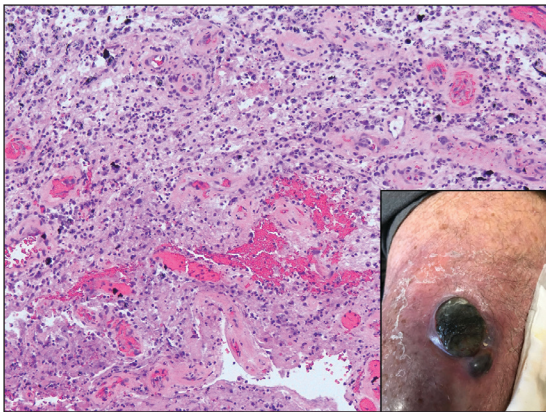


Enlarging Pigmented Lesion on the Thigh

Meaghan C. Dougher, MD; Thomas Helm, MD; Matthew F. Helm, MD

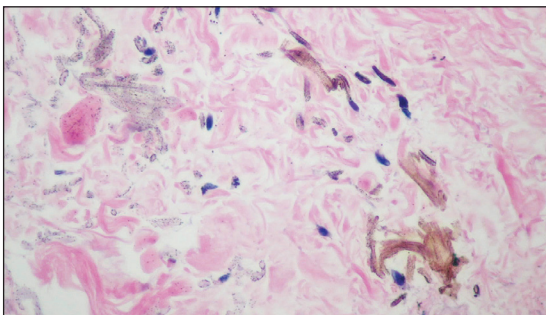
Eligible for 1 MOC SA Credit From the ABD

This Dermatopathology Diagnosis in our print edition is eligible for 1 self-assessment credit for Maintenance of Certification from the American Board of Dermatology (ABD). After completing this activity, diplomates can visit the ABD website (<http://www.abderm.org>) to self-report the credits under the activity title "Cutis Dermatopathology Diagnosis." You may report the credit after each activity is completed or after accumulating multiple credits.



H&E, original magnification $\times 200$; inset courtesy of KJ Singh, MD (Buffalo, New York).

An 80-year-old man presented with a pigmented lesion on the left lateral thigh near the knee that had been gradually enlarging over several weeks (top [inset]). He underwent a left knee replacement surgery for advanced osteoarthritis many months prior that was complicated by postoperative *Staphylococcus aureus* infection with sinus tract formation that was persistent for 6 months and treated with a topical medication. A pigmented lesion developed near the opening of the sinus tract. His medical history was remarkable for extensive actinic damage as well as multiple actinic keratoses treated with cryotherapy but no history of melanoma. An excisional biopsy was performed (top and bottom).



H&E, original magnification $\times 400$.

THE BEST DIAGNOSIS IS:

- blue nevus
- drug-induced pigmentation
- localized cutaneous argyria
- regressed melanoma
- tattoo ink reaction

PLEASE TURN TO **PAGE 82** FOR THE DIAGNOSIS

Dr. Dougher is from the Department of Pathology and Laboratory Medicine, Hospital of the University of Pennsylvania, Philadelphia. Dr. T. Helm is from the Department of Dermatology, Jacobs School of Medicine, University at Buffalo, New York. Dr. M. Helm is from the Department of Dermatology, Penn State Health Milton S. Hershey Medical Center, Pennsylvania.

The authors report no conflict of interest.

Correspondence: Meaghan C. Dougher, MD, 3400 Spruce St, 6 Founders, Philadelphia, PA 19104 (meaghan.dougher@penmedicine.upenn.edu). doi:10.12788/cutis.0830

THE DIAGNOSIS: Localized Cutaneous Argyria

The differential diagnosis of an enlarging pigmented lesion is broad, including various neoplasms, pigmented deep fungal infections, and cutaneous deposits secondary to systemic or topical medications or other exogenous substances. In our patient, identification of black particulate material on biopsy prompted further questioning. After the sinus tract persisted for 6 months, our patient's infectious disease physician started applying silver nitrate at 3-week intervals to minimize drainage, exudate, and granulation tissue formation. After 3 months, marked pigmentation of the skin around the sinus tract was noted.

Argyria is a rare skin disorder that results from deposition of silver via localized exposure or systemic ingestion. Discoloration can either be reversible or irreversible, usually dependent on the length of silver exposure.¹ Affected individuals exhibit blue-gray pigmentation of the skin that may be localized or diffuse. Photoactivated reduction of silver salts leads to conversion to elemental silver in the skin.² Although argyria is most common on sun-exposed areas, the mucosae and nails may be involved in systemic cases. The etiology of argyria includes occupational exposure by ingestion of dust or traumatic cutaneous exposure in jewelry manufacturing, mining, or photographic or radiograph manufacturing. Other sources of localized argyria include prolonged contact with topical silver nitrate or silver sulfadiazine for wound care, silver-coated jewelry or piercings, acupuncture, tooth restoration procedures using dental amalgam, silver-containing surgical implants, or other silver-containing medications or wound dressings. Discontinuing contact with the source of silver minimizes further pigmentation, and excision of deposits may be helpful in some instances.³

Histopathologic findings in argyria may be subtle and diverse. Small particulate material may be apparent on careful examination at high magnification only, and the depth of deposition can depend on the etiology of absorption or implantation as well as the length of exposure. Short-term exposure may be associated with deposition of dark, brown-black, coarse granules confined to the stratum corneum.¹ Frequently, cases of argyria reveal small, extracellular, brown-black, pigmented granules in a bandlike distribution primarily around vasculature, eccrine glands, perineural tissue, hair follicles, or arrector pili muscles or free in the dermis around collagen bundles. The granules can be highlighted by dark-field microscopy that will display scattered, refractile, white particles, described as a "stars in heaven" pattern.³ Rare ochre-colored collagen bundles have been reported in some cases, described as a pseudo-ochronosis pattern of argyria.⁴

Given the clinical history in our patient, a melanocytic lesion was considered but was excluded based on the histopathologic findings. Regressed melanoma clinically may resemble cutaneous silver deposition, as tumoral melanosis can be associated with an intense blue-black presentation. Histopathology will reveal an absence of melanocytes with residual coarse melanin in melanophages (Figure 1) rather than the particulate material associated with silver deposition. Although argyria can be associated with increased melanin in the basal epidermal keratinocytes and melanophages in the papillary dermis, silver granules can be distinguished by their uniform appearance and location throughout the skin (dermis, around vasculature/adnexal structures vs melanin in melanophages and basal epidermal keratinocytes).^{3,5,6}

Blue nevi typically present as well-circumscribed, blue to gray or even dark brown lesions most often located on the arms, legs, head, and neck. Histopathology reveals spindle-shaped dendritic melanocytes dissecting through collagen bundles in the dermis with melanophages (Figure 2). Pigmentation may vary from extensive to little or even none. Blue nevi are demarcated and may be associated with dermal sclerosis.⁷

Drug-induced hyperpigmentation has a variable presentation both clinically and histologically depending on the type of drug implicated. Tetracyclines, particularly minocycline, are known culprits of drug-induced pigmentation, which can present as blue-gray to brown discoloration in at least 3 classically described patterns: (1) blue-black pigmentation around scars or prior inflammatory sites, (2) blue-black pigmentation on the shins or upper extremities, or (3) brown pigmentation in photosensitive areas. Histopathology reveals

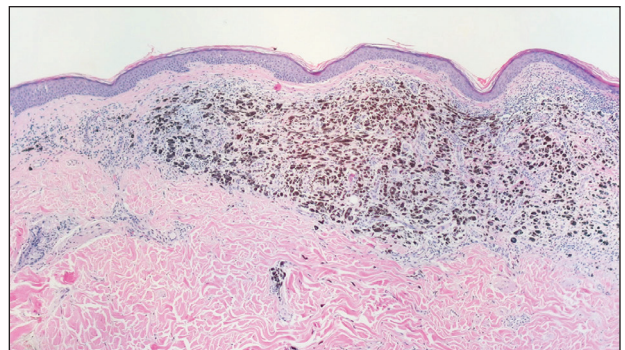


FIGURE 1. Regressed melanoma. There is a dense nodular infiltrate of melanophages with melanin pigment and surrounding inflammation in the dermis with no residual atypical melanocytes (H&E, original magnification $\times 50$).

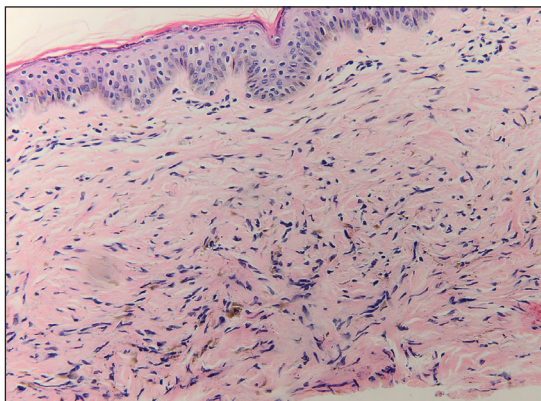


FIGURE 2. Blue nevus. Spindle-shaped dendritic melanocytes dissect through sclerotic collagen bundles in the dermis (H&E, original magnification $\times 200$).

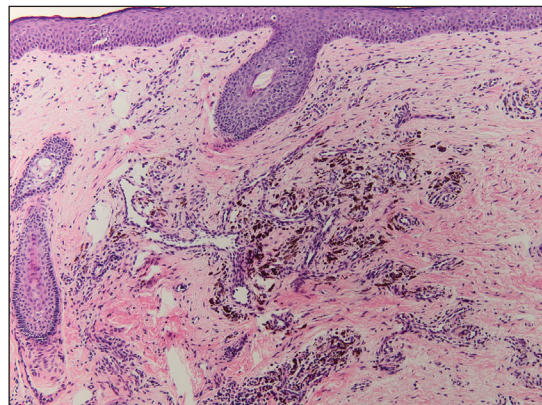


FIGURE 3. Tetracycline-induced pigmentation. Brown granules appear in the dermis with lymphohistiocytic inflammation (H&E, original magnification $\times 100$).

brown-black granules intracellularly in macrophages or fibroblasts or localized around vessels or eccrine glands (Figure 3). Special stains such as Perls Prussian blue or Fontana-Masson may highlight the pigmented granules. Widespread pigmentation in other organs, such as the thyroid, and history of long-standing tetracycline use are helpful clues to distinguish drug-induced pigmentation from other entities.⁸

Tattoo ink reaction frequently presents as an irregular pigmented lesion that can have associated features of inflammation including rash, erythema, and swelling. Histopathology reveals small clumped pigment in the dermis localized either extracellularly preferentially around vascular structures and collagen fibers or intracellularly in macrophages or fibroblasts (Figure 4). Considering the pigment is foreign material, a mixed inflammatory infiltrate can be present or more rarely the presence of pigment may induce pseudoepitheliomatous hyperplasia. The inflammatory reaction pattern on histology can vary, but granulomatous and lichenoid patterns frequently have been described. Other helpful clues to suggest tattoo pigment include refractile granules under polarized light and multiple pigmented colors.³

Dermal melanocytosis also may be considered, which consists of blue-gray irregular macules to patches on the skin that are frequently present at birth but may develop later in life. Histopathology reveals pigmented dendritic to spindle-shaped dermal melanocytes and melanophages dissecting between collagen fibers localized to the deep dermis. In addition, some hematologic or vascular disorders, including resolving hemorrhage or cyanosis, may be considered in the clinical differential. Deposition disorders such as chrysis and ochronosis could exhibit clinical or histopathologic similarities.^{3,8}

Occasionally, prolonged use of topical silver nitrate may result in a pigmented lesion that mimics a melanocytic neoplasm or other pigmented lesions. However,

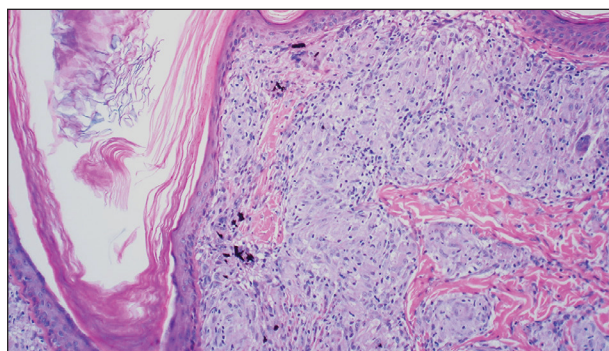


FIGURE 4. Tattoo ink reaction. Large black heterogeneous particles are present with associated granulomatous inflammation (H&E, original magnification $\times 100$).

these conditions can be readily differentiated by their characteristic histopathologic findings along with detailed clinical history.

REFERENCES

- Ondrasik RM, Jordan P, Sriharan A. A clinical mimicker of melanoma with distinctive histopathology: topical silver nitrate exposure. *J Cutan Pathol.* 2020;47:1205-1210.
- Gill P, Richards K, Cho WC, et al. Localized cutaneous argyria: review of a rare clinical mimicker of melanocytic lesions. *Ann Diagn Pathol.* 2021;54:151776.
- Molina-Ruiz AM, Cerroni L, Kutzner H, et al. Cutaneous deposits. *Am J Dermatopathol.* 2014;36:1-48.
- Lee J, Korgavkar K, DiMarco C, et al. Localized argyria with pseudo-ochronosis. *J Cutan Pathol.* 2020;47:671-674.
- El Sharouni MA, Aivazian K, Witkamp AJ, et al. Association of histologic regression with a favorable outcome in patients with stage 1 and stage 2 cutaneous melanoma. *JAMA Dermatol.* 2021;157:166-173.
- Staser K, Chen D, Solus J, et al. Extensive tumoral melanosis associated with ipilimumab-treated melanoma. *Br J Dermatol.* 2016;175:391-393.
- Sugianto JZ, Ralston JS, Metcalf JS, et al. Blue nevus and "malignant blue nevus": a concise review. *Semin Diagn Pathol.* 2016;33:219-224.
- Wang RF, Ko D, Friedman BJ, et al. Disorders of hyperpigmentation. part I. pathogenesis and clinical features of common pigmentary disorders. *J Am Acad Dermatol.* 2023;88:271-288.