Our study is limited because it was conducted at a single location with 30 physicians. Although only dermatology appointments are demonstrated in this manuscript, we have found similar results in other departments in our institution.

In conclusion, targeted interventions at patients likely to miss appointments could decrease the negative financial impact while limiting the expense and possible annoyance of reminding others unnecessarily. Patients who are younger, have been waiting a long time, or have less comprehensive insurance seem to be most likely to benefit from reminders.6

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OBSERVATION

Anti-Laminin γ1 Pemphigoid Accompanied by Autoantibodies to Laminin α3 and γ2 Subunits of Laminin-332

Anti-laminin γ1 pemphigoid (ALG1P) is an autoimmune subepidermal bullous disease characterized by autoantibodies to a 200-kDa acidic noncollagenous glycoprotein of the lower lamina lucida. In contrast, anti-laminin-332 mucous membrane pemphigoid (MMP) is an autoimmune blistering disease characterized by autoantibodies to various subunits of laminin-332 of the basement membrane. We report the first case to our knowledge of ALG1P with IgG autoantibodies for 3 distinct laminins: α3 and γ2 subunits of laminin-332 and laminin γ1.

Report of a Case | A man in his 70s was referred for tense blisters and erosions on the trunk and extremities (Figure 1A and B). No mucosal involvement was observed. He had undergone a dialysis treatment for chronic glomerulonephritis. A skin biopsy specimen taken from a bulla on the right thigh at the previous hospital demonstrated subepidermal separation with infiltration of neutrophils and eosinophils in the blister cavity and the upper dermis (Figure 1C and D). Direct immunofluorescence (IF) of the perilesional skin showed linear deposition of C3 at the basement membrane zone (BMZ). Indirect IF of healthy control human skin showed IgG anti-BMZ antibodies at a 1:20 titer (Figure 1E), which reacted with the dermal side of 1M sodium chloride-split skin (Figure 1F). In immunoblotting of healthy control human dermal extracts, IgG antibodies reacted with the 200-kDa laminin γ1 (Figure 2A). Furthermore, immunoblotting of purified human laminin-332 demonstrated IgG autoantibodies to the 145-kDa and 165-kDa α3 subunits and the 105-kDa γ2 subunit of laminin-332 (Figure 2B). Traces of the 140-kDa β3 subunit were also detected, but the band was too faint to be significant. Although
treatment with oral prednisolone, 25 mg/d (0.5 mg/kg/d), alleviated the symptoms, a few blisters still appeared. The addition of colchicine to his treatment regimen, 0.5 mg/d, suppressed blisters completely.

Discussion | Immunoblotting detected IgG autoantibodies to α3 and γ2 subunits of laminin-332 and laminin γ1. Clinically, most reported cases of ALG1P present with tense blisters and urticarial lesions without mucosal involvement, closely resembling bullous pemphigoid.1 In contrast, anti-laminin-332 MMP, which accounts for 10% to 20% of MMP, shows mucosal involvement. Because our case did not show mucosal involvement, a diagnosis of MMP is unlikely. Considering clinical findings, we diagnosed our case as ALG1P accompanied by autoantibodies to α3 and γ2 subunits of laminin-332.

Our patient was receiving dialysis treatment for chronic glomerulonephritis. Mitate et al2 also reported a case of pemphigoid with antibodies to both laminins γ1 and γ2 after rejection response to a transplanted kidney. Laminin is a major component of the renal glomerular BMZ and mesangium. Setty et al3 reported that IF studies with laminin chain–specific antibodies detected expression of α2, β1, and γ1 subunits in the normal mesangium and expression of α5, β2, and γ1 subunits in normal glomerular BMZ. In our case, it may be speculated that the autoantibodies to laminin γ1 cause both subepidermal blisters in the skin and glomerulonephritis in the kidney.

Recently, the C terminus of laminin γ1 has been identified as target antigen in anti-p200 pemphigoid, and the disease was renamed as ALG1P.4 However, Vafia et al5 reported that human IgG specific to laminin γ1 did not induce dermal-epidermal separation ex vivo, although serum samples from patients with “anti-p200 pemphigoid” did.6 They concluded that autoantibodies in anti-p200 pemphigoid serum samples are pathogenic, while pathogenicity is not mediated by autoantibodies against laminin γ1. Further studies are needed to identify the pathogenically relevant autoantigen in anti-p200 pemphigoid.
In summary, we report the first case to our knowledge of ALG1P with IgG autoantibodies for 3 distinct laminins. It remains unknown whether the reactivity with multiple components of BMZ is caused by independent autoantibodies or cross-reactive autoantibodies. Accumulation of cases like our case should give us a clue to answer this question.

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COMMENT & RESPONSE

IgG4-Related Skin Disease

To the Editor We read with interest the article recently published in JAMA Dermatology that reported successful treatment of IgG4-related disease (IgG4-RD) of the skin with thalidomide.1 A recently described disease entity, IgG4-RD can affect virtually any organ of the body, and while skin involvement is rare, it may manifest clinically as nonspecific skin papules, plaques, and nodules.2 Ingen-Housz-Oro et al3 included a diagnosis of IgG4-RD in the skin of 2 patients with skin nodules based on evaluation of skin biopsy specimens showing dense lymphocytic infiltrates with lymphoid follicles, dermal fibrosis, and an IgG4 to IgG ratio exceeding 75%. Although these patients may indeed have had isolated skin involvement by IgG4-RD, we highlight herein recent advances in the diagnosis of IgG4-RD to emphasize the importance of correlating clinical features, histopathologic evidence, and immunophenotypic data derived from careful interpretation of IgG4 and IgG stains.

Ingen-Housz-Oro et al3 included a photomicrograph of an IgG4 stain (Figure 3C in their article, original magnification ×100), which shows a relatively modest collection of IgG4+ cells surrounding and within a lymphoid follicle. In the most involved areas of this photomicrograph, we estimate that the IgG4 cell density is no higher than 50 per high power field (HPF). IgG stain was not pictured, thus precluding our ability to verify the reported IgG4 to IgG ratio. A recent consensus statement on the pathology of IgG4-RD cautioned against establishing a diagnosis of IgG4-RD based only on an elevated tissue IgG4 to IgG ratio, particularly when the absolute number of IgG4 cells is relatively low.3 This statement also proposed that—regardless of how many histopathologic features characteristic of IgG4-RD are present (ie, dense lymphoplasmacytic infiltrate, fibrosis [usually storiform in nature], and obliterator phlebitis)—the low threshold for IgG4 cell density in IgG4-related skin disease be set at 200/HPF. This recommendation was founded on recognition that moderately elevated IgG4 cell density is a nonspecific finding, as has been shown in extracutaneous organs4 and the skin.5 It is true that the clinicopathologic and immunophenotypic findings certainly raise the possibility of IgG4-related skin disease in the patients reported by Ingen-Housz-Oro et al.3 However, we advocate caution...