The dermatologic and histologic spectrum of hypereosinophilic syndrome

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INTRODUCTION

Hypereosinophilic syndrome (HES) is characterized by persistent eosinophilia in the blood or peripheral tissues, organ damage and/or dysfunction attributable to tissue hypereosinophilia, and exclusion of other disorders or conditions as the major reason for organ damage. The cutaneous and histologic manifestations of HES are variable and include psoriasiform dermatitis, urticaria, angioedema, atopic dermatitis, and erythroderma.[1] Here, we report 2 cases of HES that presented with variable skin and biopsy findings.

Abbreviation used:

HES: hypereosinophilic syndrome

CASE DESCRIPTION

Patient 1

A 67-year-old man presented with a 2-month history of diffuse, itchy rash involving the scalp, face, arms, and trunk (Fig 1, *A*), characterized by widespread pink-to-brown, small, round-to-oval, thin papules with overlying scale (Fig 1, *A*). A biopsy showed regular psoriasiform acanthosis, with areas of compact hyperkeratosis, parakeratosis, and focal collections of neutrophils in the stratum corneum (Fig 2, *A* and *B*). The dermis showed a perivascular lymphocytic inflammatory infiltrate (Fig 2, *C*). Thought to be partially treated psoriasis or pityriasis rubra pilaris, the patient began risankizumab; however, the rash was unresponsive. Two months later, the patient was incidentally found to have an absolute eosinophil count of 2.51×10^9/L, which increased to 4.47×10^9/L 1 month later.

The symptomatology was solely lymphadenopathy based on a CT scan, eosinophilia, and the rash with no gastrointestinal or cardiac symptoms. A bone marrow biopsy revealed hypercellularity, with 20% to 30% eosinophils. Plasma cells were increased at 5% to 6%, with no increase in blasts or mast cells. Peripheral T-cell gene rearrangement studies showed a clonal T-cell population. No mutations in *PDGFR-α/β*, *FGFR1*, or *BCR-ABL1* were detected using fluorescence in situ hybridization. Next-generation sequencing found a DNMT3A W313 variant of indeterminate potential. No abnormalities in *FLT3*, *IDH1*, *IDH2*, or *NPM1* were detected. This was consistent with the diagnosis of HES. Mepolizumab was the desired treatment; however, because of difficulty receiving injections, the patient began prednisone at 60 mg with a prolonged taper and hydroxyurea at 500 mg once daily, which improved his cutaneous findings.

Patient 2

A 56-year-old man presented to the hospital with severe diarrhea, acute kidney injury, an absolute eosinophil count of 10.42×10^9/L, and a 3-week history of a rash. The rash consisted of multiple ill-defined, round, pink patches with overlying rough scale spreading from the abdomen to extremities (Fig 1, *B* and *C*).

A skin biopsy showed irregular acanthosis, spongiosis, overlying serous crust (Fig 3, *A* to *C*), and a perivascular mixed inflammatory infiltrate with few scattered eosinophils (Fig 3, *D*).

Test results were negative for strongyloidiasis, trichomoniasis, stool ova and parasites, stool enteric pathogens, filarial parasites, norovirus, and aspergillus. Colonoscopy showed pandiverticulosis,

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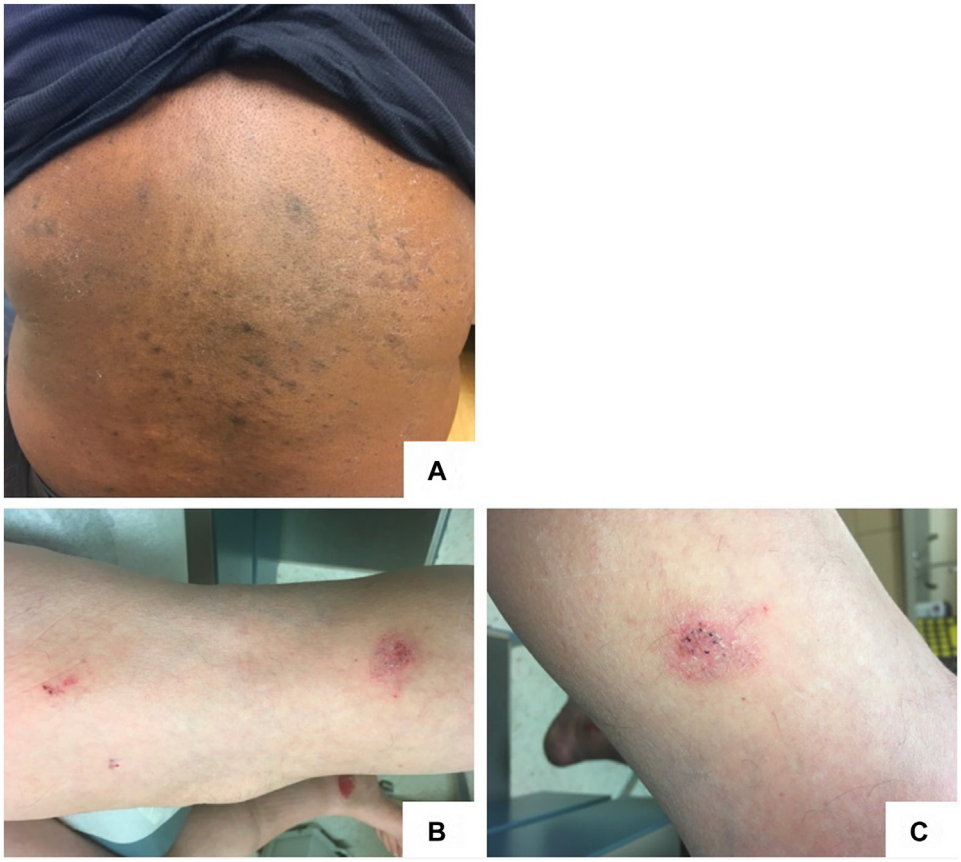

Fig 1. Cutaneous findings of hypereosinophilic syndrome. **A,** Patient 1 presented with widespread pink-to-brown, small, round-to-oval, thin papules with overlying scale. (**B, C**) Patient 2 presented with multiple ill-defined, round, pink patches with overlying rough scale.

with an eosinophilic infiltrate and chronic inflammation. A bone marrow biopsy was normocellular, with increased eosinophils (15%) and no mast cells or blasts. No mutations in *PDGFR-α/β*, *FGFR1*, or *BCR-ABL1* were detected using fluorescence in situ hybridization. A 54-gene myeloid panel was negative. This was consistent with the diagnosis of HES.

The patient recovered from the acute kidney injury; however, the rash and diarrhea persisted. Idiopathic retroperitoneal fibrosis developed in the patient, with a new diagnosis of asthma, diagnosed using pulmonary function testing. The desired medication, mepolizumab, was denied by insurance. Dupilumab was discussed because of persistent respiratory symptoms but was decided against because retroperitoneal fibrosis was the primary concern. A prolonged prednisone taper starting at 60 mg daily and rituximab infusions for concomitate retroperitoneal fibrosis improved the skin findings and diarrhea.

DISCUSSION

HES is a multisystem disease characterized by overproduction of eosinophils, resulting in eosinophil-mediated end-organ damage. It is subdivided by pathophysiology into neoplastic (primary HES), reactive (secondary HES), and idiopathic processes. HES is rare, and although its true prevalence is unknown, 1 study estimated it to be between 0.36 to 6.3 per 100,000.[2] Its clinical manifestations range from asymptomatic eosinophilia to end-organ failure. It occurs in adults aged 20 to 50 years and involves the lungs, skin, gastrointestinal tract, heart, and/or nervous system.[3,4] Its dermatologic manifestations are greatest at 37%, followed by pulmonary (25%), gastrointestinal (14%), and cardiac (5%).[4] Another study estimated dermatologic involvement in 69% of patients.[5] The dermatologic manifestations include eczema, erythroderma, lichenification, urticaria, mucosal ulcers, and lymphomatoid papulosis—like lesions.[1]

HES is classified into variants, including myeloproliferative HES, T-lymphocytic HES, familial HES, and organ-restricted HES. Myeloproliferative HES displays the features of myeloproliferative disorders, including increased serum vitamin B12,

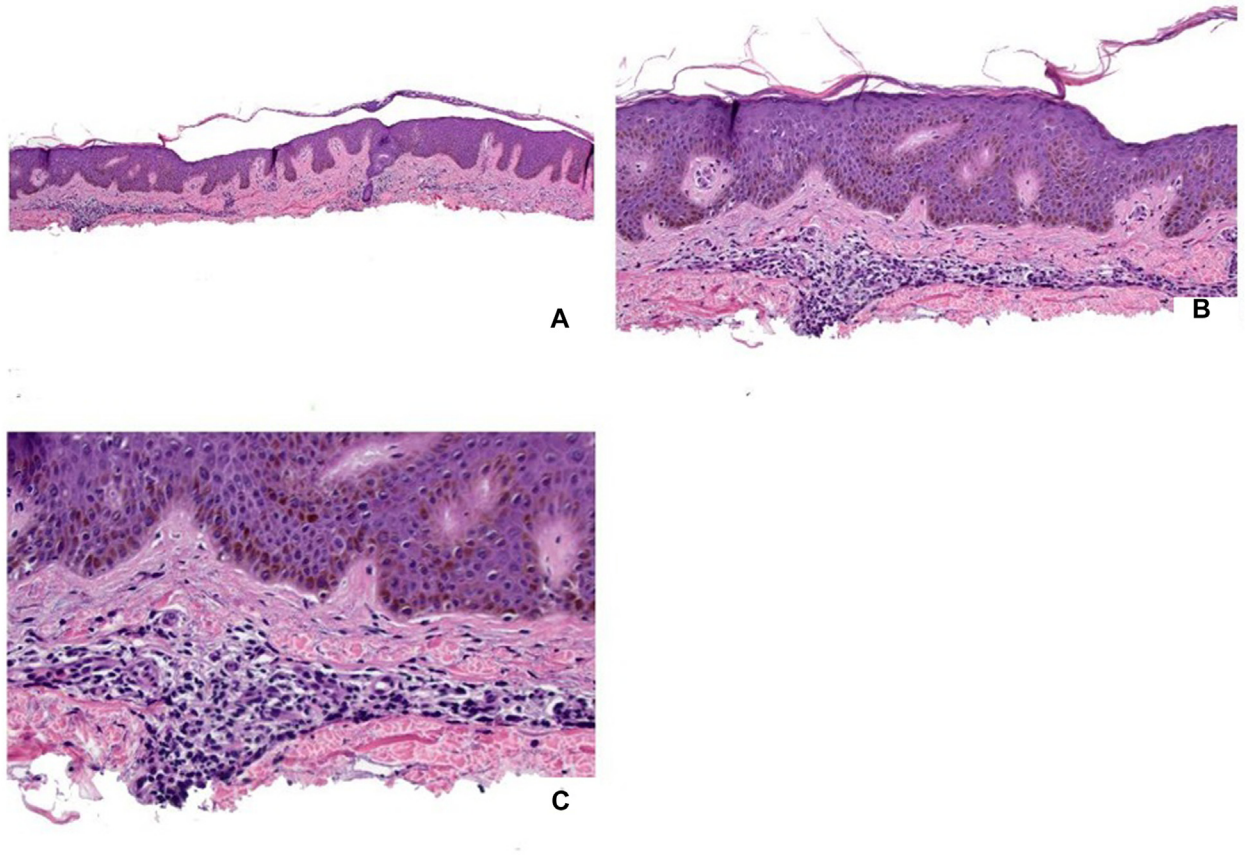

Fig 2. Histologic findings of hypereosinophilic syndrome in patient 1. (**A, B**) The sections show regular acanthosis, with focal areas of compact hyperkeratosis with parakeratosis and focal collections of neutrophils in the stratum corneum. (**A** and **B,** Hematoxylin-eosin stain; original magnifications: **A,** ×2; **B,** ×10.) **C,** Within the dermis, there is a perivascular lymphocytic inflammatory infiltrate (Hematoxylin-eosin stain; original magnification: ×10.)

anemia, thrombocytopenia, and hepatosplenomegaly.[6] T-lymphocytic HES includes clonal and reactive processes, with expansion of cytokine-producing, immunophenotypically aberrant T-cell populations.[5] It is characterized by skin and soft-tissue involvement; however, cardiovascular, pulmonary, and rheumatologic involvement can also occur. Familial HES involves autosomal dominant transmission of eosinophilia by chromosome 5q31-33 gene. Organ-restricted HES is characterized by single-organ damage, with blood eosinophilia of $\geq 1500/\mu L$.[6]

The role of skin biopsy in HES is largely unknown. In a study of 56 patients with HES, the histologic pattern and eosinophil counts varied. The common findings were epidermal thickening (30%), intraepidermal eosinophilia/neutrophilia (22%), karyorrhexis (17%), acanthosis (22%), and hyperkeratosis (13%).[7] Furthermore, 43% of biopsies showed >10 eosinophils per high-power field, and 26% of biopsies had 0 to 1 eosinophils per high-power field.[7] Skin specimens in a more recent study showed a spongiotic pattern (31%), with abundant inflammation (50%), including eosinophils (85%).[8]

The diagnosis of HES is made based on the presence of hypereosinophilia with end-organ damage. Hypereosinophilia is characterized by an absolute eosinophil count of $>1.5 \times 10^9/L$ in peripheral blood, eosinophils exceeding 20% of nucleated cells in the bone marrow, or extensive deposition of eosinophils in peripheral tissue. Initial workup should include thorough history, physical examination, and blood work to evaluate for organ involvement and exclude conditions that cause eosinophilia, including infection, asthma, malignancy, atopy, rheumatologic conditions, and medications.

If diagnosis of HES is suspected, evaluation of the heart, lungs, and hematologic system, such as peripheral blood T-lymphocyte phenotyping using flow cytometry and T-cell receptor rearrangement studies, should be performed. Bone marrow should

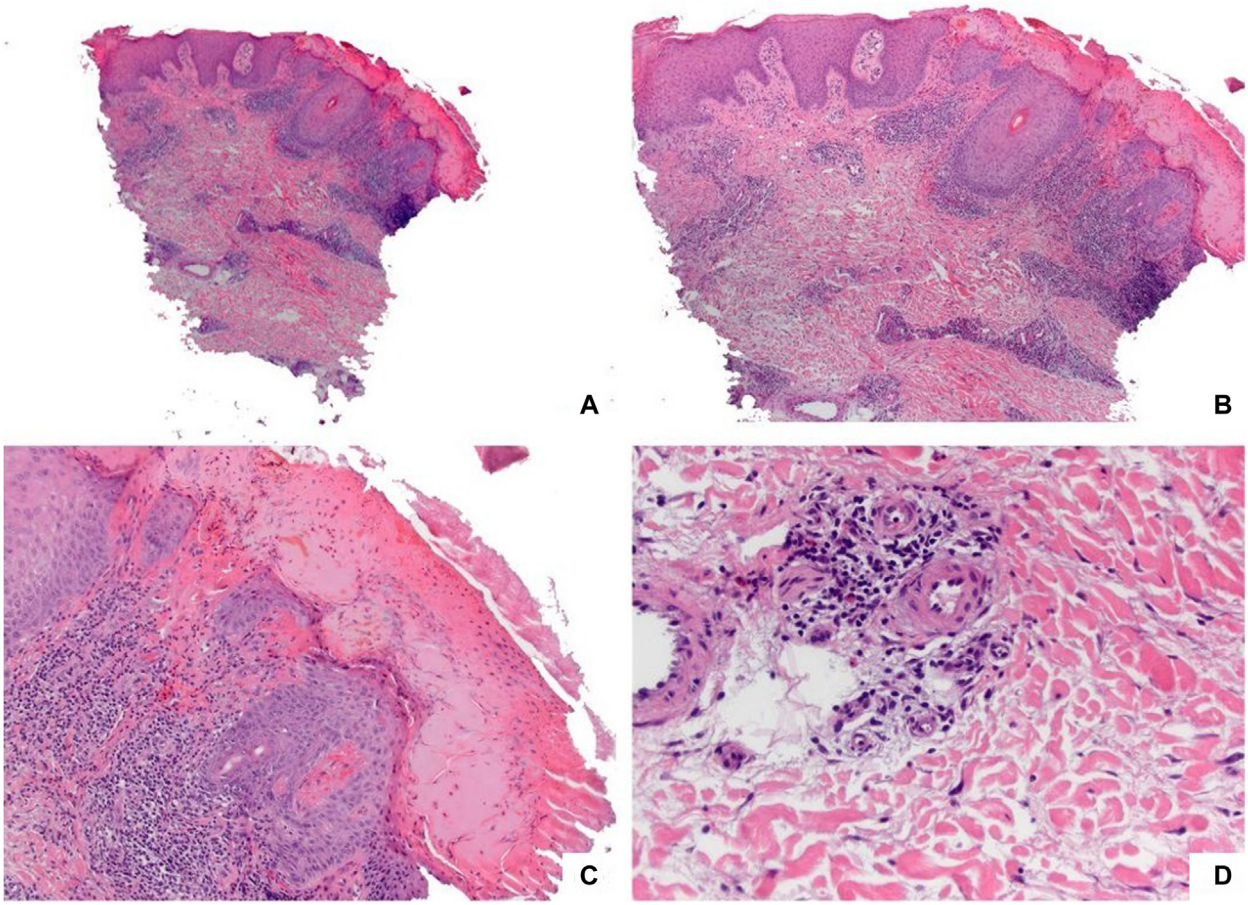

Fig 3. Histologic findings of hypereosinophilic syndrome in patient 2. There is irregular psoriasiform acanthosis, with spongiosis and overlying serous crust (**A** to **C,** Hematoxylin-eosin stain; original magnifications: **A,** ×2; **B,** ×4; **C,** ×10.) **D,** Within the dermis, there is a moderate perivascular mixed inflammatory infiltrate with few scattered eosinophils (Hematoxylin-eosin stain; original magnification: ×20.)

be assessed for cellularity, dysplasia, CD34 expression, reticulin fibrosis, mast cells, and karyotype. Molecular studies for *FGFR1*, *PDGFRA*, and *PDGFRB* fusion genes—*BCR-ABL1*, *JAK2 V617F*, *KIT*, *D816V*—and clonal T-cell receptor rearrangements can be performed.[9]

Treatment is not based on skin findings. Prednisone is the treatment of choice aside from *FIP1L1-PDGFRA*, a fusion disease that is responsive to imatinib.[9] Mepolizumab or hydroxyurea can be added if additional therapy is required. Prognosis is variable and dependent on the clinical variant.

Conflicts of interest

None disclosed.

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