

Pemphigus Erythematosus Associated With Anti-DNA Antibodies and Multiple Anti-ENA Antibodies: A Case Report

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Pemphigus erythematosus (PE) is an autoimmune blistering disease combining features of pemphigus foliaceus (PF) and systemic lupus erythematosus (SLE). We report a case of PE associated with anti-double-stranded DNA (anti-dsDNA), anti-Smith (anti-Sm), anti-Ro (anti-SSA), and antiribonucleoprotein (anti-RNP) antibodies. This case required extensive immunosuppressive therapy. We treated our patient with a combination of systemic steroids, intramuscular gold injections, azathioprine, and hydroxychloroquine. The patient's response was complete remission—evaluated clinically, serologically, and immunohistochemically.

Pemphigus erythematosus (PE) is an autoimmune blistering disease combining features of pemphigus foliaceus (PF) and systemic lupus erythematosus (SLE). The most common manifestations of SLE in patients with PE are a butterfly rash, a positive result on the lupus band test (LBT), and antinuclear antibodies (ANAs). In this article, we report a case of PE associated with anti-double-stranded DNA (anti-dsDNA), anti-Smith (anti-Sm), anti-Ro (anti-SSA), and antiribonucleoprotein (anti-RNP) antibodies. To our knowledge, only 3 reports have linked anti-dsDNA antibodies, a highly specific marker for SLE, and PE¹⁻³; in addition, the presence of extractable nuclear antigen (ENA) antibodies such as anti-Sm, anti-Ro, and anti-RNP antibodies has been reported only once.³ Our case also was

notable in that controlling it required extensive immunosuppressive therapy. We treated our patient with a combination of systemic steroids, intramuscular gold injections, azathioprine, and hydroxychloroquine. The patient's response was complete remission—evaluated clinically, serologically, and immunohistochemically.

Case Report

A 44-year-old African American woman presented with a 1-month history of generalized skin eruption. Initial manifestations were several small blisters on the central chest that spread rapidly as scaling erythema and crusted erosions of the trunk, face, and scalp. The patient was not using any medication. Laboratory findings included serologic studies positive for ANA (1:640) and anti-dsDNA antibodies. Staining of a skin biopsy specimen with hematoxylin and eosin showed subcorneal blistering. Results of serum analysis by indirect immunofluorescence showed deposits of immunoglobulin G (IgG) in an intercellular pattern on an epithelial substrate.

A presumptive diagnosis of PE led to a trial of prednisone 20 mg daily. Deterioration continued despite dose increases to 50 mg daily. Adjunctive therapy with weekly 50 mg intramuscular injections of gold had no effect.

Three months later, the patient was referred to us. She reported a paternal history of psoriasis, no significant past medical illnesses, and arthralgia that began in both knees when the rash appeared. During the physical examination, she was in considerable discomfort. Scaling and desquamation were extensive, involving most of the scalp, face, and trunk. Many lesions were annular and target-shaped and had dusky centers and surrounding erythema (Figure 1). The patient also had a malar rash.

Skin biopsy specimens for routine histology and direct immunofluorescence studies were obtained

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Figure 1. Annular and target-shaped plaques with dusky centers and surrounding erythema on the back.

from clinically involved and normal-appearing skin, respectively. Evidence of suprabasilar acantholysis and marked hydropic degeneration was seen at the dermal-epidermal junction on light microscopy (Figure 2). Diseased and normal skin had strongly positive deposits of IgG, IgM, and C3 in an intercellular pattern and along the dermal-epidermal junction. Results of indirect immunofluorescence studies of serum showed immunoglobulin and complement intercellular deposits at a titer of 1:160. Other significant laboratory findings included ANA (1:640) arranged in a speckled pattern; anti-dsDNA antibodies (11.9 IU/mL; reference range, ≤ 2.5 IU/mL); and anti-Sm, anti-Ro, and anti-RNP antibodies. Complete blood cell count and results of biochemistry profile and urinalyses were within normal limits. Results of several other tests—for anti-SSB antibody (La), anticardiolipin antibodies, cryoglobulins, rapid plasma reagin, and glucose-6-phosphate dehydrogenase—were negative or within reference range.

Increasing the dose of prednisone to 80 mg daily and continuing weekly intramuscular injections of gold 50 mg dramatically reduced truncal erythema and scaling within several weeks. The rash on the patient's scalp and face persisted. One month later, azathioprine 50 mg 3 times daily was added, and the dose of prednisone was tapered. Because of persistent rash after 3 more months, hydroxychloroquine 200 mg twice daily was added. The scalp and facial rash improved slowly. Two months later, only sparse scaling papules remained. These were treated with 10% glycolic acid lotion.

A year after the rash started, the patient's disease remitted completely. Although results of anti-dsDNA, anti-Sm, and anti-Ro antibody tests and indirect immunofluorescence studies were negative, ANA titers remained at 1:40.

Six months later, an attempt to discontinue prednisone resulted in a mild flare of facial erythema and scaling. The patient had no recurrences while on a maintenance regimen of prednisone 5 mg daily, intramuscular gold 50 mg monthly, and azathioprine 50 mg twice daily. Antimalarial therapy was discontinued without effect 2 years after the rash started.

Comment

PE affects the sexes equally and occurs in all age groups.⁴ The chief cutaneous findings of PE are erythematous crusted scaling plaques in a seborrheic distribution, with or without flaccid bullae or erosions, and a malar rash. Oral mucous membranes are usually not involved. Suprabasilar acantholysis may be present (as it is in PF) and may be seen histologically.

The most characteristic PE findings are those from immunofluorescence studies. Results of direct immunofluorescence examination of perilesional skin almost always show antibodies in intercellular spaces and often show antibodies at the dermal-epidermal junction (positive result on LBT). In a review by Amerian and Ahmed,⁴ 68% of patients whose immunofluorescence results were reported had antibodies in both locations; the other 32% had antibodies only in intercellular spaces. Of the

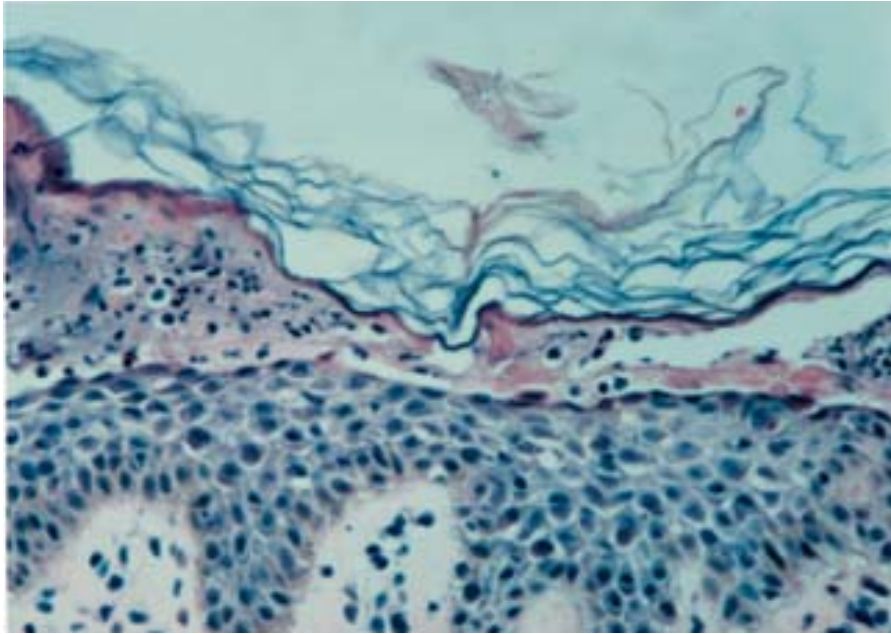


Figure 2. Suprabasilar acantholysis and marked hydropic degeneration at the dermal-epidermal junction (H&E, original magnification $\times 200$).

12 PE cases reported to our knowledge since 1986, 11 involved antibodies in both locations.^{2,3,5-11}

Clinical manifestations of SLE in patients with PE are typically mild. Although PE has been linked to SLE on 4 or more SLE-defining criteria, serologic or immunofluorescence studies often provide the most significant SLE-associated findings.³ In their review of 116 cases of PE, Amerian and Ahmed⁴ found that 77% of patients who had an LBT had a positive result, and 40% of patients tested for ANA had a positive result. In more recent years, 80% of PE cases for which ANA results were reported were positive for ANAs; this higher sensitivity may be related to use of more sensitive substrates, such as Hep-2 cells.^{1-3,6-11}

Tests for ANA subsets (eg, anti-dsDNA and anti-ENA antibodies) are also important in defining SLE. Anti-dsDNA antibodies are highly specific for SLE, occur in 50% to 60% of patients with SLE, and are associated with immune complex SLE renal disease. ENAs include the Sm, Ro, RNP, SSB/La, and Scl-1 antigens. Anti-Sm antibodies, though present in only 20% of patients with SLE, are very specific for SLE. Anti-RNP antibodies are not specific for SLE and occur in higher titers when associated with mixed connective tissue disease, a condition in which their presence has a greater diagnostic role.

Anti-dsDNA and anti-ENA antibodies are seldom found in PE. In the cases reviewed by Amerian and Ahmed,⁴ anti-dsDNA antibodies were not present. In a case reported by Ochsendorf et al,¹ an 80-year-old woman with PE had ANA and anti-dsDNA antibodies. Wieselthier et al² reported the case of a

34-year-old woman who developed PE in association with anti-dsDNA antibodies 8 years after initially presenting with signs and symptoms of SLE (fatigue, arthralgia, leukopenia, ANA positivity). A third case involved a 27-year-old African American woman who presented with findings typical of PE and whose condition then progressed to full-blown SLE with pulmonary thrombus and polyserositis. Samples drawn for serologic analysis at the time of the patient's systemic flare had an anti-dsDNA titer of less than 1:40 and an anti-Sm titer of 1:100. To our knowledge, there have been no other reports of anti-ENA antibodies occurring in association with PE.

Notably, our patient's case linked the classic rash of PE with anti-dsDNA and anti-ENA antibodies but without the systemic abnormalities of SLE. In addition, inducing clinical and serologic remission of this case required a combination of prednisone, intramuscular gold injections, azathioprine, and hydroxychloroquine. Unlike previously reported PE cases involving these antibodies, our patient did not have the systemic manifestations of SLE (eg, serositis, renal disease). Interestingly, the response of the cutaneous disease to treatment co-occurred with a decrease in titers of SLE-associated antibodies. This patient's case suggests that presence of highly SLE-specific autoantibodies in patients with PE can be a marker for recalcitrant disease.

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