COVID CONCEPTS

Pemphigus Foliaceous after COVID-19 Infection and Bamlanivimab Infusion

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ABSTRACT

We report a case of pemphigus foliaceous (PF) in the setting of bamlanivimab, a novel monoclonal antibody for the treatment of COVID-19. PF is a rare autoimmune blistering disease caused by autoantibodies directed against desmoglein-1 (DSG1). Drugs and viruses have been implicated as inciting factors of pemphigus in predisposed patients. Given the current pandemic, the presentation of PF following COVID-19 infection and bamlanivimab infusion is of special interest and further investigation may be warranted.

INTRODUCTION

To the authors' knowledge, this is the first report of pemphigus foliaceous (PF) in the setting of COVID-19 infection and subsequent treatment with bamlanivimab. Bamlanivimab was previously granted emergency use authorization for administration as a single 700-mg IV infusion after a positive COVID-19 test result and within 10 days from symptom onset. Bamlanivimab binds to the spike protein of SARS-CoV-2 and blocks attachment to the human ACE2 receptor.[1]

CASE REPORT

A 66-year-old male presented to the dermatology clinic with a cutaneous eruption of 3 months duration which began after receiving monoclonal antibody bamlanivimab infusion for a diagnosis of COVID-19. He did not require hospital admission or home oxygen therapy after the initial diagnosis and recovered completely from the COVID-19 infection without sequela. His current medications include lisinopril, rivaroxaban, and metoprolol succinate ER for which he had been taking for years prior. Physical examination revealed numerous well-demarcated erythematous crusted plaques with "cornflake" scale involving the central face, chest, abdomen, and back in a predominantly seborrheic distribution **(Figure 1 and 2)**. A perilesional biopsy revealed subcorneal acantholysis in the granular layer **(Figure 3 and 4)**. Direct immunofluorescence (DIF) revealed cell surface deposits of IgG throughout the epidermis confirming the diagnosis of pemphigus foliaceous (PF). He achieved full resolution after 4 doses of the anti-CD-20 antibody, rituximab.

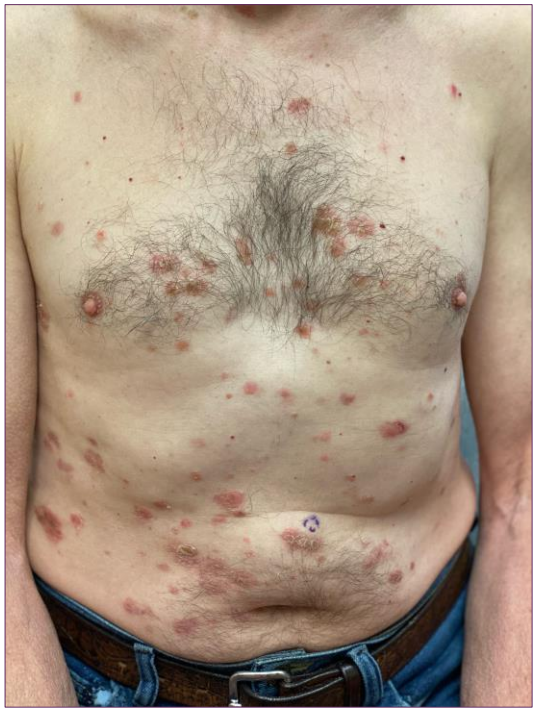

Figure 1.

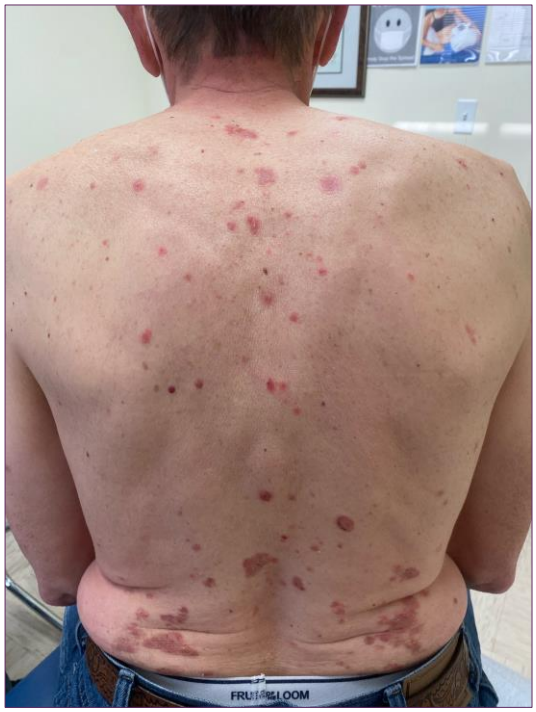

Figure 2.

DISCUSSION

PF is a rare immunobullous disease caused by a production of IgG autoantibodies directed against the intercellular adhesion protein, DSG1.[2] DSG1 autoantibodies cause separation of keratinocytes at the granular layer of the epidermis producing fragile subcorneal blisters leading to erosive lesions.[2,3] In contrast to pemphigus vulgaris, mucosal surfaces are spared in PF as there is an absence of desmoglein-3 autoantibodies.[4] Histology in PF may be nonspecific because the epidermis has a normal appearance if the thin blister has already detached. DIF reveals intercellular IgG deposition within the epidermis, with the most intense staining in the upper epidermis. Several pathways leading to acantholysis have been described including biochemical modification of antigens and indirect mechanisms that alter immune response.[5]

The literature classically divides drug-related pemphigus based on chemical structure: thiol drugs, phenolic drugs, and non-thiol/phenolic drugs. Thiol drugs are thought to disturb cell adhesion by changing the antigenic conformation of desmoglein, inhibiting enzymes that cause keratinocyte aggregation, and activating enzymes that cause keratinocyte disaggregation.[5,6] Phenolic drugs trigger release of cytokines that activate proteases resulting in acantholysis.[6] Non-thiol/phenolic drugs may cause pemphigus through various mechanisms such as over-activation of the immune system.[5]

PF is the most common variant of drug-induced pemphigus when caused by thiol containing drugs.[7] Although this patient is taking lisinopril, which contains an amide group, drug-induced pemphigus is more rare among angiotensin converting enzyme inhibitors other than captopril. Additionally,

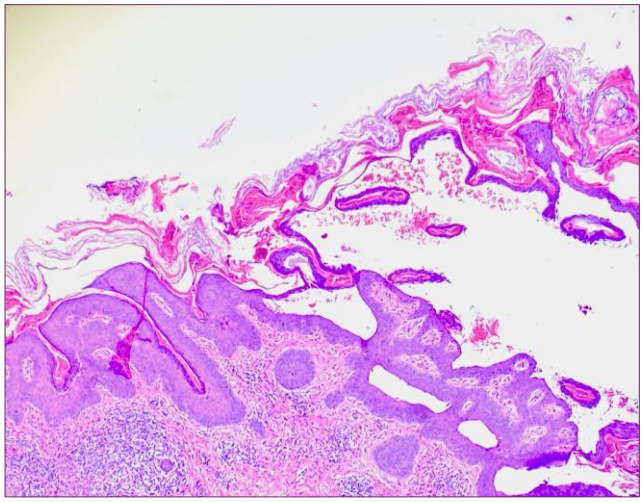

Figure 3.

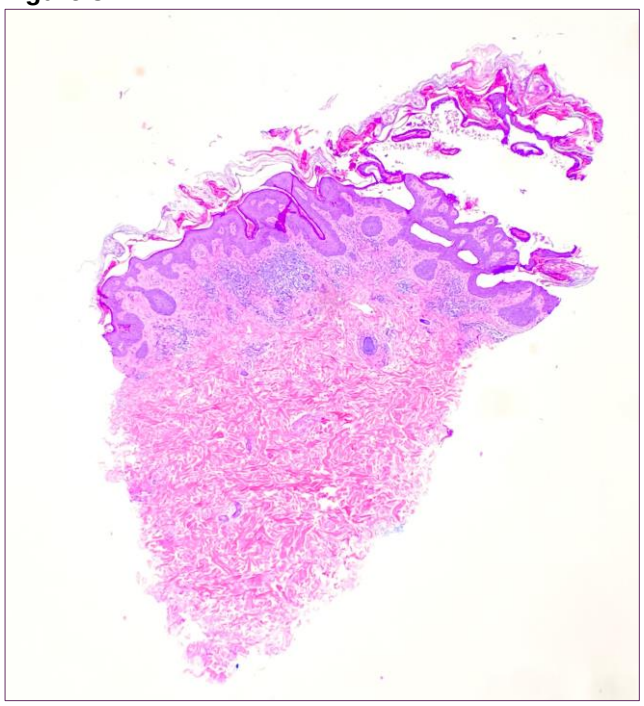

Figure 4.

metoprolol could be considered as a possible inciting drug as there are reports of beta-blockers causing drug-induced pemphigus.[7] Bamlanivimab is favored as the most likely inciting agent in this case based on timeline of disease presentation. A review of 170 drug-induced pemphigus cases found that patients developed pemphigus within a mean of 154.27 days.[8] The patient had been taking metoprolol and lisinopril for years prior. In addition, the patient continues to take metoprolol and lisinopril and has remained clear after treatment with rituximab.

We hypothesize that bamlanivimab caused PF through an indirect immune mechanism to activate autoantibodies against DSG1, although the exact mechanism of acantholysis remains to be determined. Previous case studies have reported viral infection, often *herpesviruses*, as an inciting factor in the development of pemphigus and thus, a paraviral eruption is also considered for the cause of the presenting PF.[9] COVID-19 infection decreases the amount of ACE2 and alters the renin-angiotensin system, which plays a role in keratinocyte differentiation.[10] The release of cytokines in the infection itself may set the stage for autoimmunity in a genetically predisposed individual. Controversy and difficulty in discerning the triggering event in pemphigus as viral infection, subsequent treatment intervention, or the combinations of both exists.[9] Nonetheless, SARS-CoV-2 and bamlanivimab may both be considered as possible implications in the development of PF. A previous case report described bullous pemphigoid (BP) in a patient admitted to the intensive care unit with COVID-19 infection, in which virus and drug-induced BP were considered as possible precipitating factors.[11] Further reports and investigation will help determine the causal relationship and clarify possible adverse drug reactions. Full recovery from active infection with COVID-19 is prudent before considering treatment of PF with rituximab. Patients with autoimmune bullous disease taking rituximab have developed more severe COVID-19 infection compared to the healthy population, possibly due to higher levels of IL-6.[12]

CONCLUSION

Further reports and investigation will help determine the causal relationship and clarify possible adverse drug reactions. Full recovery from active infection with COVID-19 is prudent before considering treatment of PF with rituximab.

Conflict of Interest Disclosures: None

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