TPE combined with CVVHF, our patients exhibited a remarkable time interval from peak denudation to re-epithelialization, which ranged from seven to 12 days. The number of TPE sessions and the duration of CVVHF varied among individuals, based on the clinical response to the treatment. Considering that the natural history of TEN may vary significantly and that our data was based on a small series of patients, one may argue that the beneficial effect of extracorporeal detoxification may have been a chance phenomenon. However, we believe that the extracorporeal treatment was effective because all our patients had severe conditions and their disease was refractory to conventional pharmacologic therapies and responded promptly to TPE combined with CVVHF.

It is our opinion that TPE combined with CVVHF therapies may be considered as an alternative treatment for severe pediatric TEN, especially when the treatment with steroids and IVIG fails. We acknowledge that more experience and research is needed before generalizing these therapies in children.

Supplementary material

Supplementary material associated with this article can be found in the online version, at doi:10.1684/ejd.2021.4042. Details about the therapeutic plasma exchange (TPE) combined with continuous venovenous hemofiltration (CVVHF) are described as follows:

For this type of treatment, central vascular access was gained through the subclavian or femoral vein using a double-lumen catheter. For the TPE, plasma was obtained by centrifugation and separation from blood cells with the use of a spectra continuous separator (Gambro Renal Products, Meyzieu, France). On each exchange, the circulating plasma was replaced with a plasma substitute, obtained by combining fresh frozen plasma and albumin 5% at a flow rate between 3-5 mL/kg/min. The volume of plasma exchange was about 1 to 1.5-fold relative to the volume of circulating plasma, calculated using the formula: [weight (kg)/13 × (1-HCT/100) ×1000] (HCT, hematocrit [in %]). The original blood cell components were returned to the patients. TPE was carried out every 2-3 days and the number of sessions was dependent on patient responsiveness and the extent of the disease.

CVVHF was performed over several consecutive days, but was suspended during the TPE course and immediately restarted after TPE was completed. CVVHF was performed using the Prismaflex monitor equipped with HF 60/100 filters and AN69 poly membrane that removed both solutes and fluid at a flow rate of 3-5 mL/kg/min. The replacement fluid was infused at 35-50 mL/kg/h in a post-dilution mode. Anticoagulation was used in all cases by adjusting an unfractionated heparin infusion to maintain activated partial thromboplastin time, two-fold higher than that for control (60-80 s). Discontinuation of TPE and CVVHF was dictated by the improvement in clinical outcomes, when the detachment of the epidermis was halted, and no further new lesions developed.

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Considerations on SARS-CoV-2 vaccines in patients with autoimmune blistering diseases

Patients affected by autoimmune bullous diseases (AIBDs) are fragile due to immunosuppressive treatment. Infections, favoured by immunosuppression, represent an important cause of death in AIBD patients [1]. No specific dermatological guidelines address the SARS-CoV-2 vaccination issue in AIBD patients [1]. According to general guidelines for AIBD management, patients receiving immunosuppressive therapy should receive non-live

vaccinations (*e.g.* against seasonal influenza, pneumococcal infection), whereas live attenuated vaccines are contraindicated [1].

Currently, all available COVID-19 vaccines are essentially comparable to non-live vaccines in terms of safety for immunosuppressed patients. Two vaccines are based on mRNA encoding the SARS-CoV-2 spike protein, a key target of neutralizing antibodies [2, 3]. Lipid nanoparticles allow mRNA delivery into cells [3, 4] where it is transitorily expressed, resulting in the production of the viral spike protein [2, 3]. Another vaccine consists of a replication-deficient chimpanzee adenoviral vector ChAdOx1, containing the SARS-CoV-2 spike protein gene [4]. A two-dose regimen of Moderna mRNA-1273, Pfizer-BioNTech BNT162b2 and AstraZeneca vaccines conferred 94.1%, 95.0% and 70.4% efficacy at preventing COVID-19, respectively [2-4]. No major safety concerns were reported [2-4]. Yet, data on the safety and efficacy of COVID-19 vaccines in immunocompromised patients are scanty.

The Advisory Committee on Immunization Practices cautions that in immunocompromised patients, immune response to vaccination may be reduced or absent, and underlines the importance of protective measures against COVID-19 even after vaccination [5]. Conversely, antibody testing is not recommended to assess immune response after vaccination with SARS-CoV-2 mRNA [5].

The best immunization window should be chosen according to the immunosuppression level and schedule. Immunosuppression occurs after ≥two weeks of glucocorticoids at the equivalent dose of 20 mg/d or prednisone at 2 mg/kg, methotrexate (MTX) at ≥0.4 mg/kg/week or azathioprine at ≥3.0 mg/kg/day (no indications are available regarding mycophenolate). Dosages below these levels may be considered as 'low-grade' immunosuppression [6]. Patients with severe AIBD might require 'high-grade' immunosuppression, especially during early phases of the disease, as opposed to AIBD patients with mild, localized or well controlled disease in maintenance therapy, who receive 'low-grade' immunosuppression [6]. Immunization should preferably occur during low-grade immunosuppression or before starting high-dose induction therapy. While no specific recommendations regarding discontinuation or tapering are warranted for glucocorticoids, MTX, azathioprine, and mycophenolate mofetil, caution is needed with rituximab [7]. It has been suggested that patients on rituximab may be vaccinated 12-20 weeks after completion of a treatment cycle [8], but reconstitution of the B cell compartment actually begins at around 6-9 months [8]. Inactivated influenza vaccine administration is not recommended within six months of receiving anti-B-cell antibodies, as an immune response from vaccination is highly unlikely [8].

In a recent study on the effects of ocrelizumab (anti-CD20 humanized antibody) on immune responses to common vaccines (tetanus toxoid, pneumococcal and influenza vaccines) in patients with multiple sclerosis, attenuated humoral responses were demonstrated [9]. Nonetheless, all considered, we believe immunization should not be postponed even if the expected efficacy might be lower.

Another issue is the introduction of anti-CD20 agents in patients already successfully vaccinated against COVID-19, as depleted B-cells may provide attenuated humoral response. In a recent study on patients affected by pemphigus vulgaris, rituximab treatment led to a statistically significant increase in anti-varicella zoster virus IgG and anti-Epstein-Barr virus IgG titres, while anti-dsg1 and anti-dsg3 specific autoantibody titres decreased significantly [10]. These findings were accompanied by significant elevation in B-cell-activating factor (BAFF), suggesting that BAFF levels might exert a differential effect on the induction of autoreactive versus pathogen-specific IgG antibody production in patients with pemphigus. Thus, starting rituximab in vaccinated patients might not necessarily reduce anti-SARS-CoV-2 antibody titres, but rather increase them.

A concern in particular might be the interference of SARS-CoV-2 with autoimmunity. A few cases of bullous pemphigoid and pemphigus vulgaris induced by other non-COVID vaccines have been reported but with no true epidemiological significance [11]. Patients with autoimmune diseases have been considered eligible participants in clinical trials [12] and preliminary data show no differences in the frequency of symptoms related to autoimmune conditions or inflammatory disorders in clinical trial participants who received a SARS-CoV-2 mRNA vaccine compared to placebo [12]. On the other hand, viral infection is a possible trigger of AIBD [13, 14] and SARS-CoV-2 seems to induce organ injury through alternative mechanisms beyond direct viral infection, including immunological injury [15]. Vaccines, by preventing a full-blown infection, may actually protect patients from a viral-triggered disease flare.

Contraindications to COVID-19 vaccination in immunocompromised individuals are the same as for the general population, namely a history of anaphylactic reactions to any components of the vaccine and ongoing moderate-severe acute illness. These are no absolute contraindications, but rather indications for vaccination deferral or prior referral to an allergist [12]. Special attention is warranted for patients with known allergies to one of the components of both mRNA vaccines, namely polyethylene glycol [2, 3].

In conclusion, on the one hand, clinicians should be aware that vaccinated AIBD patients could still develop COVID-19 because of a partial response, and therefore should continue all protective measures - as stated by CDC recommendations [5]. On the other hand, as AIBD patients are often elderly (bullous pemphigoid) or on high-dose immunosuppressive treatment (pemphigus vulgaris), they are at risk of severe COVID-19 and it is reasonable to immunize them according to the most appropriate window for each patient, even if the patient is on immunosuppressive therapy. ■

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Rheumatoid vasculitis mimicking cryptococcal infection

Rheumatoid vasculitis (RV) is a severe complication of rheumatoid arthritis (RA), characterized by cutaneous and systemic vasculitis affecting small or medium-sized vessels [1]. Differential diagnoses include other vasculitides and infections due to immunosuppressive treatment for RA. Disseminated cryptococcosis, which occurs primarily in immunocompromised patients, is a life-threatening systemic infection that can present with various skin manifestations, including papules, nodules, purpura, and ulcers [2]. Histological diagnosis of cryptococcosis is based on the identification of encapsulated yeast forms highlighted with periodic acid-Schiff (PAS) and mucicarmine stains. Here, we report an unusual case of RV that clinically and histologically mimicked disseminated cryptococcosis.

An 86-year-old man was admitted for fatigue, weakness, and skin lesions of the extremities. He had been receiving tocilizumab for RA, but this was discontinued two months before admission due to bacterial pneumonia. Physical examination revealed multiple purpuric papules and plaques on the extremities (*figure 1A*). Laboratory test results revealed normal leukocyte counts (4,290; normal range: 3,300-8,600/μL), elevated C-reactive protein levels (12.84; normal range: 0.00-0.14 mg/dL), and decreased C3 complement levels (46.3; normal range: 73-138 mg/dL). The patient was positive for rheumatoid factor (99.8; normal range: 0.0-15.0 IU/mL) and anti-cyclic citrullinated peptide antibody (352.0; normal range: 0.0-4.4 U/mL), and negative for proteinase-3- and myeloperoxidase (MPO)-anti-neutrophil cytoplasmic antibodies (ANCA). Clinically, the lesions were suggestive of RV or septic vasculitis, and treatment with empiric antibiotics (intravenous ampicillin/sulbactam) was initiated. Skin biopsy demonstrated leukocytoclastic vasculitis of the dermal vessels with infiltration of lymphocytes and neutrophils (*figure 1B, C*). Additionally, there were numerous yeast-like pale basophilic bodies surrounded by capsule-like vacuolated spaces in the dermis (*figure 1D*), suggesting cryptococcal yeast forms. However, PAS and mucicarmine staining failed to reveal basophilic bodies or surrounding vacuolated spaces, respectively (*figure 1E*). These cells were diffusely positive for MPO (*figure 1F*). Furthermore, blood and tissue cultures for bacteria and fungi, as well as a serum cryptococcal antigen test, were negative. Based on these findings, the patient was diagnosed with RV mimicking cryptococcal infection. Although additional immunosuppressive therapy was considered, rapid progression of multiple organ failure resulted in the death of the patient on Day 14 of hospitalization.

Histological mimics of cryptococcosis have recently been recognized for two skin diseases: neutrophilic dermatosis and leukocytoclastic vasculitis [3, 4]. The most characteristic feature is pale basophilic bodies with surrounding vacuolated spaces resembling cryptococcal organisms. Although the mimickers are indistinguishable from cryptococcosis on routine haematoxylin-eosin preparations, negative staining with PAS and mucicarmine is helpful for the diagnosis. Neutrophilic dermatoses mimicking cryptococcosis have been more frequently reported, and the term