurrence and subsequently died. Seven of the remaining nine patients treated by wide local excision alone were alive and disease free after follow-up. Two patients were lost to follow-up. Of note, 24 out of 27 patients with a positive SLNB received adjuvant therapy in the form of IFN-α2b or a 'vaccine'.

The patient who died was a 46-year-old woman diagnosed with a Spitz nevus by three dermatopathologists. Upon retrospective review, the original biopsy was re-evaluated as AST with a depth of 1.1 mm. She was initially treated with a wide local excision but the lesion extended to a peripheral margin and so she was subsequently managed by close observation. Metastatic disease developed 2 years after the initial excision.

Expert commentary

Atypical Spitz tumors are uncommon melanocytic tumors for which it is difficult to predict malignant behavior and, consequently, they are difficult to manage clinically. Indeed, investigation of key molecular aberrations in AST, such as mutations of the *HRAS* gene, have suggested that these lesions may merely represent a group of Spitz nevi and Spitzoid melanomas that are unclassifiable by light microscopy and not in fact genetically distinct entities [2]. This is a position that has been championed by Ackerman and colleagues for some time and is analogous to the viewpoint that 'classical' atypical nevi are a mixture of benign nevi and early melanomas, rather than precursors of melanomas *per se* [5–8].

Ludgate and colleagues report the largest cohort of AST patients to date [4]. The number of patients in this study, 67, is similar to the total number of patients previously reported in the literature as a whole. In addition, the current study had appreciably longer follow up for patients with a positive SLNB (mean follow-up time 43 months), compared with similar patients in previous reports (mean follow-up 29 months). In contrast to previous reports, patients in the current study were treated and followed up at a single institution, which lends additional credibility to their data. All patients with a positive SNLB were alive and disease free after follow-up, a finding in-keeping with previous studies. Thus, an informal meta-analysis encompassing all patients with positive SLNB reported in the literature to date (n = 58) indicates that positive SLNB is not predictive of a poor prognosis, which questions the role of this procedure in the management of AST. The authors in the current study argue that, where SLNB is performed, a negative result provides reassurance to the patient. They do not consider the converse situation, however, in which a patient is faced with a positive SLNB but cannot be given evidence-based counseling about the implications of their result.

There is considerable evidence to suggest that typical Spitz nevi may represent a distinct group of melanocytic tumors that arise independently of *BRAF* and *NRAS* mutations, unlike the vast majority of common acquired nevi and common melanomas [1]. The evidence that this may be the case in AST is far less robust although DNA copy number aberrations (including loss of the *p16* tumor-suppressor gene locus) have been reported in ASTs [9–11]. This paucity of evidence is, in the most part, likely to be due to the rarity of these lesions and the considerable ambiguity concerning their diagnosis. As yet, there are no data within the published literature to demonstrate a consistent genetic signature or molecular marker of the AST phenotype. As mentioned earlier, some might argue that this is because the existence of AST as a distinct entity, rather than merely a mixture of diagnostically difficult benign Spitz nevi and malignant common melanomas, can been questioned [1,2].

It should be noted that, although not proven in the setting of common melanoma [12–14], the possibility remains that SLNB may be therapeutic in AST. Were this the case, it would suggest that ASTs are indeed biologically unique with a behavior that is distinct from other types of melanoma. It is also possible that, for similar reasons, adjuvant immunotherapy may be beneficial in ASTs with a positive SLNB (89% of AST patients in the study of Ludgate and colleagues received adjuvant therapy). In practice, due to the rarity of AST it might not be possible to conduct a sufficiently large clinical trial to answer these questions, unless perhaps it is led by an organization with expertise in coordinating multicenter, international, randomized controlled trials for rare diseases, such as the UK Dermatology Clinical Trials Network [15].

Five-year view

In 5 years time, 10-year follow-up data should be available for this cohort of patients. This would remedy one of the major shortcomings of this field of research, namely limited follow-up

data, from which it is difficult to draw significant conclusions. Such data would serve as an invaluable resource for evaluating the prognosis of this ambiguous type of melanocytic proliferation.

Furthermore, continuing research into the molecular pathology of these tumors, in particular the analysis of DNA copy aberrations, may help separate those ASTs with a good prognosis from those with a malignant phenotype. Future molecular research may also answer the question of whether ASTs are a genuine entity rather than a convenient term for a mixture of diagnostically difficult lesions. Were they shown to be a genetically distinct, this might enable the identification of therapeutic targets for tailored therapy [1,2]. Large and well-coordinated multicenter international studies will be important if we are to make significant future progress.

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Key issues

- Predicting the biological behavior of atypical Spitz tumors (AST) via histology can be impossible because they have features of both Spitz nevi and malignant melanoma.
- The majority of ASTs have an excellent prognosis; however, there are well-documented cases where patients have progressed to metastatic disease and death, therefore, ASTs represent a considerable management challenge.
- Sentinel lymph node biopsy (SLNB) is associated with a significant morbidity.
- SLNB is unlikely to improve survival in patients with AST, although this is not proven in the current data.
- There is no evidence that SLNB provides prognostic information in the setting of AST.
- Advances in our understanding of the molecular pathology of AST may improve diagnosis, enable accurate prognostication, and facilitate targeted therapy.

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