

Haemophagocytic Lymphohistiocytosis Following Severe Erysipelas with EBV Reactivation

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Secondary haemophagocytic lymphohistiocytosis (HLH) is a potentially life-threatening hyperinflammatory syndrome that may mimic sepsis and should be considered in patients with persistent fever, cytopenias, organomegaly and marked hyperferritinaemia (1). Dermatological manifestations of HLH are heterogeneous, but erysipelas or cellulitis as a precipitating event is very rarely documented; cellulitis-like presentations may also reflect opportunistic infection or occult lymphoma (2–9). We report a case of steroid-responsive HLH developing during treatment of severe streptococcal erysipelas, accompanied by transient EBV-DNAemia.

copies/mL, while CMV-DNA was negative. Hepatitis screening revealed positive anti-HCV antibodies and a positive confirmatory line immunoassay, but HCV-RNA was negative; HBV-PCR was also negative.

Flow cytometry was limited by low cellularity but showed T-cell predominance, an inverted CD4/CD8 ratio of 0.48, low B-cell numbers and no evidence of a circulating malignant population. Bone marrow examination, performed after initiation of intravenous high-dose corticosteroid therapy, did not reveal haemophagocytosis. However, absence of haemophagocytosis, particularly after treatment initiation, did not exclude

CASE REPORT

A 44-year-old patient was transferred to our dermatology department because of severe erysipelas of the left leg, accompanied by chills, fever, extensive erythematous swelling, blistering and erosions, with marked distal accentuation (**Fig. 1**). Initial laboratory evaluation showed marked leukocytosis and elevated C-reactive protein (CRP). A profoundly increased anti-streptolysin titre of 17,586 U/mL supported ongoing or recent streptococcal immune stimulation, whereas repeated blood cultures remained negative for bacterial and fungal growth.

Despite gradual improvement of the cutaneous findings and initial defervescence during 3 weeks of broad-spectrum combination antibiotic therapy, the patient developed recurrent high fever of up to 39.7°C and marked pancytopenia, with leukocytes decreasing to $0.53 \times 10^9/L$, platelets to $54 \times 10^9/L$ and erythrocytes to $2.82 \times 10^{12}/L$. Peripheral blood smear showed pronounced erythrocyte anisocytosis, reduced platelets and almost complete absence of nucleated cells, with no circulating blasts or pathological cells. Laboratory findings revealed hyperferritinaemia up to 28,256 µg/L, hypertriglyceridaemia up to 413 mg/dL, hypofibrinogenaemia of 1.52 g/L, elevated soluble interleukin-2 receptor levels of 176 RU/mL, markedly increased lactate dehydrogenase of 4,385 U/L and CRP peaking at 326.44 mg/L. Abdominal ultrasound demonstrated hepatosplenomegaly. Liver involvement was reflected by AST elevation up to 518 U/L, whereas ALT was only moderately increased up to 57 U/L. EBV-DNA was detectable at 8,520



Fig. 1. Severe erythema, blistering, swelling and erosions involving the entire left leg, most pronounced on the lower part.

HLH. Hence, the HScore, a validated clinical and laboratory score estimating the probability of reactive HLH, was 284, corresponding to a >99% probability of HLH (1).

High-dose intravenous corticosteroid therapy resulted in rapid clinical and laboratory improvement. The patient became afebrile within the first days, ferritin and transaminases decreased markedly, and EBV-DNA became undetectable after 99 of treatment. After 5 weeks, the patient was discharged with complete normalization of the blood count and undetectable EBV-DNA in EDTA blood. Ferritin had decreased to 624, transaminases were nearly normal, and CRP had fallen to 15.51, while triglycerides remained moderately elevated. Corticosteroids were tapered gradually, and close short-term clinical and laboratory monitoring was scheduled.

DISCUSSION

This case illustrates the diagnostic difficulty of HLH emerging in the setting of an apparently improving bacterial skin and soft-tissue infection. The exceptionally high anti-streptolysin titre supported a strong streptococcal immune stimulus, but erysipelas alone is not an established HLH trigger. EBV-DNAemia was only moderate and became rapidly undetectable under corticosteroid therapy; therefore, EBV should be interpreted as a plausible contributor or amplifier of immune activation rather than as proven primary cause of HLH in this case (10). Moreover, LDH was strikingly elevated, supporting extensive systemic cell turnover and tissue injury, although not part of formal HLH criteria. Alternative infectious and malignant conditions were considered: repeated blood cultures remained negative, CMV-DNA, HBV-PCR and HCV-RNA were negative, and peripheral blood smear and flow cytometry did not provide evidence of leukaemia or a circulating lymphoid malignancy; bone marrow examination did not reveal haemophagocytosis. Nevertheless, cellulitis-like lesions in HLH should prompt careful exclusion of mimickers, particularly disseminated fungal infection and subcutaneous panniculitis-like T-cell lymphoma (7–9).

In this clinical context, recurrent fever, cytopenias and hyperferritinaemia despite improving skin findings should prompt immediate HLH work-up.

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Consent for publication: Written informed consent for publication of the clinical details and clinical images was obtained from the patient.

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