Mucocutaneous Granulomatous Disease in a Patient With Hermansky-Pudlak Syndrome

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An albino woman in her mid-40s with a 30-year history of Crohn disease (CD) was referred for evaluation and treatment of recurrent, exquisitely tender, persistent ulcerations involving the vulvar, perianal, inguinal, and left axillary skin. She noted that her ulcers had partially responded to prednisone, infliximab, and azathioprine administered for her CD several years ago. Her gastrointestinal CD was quiescent, but she continued to have skin manifestations that had been diagnosed as hidradenitis suppurativa. On multiple occasions, exudate cultures from the ulcers grew mixed flora. She had been treated with long-term antibiotics, including cephalaxin monohydrate, trimethoprim-sulfamethoxazole, doxycycline hyclate, metronidazole hydrochloride, and rifampin without improvement. A left axillary ulcer had been excised 1 year prior, but it recurred soon after surgery.

In addition to CD, the patient’s medical history included oculocutaneous albinism with horizontal nystagmus, episcleritis, emphysema, and interstitial lung disease. Her surgical history included a proctocolectomy and end-ileostomy and perianal fistula repair for CD. She had required a blood transfusion following her gastrointestinal surgery but had had no other problems with excessive bleeding.

Her family history was significant for 2 sisters with albinism; her only child, a son, does not have albinism. There was no family history of gastrointestinal diseases.

Physical examination revealed an afebrile and mildly dyspneic woman with pale skin, white hair, light blue eyes, and horizontal nystagmus (Figure 1). Examination of her groin revealed well-demarcated, deep, tender, linear, inguinal and vulvar ulcers with surrounding erythematous, indurated, pink plaques and scaly patches extending to the medial thighs (Figure 2A). The vulva was diffusely swollen, and indurated firm nodules were present on the labia majora and labia minora. Erythematous indurated plaques with central ulceration extended along the bilateral gluteal folds. Examination of her left axilla revealed a deep, crusted ulcer overlying a surgical scar. All ulcers exuded serosanguineous or thick yellow discharge. There were no sinus tracts, comedones, or fistulas in any of the affected sites.

Biopsy samples from the vulvar ulcer and axilla demonstrated deep dermal and subcutaneous lymphoplasmacytic infiltrates with noncaseating granulomas including numerous multinucleated giant cells (Figure 3). Tissue cultures from the vulvar ulcers were negative for atypical mycobacteria and fungi. Mixed flora were cultured from ulcer exudate, including Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa. Tuberculin skin test and serologic analysis for lymphogranuloma
loma venereum had negative results. Routine laboratory studies, including complete blood cell count with differential and a comprehensive metabolic panel, had unremarkable results.

Because of her constellation of cutaneous and systemic findings, the patient was evaluated for Hermansky-Pudlak syndrome (HPS). Electron microscopic examination of her platelets revealed an absence of dense bodies, a finding considered pathognomonic for HPS. Genetic testing identified a homozygous mutation of the HPS1 gene (c.1189 del C), thus confirming the diagnosis of HPS.

The patient was treated with prednisone, azathioprine, and nabumetone and initially experienced improvement of pain and swelling in the vulvar area, although the ulcers remained unchanged in size. Several months later, however, she developed increased vulvar pain and edema. A combined medical and surgical approach was commenced, including infliximab infusions at a dose of 10 mg/kg monthly, prednisone 30 mg daily, and surgical debridement of granulation tissue in the vulvar ulcers followed by the use of a negative-pressure wound therapy system. No bleeding complications arose as a result of the surgical debridement. She continued to improve 12 months after starting this regimen, with nearly complete healing of the vulvar ulcers, pain relief, and reduction in edema and erythema (Figure 2B). The prednisone dosage was decreased to 10 mg daily, and she continues to receive infliximab 10 mg/kg infusions every 4 weeks; attempts to reduce the dosages of these medications have been unsuccessful because of cutaneous disease flares.

Discussion

Hermansky-Pudlak syndrome is a rare autosomal-recessive genodermatosis. All patients have oculocutaneous albinism and
Granulomas and Hermansky-Pudlak Syndrome

Case Report/Case Series

Researcm

lial cells. To date, 8 HPS genes have been identified; these
mutations in genes that encode proteins involved in the biogen-
esis and function of intracellular organelles found in
melanocytes, platelets, T cells, neutrophils, and lung epithe-

dotic lysosome-related organelles complexes. Def-

its in these distinct genes result in 1 of 8 subtypes of HPS2
(Table). An inability to form melanosomes in melanocytes and
dense bodies in platelets causes the oculocutaneous albi-

ation, which on biopsy showed nonnecrotizing granulomas.1 An

these 2 cases support the possibility of metastatic cutaneous involvement of granulo-
matous colitis in HPS. Herein we review the features of cutane-
ous CD and HPS, genetically distinct diseases that share a
common granulomatous inflammatory reaction pattern.

Hermansky-Pudlak syndrome (OMIM 203300) is a rare, au-
tosomally recessive, multisystem disorder resulting from mu-
tations in genes that encode proteins involved in the biogen-
esis and function of intracellular organelles found in
melanocytes, platelets, T cells, neutrophils, and lung epithe-

dation, or transport of lysosomes appear to be central to the
pathogenesis.

Patients with mutations in the HPS1 gene tend to have
more severe disease and a greater likelihood of pulmonary
fibrosis and granulomatous colitis.3 A granulomatous reaction
to intracellular ceroid lipofuscin, a compound believed to be
derived from lipid peroxidation of polyunsaturated
lipids of subcellular membranes in the lungs and gastroin-
testinal tract of patients with HPS, may lead to the pulmo-
nary and gastrointestinal manifestations of HPS.3 Patients
with HPS may be unable to eliminate this compound as a
result of the aberrant genesis or function of lysosomes.3 On
histopathological examination, however, granulomas are
not always formed in proximity to ceroid deposits.3 In some
cases, however, no ceroid deposits are observed,4 and the
clinical and histopathologic features of the enterocolitis of
HPS can be identical to those of CD. This has prompted
speculation that there may be a genetic linkage between
HPS and CD.3

The pulmonary fibrosis and the enterocolitis associated
with HPS are often recalcitrant to medical therapy. Several
recent reports have documented successful treatment of
some patients with agents used to treat intestinal CD includ-
including the tumor necrosis factor inhibitor infliximab.4

Table. Features of Hermansky-Pudlak Syndrome (HPS) Subtypes

<table>
<thead>
<tr>
<th>HPS Subtype</th>
<th>Gene</th>
<th>Protein</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPS1</td>
<td>HPS1</td>
<td>BLOC-3</td>
<td>Restrictive lung disease, granulomatous colitis</td>
</tr>
<tr>
<td>HPS2</td>
<td>AP3B1</td>
<td>APC-3</td>
<td>Neutropenia, recurrent infections</td>
</tr>
<tr>
<td>HPS3</td>
<td>HPS3</td>
<td>BLOC-2</td>
<td>Mild hypopigmentation, no lung or GI disease</td>
</tr>
<tr>
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<td>HPS4</td>
<td>BLOC-3</td>
<td>Restrictive lung disease, granulomatous colitis</td>
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<td>HPS5</td>
<td>BLOC-2</td>
<td>Mild hypopigmentation, no lung or GI disease</td>
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<td>HPS8</td>
<td>BLOC1S3</td>
<td>BLOC-1</td>
<td>Mild hypopigmentation, no lung or GI disease</td>
</tr>
</tbody>
</table>

Abbreviations: APC, adaptor protein complex; BLOC, biogenesis of lysosome-related organelles complex; GI, gastrointestinal.

Albinism and bleeding diathesis are common to all subtypes.

Figure 3. Cutaneous Granulomatous Inflammation From the Vulva

A, Histopathologic evaluation of stained sections of vulvar (shown) and axillary (not shown) biopsy samples revealed deep dermal and subcutaneous granulomatous inflammation (hematoxylin-eosin [H&E], original magnification ×100). B, High-power magnification of the lymphoplasmacytic infiltrate with noncaseating granulomas including numerous multilabeled giant cells (H&E, original magnification, ×400).
Crohn disease is a multisystem granulomatous inflammatory disease that typically begins in the gastrointestinal tract. The disease may involve any portion of the gastrointestinal tract. Dermatologic findings are the most common extraintestinal manifestations of intestinal CD, occurring in 10% to 75% of patients.5-7 Other extraintestinal manifestations of CD include inflammatory arthropathies, hepatobiliary disease, ocular disease (episcleritis, scleritis, and uveitis), osteoporosis, anemia, nephrolithiasis, urinary tract fistulas, and renal amyloidosis.8

The cutaneous manifestations of CD can be generally classified into nutritional deficiency-associated dermatoses (acrodermatitis enteropathica and pellagra resulting from zinc and niacin deficiency, respectively, among patients with CD), reactive dermatoses (pyoderma gangrenosum, erythema nodosum, palmar plantar pustulosis, Sweet syndrome, oral aphthae, epidermolysis bullosa acquisita, necrotic or granulomatous vasculitis, hidradenitis suppurativa, finger clubbing, palmar erythema, pyoderma faciale, and pathergy reactions9), and cutaneous granulomatous disease.

Cutaneous granulomatous disease is the most common cutaneous manifestation of CD. It may be contiguous or noncontiguous with the gastrointestinal tract. Contiguous disease affects 36% to 80% of patients with CD and is the most common form of all CD-related skin diseases.2 Noncontiguous or “metastatic” granulomatous disease, conversely, is the rarest skin manifestation of CD and is defined as the presence of nonseating granulomas arising in the skin at a site distant to and separate from the intestine.5 Patients with granulomatous skin disease are more likely to have extensive gastrointestinal disease.5

Clinical features of metastatic cutaneous CD vary by patient age and anatomic site. The genital skin is the most common site of metastatic cutaneous CD in both adults (59%) and children (75%).5 In children, genital swelling with or without erythema is the most common presentation, but ulceration is uncommon.5 In contrast, adult metastatic cutaneous CD is ulcerative in the majority of cases.5 Deep “knife-like,” linear ulcerations are characteristic, and these preferentially affect the vulva and intertriginous areas. Vegetative, papillomatous nodules mimicking condyloma have been described.6,9 Genital infiltration and edema with or without erythema have also been reported in adults.5-9 Nongenital metastatic CD more commonly presents with erythematous or violaceous nodules and plaques.10 Up to 20% of adults and 86% of children present with cutaneous disease prior to the diagnosis of intestinal disease, which makes diagnosis more challenging.11,12

Emanuel and Phelps13 recently reviewed the histopathologic characteristics of 12 cases of metastatic cutaneous CD. All cases were characterized by a superficial and/or deep granulomatous dermatitis. Granulomas consisting of epithelioid histiocytes were present in 8 cases. Granulomas with Langhans-type giant cells were also common. Five of 12 cases showed ulceration. Granulomatous vasculitis was present in 2 cases, and in 2 others, massive papillary dermal edema was noted.

The clinical differential diagnosis of metastatic cutaneous CD may include infectious etiologies such as cellulitis, erysipelas, tuberculosis, deep fungal infection, tertiary syphilis, filariasis, actinomycosis, schistosomiasis, leishmaniasis, lymphogranuloma venereum, granuloma inguinale, and chronic herpes simplex virus infection. Appropriate cultures and serologic studies should be used to exclude infectious etiologies. Metastatic cutaneous CD may also be mistaken for dermatitis, foreign-body reactions, intertrigo, Behçet disease, Wegener granulomatosis, lichenoid eruptions, hidradenitis suppurativa, pyoderma gangrenosum, or sarcoidosis. Hidradenitis suppurativa can be ruled out clinically by the absence of interconnecting sinuses and comedones. Deep, linear ulcerations in flexural skin and vegetative papillomatous nodules in the vulva are characteristic findings of genital metastatic cutaneous CD.

The pathogenesis of metastatic cutaneous CD is unclear, but it has been postulated that T lymphocytes react with unknown antigens in the skin and lead to the granulomatous infiltrates of metastatic cutaneous CD.6,8,14 Metastatic cutaneous CD, particularly genital disease, often responds poorly to treatment. There are no randomized, controlled studies of therapy for this entity. Antibiotics, immunosuppressive medications, and anti-inflammatory agents have been used with limited success.

Conclusions

Our patient’s history of albinism, pulmonary fibrosis, and colitis were suggestive of HPS, which was then confirmed ultrastructurally and genetically. Her gastrointestinal biopsies revealed the histopathologic features typical of both metastatic CD and HPS. It is unclear whether the cutaneous findings in this case are manifestations of CD or, in fact, sequelae of HPS. Cutaneous granulomatous disease has been reported in only 1 other patient with HPS; this is likely due to the rarity of HPS in general. Clinicians should be aware of the possibility of skin manifestations in patients with HPS. Further observation of patients with this rare disease is required to determine whether such cutaneous findings are due to HPS or whether skin lesions originate from a separate disease process, such as CD, that may be in some way genetically linked with HPS.
Langer Lines

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The orientation of surgical incisions over the skin is widely considered to affect scarring and the final cosmetic outcome for patients. When most surgeons visualize lines on the skin surface to guide such incisions, it is Langer lines (also known as skin cleavage or tension lines) that most readily come to mind. Karl Langer (1819-1887), the man behind the famous lines, was born in Vienna, Austria, where he spent most of his life and later became professor of anatomy at Joseph’s Academy. 1 In 1861, Langer began publishing a series of 5 articles detailing his seminal work on the physical and mechanical properties of the skin. 2 In the first of these articles, Langer credited Dupuytren and Malgaigne for their earlier observations. In 1834, Dupuytren reported seeing a young man who had attempted to commit suicide by stabbing himself over the heart 3 times. The patient claimed to have used a round awl as the instrument, but he did not fashion round stab wounds on his chest. This led Dupuytren to study the matter in cadavers and documenting in the directions in which the resulting wounds narrowed and broadened, if at all. 2,3 By way of these incredibly meticulous efforts, Langer was able to draw his famous lines. Unfortunately, Langer’s work was largely unappreciated and ignored during his lifetime. 2 In fact, because his original publications were written in the classical scientific German of his era, with hints of his local Austrian dialect, it was not until 1978 that a translation of his work was made available to the English-speaking world. 1

Today, elective surgical incisions may not follow Langer lines in all body areas, and other guides, such as relaxed skin tension lines running perpendicular to the direction of muscle contraction, may serve patients better. However, the concept of skin tension lines has helped improve the practice of surgery and forensic medicine, and Langer’s work has been instrumental in our understanding of the many fascinating properties of the skin.

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