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CASE REPORT

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Linear IgA bullous dermatosis and elevated bullous interleukin-6 levels: Responsive to treatment with Anti-IL-6 receptor monoclonals

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Abstract

Linear IgA bullous dermatosis (LABD) is a rare autoimmune/inflammatory skin condition. Here, we report on a patient who developed treatment resistant LABD. At diagnosis, elevations of IL-6 and C-reactive protein in the blood and extreme elevations of IL-6 in LABD bullous fluid were seen. The patient responded well to tocilizumab (anti-IL-6 receptor) treatment.

KEYWORDS

anti-IL-6 receptor antibody, IgA bullous dermatosis, interleukin 6, kidney transplant, pancreatic cancer

1 | INTRODUCTION

Linear IgA bullous dermatosis (LABD) is a rare bullous skin disease characterized by subepidermal vesiculobullous disease. Although the etiology is uncertain, most cases are deemed drug-induced or more recently vaccine-related with other cases related to genetic pre-dispositions and paraneoplastic immune responses, with one identified report associated with pancreatic cancer.[1,2]

Previous reports have shown that IgA anti-basement membrane zone antibodies directed at the 97 kDa portion of bullous pemphigoid antigen-2 are responsible for disease manifestations.[1] Determinants of the pathophysiology of the IgA autoantibodies reflect induction by infectious agents, autoimmunity (i.e., inflammatory bowel disease), and malignancies.[1,2] However, an understanding of the immune activation events responsible for pathogenic IgA antibodies and their relation to LABD are unknown.

2 | CASE REPORT

Here, we report on a 69-year-old African American female who progressed to end stage renal disease (ESRD) after a long history of systemic lupus erythematosus (SLE). The patient subsequently received a deceased donor kidney transplant in 2009 without complications. The patient was maintained on standard immunosuppression with tacrolimus with target levels of (5–7 ng/mL), cellcept (500 mg bid) and prednisone 5 mg daily. The patient's kidney transplant has continued to function normally with serum creatinine of 0.7–0.8 mg/dL with no evidence of rejection. In 2017, the patient was diagnosed

with pancreatic adenocarcinoma and treated with surgery and chemotherapy (gemcitabine) subsequently obtaining a full remission.

In October 2020, the patient developed severely pruritic bullous and vesicular rash with initial distribution on the extremities that later extended to the entire body (Figure 1A). A biopsy showed evidence for LABD (Figure 1B,C). The patient was shortly thereafter diagnosed with recurrence of her pancreatic cancer. The extent of the patient's LABD was significant as she reported soaking of her bed sheets with fluid from ruptured bullae. She was treated with multiple agents including high dose steroids, topical steroids, colchicine, tetracycline, and anti-CD20 (ruxience) without significant benefit. Dapsone was not considered due to G6PD deficiency.

The patient continued baseline immunosuppression maintaining stable kidney function; however, her CRP (26.5 mg/L, NL <5 mg/L) and plasma IL-6 (177 pg/mL, NL <5 pg/mL) were elevated. We then aspirated serous fluid from the distended bullae on the right knee with concomitant serum for analysis of IL-6 levels. The fluid showed >10,000 pg/mL IL-6 (Figure 1A).

Based on these findings and after obtaining informed consent from the patient, we began tocilizumab (anti-IL-6R) therapy. Initially, doses of 8 mg/kg were given 2 weeks apart due to initial difficulty in lowering the CRP, then monthly. The patient showed improvements with reduction in the number and size of bullae with her second dose. At her eighth dose, she demonstrated signs of remission, and with her eleventh dose, resolution of all bullae and pruritus (Figure 1D). Of note, the patient's CRP was significantly reduced with tocilizumab (<1 mg/L) therapy indicating inhibition of IL-6/IL-6R signaling. Measurement of serum and bullous fluid IL-6 1-month post-initiation of tocilizumab showed no significant changes from baseline. This is expected since fluid phase IL-6/IL-6R complexes are detected in the IL-6 assay but do not transduce signals when bound by anti-IL-6R. This

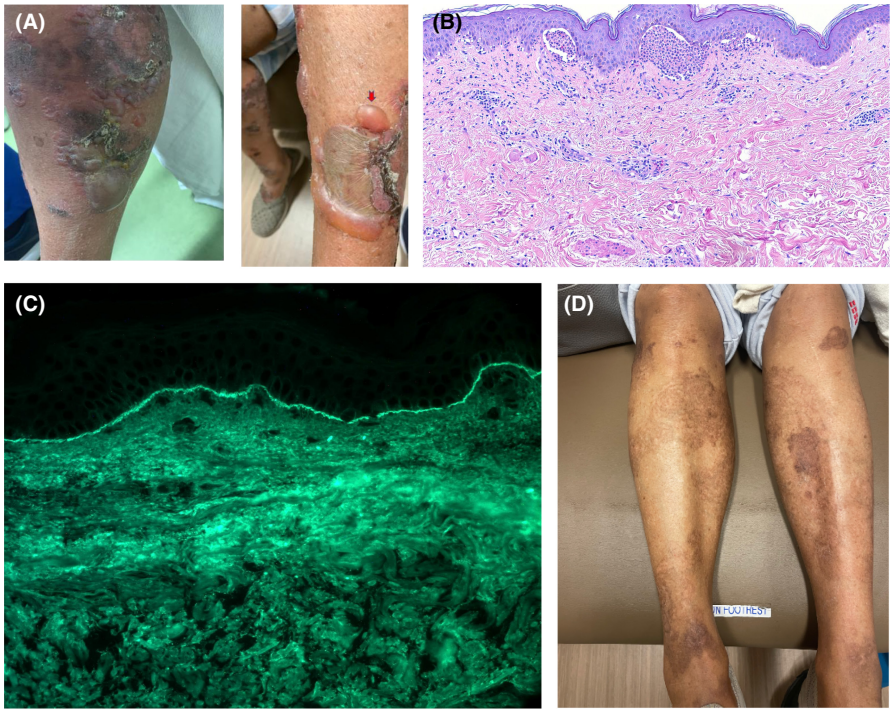

FIGURE 1 (A) This figure shows the bullous lesions on patient's knee and legs. At time of photograph, the patient had extensive bullous lesions over her entire body except for her face. Large bullous lesions were noted on the lower extremities. The arrow indicates where bullous fluid was aspirated for IL-6 determinations. The patient was noted to have elevated CRP (26.5 mg/L, Normal <5 mg/L) and IL-6 levels in plasma (177 pg/mL, normal <5 pg/mL). IL-6 fluid in aspirate was >10,000 pg/mL. (B) This figure shows the histopathology of lesioned tissue obtained from biopsy. For the H&E: Subepidermal micro abscesses within the cleft formed by the subepidermal bullous dermatosis. (200× magnification). (C) This pattern of linear basement membrane zone deposition with IgA is typical for linear IgA bullous dermatosis. IF staining for IgA shows continuous strong linear deposition along the basement membrane zone; IF stains for other immunoreactants show IgG: negative; IgM: negative; C3: negative; Fibrinogen: patchy staining of connective tissue fibers in the dermis. Photomicrograph shows linear IgA deposition along the basement membrane zone in continuous strong pattern (200× magnification) (see arrow). (D) This figure shows photo of patient's skin after completion of her eleventh dose of tocilizumab given over an 8-month period. She now has complete resolution of her LABD. CRP levels dropped significantly over the course of therapy as an indirect indication of effective inhibition of IL-6/IL-6R signaling and was associated with improvements in skin lesions.

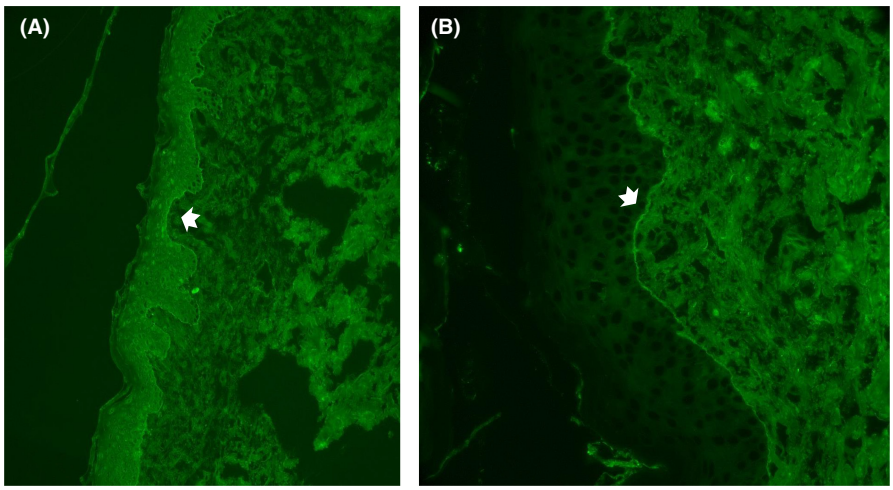

FIGURE 2 (A, B) These figures show indirect immunofluorescent assays of serum and bullous fluid obtained prior to initiation of tocilizumab therapy. (A): (200×) Deposition of IgA detected on donor skin by immunofluorescence at a 1:10 dilution of patient's blister fluid. (B): (400×) Deposition of IgA detected on donor skin by immunofluorescence at a 1:10 dilution of patient's serum. Patient serum and bullous fluid underwent a range of dilutions from 1:1 to 1:500; final dilutions used were serum at 1:50 and bullous fluid at 1:10. 2 m thick normal skin frozen sections were incubated with the dilute serum or bullous fluid for 1 h. After rinsing, slides were incubated with the secondary fluoresceinated anti-human IgA antibody (Agilent F0204, 1:20 dilution) for 45 min followed by rinsing and cover slipping. Results indicate the presence of IgA anti-basement zone antibodies in the patient's sera and bullous fluid.

has been reported by others and was consistent with the observations in our patient as CRP declined to <1 mg/L with tocilizumab treatment.[3] We then analyzed serum and bullous fluid pre-tocilizumab for IgG and IgA binding to normal skin biopsies using indirect immunofluorescence (Figure 2A,B). Here, we saw linear IgA staining of the basement membrane zone in normal skin using both serum and bullous fluid. No IgG staining was seen.

3 | DISCUSSION

Our finding of elevations in bullous fluid IL-6 levels (>10,000 pg/mL) has not, to our knowledge, been reported. A review of the literature indicates that IL-6 has been identified in serum and biopsies of patients with bullous pemphigus (BP).[4] Other reports show a predominance of Th2 cytokines (IL-13) and IgE autoantibodies in BP.[5] We could not identify any reports of cytokine-directed therapies based on analysis of bullous fluid cytokines in BP or LABD. However, we feel that analysis of cytokines in bullous fluid could be useful in providing direction for more focused therapeutic approaches as was seen here.

IL-6 is considered a critical cytokine for immune activation, antibody production, and pro-inflammatory activities. IL-6-activated pathways are involved in B-cell, plasma cell, and Th17 cell activation and differentiation.[6] Dysfunctional IL-6 production or enhanced receptor responses to IL-6 signaling are associated with several autoimmune diseases, including IgA nephropathy (IgAN), where increased plasma concentrations of IL-6 are directly associated with increased plasma concentration of aberrantly galactosylated IgA and disease activity.[7] In our patient we noted that tocilizumab also decreased serum IgA levels (666 mg/dL–>434 mg/dL).

Recent reports have also identified persistent elevation of IL-6 and CRP as markers of a sixfold increase in mortality for pancreatic cancer patients and IL-6 as an important growth factor for pancreatic cancer cells.[8,9] It is important to note that the patient was diagnosed with recurrence of pancreatic cancer shortly after development of her LABD. However, we cannot make a definitive association of pancreatic cancer and LABD in this case. She now continues her tocilizumab therapy monthly and is also treated with gemcitabine. It should also be emphasized that physicians have a heightened awareness of rare skin lesions such as LABD and their possible relation to malignancies. Here, promptly biopsying these lesions should yield clarification of etiology and direction regrading therapeutics.

In summary, IL-6-directed therapy with tocilizumab resulted in resolution of LABD. Thus, analysis of cytokines from bullae associated with LABD and other bullous dermatoses could be of diagnostic and potentially therapeutic value, especially in patients with therapeutic resistant forms of LABD. Although we could not definitively identify a relationship with LABD and recurrence of pancreatic adenocarcinoma, the previously reported association of IL-6 and elevated CRP levels with poor prognosis suggest a possible association.

AUTHOR CONTRIBUTIONS

Bonnie Balzer: Data curation; methodology; writing – review and editing. **Cynthia Nast:** Data curation; investigation; methodology. **Janet Atienza:** Data curation; investigation. **Katherine Lim:** Data curation; project administration. **Sanjeev Kumar:** Conceptualization; investigation; methodology. **Nicholas N. Nissen:** Investigation; resources. **Bongha Shin:** Data curation; formal analysis.

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CONFLICT OF INTEREST STATEMENT

Stanley C. Jordan, MD has grants and consultation agreements with CSL Behring, Regeneron, CareDx, Vera Inc. Argenx and Hansa biopharma. The other authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data will be made available upon reasonable request.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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