Spitz melanocytoma vs melanoma: a case involving the use of molecular testing

Harriet Hunter
Jonathan Potts
Paul Craig

This Short Case is brought to you in association with the Pathological Society of Great Britain and Ireland. Each month we feature a Short Case written by a member of the Trainees' Subcommittee of the Pathological Society of Great Britain and Ireland. This case, including its scanned slides, is published on the Pathological Society's website www.pathsoc.org/index.php/trainees/case-of-the-month (previous cases can be accessed by members via the education portal login). The Short Case includes a series of Test Yourself Questions at the end to check your understanding of the case. We hope you enjoy reading it.

Pathological Society
Understanding Disease — Guiding Therapy

Abstract

This case is of a melanocytic lesion that was eventually classified as a spitzoid melanoma, after molecular testing. The differential diagnosis was between a Spitz melanocytoma (Atypical Spitz tumour) and a spitzoid melanoma. This is a subjective and ambiguous area of pathology, where the use of molecular testing can provide useful diagnostic information. In this case, a BRAF V600E mutation, and lack of kinase fusions, led to the diagnosis of a spitzoid melanoma, rather than a true member of the Spitz family.

Keywords Atypical Spitz naevus; atypical Spitz tumour; naevus; Spitz; Spitz melanocytoma; spitzoid melanoma

Case report

A 49-year-old man presented with an inflamed and itchy naevus on the lower back, which was excised with a 3 mm margin. Macroscopic examination showed a well demarcated papule of 5 mm dimeter, with uniform pigmentation.

Microscopy showed predominantly intradermal melanocytic proliferation, which was symmetrical (Figure 1). There was minimal morphological maturation with depth. The cells showed epithelioid morphology, with abundant cytoplasm (Figure 2). There was nuclear pleomorphism with prominent nucleoli and occasional nuclear inclusions. A possibly atypical dermal mitosis was identified (Figure 3).

Immunohistochemistry showed a complete loss of p16 (Figure 4). BAP-1 showed retained nuclear expression (Figure 5).

The provisional conclusion was an atypical epithelioid compound melanocytic lesion. The differential diagnosis on morphology included a Spitz melanocytoma (atypical Spitz tumour), a Spitz melanoma, or a spitzoid conventional melanoma. The distinction between these entities is highly subjective on morphology alone, so molecular testing was required. Although the morphological differential would have also included a BAP1 inactivated melanocytoma, this was ruled out immunohistochemically by the retention of nuclear BAP1.

Molecular tests were requested, including a melanoma NGS panel and an RNA fusion panel. The RNA fusion panel showed no evidence of kinase fusions. The NGS panel detected an activating BRAF V600E mutation. With these results, the

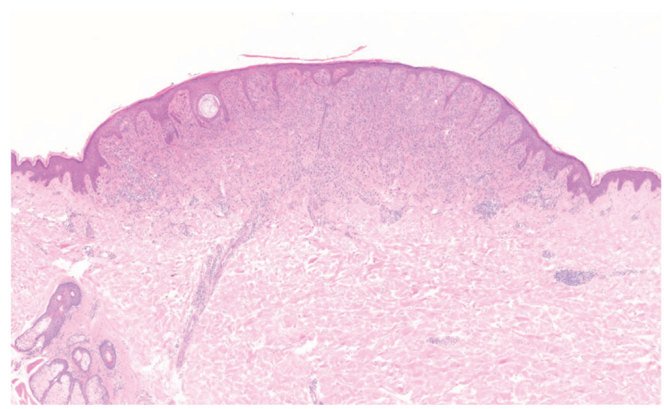

Figure 1 Low power (x20) H&E — symmetrical architecture, dermal location.

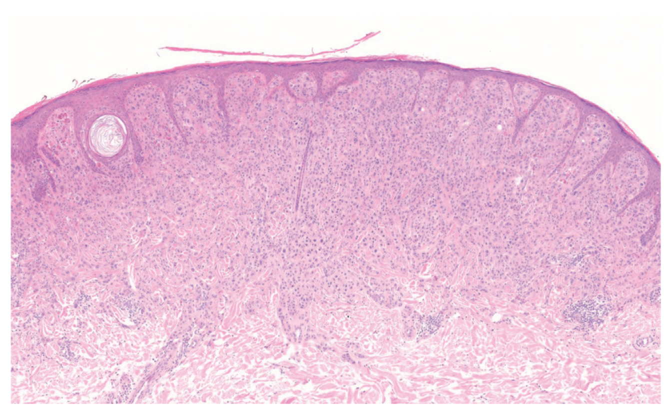

Figure 2 Low power (x50) H&E — epithelioid morphology, lack of maturation.

***Harriet Hunter** MA (Cantab) MBBChir Histopathology Specialist Registrar, North Bristol NHS Trust, UK. Conflicts of interest: none declared.*

***Jonathan Potts** BSc MBChB FRCPath Histopathology Consultant, North Bristol NHS Trust, UK. Conflicts of interest: none declared.*

***Paul Craig** MBBS FRCPath DipRCPath (Derm) FRCPA Histopathology Consultant, North Bristol NHS Trust, UK. Conflicts of interest: none declared.*

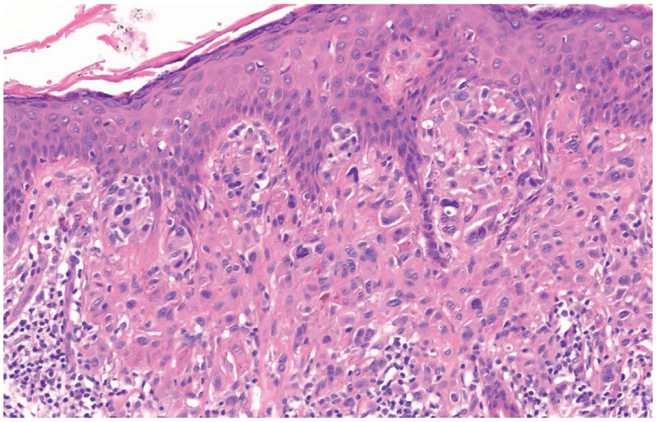

Figure 3 High power (x200) H&E — nuclear pleomorphism, atypical mitotic figure.

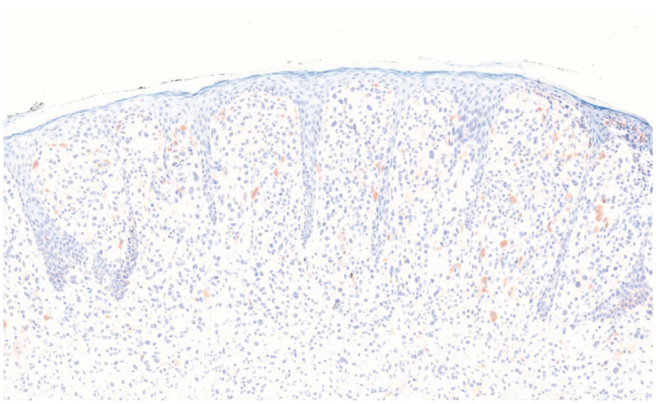

Figure 4 p16 stain is negative.

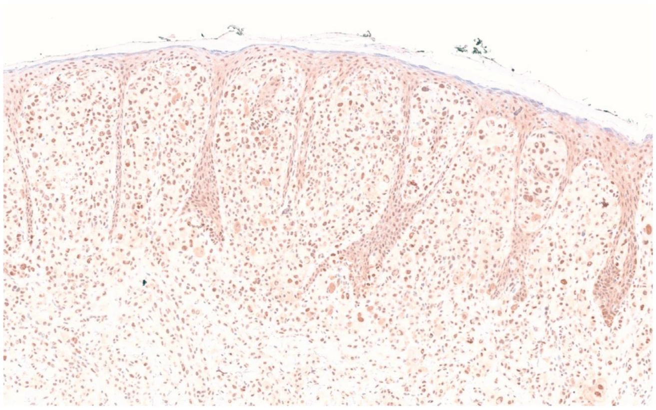

Figure 5 BAP1 nuclear staining is retained.

diagnosis of a spitzoid melanoma was favoured over a true Spitz neoplasm.

Discussion and conclusion

What are Spitz tumours?

Spitz tumours are a family of melanocytic lesions with distinctive morphological and molecular features. Spitzoid features include large epithelioid or spindled melanocytes, eosinophilic Kamino bodies, and a distinctive nested architecture with clefting at the periphery of the nests.[1] The spindled melanocytes are often arranged in parallel, like a bunch of bananas or a shoal of fish. Spitz tumours behave across the benign-malignant spectrum, ranging from the benign Spitz naevus to the malignant Spitz melanoma, or malignant Spitz tumour. Molecularly, Spitz tumours are characterized by either kinase gene fusions or HRAS mutations, and lack the BRAF or NRAS activating point mutations common in conventional naevi and melanomas.[2]

Features of Spitz melanoma include asymmetry, epidermal consumption or ulceration, and extension into the deep dermis, with deep mitoses and lack of morphological maturation. Molecular features include the characteristic kinase fusions, along with additional mutations such as TERT promotor activation.[1]

Intermediate cases with some atypical features, but falling short of frank malignancy, are termed Spitz melanocytomas or atypical Spitz tumours (AST). This is a challenging and subjective area of diagnosis. Since Spitz melanocytomas are generally indolent with a low risk of progression, there is a risk of overtreatment if they are managed as melanoma. Conversely, since a greater degree of atypia may be tolerated in a lesion of Spitzoid lineage compared to a conventional pathway, it is important not to misclassify conventional melanomas as Spitz melanocytomas. A conventional melanoma with spitzoid features, but not molecularly of the Spitz lineage, is called a spitzoid melanoma.

How can IHC and molecular tests help?

Although no single IHC marker can distinguish Spitz melanocytomas from melanomas, a panel of HMB-45, p16, and Ki67 has been suggested to be of use. Features of strong deep HMB-45 staining, complete loss of p16, and Ki67 index >10% are all more suggestive of melanoma.[3] PRAME is a relatively new marker said to be preferentially expressed in melanoma compared to benign melanocytic lesions, however expression has also been reported in Spitz naevi and Spitz melanocytomas.[4]

DNA and RNA next generation sequencing panels allow relevant mutations and gene fusions to be detected. A benign Spitz naevus will generally have a single genetic alteration, usually either a kinase fusion or HRAS mutation. While these molecular features are seen throughout the spectrum of Spitz lesions, atypical and malignant Spitz tumours often have additional abnormalities such as PTEN mutations and TERT promotor mutations.[5] If an atypical or malignant spitzoid lesion has a BRAF or NRAS point mutation (rather than a fusion), it should be classified as a spitzoid melanoma, and managed as a conventional melanoma. These tend to have a worse prognosis than true members of the Spitz family.[3] ◆

REFERENCES

1 Elder DE, Barnhill RL, Bastian BC, et al. Melanocytic neoplasms. In: WHO Classification of Tumours Editorial Board. Skin tumours [Internet; beta version ahead of print] 2023. Lyon (France): International Agency for Research on Cancer (WHO classification of tumours series, 5th edn; vol. 12). Available from: https://tumourclassification.iarc.who.int/chapters/64 [cited 2024/08 04].

2 Hagstrom M, Fumero-Velasquez M, Dhillon S, et al. An update on genomic aberrations in Spitz naevi and tumours. *Pathology* 2023; **55:** 196–205.

3 Wiesner T, Kutzner H, Cerroni L, et al. Genomic aberrations in spitzoid melanocytic tumours and their implications for diagnosis, prognosis and therapy. *Pathology* 2016; **48:** 113–31. https://doi.org/10.1016/j.pathol.2015.12.007. Epub 2016 Jan 18. PMID: 27020384; PMCID: PMC4817351.

4 Raghavan SS, Wang JY, Kwok S, et al. PRAME expression in melanocytic proliferations with intermediate histopathologic or spitzoid features. *J Cutan Pathol* 2020; **47:** 1123–31. https://doi.org/10.1111/cup.13818. Epub 2020 Sep 10. PMID: 32700786.

5 Cheng TW, Ahern MC, Giubellino A. The spectrum of Spitz melanocytic lesions: from morphologic diagnosis to molecular classification. *Front Oncol* 2022; **12**: 889223. https://doi.org/10.3389/fonc.2022.889223. PMID: 35747831; PMCID: PMC9209745.

Practice points

- Tumours of the Spitz family can exhibit the full range of benign to malignant behaviour. Important features of malignancy include: asymmetry, epidermal consumption, necrosis, frank cellular atypia, deep invasion, and lack of maturation
- Distinguishing spitzoid melanoma and Spitz melanocytoma is a subjective area of clinical practice. The use of molecular tests is an important adjunct to diagnosis
- If an atypical or malignant lesion with Spitz features shows a BRAF or NRAS mutation (rather than fusion), it should be classified as a spitzoid melanoma. These have a worse prognosis

Self-assessment multiple choice questions

1. Which two molecular features are characteristic of Spitz nevi?

a. Kinase fusions
b. BRAF point mutations
c. TERT promotor mutations
d. P53 mutations
e. HRAS activating mutations

2. If a frankly malignant spitzoid lesion has a BRAF V600E mutation, how should it be classified?

a. Spitz melanoma
b. Atypical Spitz tumour
c. Spitz melanocytoma
d. Spitzoid conventional melanoma
e. Malignant Spitz tumour

3. Which of the following is not a feature of Spitz tumours?

a. Spindled or epithelioid melanocytes
b. Nests like bunches of bananas
c. Nests like bunches of grapes
d. Clefting
e. Nests like shoals of fish

Answers:

1. A, E.
2. D
3. C

