BRAF Mutated and Morphologically Spitzoid Tumors, a Subgroup of Melanocytic Neoplasms Difficult to Distinguish From True Spitz Neoplasms

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Abstract: Drivers of Spitz neoplasms include activating point mutations in *HRAS* and Spitz-associated genomic fusions. It has become evident that some *BRAF*-mutated melanocytic neoplasms can morphologically mimic Spitz tumors (STs). These have been termed *BRAF* mutated and morphologically spitzoid (BAMS). In this study, 17 experts from the International Melanoma Pathology Study Group assessed 54 cases which included 40 BAMS and 14 true STs. The participants reviewed the cases blinded to the genomic data and selected among several diagnostic options, including BAMS, ST, melanoma, and other. A total of 38% of all diagnostic selections in the BAMS cases were for BAMS, whereas 32% were for ST. In 22 of the BAMS cases, the favored diagnosis was BAMS, whereas in 17 of the BAMS cases, the favored diagnosis was ST. Among the 20 cases in the total group of 54 with the highest number of votes for ST, half were BAMS. Of BAMS, 75% had a number of votes for ST that was within the SD of votes for ST seen among true ST cases. There was poor interobserver agreement for the precise diagnosis of the BAMS (kappa = 0.16) but good agreement that these cases were not melanoma (kappa = 0.7). BAMS nevi/tumors can closely mimic Spitz neoplasms. Expert melanoma pathologists in this study favored a diagnosis of ST in nearly half of the BAMS cases. There are BAMS cases that even experts cannot morphologically distinguish from true Spitz neoplasms.

Key Words: melanoma, dysplastic nevi, Spitz nevi, atypical Spitz tumors, Spitz melanoma, BRAF

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Genomics is rapidly being integrated into the diagnostic algorithm for challenging melanocytic neoplasms which may have histomorphological ambiguity.

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According to the World Health Organization classification, fourth edition,[1] a Spitz neoplasm is defined by spitzoid morphology and a primary driver which is either a Spitz-associated genomic fusion or *HRAS* activating point mutation.[2] Conversely, melanocytic tumors with spitzoid features and *BRAF* or *NRAS* mutations are excluded from the category of true Spitz neoplasms.[2,3] This has allowed for a more reproducible and concise classification of Spitz neoplasms.

In one study, among morphologically spitzoid neoplasms, those cases with the highest risk for aggressive behavior were cases that were not true Spitz but rather tumors that harbored *BRAF* or *NRAS* mutations, often with a telomerase reverse transcriptase (TERT) promoter mutation.[4] As a result of more routine utilization of genomics, it has become apparent that there is a spectrum of *BRAF* and *NRAS* mutated melanocytic neoplasms, ranging from benign to malignant, that can closely mimic Spitz neoplasms morphologically.[2] In this study, we were specifically interested in whether expert pathologists could distinguish between benign and intermediate-grade melanocytic neoplasms with spitzoid morphology and a *BRAF* activating point mutation, that is, tumors, in general, mapping to MPATH-Dx V2.0 class II[5] from comparable true Spitz neoplasms. To assess this, we invited expert melanoma pathologists from the International Melanoma Pathology Study Group to evaluate and diagnose a series of 54 cases consisting of both *BRAF*-mutated nevi/tumors with spitzoid features (*BRAF* mutated and morphologically spitzoid [BAMS] nevi/tumors) and true fusion or *HRAS* mutated Spitz tumors (STs). Our findings suggest that there is a subset of melanocytic neoplasms with *BRAF* mutations and spitzoid morphology that even expert melanoma pathologists cannot reliably distinguish from true STs by morphology alone.

MATERIALS AND METHODS

Case Selection

Study approval and waiver of consent for the use of de-identified information was obtained through Northwestern University's Institutional Review Board (IRB; STU00001127). We queried medical records between 2014 and 2022 to identify melanocytic neoplasms that fit into the following diagnostic groups: STs, including Spitz nevi, atypical STs, and Spitz melanocytomas, as well as BAMS nevi/tumors. Cases diagnosed as melanoma were excluded. The presence of a *BRAF* mutation or any Spitz-related mutations as defined by the World Health Organization as melanocytic nevi with characteristic spitzoid cytomorphologic features harboring an *HRAS* mutation or a kinase fusion involving *ALK*, *ROS1*, *NTRK1-3*, *RET*, *MET*, *BRAF,* or *MAP3K*[1,6–8] was confirmed by either fluorescence in situ hybridization (FISH), immunohistochemistry (IHC) or through next-generation sequencing done at the time of clinical care or later for research purposes. In total, 14 ST cases and 40 BAMS cases were included.

IHC, Genetic Sequencing, and FISH

FISH studies were performed in 18 cases in the Northwestern Medicine Dermatopathology laboratory as an additional test for melanoma at the time of clinical diagnosis.[9] This analysis was performed as previously described,[10–12] using probes targeting 6p23, 6p25, Cep6, CEP9, 9p21, and 11q13. All cases had negative results in the FISH studies.

IHC was performed on 36 BAMS cases using a 1:100 dilution of anti-*BRAF* antibody (V600E mutated; Abcam) and the Leica Bond MaxAutostainer (Leica Biosystems). The Bond Polymer Refine Red Kit (Leica Biosystems) was used for retrieval, antibody incubation, washing, and staining. Positive and negative control slides were also run with all samples, and cases were read by a study investigator for assessment of positive staining as determined by uniform strong staining throughout the neoplasm. Twenty-eight cases (14 BAMS and 14 Spitz) were sequenced through either the Tempus xT or Tempus xO panel at the time of clinical care or later for research purposes. DNA and messenger RNA whole transcriptome sequencing used the Illumina Hiseq. 4000 System and the Tempus xT and xO DNA sequencing platform which included a 648 or 1711 gene panel, respectively.[13,14]

Survey Administration

Cases were split into 2 separate diagnostic categories of true STs or BAMS nevi/tumors. We developed a survey that included a hematoxylin and eosin slide of each case, as well as pertinent patient information, including sex, age, and site of the biopsy. No information on the final diagnosis or any additional genetic or diagnostic test results on the cases were presented. Four distinct diagnostic answer choices were provided for each case for the reviewer to choose from: BAMS (1), ST (2), other (3), or melanoma (4). The survey was administered at the International Melanoma Pathology Study Group Workshop in Edinburgh, Scotland, October 16, 2022, and completed by 17 world expert board-certified dermatopathologists who submitted their responses before the related lecture at the conference.

Statistical

To calculate interrater agreement, the Free-Marginal Multirater Kappa score (multirater ðfree) was used to assess each survey. This score is an alternative to the Fleiss Kappa score and other bi-rater free-marginal Kappa scores. The multirater ðfree is indicated when reviewers are not restricted to vote in accordance with a set number of cases belonging to a single category, thereby preventing limitations on their voting decisions across independent cases.[15] Cohen Kappa interpretation system was used to categorize the level of agreement illustrated by each calculated multirater ðfree: 0 to 0.20 as none, 0.21 to 0.39 as minimal, 0.40 to 0.59 as weak, 0.60 to 0.79 as moderate, 0.80 to 0.90 as strong, and above 0.90 as almost perfect.[16] Both the χ^2 tests and the Free-Marginal Multirater Kappa score were calculated in Microsoft Excel and the significance level for the χ^2 tests was set at $P = 0.05$.

RESULTS

A total of 54 cases were included in the study which included 40 BAMS tumors and 14 genomically confirmed STs (Table 1). Of the BAMS cases, 35 harbored a missense p.V600E mutation and the remaining 5 cases harbored one of each of the following missense mutations: p.V600R, p.V600K, p.S110C, p.S323L, and p.E545Q. The BAMS group included 9 males and 31 females with an average age of 27 years old which ranged from 4 to 63 years old. Of the 40 BAMS tumors, 52.5% were located on the extremities, 35% on the trunk, and 12.5% on the head and neck. The ST group included 7 males and 7 females with an average age of 19 years old which ranged from 4 to 35 years old. Among the 14 ST sites, 65% were located on the extremities, 21% on the trunk, and 14% on the head and neck (Table 2). There was no statistically significant difference in age or distribution in comparing the BAMS and ST cases. The 17 participants assessing the 40 BAMS tumors made a total of 678 diagnostic selections (17 participants X 40 BAMS cases = 680 diagnostic selections among the BAMS cases and 2 participants did not vote for case 13). A total of 39.4% (267 votes) of the diagnostic selections were for BAMS, whereas 32.3% (219 votes) of the diagnostic selections were for ST. Of the diagnostic selections, 19% (129 votes) made in the BAMS cases were for "other," whereas 9.3% (63 votes) of the total diagnostic selections were for melanoma. In the ST group, a total of 45 of the diagnostic selections were for BAMS (19%), compared with 157 selections for ST (67%). The group accuracy in the BAMS group was 39% compared with 67% in the ST group.

In assessing the diagnostic selections within the 40 individual BAMS cases, the selected diagnosis was either favored or tied for BAMS in 22 cases, ST in 17 cases, and other in 1 case (Figs. 1–4). In fact, among the 20 cases with the highest number of votes for ST, half of them were BAMS and more than 75% of the BAMS had enough votes for ST from the expert panel to fall within the SD percentage of ST votes seen from the true ST cases. Among the 14 ST cases (Figs. 5), 1 had nearly the same number of diagnostic selections of BAMS as ST.

In 91% of the BAMS cases, a diagnostic selection of a benign diagnosis other than melanoma was selected. The Free-Marginal Multirater Kappa score (multirater ðfree) [15] for assessing these cases as melanoma or not was 0.70, which demonstrates moderate agreement.[16] The overall multirater ðfree for precise diagnostic agreement in the BAMS cases was 0.16 which reflects poor agreement among the expert panel. For the ST cases, the multirater ðfree for diagnosing these as melanoma or not was 0.75 which also reflects moderate overall agreement. The overall multirater ðfree for precise diagnostic agreement in the ST group was 0.40, demonstrating weak agreement.

DISCUSSION

Our study suggests there is a subset of benign and intermediate-grade BRAF-mutated melanocytic neoplasms that can closely mimic true Spitz neoplasms.[17] However, there is uncertainty regarding how to best classify these melanocytic neoplasms.[6] One specific example would be BAP1-associated melanocytic nevi/tumors. These lesions can have spitzoid morphology and seem to mostly be indolent despite the presence of some concerning histologic features.[18] In this example, as genomics is very specific, BAP1 neoplasms constitute their own class. However, there are other examples of melanocytic tumors with alternative genetics in which the primary driver may be a *BRAF* mutation with spitzoid morphology.[7] A previous study of BAMS neoplasms showed that 35% had additional mutations involving the *KMT* gene family, either KMT2C or KMT2D.[2] However other genomic aberrations are also possible.

In this study, we specifically aimed to determine whether a group of international melanoma pathology experts from the International Melanoma Pathology Study Group could distinguish between a series of BAMS nevi or tumors and true STs with Spitz-associated genomic fusions or an *HRAS* mutation. Blinded assessment of the BAMS group by the expert panel had nearly equal numbers of diagnostic selections of BAMS and ST, 38% and 32% of all votes, respectively. Hence, the group's diagnostic accuracy was relatively low in assessing these cases. Further, the overall Free-Marginal Multirater Kappa measuring the level of agreement among the experts in assessing these cases was 0.22, which reflects minimal agreement among the reviewers. Conversely, there was agreement in the group regarding whether they felt the BAMS cases were not melanoma with a Free-Marginal Multirater Kappa score of 0.70.

In assessing the 40 unique individual BAMS cases, there were 17 in which the favored diagnosis by the group was ST. The 20 cases from the overall data set of 54 which had the highest number of votes for ST consisted of an equal number of BAMS (n = 10) and STs (n = 10). In fact, over 75% of the BAMS cases had enough votes for ST that they fell within the SD of the number of votes for ST seen in true ST cases. In addition, as previously noted, 91% of the total votes on the BAMS cases were for a diagnosis other than melanoma. These findings support the supposition that there is a group of melanocytic neoplasms with *BRAF* mutations that expert pathologists favor as benign and cannot confidently distinguish from true STs by morphology.

Observationally, there are some morphologic features that are more typical of BAMS than true Spitz. While most of the BAMS cases had eosinophilic glassy cytoplasm similar to Spitz, some of the BAMS have more smudged hyperchromatic nuclei compared with the characteristic vesicular nuclei with open chromatin seen in most true Spitz. Also, in our broader experience, the BAMS group has a higher frequency of prominent melanin pigment and melanophages (22/40 cases, 55%). However, this was not true in this series, since by random chance, there was a relatively high percentage of pigment in the true Spitz cases in this series (10/14 cases, 71%).

Although in this study we focused on benign and intermediate grade *BRAF*-mutated melanocytic neoplasms, these mimickers of Spitz may be malignant or benign.[4]

TABLE 1. Clinical Data and Genomics of BAMS and ST Cases

Case	Age	Sex	Location	DDx*	Genomics†
1	39	F	Left anterior shin	1	BAMS
2	26	M	Left finger	1	BAMS
3	21	F	Left upper arm	1	BAMS
4	8	M	Left infra-orbital cheek	1	BAMS
5	15	M	Mid posterior neck	1	BAMS
6	11	F	Left thigh	2	*ALK* fusion AST
7	12	F	Right flank	1	BAMS
8	14	M	Left calf	2	MAP3K8 truncated AST
9	59	M	Left upper abdomen	1	BAMS
10	39	F	Left arm	1	BAMS
11	32	F	Back	1	BAMS
12	18	M	Right mandible	2	NTRK3::MYO5A fusion AST
13	12	M	Back	1	BAMS
15	12	M	Left back	1	BAMS
16	17	F	Right posterior shoulder	1	BAMS
17	20	F	Left buttock	1	BAMS
18	13	F	Right upper arm	1	BAMS
19	35	F	Right buttock	2	BRAF fusion AST
20	38	F	Left back	1	BAMS
21	44	F	Right thigh	1	BAMS
22	39	M	Left leg	1	BAMS
23	19	F	Left foot	1	BAMS
24	25	M	Right thigh	2	BRAF::MYO5A fusion AST
25	21	F	Upper mid back	1	BAMS
26	33	F	Right upper arm	1	BAMS
27	61	F	Left base of fourth toe	1	BAMS
28	4	F	Right foot	1	BAMS
29	8	F	Right upper back	1	BAMS
30	6	M	Left forearm	2	MAP3K8 truncated AST
31	32	F	Left abdomen	1	BAMS
32	21	M	Left calf	1	BAMS
33	12	M	Left ear	1	BAMS
34	40	F	Right thigh	1	BAMS
35	10	F	Left hip	2	MAP3K8 fusion AST
36	20	F	Right scapula	2	NTRK3::MYO5A fusion AST
37	39	F	Left upper arm	1	BAMS
38	44	F	Mid sternum	1	BAMS
39	10	F	Right knee	1	BAMS
40	32	F	Right forearm	2	BRAF::MLANA fusion Spitz nevus
41	26	F	Right hip	1	BAMS
42	63	F	Right thigh	1	BAMS
43	37	F	Right knee	1	BAMS
44	4	M	Right thigh	2	*HRAS*-mutated Spitz nevus
45	15	F	Back	1	BAMS
46	37	F	Right knee	1	BAMS
47	17	F	Right thigh	2	NTRK3::SQSRM1 fusion ST
48	21	F	Left back	1	BAMS
49	4	F	Left earlobe	1	BAMS
50	26	F	Left wrist	2	MAP3K8::SVIL fusion Spitz nevus
51	40	F	Left thigh	1	BAMS
52	32	M	Right lower back	2	NTRK1::LMNA fusion Spitz nevus
53	30	F	Right jawline	1	BAMS
54	33	F	Right thigh	1	BAMS
55	11	M	Right upper arm	2	RET::K1F5B fusion Spitz nevus

*1 = BAMS, 2 = Spitz.
†BAMS = BRAF mutated and morphologically Spitz tumor.
AST indicates atypical Spitz tumor.

From these findings, we conclude that for morphologically ambiguous cases with spitzoid features in which melanoma is in the differential diagnosis, assessing for the genomic driver may be critical.[19] While much more morphologic atypia, such as ulceration or brisk mitotic activity, may be tolerated in a true Spitz with a fusion driver, the same findings in a *BRAF*-mutated neoplasm would be much more concerning for malignancy.[20] Hence, IHC for *BRAF*V600E or genomic studies can play a significant role in solving some of these cases.[21]

In deciding when ancillary studies may be indicated, there are 2 primary factors that impact the pretest probability of the lesion being a true Spitz. The first factor is age, and the second factor is how characteristically spitzoid the morphology is. If the patient is young and the morphology is classic, then the likelihood of a true Spitz becomes quite high and, in most cases, additional molecular testing is not necessary. However, the older the patient is the more characteristic the histology needs to be. In older patients in which the morphology is perhaps somewhat spitzoid but not completely characteristic, additional ancillary testing would be very important to check with *BRAF* or *NRAS* IHC or molecular studies. If the tumor has an activating mutation in *BRAF* or *NRAS* and melanoma is in the morphologic differential diagnosis, then additional testing with FISH, comparative genomic hybridization, or assessment for a TERT promoter mutation would be very important. For the benign and intermediate-grade cases, it is unknown whether these lesions have a higher risk of transformation or less stability than

TABLE 2. Summary of Clinical Data and Diagnostic Selections in ST (N = 14) and BAMS (N = 40) Cases

Clinical and histologic	ST (N = 14)	BAMS (N = 40)	*P*
Clinical			
Age (y)			
Mean	18.6	27.4	0.22
Median	17.5	26	—
Range	4-35	4-63	—
Sex			
Female	7	9	—
Male	7	31	—
Location; n (%)			0.40
Head/neck	2 (14.3)	5 (12.5)	0.58
Trunk	3 (21.4)	14 (35)	0.43
Extremities	9 (64.3)	21 (52.5)	0.28
Votes; n (%)			
BAMS	45 (19)	267 (39.4)	—
ST	157 (67)	219 (32.3)	—
Other	16 (7)	129 (19)	—
Melanoma	16 (7)	63 (9.3)	—

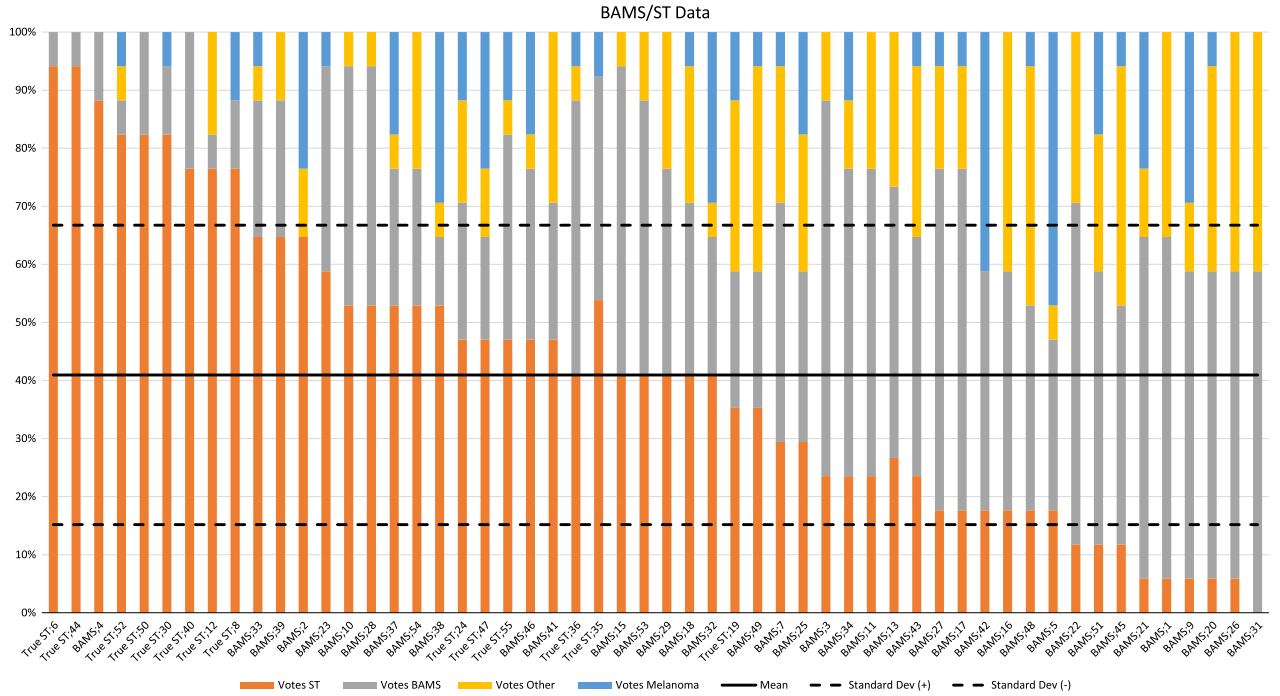

FIGURE 1. Voting results of each of the 54 cases utilized in the survey.

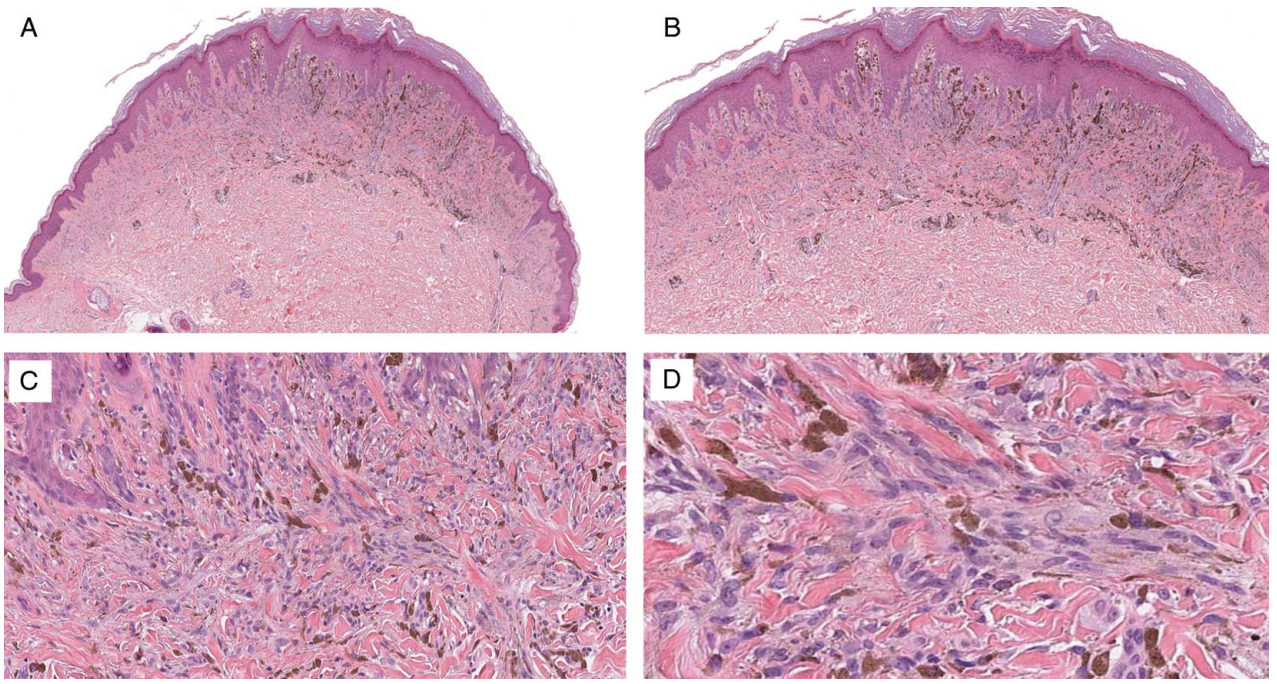

FIGURE 2. Case #39, BAMS. Low power magnification (A and B) shows a compound melanocytic neoplasm with overlying epidermal hyperplasia and a plaque-like silhouette from a 10-year-old. Higher power magnification (C and D) shows fascicles of spindle-shaped melanocytes with vesicular nuclei and abundant amphophilic pigmented cytoplasm (hematoxylin and eosin [H&E]).

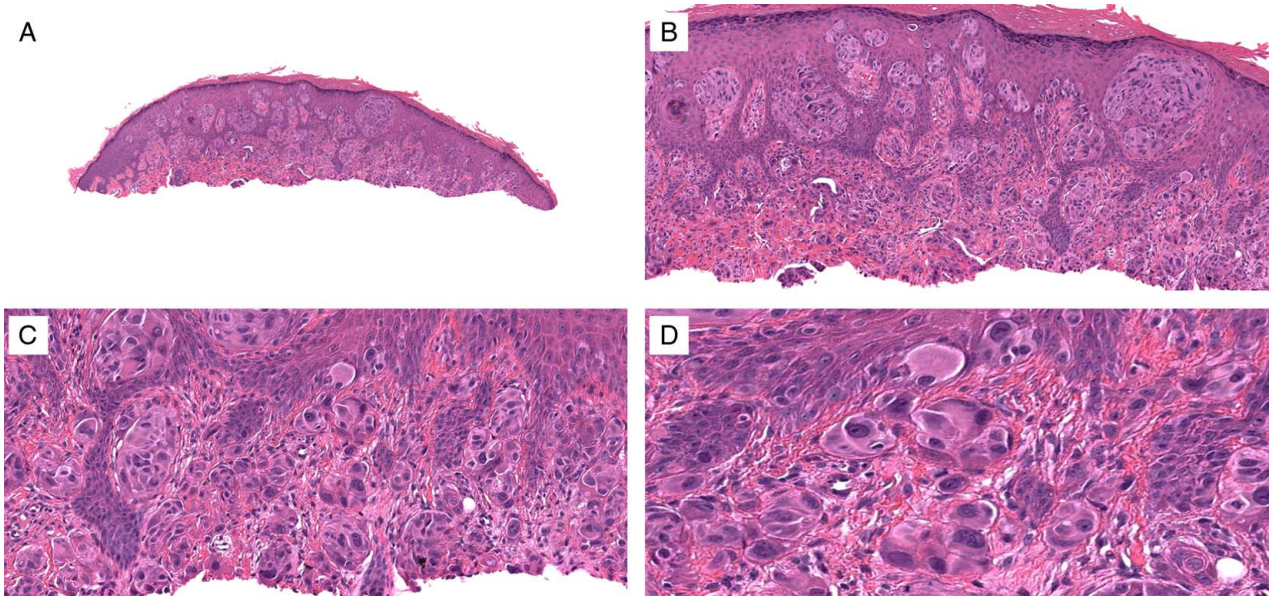

FIGURE 3. Case #33, BAMS. Low power magnification (A and B) demonstrates a compound spitzoid melanocytic neoplasm with overlying epidermal hyperplasia from a 12-year-old. Higher power magnification (C and D) shows prototypical spitzoid morphology with many of the cells having vesicular nuclei prominent nucleoli and abundant glassy eosinophilic cytoplasm (H&E).

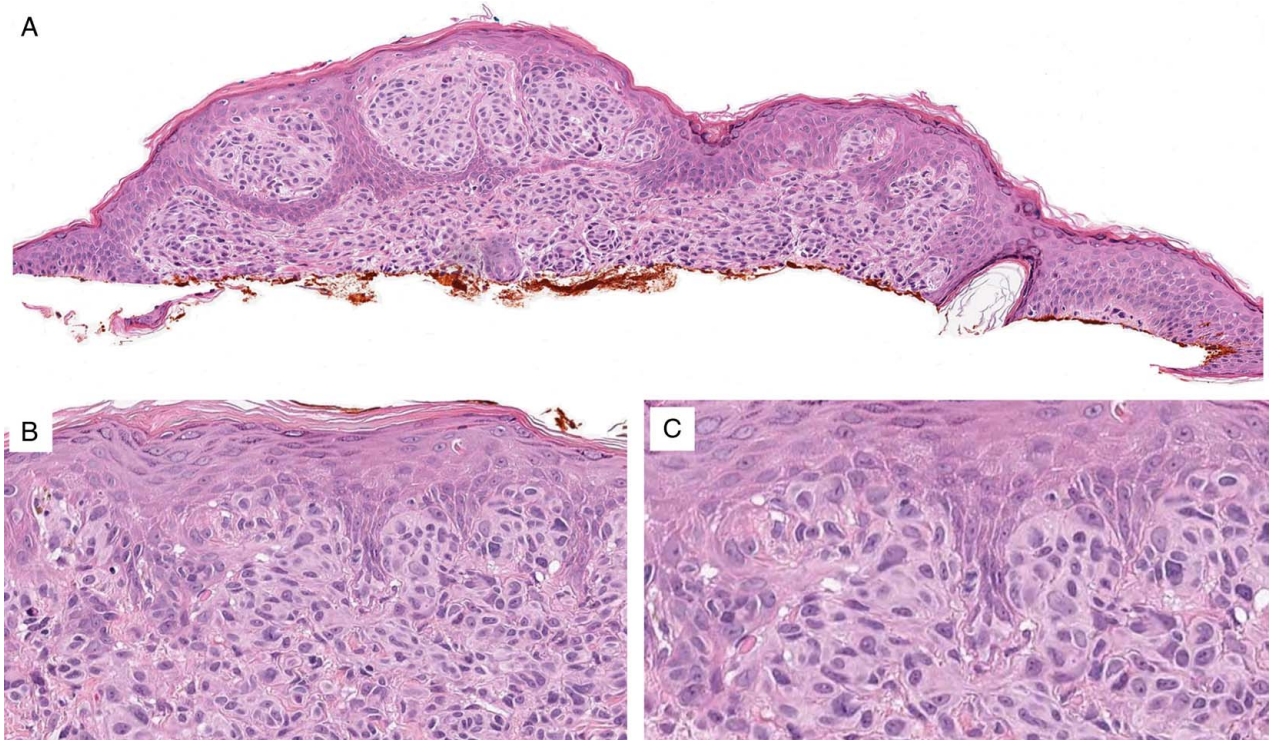

FIGURE 4. Case #4, BAMS. Low power magnification (A) shows a compound melanocytic neoplasm with overlying epidermal hyperplasia and epithelioid melanocytes with spitzoid cytomorphology from an 8-year-old. Higher power magnification (B and C) demonstrates cells with vesicular nuclei and abundant eosinophilic cytoplasm (H&E).

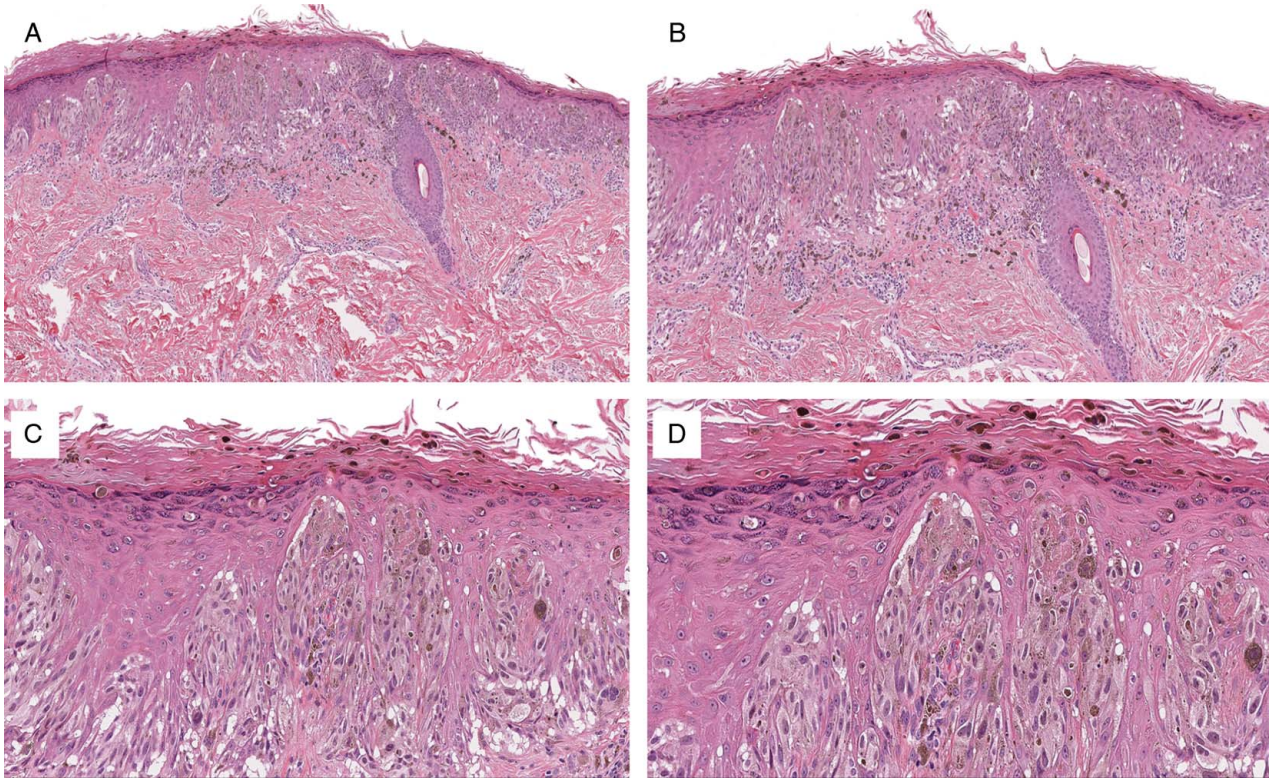

FIGURE 5. Case #30, a MAP3K8 fusion atypical ST. Low power magnification (A and B) demonstrates a compound but predominantly intraepidermal, well-nested, and circumscribed melanocytic proliferation with overlying epidermal hyperplasia. On higher power magnification (C), there are clefting spaces between the hyperplastic epidermis and the junctional melanocytic nests. At the highest magnification (D), the cells have vesicular nuclei and abundant cytoplasm which is granular and pigmented to slightly vacuolated appearing (H&E).

true Spitz neoplasms. Further studies are needed to better assess this question.

Limitations to this study include the fact that the study participants were informed of the concept of BAMS nevi/tumors before initiation of the study. Hence, they were aware that the focus of the study was on Spitz mimickers with *BRAF* mutations. It is possible without this prompting that the number of votes for ST in the BAMS group may have been even greater. Further, the participants were limited to histologic assessment without IHC results or any additional genomic testing results. In conclusion, there is a group of benign and intermediate-grade melanocytic neoplasms with *BRAF* mutations which even expert pathologists have trouble distinguishing from true Spitz neoplasms.

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