Chapter 13
Miscellaneous Dermatoses: Invisible Dermatoses and Inflammatory Processes that Clinically Mimic Tumors

Keywords Tinea versicolor • Erythrasma • Post inflammatory pigment alteration • Vitiligo • Rosacea • Chondrodermatitis nodularis helicis

Sometimes when viewing a biopsy, there are no obvious abnormalities noted at low magnification. This situation is referred by some authors as the "nothing lesion." Such a specimen warrants careful scrutiny beginning at the stratum corneum and working down to the subcutis, looking for subtle changes in the keratin layer (fungal infection), basal layer (melanocytes, melanin deposition,and basal vacuolization), papillary dermis (vascular wall thickening, amyloid deposition, mast cell infiltrates), dermis and adnexae (changes in collagen, elastic tissue, mucin deposition,and alterations in adnexae). Depending on the clinical question being asked, special stains may be very helpful in detecting organisms or deposited material.

This discussion will focus on entities that fall into this category of "invisible" dermatoses. By being aware of the clinical presentation, subtle histologic changes that characterize these lesions, and liberal use of special stains, a specific diagnosis can usually be rendered. This section of the chapter will also briefly discuss entities that occur elsewhere in the book. And the reader is referred to those chapters for more complete coverage.

Tinea Versicolor

Clinical Features

Tinea versicolor is caused by dimorphic, lipophilic organisms in the genus *Malassezia,* formerly known as *Pityrosporum*. It is characterized by hyperpigmented to hypopigmented macules with variable scale, typically located on the trunk. Patients often present toward the end of summer because their tan is uneven.

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Microscopic Features

The scale is typically a normal basket weave configuration with occasional parakeratosis. The epidermis is usually normal. A slight superficial perivascular infiltrate of lymphocytes may be seen or appear entirely normal. Hyphal and yeast forms (spaghetti and meatballs pattern) may be visible on routine histologic examination (Fig. 13.1) (Table 13.1) or highlighted with PAS or GMS stains. Sometimes, the organisms create empty spaces in the stratum corneum that can be detected on H&E slides. When cut at right angles, the hyphae appear like donuts.

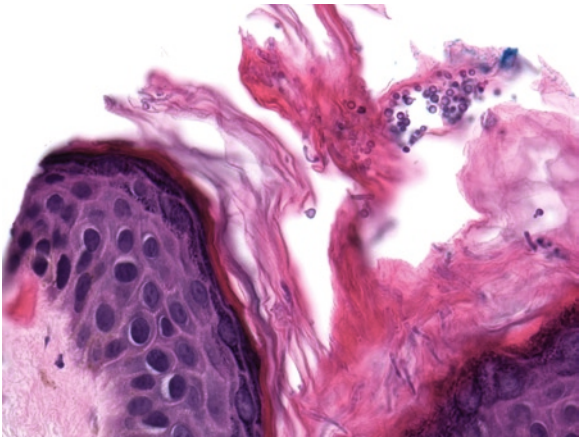

Fig. 13.1 *Tinea versicolor* is characterized by the presence of yeast and hyphae in otherwise normal looking skin

Table 13.1 Key microscopic features: tinea versicolor

- Hyphae and yeast in stratum corneum (spaghetti and meatballs pattern)
- Epidermis is usually normal
- Relatively noninflammatory

Differential Diagnosis

Dermatophyte infection is considered in the differential diagnosis histologically. The absence of neutrophils in the stratum corneum and normal epidermis are clues to tinea versicolor. Pigment disorders such as vitiligo or post inflammatory hypopigmentation may be a clinical consideration, and that history should always prompt consideration of tinea versicolor (Table 13.2).

Table 13.2 Practical tips: tinea versicolor

- Clinically can present as pigment disorder (e.g., vitiligo)
- Consider PAS stain

Corynebacterial Infection

Clinical Features

Corynebacterium overgrowth is seen in both erythrasma and pitted keratolysis. Erythrasma is the most common cause of interdigital foot infection. It may also involve intertriginous areas. The infection is found frequently in patients who are overweight or have diabetes mellitus. Lesions typically present as well-defined red-brown fine scaly patches. Pitted keratolysis presents as often malodorous, discrete pits on the plantar surfaces. Both infections demonstrate characteristic coral-red fluorescence by Wood's lamp examination.

Microscopic Features

Both erythrasma and pitted keratolysis are characterized by filamentous bacteria in the cornified layer (Fig. 13.2) (Table 13.3). A PAS stain or Gram stain highlights small, round coccobacilli.

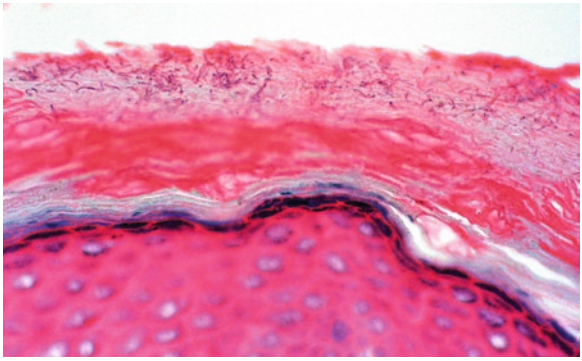

Fig. 13.2 *Erythrasma* (and pitted keratolysis) is characterized by filamentous bacteria in the stratum corneum

Table 13.3 Key microscopic features: erythrasma and pitted keratolysis (cornybacterial infection)

- Normal appearing axillary or acral skin
- Filamentous bacteria in stratum corneum

Differential Diagnosis

The differential diagnosis clinically is usually candidiasis for intertriginous cases and dermatophyte for foot infections. Erythrasma and pitted keratolysis lack the inflammatory changes and the organisms are much smaller (Table 13.4).

Table 13.4 Practical tips: erythrasma and pitted keratolysis

- Consider these diagnoses in biopsies of normal appearing axillary or acral skin
- Gram or PAS stains helpful

Post Inflammatory Pigment Alteration

Clinical Features

Post inflammatory pigment alteration usually presents as hyperpigmented or hypopigmented macules. It is the result of a previous, resolving inflammatory process. Clinically, it may still have some features resembling the disease and biopsies may be submitted with a clinical diagnosis of an inflammatory skin disease.

Microscopic Features

The epidermis is usually normal in appearance or may exhibit subtle alterations (e.g., minimal spongiosis or acanthosis). Within the dermis, there is a scant to mild perivascular lymphocytic infiltrate with scattered melanophages (Fig. 13.3; Table 13.5).

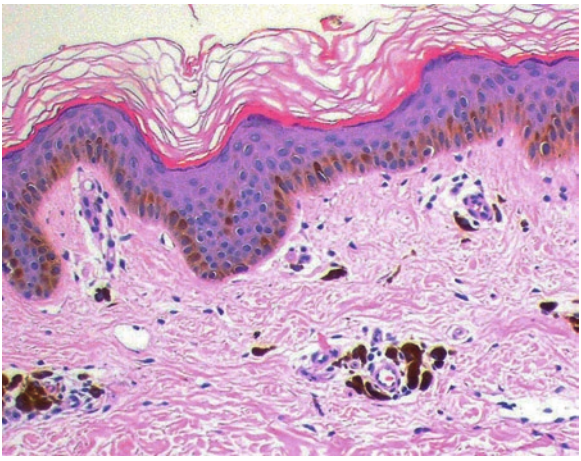

Fig. 13.3 *Post inflammatory pigment alteration*. The epidermis is unremarkable and there are perivascular melanophages

Table 13.5 Key microscopic features: post inflammatory pigment alteration

- Unremarkable epidermis
- Mild perivascular lymphocytic infiltrate with melanophages

Differential Diagnosis

The histologic differential diagnosis includes other vitiligo. Melanophages are more prominent in post inflammatory pigment alteration and there is no reduction in the number of melanocytes in post inflammatory pigment alteration. Ashy dermatosis, also called erythema dyschromicum perstans, is in the histologic differential diagnosis. It is a widespread dermatitis that presents as ash-colored or brown hyperpigmented macules that is most common in Latin America or in patients with Hispanic ancestry. It is a mild interface dermatitis that has a component of post inflammatory pigment alteration. Active lesions will demonstrate interface change in addition to dermal melanophages and a mild perivascular lymphocytic infiltrate. The interface change may be subtle and multiple levels may be needed. In biopsies submitted as solitary lesions, the possibility of a regressed melanocytic lesion or resolved benign lichenoid keratosis should be considered. In this situation, additional levels are recommended to help exclude these possibilities. Immunohistochemical stains for melanocytic markers can also be considered to help exclude an occult residual melanocytic tumor (Table 13.6).

Table 13.6 Practical tips: post inflammatory pigment alteration

- Clinically may be hyperpigmented or hypopigmented
- Consider immunostains to rule out vitiligo
- Consider PAS stains to rule out tinea versicolor
- If patient is of Hispanic descent, consider ashy dermatosis and look for evidence of interface change
- If lesion is solitary, consider regressed melanocytic lesion
  - Get deeper levels
  - Consider immunostains to evaluate for occult melanocytic tumor

Vitiligo

Clinical Features

Vitiligo is an acquired condition where melanocytes are absent from affected skin. Lesions are characterized by circumscribed, hypopigmented round or oval macules or patches. Vitiligo is a progressive disorder in which some or all of the melanocytes in the affected skin are selectively destroyed. Average age of onset is 20 years; face, neck and scalp are most commonly affected. Vitiligo is a complex disorder. Pathophysiologic hypotheses to explain this pathology include autocytotoxic, neural, and immunologic mechanisms, the details of which are beyond the scope of this book.

Microscopic Features

Ideally, the biopsy should include both lesional and nonlesional skin. In normal skin, melanocytes are distributed as one per approximately seven keratinocytes. In contrast to keratinocytes, basilar melanocytes often have halos surrounding the nucleus with some cytoplasm still clinging to the nucleus. Vitiligo is defined as a greatly reduced or absence of melanocytes and melanin. Practically speaking, it may be very difficult to recognize and distinguish melanocytes from basal keratinocytes on routine examination. For this reason, it is advisable to order a panel of special stains when evaluating for this possibility. Masson–Fontana stain demonstrates loss of melanin pigment in the basilar epithelium of vitiliginous skin. Immunohistochemical stains are the preferable means for evaluation, as they are more sensitive. Immunohistochemical staining with Melan-A or Mart-1 stains are better than S100 protein stains because of their relative specificity for melanocytes (Fig. 13.4). Immunostains for S100 protein will also highlight intraepidermal Langerhans cells. However, there are some potential interpretation pitfalls with Melan-A or Mart-1. In inflammatory process with active interface change, there may be false positivity of non-melanocytes with these stains. An immunohistochemical stain for microphthalmia transcription factor (MITF) can be useful, as it is a fairly specific nuclear marker of melanocytes. Early lesions of vitiligo can show superficial perivascular lymphocytes (inflammatory vitiligo); however, dermal melanophages favor nonspecific postinflammatory alteration over vitiligo (Table 13.7).

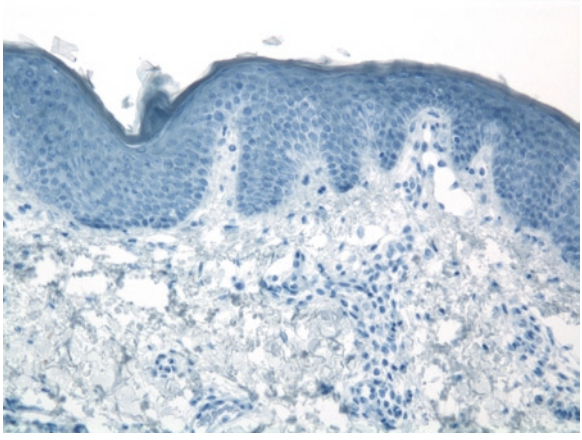

Fig. 13.4 *Vitiligo*. An immunohistochemical stain for Melan-A demonstrates an absence of melanocytes

Table 13.7 Key microscopic features: vitiligo

- Absence of melanocytes on H&E
- Immunostains ideal to prove reduction/absence of melanocytes

Differential Diagnosis

The primary differential diagnosis is postinflammatory pigment alteration. Tinea versicolor could also be considered. Neither of these entities has reduced numbers of melanocytes in the epidermis (Table 13.8).

Table 13.8 Practical tips: vitiligo

- Normal skin has ~1 melanocyte per 7 keratinocytes
- Exclude tinea versicolor with PAS or GMS stains
- Melan-A or Mart-1 immunostains superior to S100 protein immunostains

Macular Amyloidosis and Lichen Amyloidosis

Clinical Features

Macular amyloidosis presents most commonly as an intensely pruritic, dusky brown pigmented papules distributed over the upper back or arms. Approximately 50% of patients have a reticulated or rippled pattern of pigmentation. Lichen amyloidosis presents as pruritic waxy papules usually on the lower legs.

Microscopic Features

Both forms are essentially the same microscopically with deposition of amyloid within the dermal papillae. The homogenous, dull-pink deposits are associated with widened dermal papillae and dermal melanophages (Fig. 13.5). In our experience, the diagnosis is best made on H&E, as often classic amyloid stains (Congo-red) are

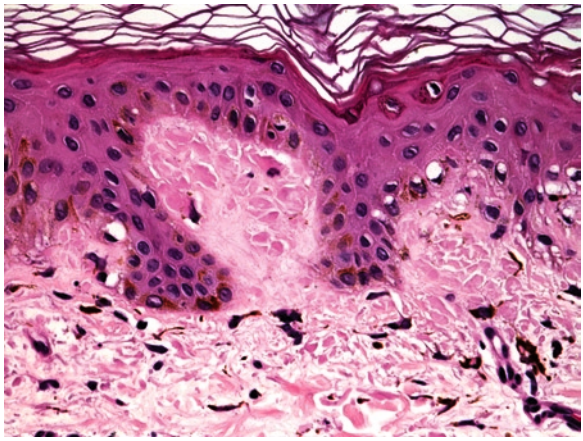

Fig. 13.5 *Macular amyloidosis*. The amyloid deposition is characterized by eosinophilic globules in the papillary dermis. Melanophages are present around the blood vessels

negative (Table 13.9). Reactive epidermal changes related to excoriation (hyperkeratosis, thickened granular layer) may be present.

Table 13.9 Key microscopic features: macular and lichenoid amyloidosis

- Homogenous dull pink papillary dermal deposits of amyloid
- Widened dermal papillae
- Melanophages

Differential Diagnosis

Distinguishing macular and lichen amyloidosis requires knowledge of the clinical presentation (Table 13.10). Systemic amyloidosis can look similar, but the deposits are usually more prominent and not just in the papillary dermis. They are more likely to be birefringent under polarized light with a Congo-red stain. Colloid milium can look identical histologically. Colloid milium is characterized by numerous yellow-brown papules on heavily sun-damaged skin.

Table 13.10 Practical tips: macular and lichenoid amyloidosis

- This form of amyloid often not birefringent on Congo red stains
- Best considered an H&E diagnosis

Other Inflammatory Diseases that Can Present as Nothing Lesions

In this section there is brief mention of other entities in the nothing lesion differential diagnosis that have been previously discussed in other chapters.

Dermatophyte Infections

Dermatophyte infections are discussed in detail in Chap. 12. Occasionally, dermatophyte infections are histologically quite subtle. Often, it is the result of prior treatment with topical steroids. Clues to occult dermatophyte infection include clinical history of poor response to topical steroids, history of an annular lesion and the sandwich sign as discussed in the previous chapter.

Cutaneous Mastocytosis

As discussed in Chap. 5, cutaneous mast cell disease is characterized by clinical heterogeneity. Urticaria pigmentosa and telangiectasia macularis eruptiva perstans

can be quite subtle histologically. Special stains are instrumental in recognizing subtle forms. Special stains such as Giemsa can be used, but an immunohistochemical stain for tryptase or CD117 are more sensitive as they also detect degranulated mast cells. See Chap. 5 for a more complete discussion.

Morphea

Clinical and histologic features of morphea are more completely discussed in Chap. 9. On scanning magnification, the "square" biopsy (as opposed to normal tapered or cone shape that occurs post-fixation) is a helpful clue to the diagnosis.

Dermal Hypersensitivity Reaction (Urticaria or Drug Eruption)

The entities have been previously discussed in more detail in Chaps. 4 and 5. For the purposes of this chapter, it is important to remember that the dermal infiltrate can appear sparse on scanning magnification, and therefore appear as a "nothing lesion." High power examination will reveal some perivascular eosinophils that are key to recognizing these dermal hypersensitivity reactions. Intravascular neutrophils may also be seen especially in the setting of urticaria.

Inflammatory Disorders Clinically Mistaken for Neoplasms

Inflammatory dermatoses can sometimes mimic cutaneous neoplasms. In our practices, the two most common inflammatory dermatoses that are frequently submitted with a clinical diagnosis of a cutaneous malignancy are rosacea and chondrodermatitis nodularis helicis. Knowledge of this is helpful in arriving at the proper diagnosis in this setting.

Rosacea (Acne Rosacea)

Clinical Features

Rosacea begins as an erythematous eruption on the central face, especially the cheeks and around the nose. Over the time, patients may develop papules and/or pustules. The papules may have surrounding telangiectasia. Occasionally, the appearance may cause a clinician to consider the possibility of a basal cell carcinoma.

Microscopic Features

The histologic findings of rosacea are variable. Fairly constant is the presence of a perivascular and perifollicular lymphocytic infiltrate (Fig. 13.6). An associated acute folliculitis may be present in occasional cases. Some cases have a relatively prominent granulomatous inflammatory infiltrate and are termed granulomatous rosacea (Fig. 13.7; Table 13.11).

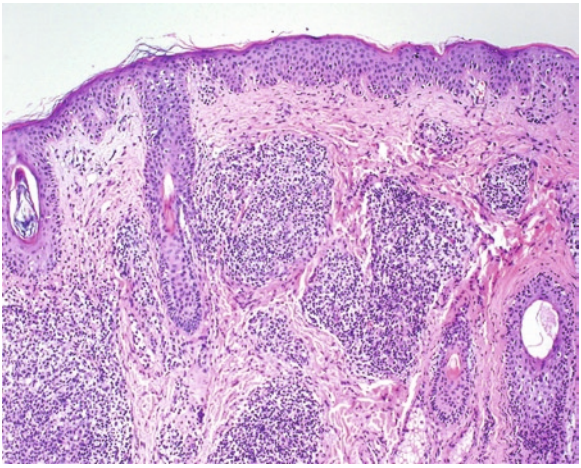

Fig. 13.6 *Rosacea* is characterized by a perifollicular and perivascular lymphohistiocytic infiltrate

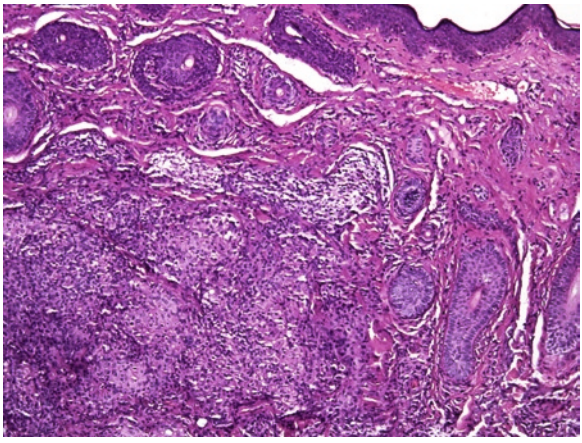

Fig. 13.7 *Granulomatous rosacea*. Within the dermis there is a brisk granulomatous infiltrate centered on follicles. The papillary dermal blood vessels are ectatic, a common finding in rosacea

Table 13.11 Key microscopic features: rosacea

- Perivascular and perifollicular lymphohistiocytic infiltrate
- Telangiectatic vessels
- May be granulomatous

Differential Diagnosis

The histologic features are often nonspecific. Rosacea is rarely biopsied except when basal cell carcinoma is a clinical concern. In such cases, it is prudent to obtain deeper levels to exclude that possibility. In granulomatous rosacea, sarcoidosis or infection could be considered. Usually the granulomas of granulomatous rosacea have a more developed lymphocytic cuff. The clinical concern for basal cell carcinoma is also a clue that suggests rosacea over sarcoidosis (Table 13.12).

Table 13.12 Practical tips: rosacea

- Occurs on central face, especially around nose
- May be submitted with clinical diagnosis of basal cell carcinoma
- Multiple levels recommended if clinical concern is basal cell carcinoma

Chondrodermatitis Nodularis Helicis

Clinical Features

Chondrodermatitis nodularis helicis, also referred to as chondrodermatitis nodularis chronica helicis, has a very specific clinical presentation. It is more common in middle aged to older patients. In men, it presents almost exclusively on the helix. In women, the antihelix is the most common location. It presents as a crusted or ulcerated nodule. Clinically, it can be confused with squamous cell carcinoma or, less frequently, basal cell carcinoma. The etiology of this process is thought to be related to chronic trauma. Some consider it a localized pressure ulcer. Supporting this are cases attributable to persistent headphone use in telephone operators in days of yore and the increased incidence on the dominant sleep side.

Microscopic Features

The epidermis is usually, but not always, ulcerated. Adjacent to the ulcer, the epidermis shows pseudoepitheliomatous hyperplasia. Immediately beneath the ulcer, there is the characteristic fibrinoid degeneration of the collagen (Fig. 13.8). Beneath the fibrinoid material is a reactive vascular proliferation, but with relatively little inflammation. Depending on how deep the process goes, a reactive proliferation of perichondrial fibroblasts and degenerative changes of the collagen may be seen (Table 13.13).

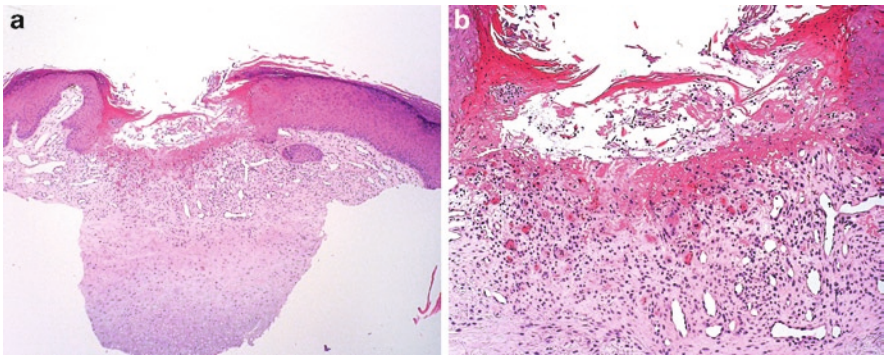

Fig. 13.8 *Chondrodermatitis nodularis helicis*. (**a**) At scanning magnification there is an epidermal ulcer overlying the cartilage. (**b**) Beneath the ulcer there is the characteristic fibrinoid change in the dermal collagen that is surrounded by a reactive vascular proliferation

Table 13.13 Key microscopic features: chondrodermatitis nodularis helicis

- Ulcerated epidermis with adjacent reactive epidermal hyperplasia
- Fibrinoid degeneration of dermal collagen
- Reactive vascular proliferation under degenerated collagen

Differential Diagnosis

The most common entity in the differential diagnosis is squamous cell carcinoma. The pseudoepitheliomatous hyperplasia must not be mistaken for squamous cell carcinoma. There may be some reactive atypia, but hyperchromasia and atypical mitotic figures are not seen. One must be careful not to over interpret the presence of adjacent actinic keratosis. As this lesion tends to occur in sun-damaged skin of older patients, adjacent actinic keratosis may be an incidental finding. The fibrinoid degeneration of the dermal collagen is the key histologic feature. Often, the biopsy is relatively shallow and does not demonstrate the underlying cartilage. The histologic findings are actually quite distinctive, and misdiagnosis is rare when one is aware of the features (Table 13.14).

Table 13.14 Practical tips: chondrodermatitis nodularis helicis

- High index of suspicion on biopsies from ear
  - Helix and antihelix almost exclusively involved
- Fibrinoid degeneration of collagen is the key microscopic feature

Sample Reports: Post Inflammatory Pigment Alteration

Example 1:

Clinical history: Hypopigmented macules, rule out vitiligo.

Diagnosis: Mild perivascular lymphocytic infiltrate with melanophages consistent with post inflammatory pigment alteration, see comment.

Comment: The epidermis is unremarkable. Within the dermis, there is a mild superficial perivascular lymphocytic infiltrate with scattered melanophages. Because of the clinical suspicion for possible vitiligo, an immunohistochemical stain for Melan-A was performed and compared to appropriate controls to assess for the number and distribution of melanocytes. There is a normal number and distribution of melanocytes. The histologic features are consistent with post inflammatory pigment alteration, which can clinically present as hypopigmented or hyperpigmented macules.

Example 2:

Clinical history: Pigmented lesion.

Diagnosis: Mild perivascular lymphocytic infiltrate with melanophages consistent with post inflammatory pigment alteration, see comment.

Comment: The epidermis is unremarkable. Within the dermis, there is a mild superficial perivascular lymphocytic infiltrate with scattered melanophages. Because of the clinical suspicion for a pigmented neoplasm, multiple deeper levels and an immunohistochemical stain for Melan-A was performed and compared to appropriate controls. No evidence of a melanocytic neoplasm is seen. The histologic features are consistent with post inflammatory pigment alteration, which can clinically present as hypopigmented or hyperpigmented macules. The possibility of a completely regressed melanocytic neoplasm or resolved benign lichenoid keratosis cannot be excluded. Clinicopathologic correlation and continued clinical follow-up is recommended.

Sample Report: Rosacea

Clinical history: Rule out basal cell carcinoma.

Diagnosis: Perivascular and perifollicular lymphohistiocytic infiltrate suggestive of rosacea, see comment.

Comment: Multiple levels were examined. Within the dermis, there is a perivascular and perifollicular lymphohistiocytic infiltrate. No evidence of malignancy is seen. The histologic features are consistent with rosacea in the appropriate clinical context. Clinicopathologic correlation is recommended.

Sample Report: Chondrodermatitis Nodularis Helicis

Clinical history: Squamous cell carcinoma.

Diagnosis: Consistent with chondrodermatitis nodularis helicis, see comment.

Comment: The epidermis is ulcerated. Beneath the ulcer, there is fibrinoid degeneration of the collagen, which is surrounded by a reactive vascular proliferation. Given the clinical presentation on the ear, the histologic features are consistent with the diagnosis of chondrodermatitis nodularis chronic helicis. Clinicopathologic correlation is recommended.

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