# Clinical and dermoscopic features of cutaneous *BAP1*-inactivated melanocytic tumors: Results of a multicenter case-control study by the International Dermoscopy Society

Oriol Yélamos, MD,[a,b] Cristián Navarrete-Dechent, MD,[a,c] Michael A. Marchetti, MD,[a] Tova Rogers, MD,[a] Zoe Apalla, MD,[d] Philippe Bahadoran, MD,[e] Nuria Blázquez-Sánchez, MD, PhD,[f] Klaus Busam, MD,[g] Cristina Carrera, MD,[b] Stephen W. Dusza, DrPH,[a] Arnaud de la Fouchardière, MD,[h] Gerardo Ferrara, MD,[i] Pedram Gerami, MD,[j] Harald Kittler, MD,[k] Aimilios Lallas, MD,[d] Josep Malvehy, MD,[b] José F. Millán-Cayetano, MD,[f] Kelly C. Nelson, MD,[l] Victor Li Quan,[j] Susana Puig, MD,[b] Howard Stevens, MD,[m] Luc Thomas, MD, PhD,[n] and Ashfaq A. Marghoob, MD[a]

*New York, New York; Barcelona and Marbella, Spain; Santiago, Chile; Thessaloniki, Greece; Nice and Lyon, France; Macerata, Italy; Chicago, Illinois; Vienna, Austria; Houston, Texas; and London, United Kingdom*

**Background:** Multiple BRCA1-associated protein 1 (*BAP1*)-inactivated melanocytic tumors (BIMTs) have been associated with a familial cancer syndrome involving germline mutations in *BAP1*.

**Objectives:** We sought to describe the clinical and dermoscopic features of BIMTs.

**Methods:** This was a retrospective, multicenter, case-control study. Participating centers contributed clinical data, dermoscopic images, and histopathologic data of biopsy-proven BIMTs. We compared the dermoscopic features between BIMTs and control patients.

**Results:** The dataset consisted of 48 BIMTs from 31 patients (22 women; median age 37 years) and 80 control patients. Eleven patients had a *BAP1* germline mutation. Clinically, most BIMTs presented as pink, dome-shaped papules (n = 24). Dermoscopically, we identified 5 patterns: structureless pink-to-tan with irregular eccentric dots/globules (n = 14, 29.8%); structureless pink-to-tan with peripheral vessels (n = 10, 21.3%); structureless pink-to-tan (n = 7, 14.9%); a network with raised, structureless, pink-to-tan areas (n = 7, 14.9%); and globular pattern (n = 4, 8.5%). The structureless with eccentric dots/globules pattern

and network with raised structureless areas pattern were only identified in BIMT and were more common in patients with *BAP1* germline mutations ($P < .0001$ and $P = .001$, respectively).

***Limitations:*** Limitations included our small sample size, retrospective design, the absence of germline genetic testing in all patients, and inclusion bias toward more atypical-looking BIMTs.

***Conclusions:*** Dome-shaped papules with pink-to-tan structureless areas and peripheral irregular dots/globules or network should raise the clinical suspicion for BIMT. ( J Am Acad Dermatol 2019;80:1585-93.)

***Key words:*** atypical Spitzoid tumor; *BAP1*; *BAP1*-inactivated melanocytic tumors; dermoscopy; melanoma; Wiesner nevus.

BRCA1-associated protein 1 (*BAP1*)—inactivated melanocytic tumors (BIMTs), also referred to as Wiesner nevi or informally bapomas, are melanocytic tumors with unique genetic profiles. While some authors consider these lesions to be variants of Spitz nevi, others think they represent a distinct entity with overlapping clinical and cytologic features.[1,2] The occurrence of multiple BIMTs has been associated with a familial cancer syndrome involving germline inactivating mutations in the tumor suppressor gene *BAP1*.[3] BAP1-associated cancer syndrome demonstrates autosomal dominant inheritance and predisposes to the development of various malignancies, such as mesothelioma, uveal melanoma, renal cell carcinoma, and cutaneous melanoma. Sporadic cases of BIMT without a syndromal association have also been described.[3,4] There are limited reports on the clinical characteristics of BIMTs,[3,5] and data regarding the dermoscopic appearances of these lesions are sparse.[6-9]

We sought to describe and correlate the clinical and dermoscopic findings associated with BIMT, features that may raise suspicion for germline *BAP1* mutations.

## METHODS

After institutional review board approval at Memorial Sloan Kettering Cancer Center, we conducted a retrospective multicenter descriptive study via the International Dermoscopy Society (IDS). Between August 2016 and November 2017, we promoted the study via the IDS website, dermoscopy conferences, and dermoscopy mailing lists. Physicians from 11

### CAPSULE SUMMARY

- Multiple BRCA1-associated protein 1 (*BAP1*)—inactivated melanocytic tumors (BIMTs) have been associated with a familial cancer syndrome involving germline mutations in *BAP1*.

- We have identified 5 dermoscopic patterns present in BIMTs.

- Dome-shaped papules with pink to tan structureless areas and peripheral irregular dots/globules or network should raise suspicion for BIMT associated with *BAP1* germline mutations.

participating centers provided deidentified clinical data using an electronic survey (age at diagnosis, lesion size, anatomic site, Fitzpatrick skin type, reason for excision, personal or family history of cancer, and the presence or absence of genetic studies in the proband and relatives), clinical and dermoscopic images, and histologic reports or scanned slides of biopsy-proven BIMTs. The diagnosis of BIMT was performed by trained dermatopathologists in each participating center using the previously published diagnostic criteria (biphasic melanocytic proliferation showing 1 banal-looking melanocytic population showing normal BAP1 expression, together with an area of atypical Spitzoid melanocytes showing the nuclear loss of BAP1[3,10,11]). During the recruitment period we received complete data on 48 BIMTs.

We then created an Access 2013 database (Microsoft Corp, Redmond, WA) to collect the data from the electronic survey and a checklist of dermoscopic terms based on the 2016 IDS dermoscopic terminology consensus.[12] In addition, because the main differential diagnosis of BIMT includes pink-to-tan papules, such as intradermal nevi, Spitz nevi, or neurofibromas, we included 80 dermoscopic images (~2:1 comparison) of lesions included in its clinical differential diagnosis as controls. Specifically, we included 51 consecutive melanocytic lesions with retained (normal) BAP1 status for which dermoscopic images were available in the Memorial Sloan Kettering Cancer Center Dermatology Service's image database system (Vectra, Canfield, Parsipanny, NJ). Among these lesions, 28 had Spitzoid features (16 compound or intradermal nevi with Spitzoid

features, 6 atypical Spitzoid tumors, and 1 Spitzoid melanoma) and 23 did not have Spitzoid features (13 compound nevi, 4 intradermal nevi, 3 junctional nevi, and 1 melanoma). We also included 29 non-melanocytic lesions within the clinical differential diagnosis of BIMT (6 neurofibromas, 5 basal cell carcinomas, 4 fibroepitheliomas of Pinkus, 4 dermatofibromas, 3 fibromas, 3 Merkel cell carcinomas, 2 xanthogranulomas, 1 pilomatricoma, and 1 angioma). A board-certified dermatologist (O.Y.) randomized all the images and prepared a slideshow including the BIMTs and the non-BIMT lesions. Two expert dermoscopists (A.A.M., M.A.M.) analyzed the lesions separately and described the dermoscopic features while blinded to the histopathologic diagnosis or clinical data. A third dermatologist (C.N-D.) resolved disagreement in cases of nonconcordance. Based on the dermoscopic features identified, one of the authors (O.Y.) grouped the BIMTs in different dermoscopic patterns. The dermoscopic structures and patterns encountered in BIMTs were then compared with the features present in control patients. We also compared whether these patterns were more commonly found in suspected sporadic versus syndromic BIMTs.

## Statistical analysis

Descriptive and relative frequencies were used to describe the distribution of dermoscopic features of the study lesions by each reviewer. Prevalence estimates for most dermoscopic features were low, and therefore prevalence-adjusted kappa values were calculated to present agreement between dermoscopic reviewers. A kappa value of 1 indicates perfect agreement, >0.8 indicates excellent agreement, 0.6 to 0.8 indicates good agreement, 0.4 to 0.6 indicates fair agreement, and <0.4 indicates poor agreement. Two-sided $P$ values < .05 were considered statistically significant. A single consensus estimate was created for each characteristic when agreement was discordant between reviewers. Fisher's exact test was used to assess the independence of the dermoscopic features between BIMT and non-BIMT lesions. All analyses were performed using Stata software (v 14.2; Stata Corp, College Station, TX).

## RESULTS
### Cohort characteristics

We collected 48 BIMTs from 31 patients (22 women). The average age at diagnosis was 36.9 years (standard deviation 15 years; range 9-73 years). Nine patients were Fitzpatrick skin type I, 15 were Fitzpatrick skin type II, and 7 were Fitzpatrick skin type III. Eleven patients had a known *BAP1* germline mutation and contributed 26 lesions. All patients with known *BAP1* germline mutations had multiple BIMTs. One patient had a germline *BRCA2* mutation and had a history of breast cancer, but no testing for *BAP1* was performed. One patient had a personal and family history of ocular melanoma and presented with multiple BIMTs, but genetic testing did not reveal evidence of a mutation in *BAP1*. Three additional patients were suspected to have syndromic BIMTs (cancer history, multiple BIMTs) but genetic results were not available. The remaining 16 patients presented with single BIMTs.

Eight patients had atypical mole syndrome, 3 of them harboring *BAP1* germline mutations. Six patients with the atypical mole syndrome were previously diagnosed with skin cancers (6 melanomas, 2 basal cell carcinomas). One patient with a germline *BAP1* mutation and atypical mole syndrome had a renal angiomyolipoma with *BAP1* loss. Among the patients without atypical mole syndrome (n = 23), 5 had a personal history of melanoma, 3 had a personal history of basal cell carcinoma, and 1 had oculocutaneous albinism. None of the patients had a personal history of renal cell carcinoma, meningioma, or lung cancer. All patients included in the study did not have local, regional, or distant metastases from BIMT.

Regarding family history, 16 patients had relatives diagnosed with cancer (9 cutaneous melanomas, 2 mesotheliomas, 2 lung carcinomas, 1 ocular melanoma, 1 renal carcinoma, 1 pancreatic cancer, 1 breast cancer, 1 prostate cancer; 1 testicular cancer, 1 throat cancer, and 1 ovarian cancer).

### Clinical characteristics of the lesions

Clinically, BIMTs presented as pink, dome-shaped papules in half of all cases (n = 24, 50%), followed by brown papules (n = 8, 16.6%), pink and brown papules (n = 6, 12.5%), red papules (n = 4, 8.33%), pink/red to orange papules (n = 4, 8.33%), and brown and pink macules (n = 2, 4.16%). The average size was 6.85 mm (standard deviation 2.01, range 4-12 mm). BIMTs were most frequently located on the head and neck (n = 17, 35.41%), followed by the trunk (n = 16, 33.33%), upper limbs (n = 12, 25%), and lower limbs (n = 3, 6.25%). The reasons for obtaining a biopsy specimen were exclusion of skin cancer in 32 cases (66.66%), study of a patient with a suspected BAP1-associated cancer syndrome in 9 cases (18.75%), patient concern in 5 cases (10.42%), and irritation of the lesion in 2 cases (4.16%).

**Table I.** Frequencies of the dermoscopic features found in the lesions, interobserver agreement, and comparison of the dermoscopic features and colors identified in BRCA1-associated protein 1—inactivated melanocytic tumors versus controls

| Dermoscopic structures, n (%) | All lesions (n = 127) | Interobserver agreement, kappa value | BIMT (n = 47) | Controls (n = 80) | Odds ratio (95% confidence interval) | P value |
|---|---|---|---|---|---|---|
| Typical network | 5 (3.9) | 0.505 | 1 (2.1) | 4 (5) | 0.413 (0.45-3.8) | .651 |
| Atypical network | 15 (11.8) | 0.108 | 6 (12.8) | 9 (11.3) | 1.15 (0.38-3.47) | .784 |
| Negative network | 4 (3.1) | 0.485 | 2 (4.3) | 2 (2.5) | 1.73 (0.236-12.731) | .626 |
| Regular globules | 3 (2.4) | 0.266 | 2 (4.3) | 1 (1.3) | 3.51 (0.31-39.8) | .554 |
| Irregular globules | 20 (15.7) | 0.804 | 14 (29.8) | 6 (7.5) | 5.23 (1.8-14.8) | .002 |
| Regular dots | 2 (1.6) | NS | 0 | 2 (2.5) | N/A | .530 |
| Irregular dots | 20 (15.7) | 0.297 | 12 (25.5) | 8 (10) | 3.086 (1.156-8.23) | .025 |
| Streaks | 1 (0.8) | NS | 0 | 1 (1) | N/A | >.99 |
| Shiny white streaks | 7 (5.5) | 0.788 | 2 (4.3) | 5 (6.3) | 0.667 (0.124-3.58) | >.99 |
| Shiny white blotches and strands | 2 (1.6) | 0.663 | 0 | 2 (2.5) | N/A | .530 |
| Blue whitish veil | 3 (2.4) | 0.392 | 0 | 3 (3.8) | N/A | .295 |
| Ulceration/erosion | 3 (2.4) | 1 | 0 | 3 (3.8) | N/A | .295 |
| Milia-like cysts | 4 (3.1) | 0.324 | 0 | 4 (5) | N/A | .296 |
| Comma vessels | 2 (1.6) | NS | 0 | 2 (2.5) | N/A | .530 |
| Dotted vessels | 50 (39.4) | 0.336 | 16 (34) | 34 (42.5) | 0.698 (0.33-1.47) | .452 |
| Arborizing vessels | 18 (14.2) | 0.367 | 3 (6.4) | 15 (18.8) | 0.295 (0.081-1.081) | .067 |
| Serpentine vessels | 41 (32.3) | 0.355 | 18 (38.3) | 23 (28.8) | 1.538 (0.718-3.295) | .327 |
| Glomerular vessels | 1 (0.8) | NS | 0 | 1 (1.3) | N/A | >.99 |
| Hairpin vessels | 2 (1.6) | NS | 0 | 2 (2.5) | N/A | .530 |
| Polymorphous vessels | 37 (29.1) | 0.285 | 12 (25.5) | 25 (31.3) | 1.846 (0.643-5.3) | .548 |
| Structureless pink to tan | 52 (40.9) | 0.346 | 33 (70.2) | 19 (23.8) | 7.6 (3.3-17) | <.0001 |
| Arrangement of dermoscopic structures | | | | | | |
|   Organized | 44 (34.6) | 0.298 | 18 (38.3) | 26 (32.5) | 1.289 (0.608-2.733) | .564 |
|   Disorganized | 83 (65.4) | 0.298 | 29 (61.7) | 54 (67.5) | 0.776 (0.366-1.645) | .564 |
| Colors seen on dermoscopy | | | | | | |
|   Brown | 83 (65.4) | 0.520 | 32 (68.1) | 51 (63.8) | 1.213 (0.565-2.605) | .701 |
|   Black | 5 (3.9) | 0.478 | 0 | 5 (6.3) | N/A | .157 |
|   Blue-gray | 17 (13.4) | 0.339 | 2 (4.3) | 15 (18.8) | 0.2 (0.04-0.88) | .029 |
|   White | 16 (12.6) | 0.229 | 2 (4.3) | 14 (17.5) | 0.2 (0.04-0.96) | .049 |
|   Red | 5 (3.9) | NS | 2 (4.3) | 3 (3.8) | 1.141 (0.184-7.087) | >.99 |
|   Pink | 93 (73.2) | 0.315 | 36 (76.5) | 57 (71.3) | 1.321 (0.575-3.031) | .542 |

*BIMT*, BRCA1-associated protein 1—inactivated melanocytic tumor; *N/A*, not available; *NS*, not significant.

## Dermoscopic characteristics of the lesions

For the dermoscopy analysis, we excluded 1 case because of poor image quality, and ultimately 47 BIMTs were included. Table I summarizes the dermoscopic features present in all the lesions. Dermoscopically, BIMT presented with pink-to-tan structureless areas (n = 33, 70.2%), brown irregular dots and globules (clods) (n = 19, 40.4%), serpentine vessels (n = 18, 38.3%), dotted vessels (n = 16, 34%), atypical network (n = 6, 12.8%), arborizing vessels (n = 3, 6.4%), negative network (n = 2, 4.3%), regular globules (n = 2, 4.3%), shiny white streaks (n = 2, 4.3%), and typical network (n = 1, 2.1%). Among these features, irregular globules were significantly more frequent in the BIMTs compared to non-BIMTs (odds ratio [OR] 5.23, P = .002), as well as structureless pink/tan areas (OR 7.6, P < .00001). Among

BIMTs, the dermoscopic feature with the highest interobserver agreement was irregular globules (kappa = 0.804).

Considering these dermoscopic findings, we grouped BIMT cases in 5 patterns: structureless pink-to-tan with irregular dots/globules located eccentrically (n = 14, 29.8%); structureless pink-to-tan with peripheral vessels (n = 10, 21.3%); structureless pink-to-tan (n = 7, 14.9%); network with raised, structureless, pink-to-tan areas (n = 7, 14.9%); and globular pattern (n = 4, 8.5%; Figs 1-3). Five cases (11.6%) did not have a specific pattern. When comparing the presence of these patterns between the BIMTs and the controls, the structureless pink-to-tan with irregular dots/globules and the network with raised structureless areas patterns were only identified in BIMTs (P < .0001; Table II). In addition,
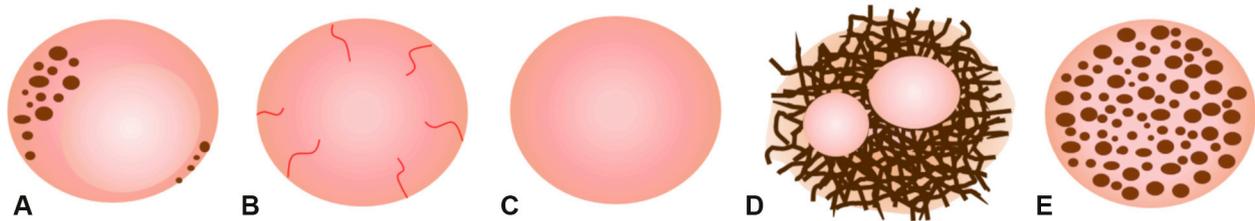
**Fig 1.** Schematics showing the 5 patterns identified in our cohort of BRCA1-associated protein 1−inactivated melanocytic tumors. **A**, Structureless pink/tan with atypical eccentric clods. **B**, Structureless pink with radial vessels. **C**, Structureless pink/tan. **D**, Network with raised structureless areas. **E**, Globular.
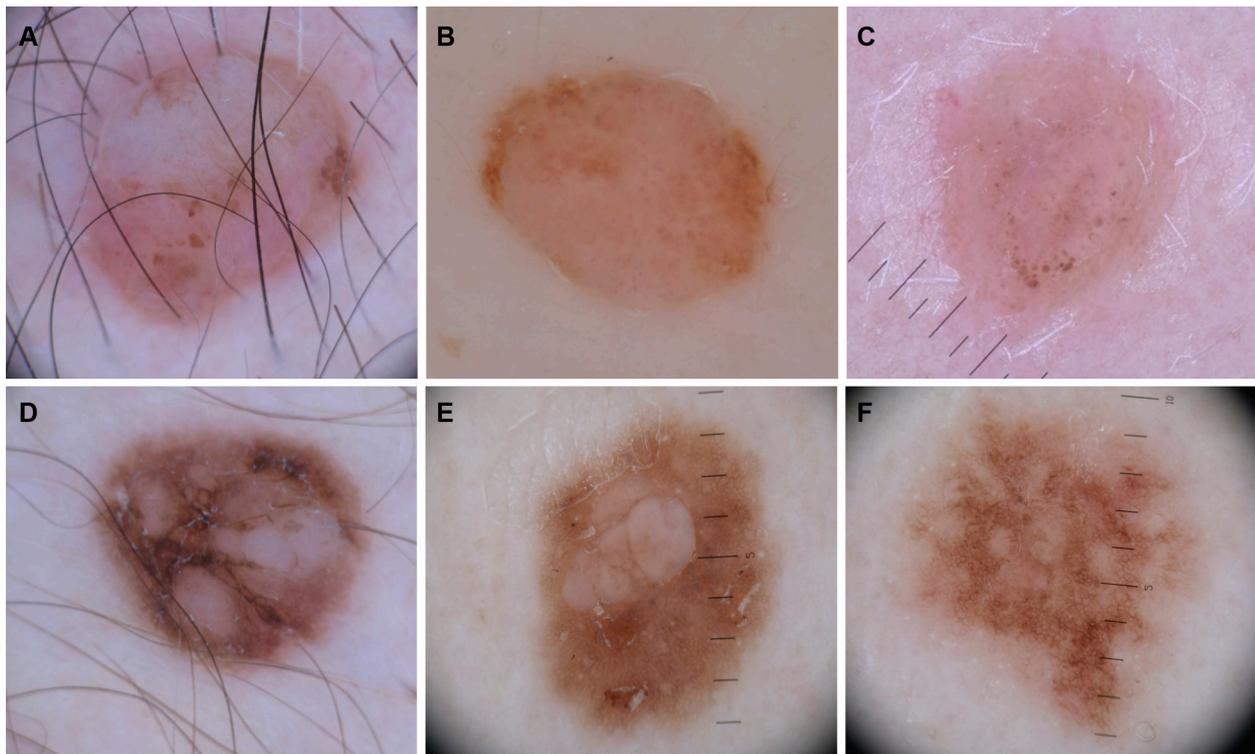


**Fig 2.** Dermoscopic patterns more frequently identified in suspected syndromic BRCA1-associated protein 1−inactivated melanocytic tumors. **A-C**, Structureless pink to tan areas with atypical eccentric clods, which occasionally can coalesce. **D-F**, Network with raised structureless areas, which generally tend to be multiple and sometimes slightly raised.

when comparing lesions on patients with multiple BIMTs associated with *BAP1* germline mutations (syndromic BIMTs) versus patients with single BIMTs (suspected sporadic BIMTs), the structureless pink-to-tan with irregular dots/globules pattern was significantly more frequent in cases harboring a *BAP1* germline mutation (46.15% vs 6.25%, OR 12.85, *P* = .007; Table III). Similarly, the pattern showing network and raised structureless areas was only present in syndromic cases. Conversely, a purely globular pattern was not observed in any syndromic case. There was no association for the remaining patterns.

## DISCUSSION

BIMTs were described by Wiesner et al[3] in 2011 in 2 unrelated families, both with germline mutations in the tumor suppressor gene called *BAP1*. Germline *BAP1* mutations are associated with a cancer syndrome that increases the risk for multiple internal and cutaneous neoplasms such as uveal melanoma (28%), pleural and peritoneal mesothelioma (22%), cutaneous melanoma (18%), and renal cell carcinoma (9%).[8,13,14] Single BIMTs have also been reported to occur sporadically and are not associated with an increased cancer risk. Therefore, because multiple BIMTs are a hallmark of germline *BAP1*
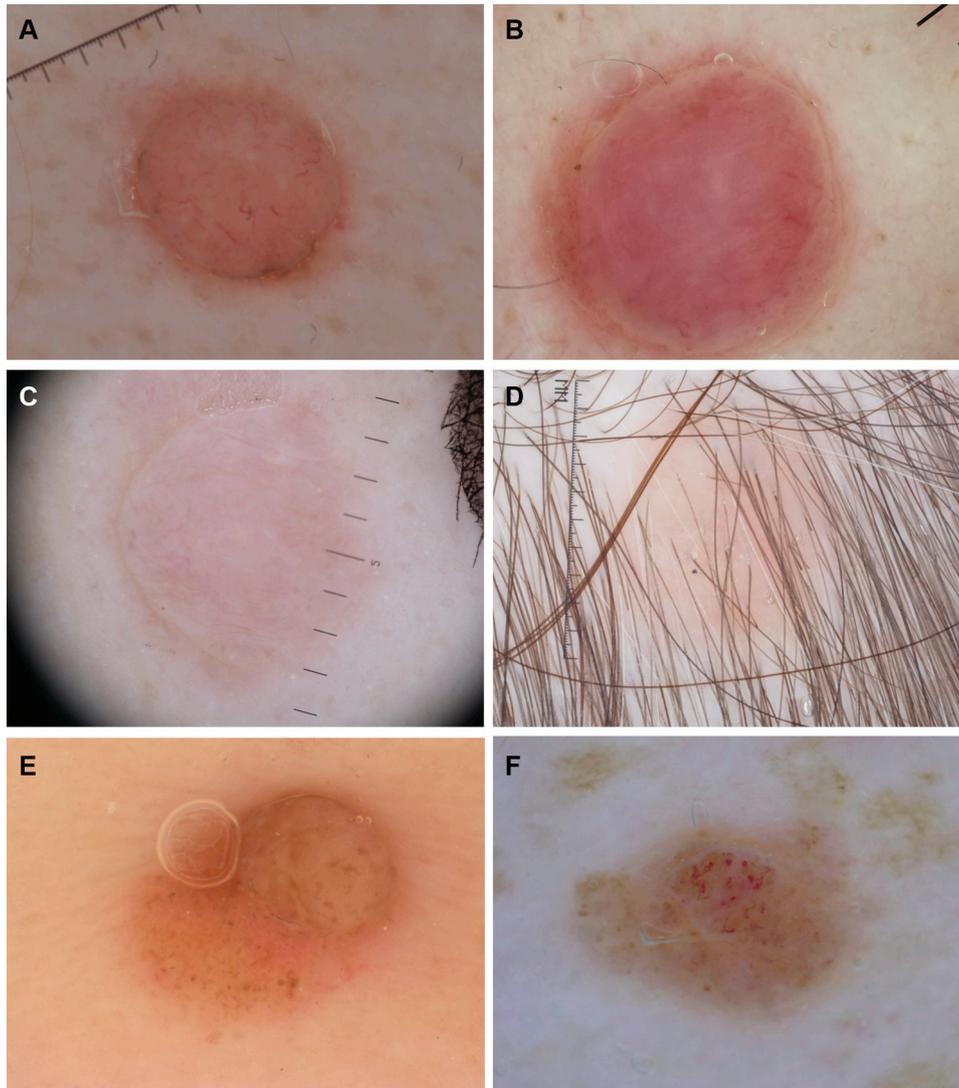
**Fig 3.** Dermoscopic patterns that are nonspecific for syndromic BRCA1-associated protein 1—inactivated melanocytic tumors. **A** and **B**, Dome-shaped papules presenting with structureless pink areas surrounded with radial vessels and a rim of peripheral pigment. **C** and **D**, Pink papules showing a structureless pink to tan pattern. **E**, Sporadic case presenting as a brown papule with irregular globules on dermoscopy. **F**, Syndromic case with a nonspecific pattern presenting with irregular globules and polymorphous vessels.

mutations, the diagnosis of BIMTs is crucial to identify individuals who are at higher risk to develop multiple cancers.

Clinically, BIMTs can be overlooked because they present as nonspecific dome-shaped, pink-to-orange papules or papulonodules, resembling banal intradermal nevi or fibromas.[3,13] Similarly, the predominant clinical presentation of BIMTs in our study is that of pink-to-tan, sometimes red-to-orange papules. However, we have also shown that BIMT can present as brown, pigmented papules and less frequently as tan macules.

Dermoscopic features of BIMTs have been anecdotally reported and include the presence of pink structureless areas with peripheral linear vessels,[6,7,9] a multicomponent pattern,[9] and pink structureless areas with peripheral pigmented globules.[8] In the present study, we identified 3 additional dermoscopic patterns: structureless pink-to-tan, network with raised structureless pink-to-tan areas, and globular patterns. Interestingly, we have identified 2 patterns that seem characteristic for BIMTs: structureless pink-to-tan with irregular eccentric dots/globules and network with raised structureless pink-to-tan areas. In addition, these 2 patterns were more frequent in patients with multiple BIMTs associated with a known *BAP1* germline mutation. On the other hand, the globular pattern seems to be a negative

**Table II.** Frequencies and comparison of the dermoscopic patterns identified in BRCA1-associated protein 1—deficient tumors versus non-BRCA1-associated protein 1—inactivated melanocytic tumors

| Dermoscopic patterns | BIMT (n = 47) | Controls (n = 80) | Odds ratio (95% confidence interval) | P value |
|---|---|---|---|---|
| Structureless pink/tan with atypical eccentric clods | 14 | 0 | 1.42 (1.1-1.7) | <.0001 |
| Structureless pink/tan | 7 | 7 | 1.11 (1.01-1.2) | .380 |
| Network with raised structureless | 7 | 0 | 1.17 (1.04-1.32) | .001 |
| Structureless pink with radial vessels | 10 | 3 | 6.93 (1.8-26.7) | .004 |
| Globular | 4 | 6 | 1.14 (0.3-4.2) | >.99 |
| Nonspecific | 5 | N/A | N/A | N/A |

*BIMT*, BRCA1-associated protein 1—inactivated melanocytic tumor; *N/A*, not available.

**Table III.** Frequencies and comparison of the dermoscopic patterns identified in patients with multiple BRCA1-associated protein 1—inactivated melanocytic tumors and known *BAP1* germline mutation versus patients with suspected sporadic cases presenting with a single BRCA1-associated protein 1—inactivated melanocytic tumor and no history of a cancer syndrome

| Dermoscopic patterns | Cases with multiple BIMTs, syndromic (n = 26) | Single BIMT, suspected sporadic (n = 16) | Odds ratio (95% confidence interval) | P value |
|---|---|---|---|---|
| Structureless pink/tan with atypical eccentric clods | 12 | 1 | 12.85 (1.47-112.170) | .007 |
| Structureless pink/tan | 4 | 3 | 1.23 (0.31-4.8) | >.99 |
| Network with raised structureless | 6 | 0 | N/A | .067 |
| Structureless pink with radial vessels | 4 | 6 | 0.30 (0.7-1.31) | .142 |
| Globular | 0 | 4 | N/A | .016 |

*BAP1*, BRCA1-associated protein 1; *BIMT*, BRCA1-associated protein 1—inactivated melanocytic tumor; *N/A*, not available.

predictor for *BAP1* germline mutations because it was not observed in any syndromic case, although only 8.5% of sporadic BIMTs presented with this pattern.

Our results should be interpreted with caution because we only included BIMTs from which biopsy specimens were obtained, and there is a chance that some BIMTs, especially sporadic lesions, may appear clinically and dermoscopically banal and would therefore not warrant obtaining a biopsy specimen. In fact, irregular dots and globules, which was the dermoscopic feature more commonly identified in BIMTs, represents a melanoma-specific structure with an OR of 1.7 to 4.8 for melanoma.[15] This could explain why the main reason for excision in the BIMTs included in our study (63.6%) was to exclude skin cancer. Interestingly, although irregular dots/globules and structureless pink-to-tan areas were identified in both BIMTs and non-BIMTs, its simultaneous presence was only seen in BIMTs (*P* < .0001). Nevertheless, we acknowledge that our sample does not include many melanomas, which seems to be an important differential diagnosis from a dermoscopic standpoint. In fact, the melanomas included in our study showed mostly a multicomponent pattern, negative network, or polymorphous vessels, which clinically made them easy

to suspect as melanomas. Therefore, further studies including a greater number of melanomas, especially melanomas showing atypical dots/globules or structureless areas, are necessary to confirm our results, because if this pattern is confirmed to be unique of BIMT that would be useful to identify patients who are at high risk for internal malignancies. In addition, this pattern may be relatively easy to identify because the identification of irregular dots/globules had excellent interobserver agreement among different observers (kappa = 0.804). Another limitation of our study is that the status of the *BAP1* gene was not known in all cases. Therefore, conclusions regarding whether one pattern is more common in syndromic versus sporadic cases should be taken with caution.

Histopathologically, BIMTs are reminiscent of Spitz nevi but lack epidermal hyperplasia, hypergranulosis, or Kamino bodies.[3,10,16] Characteristically, BIMTs present with 2 populations of cells: a more conventional-looking nevus cells population located mostly at the periphery and a second one with atypical, epitheloid cells with spitzoid characteristics, which typically lack melanin.[3,10,11] Immunohistochemially, the atypical spitzoid population presents with nuclear loss of BAP1 and positive staining for VE1 (revealing a *BRAF* mutation).[10,16] Therefore, we believe the
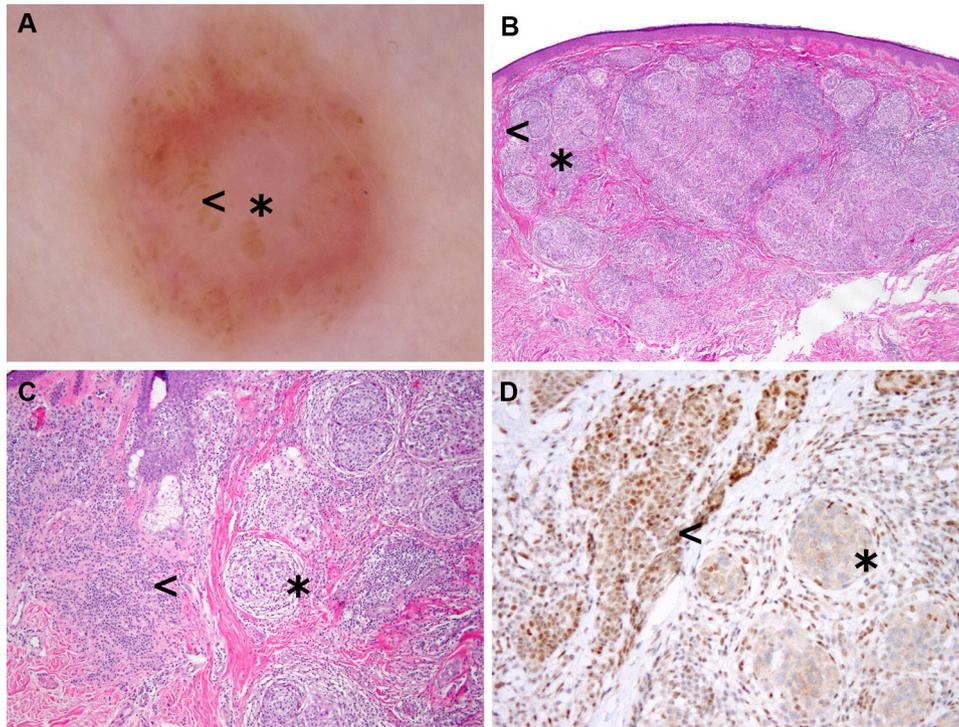
**Fig 4.** Correlation between dermoscopy and histopathology in a BRCA1-associated protein 1−inactivated melanocytic tumor. **A**, Dermoscopy shows a pinkish lesion with central structureless pink to tan areas (asterisk) with atypical dots and globules located mostly at the periphery (arrowhead). **B** and **C**, Histologically, this lesion has a central melanocytic population composed of spitzoid nests located in the dermis (asterisk), surrounded by a more banal-looking melanocytic population located in the periphery (arrowhead). **D**, Immunohistochemical stains for BRCA1-associated protein 1 show that spitzoid population (asterisk) corresponds to the BRCA1-associated protein 1−inactivated population, whereas the pigmented banal melanocytes on the periphery retain BRCA1-associated protein 1.

structureless areas identified with dermoscopy correspond to the BAP1-inactivated melanocytes, whereas the pigmented dots/globules, network, or peripheral pigment correspond to the more conventional-looking melanocytic population (Fig 4). We hypothesize that the different dermoscopic patterns could correspond to different subtypes of BIMTs with a larger or smaller component of either one or the other component of this biphasic proliferation. In other words, BIMT can present with a dermoscopic spectrum that ranges from globular to structureless, depending on the predominant melanocytic population. One could hypothesize that BIMTs undergo a genetic hit that prompts the melanocytes to inactivate *BAP1*, resulting in increased structureless areas. However, further prospective studies should confirm this hypothesis and evaluate whether these patterns occur de novo or evolve over time.

In addition, the relevance of these different patterns and whether they are associated with a better or worse prognosis is unknown. BIMTs are generally indolent,[10,17] although malignant transformation has been described.[13] Interestingly, 11 patients with BIMTs had a personal history of cutaneous melanoma and had 9 relatives with cutaneous melanoma. Some of these cases were diagnosed as spitzoid melanomas, and therefore it is possible that some of these lesions were in fact BIMTs removed before 2011 when BIMT was initially described.[3] The fact that none of the patients had local or regional recurrence may support this statement. Studies with long-term follow-up are necessary to evaluate the behavior of BIMT and its true malignant potential.

In summary, a subset of BIMT harbors unique dermoscopic features that are not present in lesions in its differential diagnosis. This is important because it may help identify individuals who are at higher risk for developing multiple malignancies. Specifically, the dermoscopic pattern of a pink-to-tan structureless area together with eccentric irregular dots/globules in a young adult should raise suspicion for BIMT associated with *BAP1* germline mutations. This could allow the identification of patients who are at

risk for developing multiple cancers and who may benefit from cancer screening. Some authors suggest that total skin examination every 6 months and annual ophthalmologic examinations may be beneficial to screen patients with *BAP1* germline mutations because these measures are noninvasive.[8] Others also recommend genetic and imaging testing.[8,18] However, there are no consensus guidelines regarding how to screen for malignancies in these patients. Based on our results, if multiple lesions showing 1 or multiple of the described patterns are identified, it may be worth excising 1 or 2 lesions to confirm the diagnosis histopathologically. However, we recommend integrating all the available data (clinical, dermoscopic, familial, and histologic) together in guiding the management of such patients. Thus, future studies are necessary to generate evidence-based guidelines on how to manage patients harboring *BAP1* germline mutations.

**REFERENCES**

1. Vilain RE, McCarthy SW, Thompson JF, Scolyer RA. BAP1-inactivated spitzoid naevi. *Am J Surg Pathol*. 2015;39:722.
2. Yeh I, Mully TW, Wiesner T, et al. Ambiguous melanocytic tumors with loss of 3p21. *Am J Surg Pathol*. 2014;38:1088-1095.
3. Wiesner T, Obenauf AC, Murali R, et al. Germline mutations in BAP1 predispose to melanocytic tumors. *Nat Genet*. 2011;43:1018-1021.
4. Wiesner T, Murali R, Fried I, et al. A distinct subset of atypical Spitz tumors is characterized by BRAF mutation and loss of BAP1 expression. *Am J Surg Pathol*. 2012;36:818-830.
5. Busam KJ, Sung J, Wiesner T, von Deimling A, Jungbluth A. Combined BRAF(V600E)-positive melanocytic lesions with large epithelioid cells lacking BAP1 expression and conventional nevomelanocytes. *Am J Surg Pathol*. 2013;37:193-199.
6. Puig S, Carrera C, Malvehy J. Nevi in patients with Bap1 germ line mutation, red-hair polymorphism, and albinism. In: Zalaudek I, Argenziano G, Giacomel J, eds. *Dermatoscopy of Non-Pigmented Skin Tumors*. Boca Raton, FL: CRC Press; 2015:61-62.
7. Rogers T, Marino ML, Raciti P, et al. Biologically distinct subsets of naevi: a review. *G Ital Dermatol Venereol*. 2016;151:365-384.
8. Haugh AM, Njauw CN, Bubley JA, et al. Genotypic and phenotypic features of BAP1 cancer syndrome: a report of 8 new families and review of cases in the literature. *JAMA Dermatol*. 2017;153:999-1006.
9. Moawad S, Reigneau M, de la Fouchardiere A, et al. Clinical, dermoscopic, histological and molecular analysis of BAP1 inactivated melanocytic nevus/tumor in two familial cases of BAP1 syndrome. *Br J Dermatol*. 2018;179:973-975.
10. Gerami P, Yelamos O, Lee CY, et al. Multiple cutaneous melanomas and clinically atypical moles in a patient with a novel germline BAP1 mutation. *JAMA Dermatol*. 2015;151:1235-1239.
11. Busam K, Sung J, Wiesner T, von Deimling A, Jungbluth A. Combined BRAF(V600E)-positive melanocytic lesions with large epithelioid cells lacking BAP1 expression and conventional nevomelanocytes. *Am J Surg Pathol*. 2013;36:193-199.
12. Kittler H, Marghoob AA, Argenziano G, et al. Standardization of terminology in dermoscopy/dermatoscopy: results of the third consensus conference of the International Society of Dermoscopy. *J Am Acad Dermatol*. 2016;74:1093-1106.
13. Wiesner T, Fried I, Ulz P, et al. Toward an improved definition of the tumor spectrum associated with BAP1 germline mutations. *J Clin Oncol*. 2012;30:E337-E340.
14. Abdel-Rahman MH, Pilarski R, Cebulla CM, et al. Germline BAP1 mutation predisposes to uveal melanoma, lung adenocarcinoma, meningioma, and other cancers. *J Med Genet*. 2011;48:856-859.
15. Wolner ZJ, Yelamos O, Liopyris K, Rogers T, Marchetti MA, Marghoob AA. Enhancing skin cancer diagnosis with dermoscopy. *Dermatol Clin*. 2017;35:417-437.
16. Llamas-Velasco M, Perez-Gonzalez YC, Requena L, Kutzner H. Histopathologic clues for the diagnosis of Wiesner nevus. *J Am Acad Dermatol*. 2014;70:549-554.
17. Gammon B, Traczyk TN, Gerami P. Clumped perinuclear BAP1 expression is a frequent finding in sporadic epithelioid Spitz tumors. *J Cutan Pathol*. 2013;40:538-542.
18. Pilarski R, Rai K, Cebulla C, Abdel-Rahman M. BAP1 tumor predisposition syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews. Seattle, WA; 1993-2018.