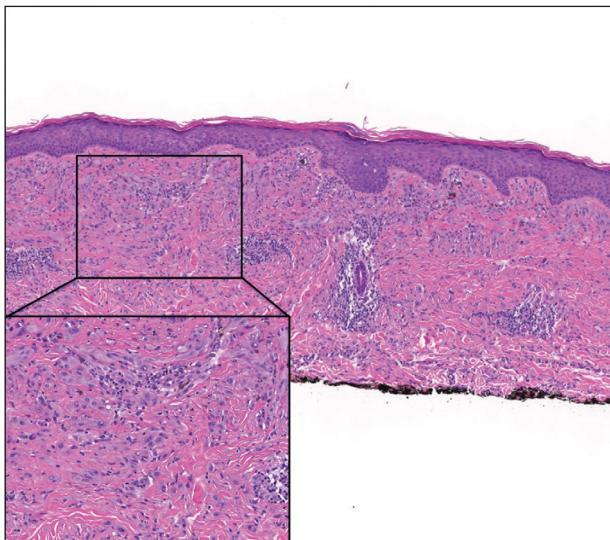


Light Brown and Pink Macule on the Upper Arm

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H&E, original magnification $\times 40$ (inset, original magnification $\times 200$).

A 37-year-old woman with a history of fibrocystic breast disease and a family history of breast cancer presented with a light brown macule on the right upper arm of 10 years' duration. The patient first noticed this macule 10 years prior; however, within the last 4 months she noticed a small amount of homogenous darkening and occasional pruritus. Physical examination revealed a 4.0-mm, light brown and pink macule on the right upper arm. Dermoscopy showed a homogenous pigment network with reticular lines and branched streaks centrally. No crystalline structures, milky red globules, or pseudopods were appreciated. A tangential shave biopsy was obtained and submitted for hematoxylin and eosin staining.

THE BEST DIAGNOSIS IS:

- cellular blue nevus
- cutaneous metastatic breast cancer
- deep penetrating nevus
- desmoplastic Spitz nevus
- multicentric reticulohistiocytosis

PLEASE TURN TO **PAGE 95** FOR THE DIAGNOSIS

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THE DIAGNOSIS: Desmoplastic Spitz Nevus

Desmoplastic Spitz nevus is a rare variant of Spitz nevus that commonly presents as a red to brown papule on the head, neck, or extremities. It is pertinent to review the histologic features of this neoplasm, as it can be confused with other more sinister entities such as spitzoid melanoma. Histologically, there is a dermal infiltrate of melanocytes containing eosinophilic cytoplasm and vesicular nuclei. Junctional involvement is rare, and there should be no pagetoid spread.¹ This entity features abundant stromal fibrosis formed by dense collagen bundles, low cellular density, and polygonal-shaped melanocytes, which helps to differentiate it from melanoma.^{2,3} In a retrospective study comparing the characteristics of desmoplastic Spitz nevi with desmoplastic melanoma, desmoplastic Spitz nevi histologically were more symmetric and circumscribed with greater melanocytic maturation and adnexal structure involvement.³ Although this entity demonstrates maturation from the superficial to the deep dermis, it also may feature deep dermal vascular proliferation.⁴ S-100 and SRY-related HMG box 10, SOX-10, are noted to be positive in desmoplastic Spitz nevi, which can help to differentiate it from non-melanocytic entities (Figure 1).

Although spitzoid lesions can be ambiguous and difficult even for experts to classify, spitzoid melanoma tends to have a high Breslow thickness, high cell density, marked atypia, and an increased nucleus to cytoplasm ratio.⁵ Additionally, desmoplastic melanoma was found to more often display “melanocytic junctional nests associated with discohesive cells, variations in size and shape of the nests, lentiginous melanocytic proliferation, actinic elastosis, pagetoid spread, dermal mitosis, perineural involvement and brisk inflammatory infiltrate.”³ Given the challenge of histologically separating desmoplastic Spitz nevi from melanoma, immunostaining can be useful. For example, Hilliard et al⁶ used a p16 antibody to differentiate desmoplastic Spitz nevi from desmoplastic melanoma, finding that most desmoplastic melanomas (81.8%; n=11) were negative for p16, whereas all desmoplastic Spitz nevi were at least moderately positive. However, another study re-evaluated the utility of p16 in desmoplastic melanoma and found that 72.7% (16/22) were at least focally reactive for the immunostain.⁷ Thus, caution must be exercised when using p16.

Preferentially expressed Antigen in MELanoma (PRAME) is a newer nuclear immunohistochemical marker that tends to be positive in melanomas and negative in nevi. Desmoplastic Spitz nevi would be expected to be negative for PRAME, while desmoplastic melanoma may be positive; however, this marker seems to be less effective in desmoplastic melanoma than in most other subtypes of the malignancy. In one study, only 35% (n=20)

of desmoplastic melanomas were positive for PRAME.⁸ Likewise, another study showed that some benign Spitz nevi may diffusely express PRAME.⁹ As such, PRAME should be used prudently.

For cases in which immunohistochemistry is equivocal, molecular testing may aid in differentiating Spitz nevi from melanoma. For example, comparative genomic hybridization has revealed an increased copy number of chromosome 11p in approximately 20% of Spitz nevus cases¹⁰; this finding is not seen in melanoma. Mutation analyses of HRas proto-oncogene, GTPase, *HRAS*; B-Raf proto-oncogene, serine/threonine kinase, *BRAF*; and NRAS proto-oncogene, GTPase, *NRAS*, also have shown some promise in distinguishing spitzoid lesions from melanoma, but these analyses may be oversimplified.¹¹ Fluorescence in situ hybridization (FISH) is another diagnostic modality that has been studied to differentiate benign nevi from melanoma. One study challenged the utility of FISH, reporting 7 of 15 desmoplastic melanomas tested positive compared to 0 of 15 sclerotic melanocytic nevi.¹² Thus, negative FISH cannot reliably rule out melanoma. Ultimately, a combination of immunostains along with FISH or another genetic study would prove to be most effective in ruling out melanoma in difficult cases. Even then, a dermatopathologist may be faced with a degree of uncertainty.

Cellular blue nevi predominantly affect adults younger than 40 years and commonly are seen on the buttocks.¹³ This benign neoplasm demonstrates areas that are distinctly sclerotic as well as those that are cellular in nature.¹⁴ This entity demonstrates a well-circumscribed dermal growth pattern with 2 main populations of cells. The sclerotic portion of the cellular blue nevus mimics that of the blue nevus in that it is noted superficially with irregular margins. The cellular aspect of the nevus features spindle cells contained within well-circumscribed nodules (Figure 2). Stromal melanophages are not uncommon, and some can be observed adjacent to nerve fibers. Although

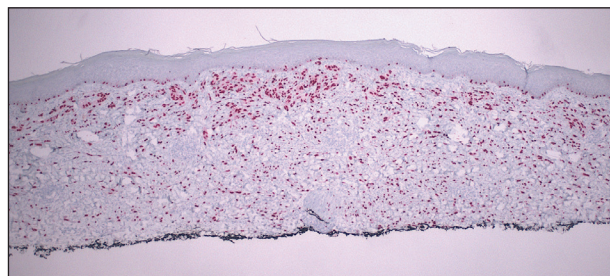


FIGURE 1. Desmoplastic Spitz nevus. Immunohistochemistry shows a neoplastic proliferation in the dermis with SOX-10 (SRY-related HMG box 10) positivity (original magnification $\times 40$).

this blue nevus variant displays features of the common blue nevus, its melanocytes track along adnexal and neurovascular structures similar to the deep penetrating nevus and the desmoplastic Spitz nevus. However, these melanocytes are variable in morphology and can appear on a spectrum spanning from pale and lightly pigmented to clear.¹⁵

The breast is the most common site of origin of tumor metastasis to the skin. These cutaneous metastases can vary in both their clinical and histological presentations. For example, cutaneous metastatic breast adenocarcinoma often can present clinically as pink-violaceous papules and plaques on the breast or on other parts of the body. Histologically, it can demonstrate a varying degree of patterns such as collagen infiltration by single cells, cords, tubules, and sheets of atypical cells (Figure 3) that can be observed together in areas of mucin or can form glandular structures.¹⁶ Metastatic breast carcinoma is noted to be positive for gross cystic disease fluid protein-15, estrogen receptor, and cytokeratin 7, which can help differentiate this entity from other tumors of glandular origin.¹⁶ Although rare, primary melanoma of the breast has been reported in the literature.^{17,18} These malignant melanocytic lesions easily could be differentiated from other breast tumors such as adenocarcinoma using immunohistochemical staining patterns.

Deep penetrating nevi most often are observed clinically as blue, brown, or black papules or nodules on the head or neck.¹⁹ Histologically, this lesion features a wedge-shaped infiltrate of deep dermal melanocytes with oval nuclei. It commonly extends to the reticular dermis or further into the subcutis (Figure 4).^{20,21} This neoplasm frequently tracks along adnexal and neurovascular structures, resulting in a plexiform appearance.²² The adnexal

involvement of deep penetrating nevi is a shared feature with desmoplastic Spitz nevi. The presence of any number of melanophages is characteristic of this lesion.²³ Lastly, there is a well-documented association between β -catenin mutations and deep penetrating nevi.²⁴

Multicentric reticulohistiocytosis (MRH) is a rare form of non-Langerhans cell histiocytosis that has the pathognomonic clinical finding of pink-red papules (coral beading) with a predilection for acral surfaces. Histology of affected skin reveals a dermal infiltrate of ground glass as well as eosinophilic histiocytes that most often

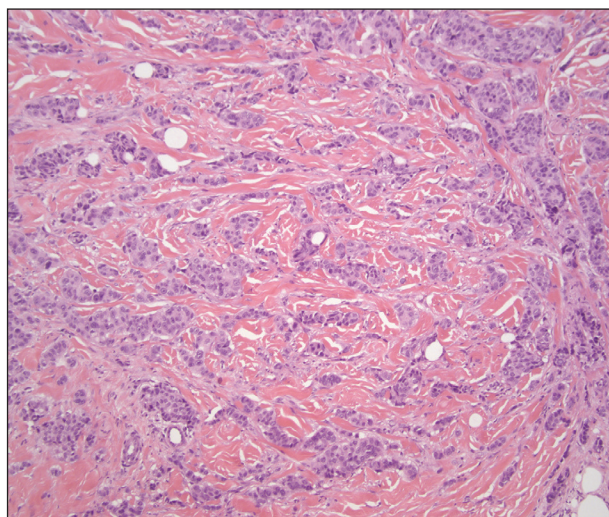


FIGURE 3. Cutaneous metastatic breast cancer. Dermal collagen infiltrated by cords and tubules of epithelial cells with occasional mucin deposition (H&E, original magnification $\times 100$). There is a high degree of atypia and pleomorphism noted within this neoplasm.

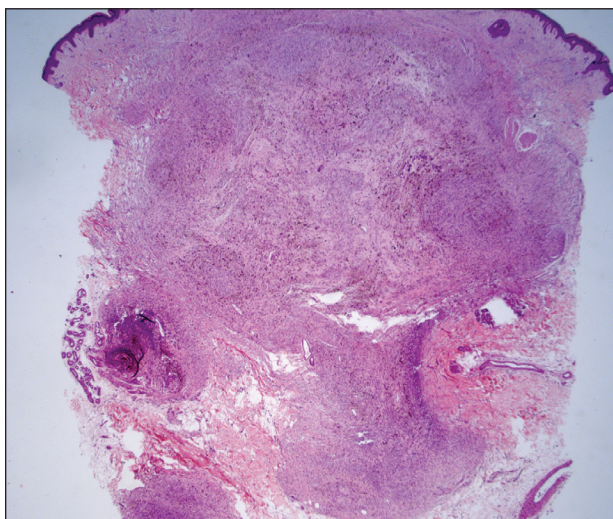


FIGURE 2. Cellular blue nevus. Well-demarcated infiltrate of spindled and dendritic melanocytes creating a dumbbell shape within the dermis and subcutis. There are variable degrees of melanin pigment, cellularity, and sclerosis (H&E, original magnification $\times 20$).

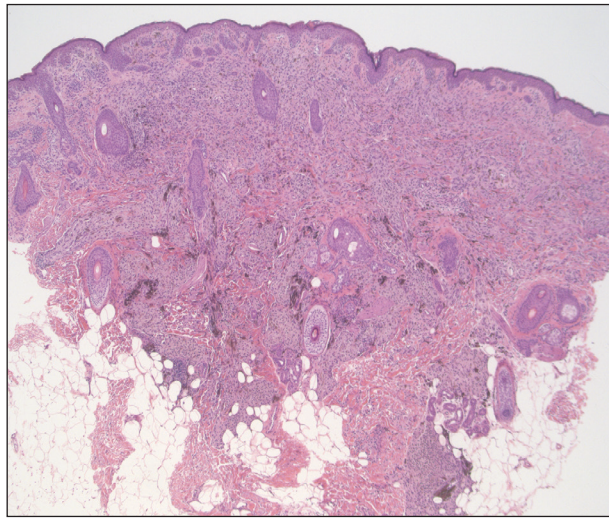


FIGURE 4. Deep penetrating nevus. Wedge-shaped infiltrate of melanocytes pushing into the reticular dermis and subcutis. Notable features include adnexal tracking and characteristic melanophages with melanin pigment (H&E, original magnification $\times 40$).

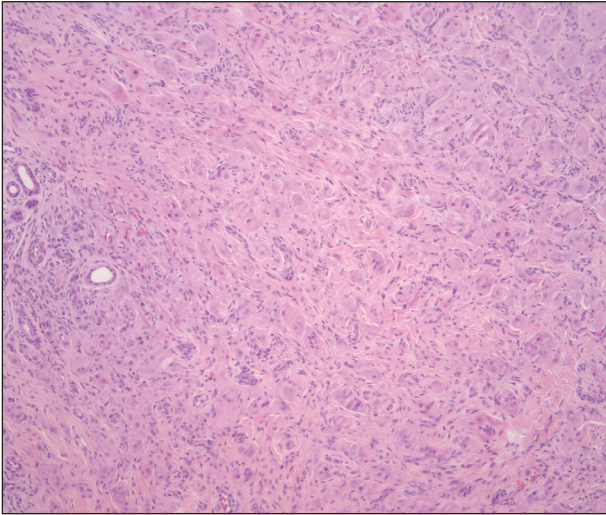


FIGURE 5. Multicentric reticulohistiocytosis. Predominantly dermal-based aggregation of 2-toned, ground glass, eosinophilic histiocytes (H&E, original magnification $\times 100$).

stain positive for CD68 and human alveolar macrophage 56 but negative for S-100 and CD1a (Figure 5).²⁵ Although MRH is rare, negative staining for S-100 could serve as a useful diagnostic clue to differentiate it from other entities that are positive for S-100, such as the desmoplastic Spitz nevus. Arthritis mutilans is a potential complication of MRH, but a reported association with an underlying malignancy is seen in approximately 25% of cases.²⁶ Thus, the cutaneous, rheumatologic, and oncologic implications of this disease help to distinguish it from other differential diagnoses that may be considered.

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