

Educational Case: Vitiligo

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see <http://journals.sagepub.com/doi/10.1177/2374289519888719>.¹

Keywords

pathology competencies, organ system pathology, skin, autoimmune disease, vitiligo, depigmenting disorders, melanocytic disorder, special stains

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Primary Learning Objective

Objective SK3.2: Immune Diseases of the Skin: Describe the clinical features and pathologic basis for the following immunologically driven diseases with a genetic component: eczema, psoriasis, and vitiligo.

Competency 2: Organ System Pathology; Topic: Skin (SK); Learning Goal 3: Immune-Related Disorders of the Skin.

Patient Presentation

A 38-year-old Caucasian male presents to the dermatologist concerned about “white” spots on his arms and legs. The spots have been present for many years and are asymptomatic. The patient has no other relevant past medical history and takes no medications.

Diagnostic Findings, Part I

Physical examination shows symmetrically located, well-demarcated 6- to 10-mm depigmented macules and patches on his forearms, dorsal hands, and distal legs. The lesions show no surface scale. No other lesions are seen on full-body examination. Potassium hydroxide (KOH) preparation test is negative for fungal organisms.

Questions/Discussion Points, Part I

What Is Your Differential Diagnosis Based on the Clinical Presentation and History?

The patient is presenting with a depigmenting disorder of his skin. The differential diagnosis would include vitiligo, postinflammatory hypopigmentation, tinea versicolor, and idiopathic guttate hypomelanosis (IGH). Vitiligo is an asymptomatic eruption of depigmented macules and papules, often symmetrically distributed. Patients may or may not have a family history of vitiligo or a history of autoimmune disease. Vitiligo is the leading differential diagnosis in this case. Postinflammatory hypopigmentation is a result of a preceding inflammatory lesion or eruption, disrupting the melanin pigment in the epidermis, and causing pigment drop-out into the dermis. The clinical result is that of a pigment change. Given the lack of history of a preexisting eruption, a postinflammatory process is unlikely. Tinea versicolor is a cutaneous fungal

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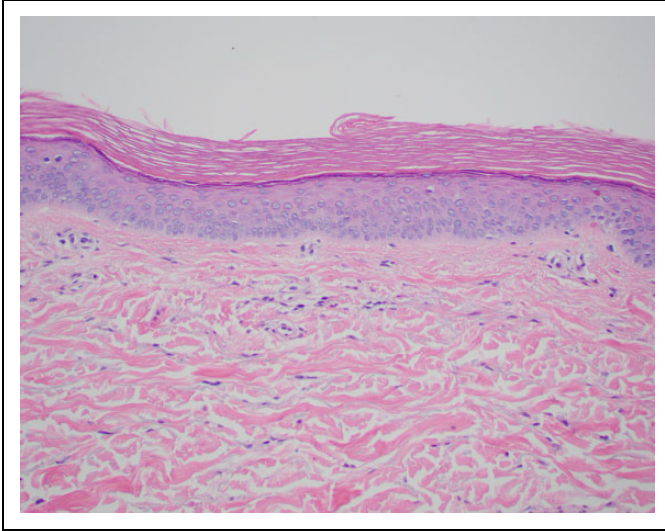


Figure 1. The patient's skin biopsy from the dorsal hand. Melanocytes are not readily identifiable along the junction. There is no appreciable inflammation within the dermis (hematoxylin and eosin, $\times 20$).

infection and can cause pigment alteration in the skin. A cutaneous fungal infection should still be considered, although the lack of scale on examination and negative KOH prep argues against this. Idiopathic guttate hypomelanosis is a sun-related condition, often seen in older adults, appearing as small 1- to 3-mm macules of depigmentation on actinically damaged skin. The lesions in this patient are larger, though are on sun-exposed areas. A skin biopsy can help to differentiate IGH from vitiligo as melanocytes are retained in IGH.

Diagnostic Findings, Part 2

A Skin Biopsy of the Dorsal Hand Is Performed for Diagnosis and Is Shown in Figure 1. How Would You Describe the Microscopic Findings in the Hematoxylin and Eosin–Stained Skin Biopsy?

Junctional melanocytes are not readily identified. There is overlying orthokeratosis. There is no appreciable inflammation in the dermis. Overall, these features are nonspecific and are of near “normal” skin for site.

A panel of stains is performed to further characterize the process, including to detect melanin pigment, identify any fungal infection present, and highlight the melanocytes within the epidermis.

A Fontana Masson Stain Is Performed and Is Shown in Figure 2. What Does a Fontana Masson Stain Detect? How Would You Interpret the Fontana Masson Stain on This Case?

A Fontana Masson stains melanin pigment. Any cell containing melanin will stain black. The Fontana Masson stain in this case showed no positive staining (no black melanin pigment seen).

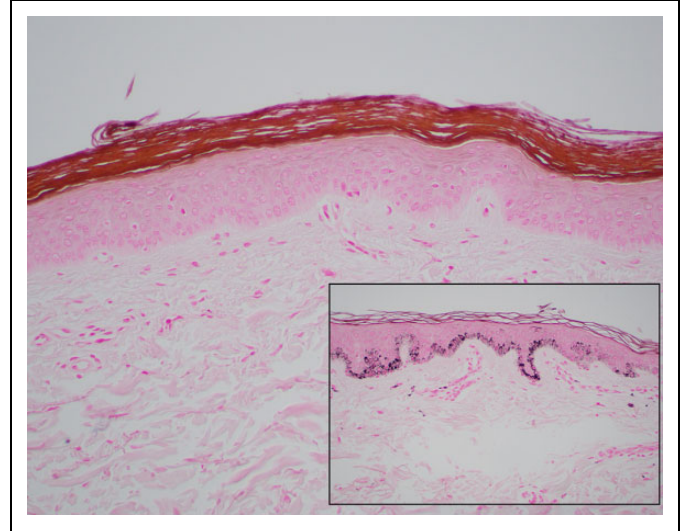


Figure 2. The patient's skin biopsy stained with Fontana Masson, a melanin pigment stain, showing no appreciable melanin in the epidermis or dermis. Inset, A Fontana Masson stain of “normal” skin showing melanin pigment (black cytoplasmic pigment) in keratinocytes along the dermal–epidermal junction (Fontana Masson, $\times 20$).

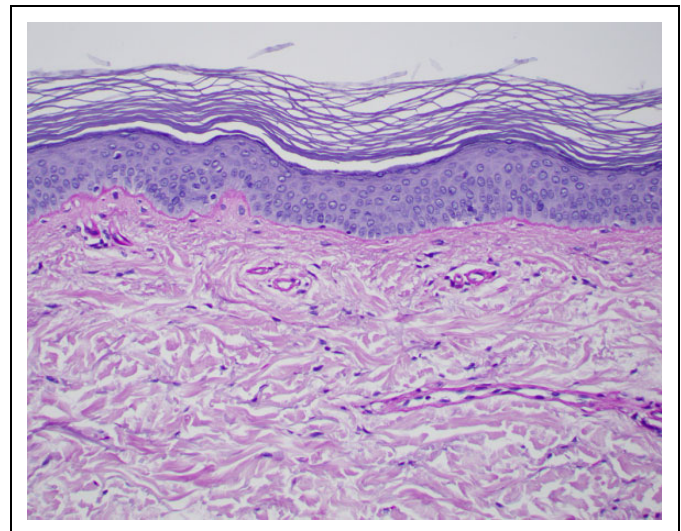


Figure 3. The patient's skin biopsy stained with periodic acid–Schiff (PAS), a fungal stain, showing no evidence of fungal hyphae in the stratum corneum, the uppermost layer of the epidermis (PAS, $\times 20$).

The inset photo shows an example of “normal” skin with basilar pigment seen.

A Periodic Acid–Schiff Stain Is Done and Is Shown in Figure 3. Why Was a Periodic Acid–Schiff Stain Performed? How Would You Interpret the Periodic Acid–Schiff Stain on This Case?

A periodic acid–Schiff (PAS) is performed in this case to detect fungal organisms present in the stratum corneum (skin surface). The PAS stain in this case was negative—there were no fungal

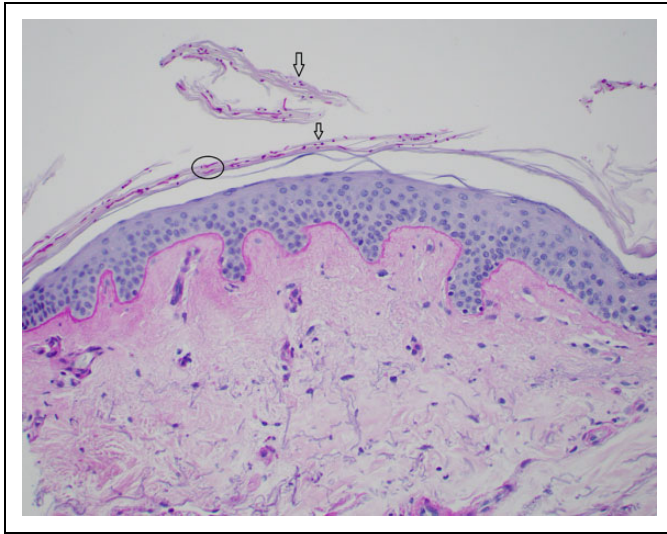


Figure 4. An example case of *Tinea versicolor*. Pictured is a skin biopsy with superficial fungal hyphae (circled) and yeast (arrows) forms seen within the stratum corneum, stained with period acid–Schiff (PAS). This is often referred to as a “spaghetti and meatballs” appearance (PAS, $\times 20$).

organisms seen. A positive example of a PAS stain is shown in Figure 4 to illustrate superficial fungal hyphae and yeast forms as would be found in *tinea versicolor*.

A SOX-10 Stain Is Performed and Is Shown in Figure 5. What Cells Are Highlighted by SOX-10 Immunohistochemical Stain? How Would You Interpret the SOX-10 Stain in This Case?

SOX-10 is a transcription factor found in neural crest cells and melanocytes. It is a nuclear stain and would be positive in melanocytes found within the epidermis. The SOX-10 stain is negative in this case, confirming a lack of melanocytes along the junction. The inset photo is of “normal” skin and highlights scattered, evenly distributed melanocytes along the junction (red nuclear stain).

How Does the Microscopic Examination Narrow Your Differential Diagnosis?

A near “normal” skin biopsy with absent melanocytes and lack of melanin pigment with a clinical history of symmetrically located, depigmented macules and patches on arms and legs is most consistent with vitiligo. Postinflammatory hypopigmentation is the result of a resolved/resolving inflammatory dermatitis. The loss of pigment is due to the inflammation in the primary process disrupting the epidermal keratinocytes, which contain melanin pigment. The keratinocytes “lose” their pigment into the dermis, causing the clinical impression of pigment alteration. The biopsy will often reveal melanophages (histiocytes containing melanin) in the upper dermis—a sign of prior inflammation. Stains are not useful in making the

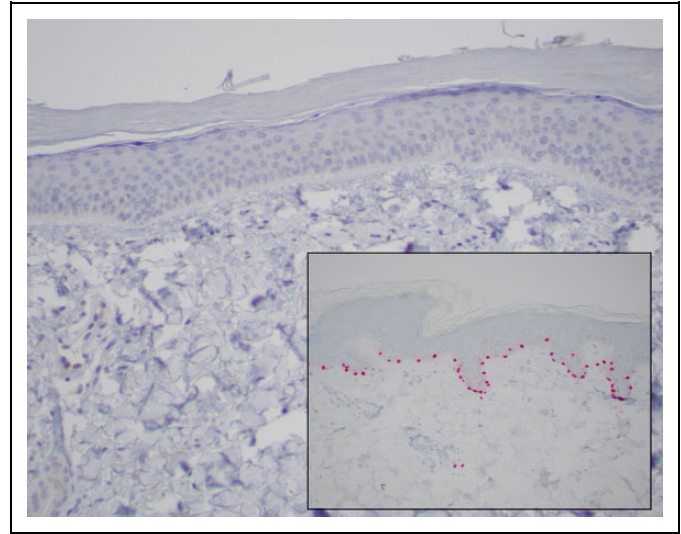


Figure 5. The patient’s skin biopsy stained with SOX-10, an immunohistochemical stain for melanocytes, showing no melanocytes along the dermal–epidermal junction. Inset, A SOX-10 stain of “normal” skin showing evenly distributed melanocytes (red nuclear stain) along the dermal–epidermal junction (SOX-10 ALK PHOS (EP268, Epitomics), $\times 20$).

diagnosis of postinflammatory pigment alteration. *Tinea versicolor* is a superficial cutaneous fungal infection caused by *Malassezia* species. It can be highlighted clinically by Wood’s lamp fluorescence or detected with a scrape preparation and KOH stain in clinic to identify the superficial fungal organisms. Clinically, the macules and patches can be either hyper- or hypopigmented and red-brown to white. Infrequently, it is biopsied, but when it is, it shows fungal hyphae and spores in the stratum corneum, resembling “spaghetti and meatballs.” For this reason, the PAS stain was ordered—and helpful in excluding this diagnosis in this patient. Idiopathic guttate hypomelanosis is a condition seen in older adults with significant sun exposure. It is characterized by small, 1- to 3-mm white macules on the legs, arms, chest, and back. On biopsy, there are patchy areas with decreased numbers of melanocytes along the dermal–epidermal junction and hyperkeratosis. The biopsy from this patient showed absent melanocytes along the junction, helping to exclude this diagnosis. These points are summarized in Table 1.

Questions/Discussion Points, Part 2

What is Vitiligo?

Vitiligo is a skin disorder characterized by depigmentation of the skin and hair follicles resulting in white, often symmetrical macules and patches on the skin surrounded by normal skin. They often increase in number and size over time. Vitiligo is classified as localized, generalized, and universal, affecting different regions of the body and with variable extent.² Over 50% of patients present before age 20, with many of these before age 10. Vitiligo is common, affecting 0.5% to 2.0% of the world’s population. There is no race or sex predilection.³ Interestingly, patients can experience the “Koebner phenomenon”

Table 1. Differential Diagnosis for Skin Disorders Showing Depigmentation.

Disorder	Clinical Presentation	Histology
Vitiligo	One or more, often symmetrical, macules and patches of depigmentation surrounded by unaffected skin; often increase in size and number over time; 50% present younger than 20 years.	Basilar keratinocyte hypopigmentation ± Mild dermal inflammation. Fontana Masson: absent melanin pigment along the dermal–epidermal junction; no dermal pigment. SOX-10 (or other melanocyte stain): absent melanocytes along the dermal–epidermal junction.
Postinflammatory hypopigmentation	Poorly demarcated hypopigmentation in area(s) of previous inflammation. May have coexistent inflammatory disorder elsewhere on body (eg, seborrheic dermatitis, lupus, psoriasis, allergic contact dermatitis).	Slightly decreased numbers of melanocytes along the dermal–epidermal junction. ± Dermal inflammation or other changes characteristic of underlying inflammatory condition. Often pigment dropout in superficial dermis (dermal melanophages).
Tinea versicolor	Hypopigmented patches with surface scale. KOH preparation test: positive for fungal organisms.	Stratum corneum containing fungal hyphae and spores (“spaghetti and meatballs”). Epidermal spongiosis and mild dermal inflammation. PAS stain positive for fungal organisms.
Idiopathic guttate hypomelanosis	Multiple 1–5 mm hypomelanotic macules on sun-exposed sites, legs, arms, chest. Adults with chronic sun exposure history.	Skip areas of decreased melanocytes along the dermal–epidermal junction. Marked solar elastosis. SOX-10 (or other melanocyte stain): highlights junctional melanocytes.

Abbreviations: KOH, potassium hydroxide; PAS, periodic acid–Schiff.

in which new lesions of vitiligo appear in areas of trauma. The clinical course of vitiligo is difficult to predict.⁴

What Causes Vitiligo?

The exact cause of vitiligo is unclear but what results is damage to melanocytes and their subsequent disappearance in the affected skin. There are several theories regarding the pathogenesis of vitiligo; the most prominent is an autoimmune condition. Other theories include a neural, self-destructive, and inherent defect—all of which are not mutually exclusive. Vitiligo may in fact represent a group of heterogeneous pathophysiologic disorders with a similar phenotype. Although most cases of vitiligo are sporadic, familial clustering is not uncommon, and human leukocyte antigen (HLA) haplotypes may contribute to vitiligo susceptibility; HLA-A2 has been identified as a high-risk haplotype. In addition, there are numerous candidate genes and genetic loci associated with vitiligo. These genes have been implicated in a number of autoimmune diseases and likely function as a general autoimmune or autoinflammatory susceptibility loci similar to HLA.² Epidemiologic studies indicate that vitiligo is inherited in a non-Mendelian, multifactorial, and polygenic pattern with incomplete penetrance.² Different phenotypes are associated with different genetic susceptibility genes and environmental exposures. Intrinsic defects in melanocytes may initiate disease through innate inflammation, including recruitment of natural killer cells and inflammatory dendritic cells. Cytotoxic CD8⁺ T cells have been shown to be involved in melanocyte destruction.^{3,5} Environmental factors also contribute, including exposure to phenolic compounds found in household products.³

How Is Vitiligo Diagnosed?

Vitiligo is a clinical diagnosis, meaning clinicians can recognize the disease and, by clinical presentation only, make the diagnosis without further testing. Wood’s lamp examination helps to confirm the diagnosis and extent of the disease by delineating lesions on the skin and is often performed in the clinic. Biopsy may also be performed to confirm the diagnosis. Histologic examination will show basal keratinocyte hypopigmentation, mild dermal inflammation, and absent melanocytes.^{6,7}

Are There Systemic Changes in Someone With Vitiligo?

Patients with vitiligo may present with systemic changes including inflammation of the ear and eye. Melanocytes are found in the uveal tract, retinal pigment epithelium, and membranous labyrinth of the inner ear. Therefore, any area with melanocytes may be affected. Patients with vitiligo and their first-degree relatives have an increased prevalence of autoimmune thyroid disease, type 1 diabetes mellitus, pernicious anemia, rheumatoid arthritis, Addison disease, lupus, Guillain-Barre syndrome, and others.² Thyroid disease is the most common condition found in patients with vitiligo.

Teaching Points

1. Vitiligo is an acquired, idiopathic condition favored to be an autoimmune disease characterized by destruction of melanocytes, the pigment producing cells in the skin.
2. Patients with vitiligo present with macules and patches of depigmentation of the skin. The clinical course is difficult to predict.

3. Melanocytes are also found in the eye and ear, and therefore, patients with vitiligo may have inflammation affecting these sites.
4. Vitiligo is associated with other systemic autoimmune diseases, most commonly thyroid disease.
5. Histologically, vitiligo shows loss of melanocytes along the dermal–epidermal junction and lack of melanin pigment in the basilar keratinocytes. Stains can be used to confirm the findings and rule out other causes of clinical depigmentation.
6. The differential diagnosis of vitiligo includes other disorders of hypopigmentation. Differentiation can be made by a combination of clinical findings and histologic features.

Declaration of Conflicting Interests

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