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Letter to the Editor

Letter to the Editor (Case report)

Brain oedema due to disseminated intravascular coagulation in a patient with adult-onset Still's disease–associated hemophagocytic lymphohistiocytosis—a case report

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Rheumatology key message

- Neurologic symptoms in adult-onset Still's disease should trigger suspicion and prompt treatment of secondary hemophagocytic lymphohistiocytosis.

Dear Editor, Adult-onset Still's disease (AOSD) is an autoinflammatory disease with to-date unexplained aetiology. Secondary hemophagocytic lymphohistiocytosis (HLH), here referred to as macrophage activation syndrome HLH (MAS-HLH) is *the* most devastating complication of AOSD [1]. Signs of evolution include antibiotic-resistant fever, hepatosplenomegaly, hyperferritinaemia, hypertriglyceridaemia, fibrinogen consumption, bi- or trilinear cytopenia, as well as hemophagocytosis in bone marrow [2]. Yet, low sensitivity and diagnostic delay of bone marrow histopathology, baseline hyperferritinaemia and organomegaly make prompt recognition of MAS-HLH particularly challenging in the context of AOSD. However, rigorous and instant immunosuppressive therapy upon recognition is lifesaving [1].

Herein, we report a 23-year-old Caucasian woman who had been diagnosed with AOSD 2 years ago based on recurrent febrile episodes including pharyngitis, cervical lymphadenopathy, salmon-coloured rash (Fig. 1A), arthritis, lymphadenopathy and hepatosplenomegaly (informed consent has been obtained from relatives). Treatment with MTX (15 mg/week s.c.), anakinra (100 mg/day s.c.) and tocilizumab (162 mg/week s.c.) was not effective, and she was dependent on low- to medium-dose glucocorticoids (up to 20 mg prednisolone per day). Ten, 6 and 2 weeks before the events reported here, the patient experienced disease flares after discontinuation (initially) or tapering (more recently) of prednisolone, respectively, and had to be treated with high-dose prednisolone (60 mg/day) to blunt fevers. Canakinumab (300 mg/4 weeks) was initiated as an approved steroid-sparing agent. Lymph node histology and bone marrow puncture were obtained to exclude lymphoma or multicentric Castleman's disease. At this stage (2 weeks prior to her final admission), suspected MAS-HLH was not confirmed by histological bone marrow examination. However, F-fluorodeoxyglucose (FDG)-PET-CT scan had revealed focal hepatic tracer enhancement of uncertain significance (Fig. 1B). Aside from mild anaemia, cytopenia was absent, and elevated serum ferritin levels (up to 4500 pg/ml) decreased upon prednisolone therapy (Fig. 1C).

Seven days post discharge, the patient returned to the emergency room with high fever which had been ongoing for 2 days despite 40 mg of oral prednisolone. In addition, she demonstrated sinus tachycardia up to 160 bpm and circulatory failure—her lactate level at admission was 5 mmol/l and

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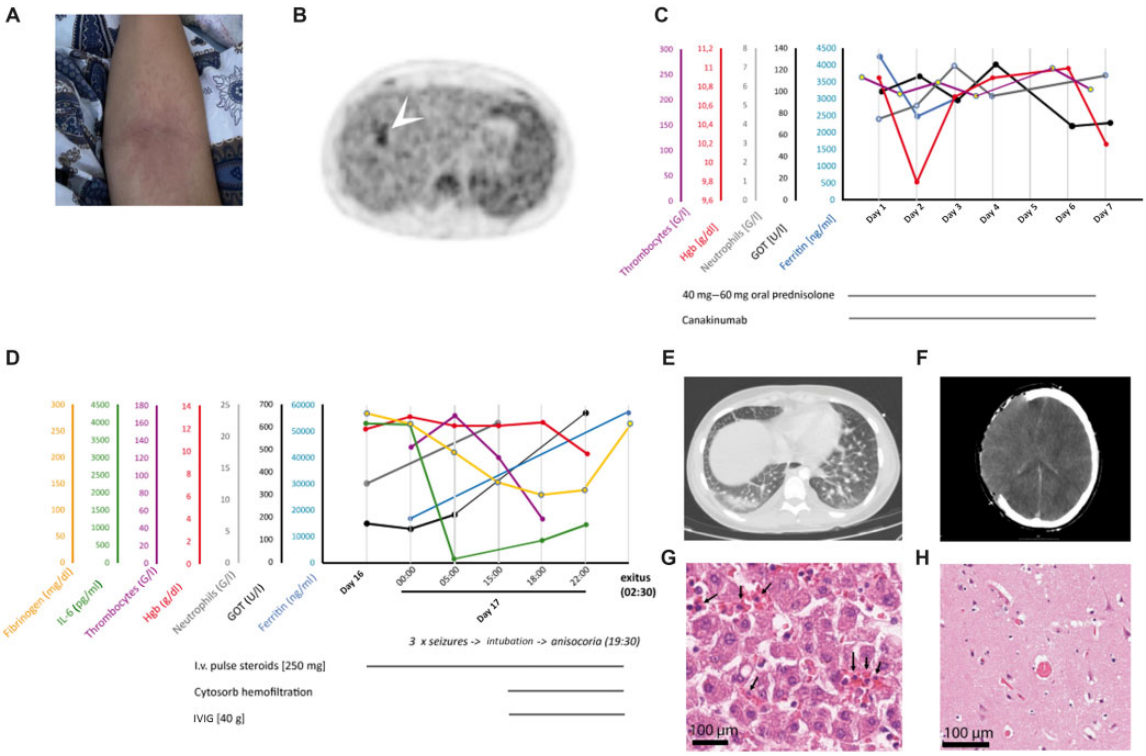

Figure 1. Clinical course and histopathological autopsy findings. **(A)** Salmon-coloured rash on the patient's elbow bend during AOSD disease flares. Permission was obtained from relatives. **(B)** PET-CT scan recorded 2 weeks prior to her final admission documenting focal F-fluorodeoxyglucose (FDG) uptake in liver (white arrow) and spleen. **(C)** Time course of patient's thrombocyte counts, haemoglobin (Hgb) levels, neutrophil counts, Glutamat-Oxalacetat-Transaminase (GOT) and ferritin levels 2 weeks prior to her final admission upon treatment with 40 mg of prednisolone and canakinumab. **(D)** Time course of patient's fibrinogen and IL-6 levels, thrombocyte counts, haemoglobin (Hgb) levels, neutrophil counts, Glutamat-Oxalacetat-Transaminase (GOT), and ferritin levels upon final admission (24 hours). **(E)** CT scan performed at day 16 upon final admission demonstrated bi-pulmonal basal infiltrates. **(F)** Cranial CT scan depicting malignant brain oedema despite hemicraniectomy. **(G)** Hematoxylin and eosin (HE) stain (×40) demonstrates hepatic sinusoidal hemophagocytosis, more precisely phagocytes incorporating erythrocytes (→) and some leucocytes. **(H)** HE stains demonstrate oedematous cortical brain tissue (frontal cortex right) with pyknotic neurons and clotted capillaries. In view of the preceding aberrations of plasmatic coagulation (raised D-Dimer, fibrinogen consumption), this was considered to reflect disseminated intravascular coagulation (DIC). There was no evidence of an additional inflammatory or malignant intracerebral disease, i.e. intravascular lymphoma, atypical infections, demyelinating or necrotizing encephalopathies

volume therapy and vasopressors were initiated. Blood cell counts revealed neutrophilic leucocytosis, stable anaemia and no sign of thrombocytopenia. The patient's fibrinogen levels were still normal (Fig. 1D). Further work-up revealed a strong systemic inflammatory response, as evidenced by massively elevated IL-6 (3974 pg/ml, Fig. 1D) and procalcitonin (37 ng/ml). The latter, however, does not allow discrimination of sepsis in the context of haematological disorders or HLH [3]. CT scan demonstrated bi-pulmonal basal infiltrates (Fig. 1E).

Due to suspicion of MAS-HLH, the patient was immediately put on high-dose i.v. prednisolone (250 mg) in addition to broad-spectrum antimicrobial treatment (Meropenem, Linezolid and Caspofungine). Vasopressor doses and lactate levels (minimum: 3 mmol/l) declined for the next 8 h. When the patient developed seizures, she was intubated. Sensitive HLH disease markers, i.e. ferritin (16 000 ng/ml) and soluble IL-2 receptor (14 256 U/ml), were massively elevated, suggesting accelerated macrophage and T cell activation, respectively [4]. In addition, fibrinogen levels dropped (Fig. 1D). Immunosuppression/immunomodulation was meanwhile escalated to Cytosorb® filtration and IVIG (40 g). Nevertheless, the patient developed progressive acute respiratory distress syndrome and anisocoria that rapidly evolved into bilateral fixed pupils secondary to fulminant brain oedema (Fig. 1F). Despite immediate hemicraniectomy, clinical brain death was inevitable, and thus further escalation of immunosuppression with plasmapheresis and etoposide were discontinued.

Thereafter, histopathologic work-up revealed massive cellular infiltrates and evidence of hemophagocytosis in the patient's spleen, lungs and liver (Fig. 1G). Retrospectively, FDG-PET liver enhancement detected earlier might have reflected early organ-specific MAS-HLH activity. Brain tissue showed oedema secondary to intravascular microthrombi due to disseminated intravascular coagulation (DIC; Fig. 1H). Thus, MAS-HLH–associated massive inflammation caused DIC, which likely led to cerebral microthrombi, ischaemia and ultimately brain oedema. Infectious disease work-up including blood cultures, virus serology, PCR screening, and histopathologic evaluation for potential differential diagnoses (such as lymphoma or acute necrotizing encephalopathy) were unremarkable. Whole-genome sequencing did not reveal underlying primary HLH or other disease-causing variants.

The fatal course teaches some lessons. First, although cerebral involvement is much more frequent in childhood primary HLH, it may be as fatal in adult MAS-HLH. In this regard, rare complications of AOSD, namely necrotizing leukoencephalopathy due to DIC and MAS-HLH, as well as thrombotic thrombocytopenic purpura with subsequent malignant brain oedema have been reported [5, 6]. Unique to our case is the poly-trauma-like dynamic from admission to malignant brain oedema within 24 h justifying rigorous immunosuppression, e.g. direct use of etoposide, in particular in cases with neurological symptoms.

Second, the HLH 2004 criteria and the Hscore [7] are suboptimal for detecting MAS-HLH in AOSD, because their clinical features, transaminitis and hyperferritinaemia are similar by nature. The MAS/systemic JIA (MS) score that has been developed for diagnosing MAS-HLH in systemic JIA might be superior, as it relies on more specific clinical parameters for detecting transition to MAS-HLH [8]. However, its validation for AOSD is pending.

Finally, more data is needed on secondary MAS-HLH with respect to early detection, risk stratification, and which immunosuppressive agents to choose in a setting in which sepsis persists as a major differential diagnosis.

Data availability statement

Further data on this case can be obtained in anonymised form from the corresponding author on reasonable request. The data underlying this article cannot be shared publicly due to privacy reasons.

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