Acute Onset of Acrokeratosis Paraneoplastica (Bazex Syndrome)

Acrokeratosis paraneoplastica, or Bazex syndrome, is a well-characterized but rare dermatosis first described by Bazex et al in 1965 in association with a malignant neoplasm of the upper aerodigestive tract. It is typically seen in men older than 40 years.²⁻⁵

Report of a Case | A 57-year-old man sought medical attention for dysphagia, chest pain, and a 40-lb weight loss over 6 months. Imaging demonstrated a distal esophageal ulcerating mass covering 50% to 75% of the esophageal circumference. Biopsy showed a poorly differentiated epithelioid malignant neoplasm; immunohistochemical staining was negative for pan-cytokeratins, melanoma, and mesenchymal markers.

On physical examination, the patient had desquamative, edematous digits of the hands and feet with hyperpigmented, lichenified plaques. He had numerous grouped and clustered tense vesicles (1-3 mm) and a few hemorrhagic bullae (Figure 1). He also had an ill-defined hyperkeratotic, violaceous patch on his nose and small vesicles on the ears. His knees exhibited hyperpigmented hyperkeratotic plaques. The patient reported that his cutaneous manifestations developed in less than a week.

Biopsy specimens from the wrist showed an acanthotic and mildly spongiotic epidermis with minimal interface, vacuolar damage, and overlying parakeratosis (Figure 2). In the dermis, there was an increased number of eosinophils and pigment incontinence. Direct immunofluorescence demonstrated broad-based band staining of fibrin at the basement membrane zone and granular deposits of C3.

Skin-directed therapies included a brief course of oral prednisone, clobetasol ointment, and aluminum acetate soaks, with mild improvement in discomfort and appearance of the skin lesions. Systemic chemotherapy was initiated to treat the metastatic, poorly differentiated epithelioid malignant condition. The patient also received palliative radiation therapy to the esophagus and salvage systemic therapy, but he died after 4 months.

Discussion | Acrokeratosis paraneoplastica is a rare paraneoplastic phenomenon with characteristic findings, though its
pathogenesis and relationship to the associated malignant condition are not well understood. Theories include tumor antigens cross-reacting with antigens of the skin BMZ, a cellular immune response with cytotoxic effects, tumor growth factors inducing hyperkeratosis (transforming growth factor α, epidermal growth factor, or insulin-like growth factor 1), or zinc and vitamin A deficiency from tumor expansion. 5,6

The eruption is generally symmetric and nonpruritic, with violaceous to pink patches and plaques with hyperkeratosis of acral sites. 3,5 The extremities and trunk can be involved. 3,6 The palms and soles may have hyperkeratosis and fissures, as in keratoderma. 5 Nail changes are frequently seen, including onycholysis and subungual debris. 4 Edema of the distal extremities and vesicular formation is infrequently seen. 3,5,7

The cutaneous manifestations present, on average, 11 months prior to the discovery of cancer, but in 20% of the cases, the malignant neoplasm is diagnosed at the time of the skin eruption. 3,6 Squamous cell carcinoma is the most commonly associated malignant condition. 5 Other cancers include poorly differentiated carcinoma, adenocarcinoma, small cell carcinoma, lymphoma, and cholangiocarcinoma. The majority of associated malignant neoplasms occur above the diaphragm and involve the upper one-third of the aerodigestive tract.

Bazex syndrome may resemble more common diseases such as psoriasis. Therefore, a biopsy is generally helpful, though the findings are typically nonspecific. Common reported findings include hyperkeratosis, acanthosis, parakeratosis, dyskeratotic keratinocytes, and perivascular infiltrates. 4,5 Immunofluorescence has been performed in a minority of cases, and its results are generally nonspecific. 5 Our patient’s clinical findings were concerning for a blistering disease, but neither hematoxylin-eosin nor direct immunofluorescence evaluation showed evidence of bullous pemphigoid or paraneoplastic pemphigus.

Symptomatic improvement can be achieved by treating the underlying malignant condition; return of skin lesions can signal tumor recurrence. 3 While skin-directed therapy might be helpful to control symptoms, the responses are variable and suboptimal.

In summary, we present herein a case of acrokeratosis paraneoplastica with rapid onset of cutaneous findings and the development of many vesicles and bullae. Furthermore, we demonstrate the diagnostic role of biopsy and immunofluorescence testing in this patient.

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Erythrokeratomia Paraneoplastica

Erythrokeratomia paraneoplastica (EBA) is a rare acquired subepidermal blistering autoimmune disease of the skin and mucosa associated with autoantibodies directed against type VII collagen, the major component of the anchoring fibrils of the dermal-epidermal junction. 1,2 Various clinical presentations of EBA have been described, including a noninflammatory mecha-nobullous form, an inflammatory bullous pemphigoid (BP)-like form, and a mucous-membrane pemphigoid-like form. These forms may show clinical overlap, and their courses are often unpredictable. 1,3

Report of a Case | A 60-year-old man was admitted for evaluation of a 3-week history of widespread pruritic cutaneous lesions. The patient had taken no drugs, and his medical history was unref-
On examination, almost his entire trunk, buttocks, and thighs were erythematous and infiltrated with papular and urticarial lesions (Figure 1). Islands of normal-appearing skin were observed. On his soles and palms, isolated lesions with a target-like appearance were noted. The head as well as the oral and genital mucous membranes were spared. During hospital admission, the patient developed isolated vesicles and serous blisters on erythematous skin on his wrist and ankle.

Light microscopy studies of a skin biopsy specimen obtained from patient’s back showed a diffuse spongiosis with a mixed perivascular inflammatory infiltrate consisting of eosinophils and neutrophils in the upper dermis (Figure 2). Direct immunofluorescence microscopy studies disclosed linear deposits of IgG and C3 along the epidermal basement membrane zone. By indirect immunofluorescence microscopy using sodium chloride-separated normal human skin, circulating IgG autoantibodies binding the dermal side of the split were detected.

Immunoblotting analysis using human dermal extracts showed a reactivity with a 290-kDa protein showing the same electrophoretic migration to the protein band recognized by the control monoclonal antibody directed against type VII collagen.

Based on the clinical features and immunopathological findings, the diagnosis of EBA was made. The patient was given oral prednisolone, 0.75 mg/kg of body weight, which resulted in rapid clearance of the lesions within 2 weeks. Corticosteroid doses were subsequently slowly tapered. At a dose of 10 mg/d, the patient experienced a relapse and began treatment with methotrexate, 15 mg subcutaneously once weekly. The prednisolone dose was then tapered to 2.5 mg/d, and the patient remained asymptomatic at 6-month follow-up.

Discussion | The clinical features of EBA are protean. The classic presentation is that of a noninflammatory mechanobullous disease characterized by the development of acral blisters that heal with atrophic scarring, milia, and hyperpigmentation or hypopigmentation. They are localized to trauma-prone surfaces such as elbows, knees, hands, and feet. Acral involvement may be mutilating. Scalp involvement occurs in up to 20% of patients. The inflammatory BP-like presentation is associated with widespread vesicles and bullae involving intertriginous and flexural areas that heal without atrophic scarring. Epidermolysis bullosa acquisita may also present as mucous membrane pemphigoid or as Brunsting-Perry pemphigoid phenotype. The potential causes of erythroderma include psoriasis, atopic dermatitis, drug reactions, and cutaneous T-cell lymphoma. With the exception of pemphigus foliaceus, the other autoimmune bullous diseases of the skin have been only anecdotally implicated as cause of erythroderma. Specifically, single cases of erythrodermic BP have been described, but our patient showed no evidence of any of these.
Our case was striking because the patient initially showed features suggestive of either a severe drug reaction or a paraviral eruption, but immunopathological studies were diagnostic for EBA. Our observation provides a further example about the polymorphous and misleading presentations of EBA. Hence, EBA should be considered as a rare cause of erythroderma.

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