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Cutaneous Clues to Hereditary Hemochromatosis: Refractory Herpes Labialis and Atypical Facial Dermatosis

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Abstract:

Hereditary hemochromatosis (HH) is a genetic iron overload disorder classically associated with hepatic, endocrine, cardiac, and rheumatologic complications. Although cutaneous hyperpigmentation is well recognized, other dermatologic manifestations may serve as early clues to systemic disease. We report a 24-year-old female presenting with recurrent herpes labialis refractory to over-the-counter antiviral therapy, constitutional symptoms, and an atypical unilateral facial eruption composed of erythematous papules and pustules coalescing into crusted plaques. Despite the patient's concern for an underlying immunocompromised state, symptoms were initially attributed to stress. The facial eruption progressed with topical clindamycin use, although resolved following empiric treatment with topical clotrimazole. The coexistence of recurrent herpes simplex virus (HSV) outbreaks and a facial eruption concerning for a fungal process prompted laboratory evaluation, which revealed elevated serum iron and transferrin saturation. Genetic testing subsequently confirmed H63D homozygous hereditary hemochromatosis. Following the discontinuation of oral contraceptive pills, restoration of physiologic menstrual blood loss, and initiation of therapeutic phlebotomy, iron indices normalized. The patient experienced marked symptomatic improvement, substantial reduction in herpes simplex virus recurrence, and complete resolution of the facial eruption. This case highlights the potential role of dermatologic findings as early indicators of systemic iron dysregulation and underscores the importance of maintaining a broad differential diagnosis in patients with persistent or atypical cutaneous presentations.

Keywords:
Hereditary hemochromatosis, herpes simplex virus, iron overload, cutaneous manifestations, immune dysregulation, perioral dermatitis.

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Introduction

Background

Hereditary hemochromatosis (HH) is an inherited autosomal recessive disorder characterized by excess intestinal iron absorption and progressive tissue deposition [1]. Iron accumulation can result in hepatic cirrhosis, hepatocellular carcinoma, diabetes mellitus, cardiomyopathy, and arthropathy, reinforcing the importance of timely diagnosis and intervention [2]. Although these complications are well established, multisystem involvement may result in atypical presentations, complicating clinical recognition [3]. While hyperpigmentation is a well-recognized

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cutaneous manifestation, other dermatologic findings may serve as early diagnostic clues [3].

Case Presentation

A 24-year-old female presented with a two-month history of unintentional weight loss of 15–20 pounds, recurrent herpes labialis outbreaks refractory to over-the-counter antivirals, and an erythematous eruption on the left mandible composed of papules and pustules coalescing into plaques with overlying crusting **(Figure 1)**. Past medical history included a three-year history of migraines with aura and use of a combined oral contraceptive containing norethindrone acetate 1 mg and ethinyl estradiol 10 µg. Family history was initially noncontributory. The patient expressed concerns regarding an immunocompromised state, although her symptoms were attributed to stress associated with graduate school.

She was prescribed valacyclovir 1 g twice daily for one week for herpes labialis with partial symptomatic improvement, followed by valacyclovir 500 mg daily for two to three weeks. Clindamycin 1% gel was prescribed for the facial eruption; however, symptoms progressed. Although her primary provider considered a fungal infection unlikely, the patient initiated over-the-counter clotrimazole 1% cream, resulting in complete resolution within four weeks **(Figure 2)**. Potassium hydroxide preparation and fungal culture were not performed, although the empiric response to topical antifungal therapy was suggestive of a fungal infection.

Due to persistent constitutional symptoms and recurrent HSV, the patient requested laboratory evaluation through her primary provider. Complete blood count demonstrated mild neutropenia (43%) (Ref: 50-70%) and relative lymphocytosis (46.6%) (Ref: 18-42%). Comprehensive metabolic panel (CMP) revealed mildly decreased alkaline phosphatase (43 U/L) (Ref: 45-117). Due to associated fatigue and weight loss, iron studies and vitamin D levels were obtained, revealing an elevated serum iron of 274 µg/dL (Ref: 50-170 µg/dL) and transferrin saturation of 82.3% (Ref: 12-57%), with normal ferritin (55 ng/mL) (Ref: 8-388 ng/mL) and total iron-binding capacity (329 µg/dL) (Ref: 250-450 µg/dL). Vitamin D was mildly decreased at 29.9 ng/mL (Ref: >30 ng/mL). Repeat laboratory testing three weeks later confirmed persistent iron overload, prompting a workup for an underlying etiology and diagnostic evaluation for hereditary hemochromatosis. Genetic testing revealed an H63D homozygous mutation in the *HFE* gene, confirming the diagnosis of hereditary hemochromatosis.

The patient was referred to hematology/oncology, where management included discontinuation of the oral contraceptive to promote physiologic iron loss through menses. Five months later, after experiencing regular menses, laboratory testing revealed a serum iron of 179 µg/dL, transferrin saturation of 59%, and ferritin of 127 ng/mL, with mild transient elevation in ALT (57 U/L). Persistent iron elevation prompted therapeutic phlebotomy of one pint of whole blood. Subsequent labs demonstrated normalization of serum iron (164 µg/dL), transferrin saturation (47%), ferritin (73 ng/mL) and liver enzymes (ALT 18 U/L, AST 20 U/L).

The patient reported marked improvement in systemic and cutaneous symptoms following iron regulation. Migraine frequency decreased from 15–20 episodes per month with aura to 2–4 episodes per month without aura. Several clinical features suggest that oral contraceptives do not independently explain the patient's migraine burden. The patient had tolerated the same continuously administered ultra-low-dose estrogen-containing oral contraceptive (10 µg ethinyl estradiol) for three years before migraine onset. The delayed onset of migraines is inconsistent with a hormonal etiology, which classically occurs within months of therapy initiation [3]. Additionally, continuous formulations containing less than 20 µg ethinyl estradiol have demonstrated reduction in menstrual migraine frequency and aura occurrence [3]. Prior neurology evaluations likewise denied oral contraceptives as a contributing factor due to low dosage. Notably, oral contraceptive therapy was resumed following iron normalization without recurrence of aura or increase in migraine frequency or

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severity. The patient also noted improved cognition, sleep quality, and reduced arthralgias. No recurrence of the facial eruption occurred, and only two to three minor, single-lesion HSV outbreaks developed over the next year, each resolving within 2–3 days of antiviral therapy. Subsequent laboratory and genetic testing in her father revealed iron and ferritin overload and a heterozygous H63D mutation, prompting hematologic referral. Following therapeutic phlebotomy, he reported improvement in cognition, weight loss and reduced fatigue, further supporting the potential clinical impact of iron regulation.

Discussion

This case demonstrates the diagnostic value of dermatologic assessment, as cutaneous findings may precede the recognition of systemic disease [4]. The patient's recurrent herpes simplex virus outbreaks and atypical facial eruption prompted further investigation, ultimately leading to the diagnosis of hereditary hemochromatosis.

Iron overload has been associated with altered immune responses and increased susceptibility to infection, as many pathogens rely on host iron as a critical nutrient [5]. Excess iron has been shown to impair innate immune responses, including the phagocytic and chemotactic functions of neutrophils and macrophages [6]. This immune dysregulation may manifest clinically as vulnerability to atypical cutaneous infections or inflammatory eruptions. In this case, recurrent cutaneous findings occurred in the setting of iron dysregulation, raising the possibility that iron overload contributed to an altered immune state reflected in the skin.

Dermatologic conditions documented in HH extend beyond hyperpigmentation, including atrophic skin, ichthyosis-like scaling, pruritus, koilonychia, alopecia, and erythematous papulonodules [7]. Opportunistic or recurrent infectious dermatoses, as seen in this case, are rarely described but may represent an early clinical clue. Persistent infectious dermatoses may warrant consideration of underlying systemic disease and laboratory evaluation for contributing metabolic sources, such as iron overload.

This case highlights the potential impact of anchoring bias on timely and accurate diagnosis, reinforcing the importance of maintaining a broad and systematic differential. Initial assessments attributed the patient's symptoms to stress, despite persistent constitutional and dermatologic findings suggestive of an underlying physiologic process. Dermatologists are often uniquely positioned to evaluate unexplained cutaneous presentations, playing a pivotal role in the recognition and intervention of systemic disease. In patients with persistent, recurrent, or atypical cutaneous findings, laboratory evaluation, including iron studies, may facilitate the earlier diagnosis and intervention of underlying systemic conditions such as hereditary hemochromatosis.

Take-Home Messages

I. Hereditary hemochromatosis may present with atypical dermatologic findings prior to the recognition of systemic disease.
II. Recurrent or treatment-refractory cutaneous infections should prompt consideration of underlying metabolic or immunologic dysfunction.
III. Iron overload may contribute to immune dysregulation and susceptibility to infectious dermatoses.
IV. Anchoring bias may delay diagnosis in patients with persistent constitutional and dermatologic symptoms.
V. Dermatologists play an important role in identifying cutaneous manifestations of systemic disease.

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Figure Legends

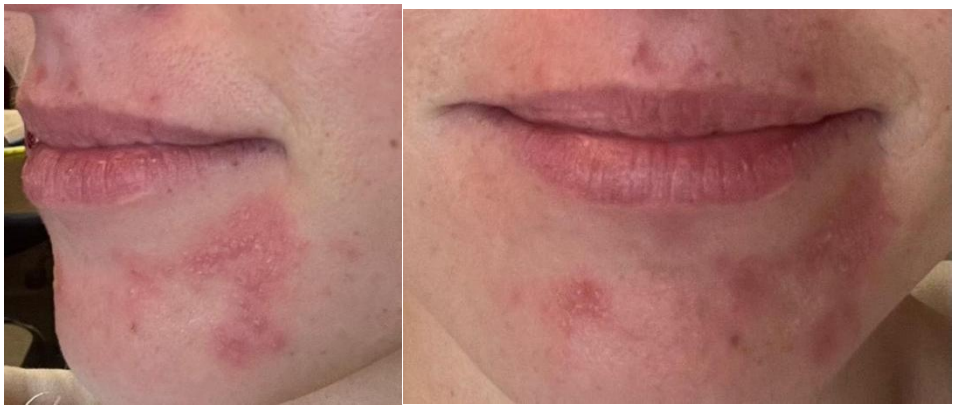

Figure 1. (A) Initial perioral and left mandibular lesion of erythematous papules and pustules coalescing into a plaque with overlying scale. (B) Frontal view demonstrating similar morphology and distribution.

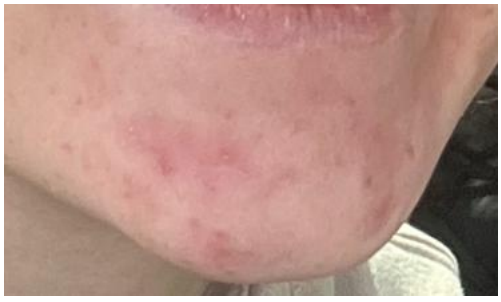

Figure 2. Resolution of the perioral and left mandibular eruption following four weeks of empiric treatment with over-the-counter clotrimazole 1% cream.