INTRODUCTION

Linear IgA bullous dermatosis (LABD) is an autoimmune, blistering disease characterized by linear deposits of IgA along the basement membrane. In cases of concurrent deposits of IgG, the disease is considered a distinct subtype of LABD called linear IgA/IgG bullous dermatosis (LAGBD). This disease has various clinical presentations including generalized vesiculobullous lesions with mucosal involvement. Omalizumab (OMZ) is a humanized monoclonal antibody against IgE and has proved effective as an off-label treatment for other bullous diseases, notably bullous pemphigoid (BP). OMZ has not previously been reported as an effective treatment for LAGBD.

CASE REPORT

A 61-year-old woman was presented to the Department of Dermatology and Allergy nine years ago with general malaise and a 3-week history of vesicular ulcerations with itching and stinging located to the inner genital labia, upper extremities, and oral mucosa. Her medications included carbamazepine, which she had received for 30 years, metoprolol, and thiazide. She had recurring oral herpes simplex but had never needed oral antiviral treatment. She had no lymphadenopathy on examination, and laboratory testing showed normal leukocytes and mild eosinophilia (0.55 × 10^9/L). Liver function, renal function, thyroid hormones, and antinuclear antibodies were all within normal ranges, and indirect immunofluorescence
HAULRIG et al. (IF) test for circulating autoantibodies was negative. The patient was initially treated with valaciclovir on suspicion of generalized herpes simplex infection, and cutaneous punch biopsies for both histopathology and direct IF were performed. Two weeks after the first visit, histology showed epidermal spongiosis, subepidermal bullae with necrosis, and infiltration of eosinophil granulocytes, while the dermis had perivascular infiltrates containing lymphocytes and histiocytic cells. Neutrophilic granulocytes were present in the dermal blood vessels but did not infiltrate the dermis. Direct IF showed IgG deposits along the basement membrane and the absence of IgA and C3. PCR tests for varicella zoster and herpes simplex were negative. On this basis, the patient was diagnosed with BP and treated with azathioprine in increasing doses up to 2 mg/kg daily, prednisolone up to 37.5 mg daily, and topical corticosteroid. The patient responded appropriately with minimal disease during the first six years of treatment while maintaining azathioprine combined with prednisolone 5mg daily. In these years, she had two skin infections with Staphylococcus aureus that required dicloxacillin treatment. After seven years of treatment, she had secondary loss of response and worsening of active disease with vesicles, pustules, and erosions clustered in rosette-like patterns, and there was involvement of the trunk and thighs. Renewed cutaneous punch biopsy for histopathology showed subepidermal bullae containing eosinophil granulocytes, sparse perivascular inflammation of eosinophil granulocytes in the dermis, and the absence of neutrophilic granulocytes, which resembled BP (Figure 1A). Direct IF from the trunk showed linear IgA and faint linear IgG depositions along the basement membrane and the absence of C3, which was consistent with LAGBD (Figure 1B). Renewed IF for circulating IgG antibodies was negative. Laboratory testing showed eosinophilia (0.75 x 10^9/L), while analyses for coeliac disease were negative. Due to the worsening of disease, the patient had four recurrent skin infections within two months caused by S. aureus with CRP up to 41 mg/L (reference range <10 mg/L) and normal leukocytes. All infections were treated with dicloxacillin in combination with frequent potassium permanganate baths.

Treatment with dapsone 50 mg daily and increased doses of prednisolone was initiated, but the patient experienced adverse effects in the form of neuropathies and hemolysis after three weeks when hemoglobin decreased from 7.7 to 6.6 mmol/L (reference range 7.3–9.5 mmol/L). Haptoglobin was increased to 2.94 g/L (reference range 0.47–2.05 g/L), and bilirubin was normal. Dapsone and prednisolone treatments were stopped, and she was then treated with sulfapyridine up to 3 grams daily divided into three doses. Her condition only slightly improved the following seven months, and treatment with oral methotrexate up to 10 mg weekly was added. Subsequently, the patient developed anemia after two months with hemoglobin decreasing from 7.7 mmol/L to 6.6 mmol/L. She showed no signs of further improvement (Figure 2A,B). Methotrexate was stopped. Fifteen months ago, the patient started subcutaneous OMZ 300 mg every four weeks in addition to sulfapyridine, which was slowly decreased to 500 mg twice daily. One month after the first injection with OMZ, the patient showed noticeable improvement, and she had almost complete remission after another month. She has currently received treatment with OMZ and sulfapyridine for 12 months with no side effects or signs of relapse (Figure 2C,D).

3 DISCUSSION

We describe a case of treatment-refractory LAGBD with onset nine years ago, which was initially diagnosed as BP. Two years ago, when the disease worsened, the vesicles had annular and herpetiform arrangements with mucosal involvement, which is a typical find in LABD but rarely reported in BP. The first biopsy at disease onset showed histopathological features of BP though immunoglobulin deposits were absent. According to the few available case reports that describe its clinical features in detail, LAGBD can resemble both LABD and BP. We are convinced that the patient in our case had LAGBD throughout the course of disease, even though the histological diagnosis was not confirmed until after eight years.

![Picture of biopsy and immunofluorescence analysis](A) Biopsy of lesional skin nine years after debut showing subepidermal bulla containing eosinophil granulocytes and perivascular inflammation. H&E stain. (B) Direct immunofluorescence analysis of a perilesional skin biopsy showing linear deposits of IgA along the basement membrane.
A wide range of drugs can induce LABD, including carbamazepine, metoprolol, and thiazide, which the patient received throughout the course of the disease. However, we do not believe that these medications were inducing the disease, since the patient had received the medications in the same doses for several years prior to disease onset, and there were no dose changes prior to worsening of disease.

The same treatment strategies are described for both LABD and LAGBD, and there are reports of successful treatments of LAGBD with prednisolone, dapsone, azathioprine, and sulfapyridine. In our case, these treatments either proved ineffective or were discontinued due to side effects. There are also reports of successful treatment with antibiotics such as dicloxacillin against LABD. The patient received multiple dicloxacillin treatments against recurring skin infections that did not affect the general skin disease. Consequently, we did try other antibiotics to achieve disease control.

Azathioprine in combination with prednisolone was the only treatment providing temporary disease control for four years until there was secondary loss of response. We refrained from initiating treatment with rituximab due to the recent pandemic with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Instead, we initiated treatment with OMZ in combination with
sulfapyridine after which the patient's skin lesions almost cleared after two months. We are convinced that OMZ was decisive for the patient's sudden treatment response since sulfapyridine treatment alone previously only had a slight effect.

OMZ is a monoclonal IgE antibody approved for inflammatory diseases including chronic spontaneous urticaria and asthma. OMZ binds free circulating IgE and thereby prevents it from inducing allergic reactions. Its usefulness as a novel off-label treatment alternative for BP has been previously reported in multiple cases, while one case reports its efficacy in the treatment of LABD.3,4,10 Although specific IgE directed against the autoantigen BP180 has been shown in BP, the exact mechanism of OMZ in BP, LABD, and LAGBD is not fully understood.11 Our case report supports the limited amount of evidence of OMZ and its usefulness in the treatment of LABD and LAGBD.

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AUTHOR CONTRIBUTIONS
Morten Bahrt Haulrig wrote the manuscript. Signe Ledou Nielsen contributed to data analysis and interpretation and final approval of the version to be published. Jesper Elberling contributed to critical revision of the article and final approval of the version to be published. Lone Skov contributed to critical revision of the article and final approval of the version to be published.

DISCLOSURE
Morten B. Haulrig has received an honorarium as a consultant for Novartis. Jesper Elberling has received lecture fees from Leo Pharma, Sanofi, Galderma, Novartis, AstraZeneca, Sanionia, and Boehringer Ingelheim. Lone Skov has been an advisor, investigator, and speaker for AbbVie, Eli Lilly, Novartis, Sanofi, Celgene, Leo Pharma, BMS, UCB, and Almirall, outside the submitted work. Lone Skov reports nonfinancial support from AbbVie, Sanofi, Janssen, and grants from Novartis, Janssen, BMS, and Sanofi.

DATA AVAILABILITY STATEMENT
Research data are not shared.

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