INTRODUCTION

The definition of an adverse drug reaction (ADR), according to the World Health Organization (WHO), is “a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man.”

Mild symptoms of skin reactions after ADR can be urticaria, purpura, maculopapular rash, etc. The severe form of ADR, also called severe cutaneous adverse reaction (SCAR), includes Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP).

The main differences between SJS, SJS/TEN overlap, and TEN are the extent of exfoliating skin surface where SJS affects <10% of the body surface, TEN >20%, and SJS/TEN overlap 10%–20%. The most common cause of SJS/TEN is pharmaceuticals. The primary action of the treatment in SJS/TEN is the withdrawal of the drug suspected of causing the condition. Predicting the...
mortality in patients with SJS/TEN can be difficult; therefore, a severity-of-illness score for toxic epidermal necrolysis (SCORTEN) was created.6

Purpura fulminans (PF) is caused by disseminated intravascular coagulation (DIC) with dermal vascular thrombosis leading to hemorrhagic infarction of the skin and is similar to TEN in the way that they are both rare, life-threatening, difficult to diagnose, and goes with high mortality.7 Both diseases can involve flu-like early symptoms and epidermal detachment.

The extensive epidermal detachment in TEN, together with the concomitant immunosuppression increases the risk of a superimposed infection. Immunosuppressed patients can sometimes reactivate viruses, a rare case described in the literature is disseminated herpes infections.8 These infections with herpes zoster and herpes simplex virus increase the morbidity and mortality, and the diagnosis can be difficult.8

We here present a rare case of a patient suffering from TEN, who later passed away due to PF as a possible complication to a superimposed disseminated herpes simplex infection.

2 | CASE REPORT

A 52-year-old, previously healthy woman, was sent to her local hospital due to sudden confusion. She suffered from liver encephalopathy and alcohol induced hepatitis from ethyl overconsumption (6 standard units/day). On day 3, post-admission blood cultures showed Staphylococcus epidermidis. Along with liver inflammation, fever, swelling of the abdomen, and upper abdominal pain, portal vein thrombosis was suspected; a CT scan with contrast was done, and piperacillin-tazobactam was started.

On day 8 post admission, flat, or slightly raised, pink spots with dark red centers were noted. One day later blisters developed over her anterior neck and back, whereof some ruptured/exfoliating and initially diagnosed as Stevens–Johnson syndrome (SJS) by a dermatologist. Approximately 5% of the total body surface area (TBSA) was affected with blisters and a progression of dark red centers. No involvement of mucous membranes was seen. The patient was later the same day referred to our burn unit due to the progression of blisters. A positive Nikolsky sign9 was noticed on arrival.

After admission to the burn center, her wounds were exuding heavily and daily changes of polyurethane wound dressings were required. (Figure 1). Blistering and exfoliation progressed further and on day 10 from initial admission the affected area was assessed to 40% TBSA. The patient scored 3 on SCORTEN, which corresponds to a mortality of 35%–58%.6 Due to heavily leaking wounds, the patient was resuscitated with Ringer’s acetate infusion (50–100 ml/h) aiming for a diuresis of 40 ml/h. Blood cultures showed significant amounts of Staphylococcus Aureus, S. Epidermidis, and Escherichia coli. Cefotaxime 2 grams TID were started.

On day 12 from initial admission, the patient suddenly developed acute liver, kidney, and respiratory failure with deranged laboratory results with INR 2.6 >-3.5, thrombocytopenia $12 \times 10^9$ g/L. Together with the patient’s relatives a consensus discussion was held leading to a do-not-resuscitate (DNR) decision. The pathological–anatomical diagnosis of a skin biopsy taken at the local hospital demonstrated superficial dermatitis and epidermal necrosis, compatible with the initial diagnosis of SJS.

On day 13 from initial admission, INR continued to increase (3.7) and kidney function deteriorated with eGFR (CystC) of $33 \text{ ml/min/1.73 m}^2$. On wound inspection, a significant progression of the depth was seen, showing the dermal plate now fully exposed. (Figure 2).

On day 14 from initial admission, fingers and toes showed a purple discoloration and suspected thrombosis. A clinical suspicion of purpura fulminans (PF) was raised. (Figure 3) Due to the patient’s poor condition and the following DNR, the decision to cease intensive care was taken.

The patient passed away later the same day. An autopsy performed a week later describes macroscopic findings as hepatomegaly with 3.5 liters of ascetic fluid, ulcerations in the bladder and lung edema. On microscopic examination, the lesions in the skin revealed morphological changes ranging from single apoptotic keratinocytes to full, transepidermal necrolysis, consistent with the previously diagnosed as SJS and later TEN. In the lesions causing the clinical suspicion of PF, there were additional findings consisting of dermal hemorrhage and numerous small thrombi in the superficial dermal capillaries, thus confirming the diagnosis.

Multinucleated giant cells with pale staining nuclear inclusion bodies were present in the dermis, thus rising suspicion of a viral infection. (Figure 4) When inspecting...
the hemorrhaged areas in the urinary bladder, similar cellular changes were revealed, (Figure 5) as well as in the hepatic parenchyma. Due to these findings, immunohistological staining was performed, showing manifestation of herpes simplex virus in the bladder and lungs. Due to autolysis, the immunohistological staining of skin and liver was judged uncertain. In the bladder, however, the immunostaining also showed positive cells intravasally (Figure 6), strengthens the suspicion of a disseminated herpes simplex infection.

3 | DISCUSSION

The underlying thrombosis in PF can lead to cutaneous hemorrhage, together with a broad epidermolysis this can mimic clinical features of TEN. A case report from Cotliar et al10 (2012) describes a meningococcal PF resembling SJS features, and this case describes the challenge of differentiating SJS/TEN from a patient with PF presenting with bullae. The histopathological analysis can be helpful, and an early clinical recognition could help prevent the progression.

Our patient most probably reacted to contrast given in connection with her CT scan, causing a reaction leading to SJS. The patient had a confirmed sepsis on blood culture with three different types of bacteria, none of them usually connected to acute infectious PF and responded poorly to given therapy. On day 14 post admission, clinical suspicion of PF was made when purple toes and fingers were noted, suggesting thrombosis.
To our surprise, the microscopic and immunochemical examination following the autopsy did not only find microthrombi in dermal venules and capillaries confirming the clinical suspicion of PF but also a disseminated herpes simplex infection, morphologically originating from the bladder. In a case-control study\(^ {11}\) (2002) aimed to differ SJS and TEN from EM by localization and skin lesions, the authors found that herpes infections played no role in the SJS-TEN overlap. This study also concluded that the herpes infection played a significant role in SJS and TEN and that it can be a main risk factor in milder forms, also described in the case-control study by Auquier-Dunant A et al.\(^ {11}\)

The combination of PF and a disseminated herpes simplex infection is very rare, and to our knowledge, no similar case has been reported. We speculate that the clinical route of this case started with the immunosuppressive state of the patient following SJS and TEN, leading to superimposed infection with three different types of bacteria, confirmed in blood cultures, and a disseminated viral infection (herpes simplex) which was discovered at the autopsy. The patient received antibiotic treatment but developed DIC and eventually PF and passed away due to systemic organ failure. The delayed diagnosis of a disseminated herpes infection has been described before,\(^ {8}\) and our patient had a similar course with a delayed diagnosis and was first diagnosed with a disseminated herpes infection following the autopsy.

**FIGURE 6** Section from the bladder, with IHC staining for herpes simplex virus, with examples of positive staining cells intravasally (arrow) and in surrounding stroma (arrowheads)

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**4 | CONCLUSION**

We describe this complex case with the diagnosis of SJS, TEN, DIC, PF, and herpes simplex infection. The combination of all these diagnoses is very rare, no similar case has been described in adults to the authors’ knowledge. We recommend a prompt diagnosis and early recognition of both bacterial and viral infections to prevent the development of PF. Patients with an initial presentation of TEN and infections should call the attention for the risk of developing PF.

The clinical and microscopic relationship with the diagnoses described above need further investigations to help manage these rare conditions.

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None.

**CONFLICTS OF INTEREST**

Herewith, I do declare that neither do I nor my co-authors have conflicts of interest and that there are no financial and personal relationships with other people or organizations that could in appropriately influence our work.

**AUTHOR CONTRIBUTION**

Author 1 initiated the process of writing the manuscript and the main writer of the manuscript. Author 2 contributed to writing the manuscript together with author 1. Author 3 contributed to a review and clinical expertise. Author 4 is the main reviewer and responsible for writing and clinical guidance.

**ETHICAL APPROVAL**

None.

**CONSENT**

Written Consent from the patient: Yes.

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

**DATA AVAILABILITY STATEMENT**

Data sharing not applicable to this article as no data sets were generated or analyzed during the current study.

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