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Case report

Catastrophic hemophagocytic lymphohistiocytosis in a young man with nephrotic syndrome

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ABSTRACT

Background: In its early stage, necrotizing fasciitis mimics a milder cutaneous infection, such as cellulitis, and is an uncommon but potentially fatal complication of nephrotic syndrome. It may trigger an uncontrolled and catastrophic immune response, such as hemophagocytic lymphohistiocytosis (HLH).
Case report: A 19-y-old man presented with steroid-resistant nephrotic syndrome and rapidly progressing *Escherichia coli* monomicrobial necrotizing fasciitis with bacteremia. The conditions developed one day after steroid therapy, leading to multiple organ dysfunction syndrome. A provisional diagnosis of HLH was promptly made, based upon the patient's fever, unremitting shock, marked pancytopenia, hyperferritinemia, hypofibrinogenemia, and the typical histiocytic hemophagocytosis in pleural effusion. Despite aggressive medical treatment and organ support, the patient died 8 days after transfer to our intensive care unit. Final bone marrow examination confirmed the diagnosis of HLH.
Conclusions: Although nephrotic syndrome associated with *E. coli* infection is common, this is the first reported case of *E. coli* monomicrobial necrotizing fasciitis with bacteremia resulting in HLH in a patient with nephrotic syndrome.

1. Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a potentially lethal syndrome, resulting from excessive activation and proliferation of non-malignant macrophages, characterized by hemophagocytosis in the reticuloendothelial system [1]. Aside from the primary form of HLH (familial), which is caused by inherited immune deficiencies that are typically symptomatic during infancy or early childhood, acquired HLH can occur throughout a patient's lifetime, triggered by underlying disorders such as severe infections, malignancies, autoimmune diseases, drug use, or AIDS [2]. Interestingly, infection-associated HLH shares its hyperinflammatory pathophysiological characteristics and clinicopathological features with severe sepsis and other related syndromes [3,4]. The predominant pathogens that cause infection-associated HLH are viruses, while bacterial infections triggering HLH are rarely reported [2,5].

2. Case report

A 19-y-old man, diagnosed with nephrotic syndrome secondary to idiopathic IgM nephropathy 6 months earlier, was admitted due to relapsed swelling of lower legs and progressive dyspnea, having gained 9 kg in the preceding week. He exhibited poor treatment response to oral prednisolone, cyclosporine, and mycophenolate, with constant heavy proteinuria (11.8–16.3 g/day) and hypoalbuminemia (1.0–1.9 g/dl). On admission, his body temperature was 36.1 °C; heart rate, 86 beats/min; respiratory rate, 20 breaths/min; blood pressure, 132/68 mm Hg; and room air SaO_2, 98%. Physical examinations revealed anasarca and diminished bibasilar breath sounds, compatible with the bilateral pleural effusion shown on the chest plain film. Laboratory tests showed urinary protein loss of 20.2 g/day, serum albumin 0.8 g/dl, serum creatinine 2.0 mg/dl, and serum IgG 473 mg/dl. Based on this data, a relapse of nephrosis and acute kidney injury was diagnosed.

After excluding notable infections, we initiated a 3-day high-dose methylprednisolone therapy (250 mg/day), with oral proton pump inhibitor and intravenous loop diuretics, human albumin and heparin. Following the 3-day treatment, the anasarca and pleural effusion had partially resolved. However, the patient subsequently developed fever

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(38.9 °C) and tender erythematous swelling with head and pain on the lateral aspect of the left thigh during the evening of the 4th day after admission. We immediately administered intravenous oxacillin (2.0 g every 4 h) for suspected cellulitis, after collecting blood cultures. Considering his worsening pain, and the redness that was rapidly spreading to the left buttock, we performed non-contrast computed tomography in the 5th day, which revealed diffuse subcutaneous swelling and extensive fluid accumulation between the subcutaneous layer and superficial muscle layer. From this result, a presumptive diagnosis of necrotizing fasciitis was made.

Twelve hours after observing the skin lesion, the patient was transferred to the intensive care unit (ICU) for acute respiratory failure and septic shock, with pancytopenia and surging C-reactive protein (CRP) levels (white cell count 700/μl, hemoglobin 5.7 g/dl, platelets 69,000/μl, CRP 27.1 mg/dl). We applied mechanical ventilator support, early goal-directed therapy with broad-spectrum antibiotics (imipenem and daptomycin) and continuous venovenous hemodiafiltration for rapidly progressive multiple organ dysfunction syndrome (MODS). MODS symptoms included coma, hypoxic respiratory failure, refractory shock with anuria, disseminated intravascular coagulation, pancytopenia with low reticulocyte index and fulminant hepatitis. Portable ultrasound revealed remarkable bilateral pleural effusion, and therefore urgent fasciotomy and thoracentesis were performed. We isolated *Escherichia coli* from all necrotic tissues, exudate, and pleural effusion. Tests for viral (cytomegalovirus, Epstein–Barr virus, herpes simplex, varicella

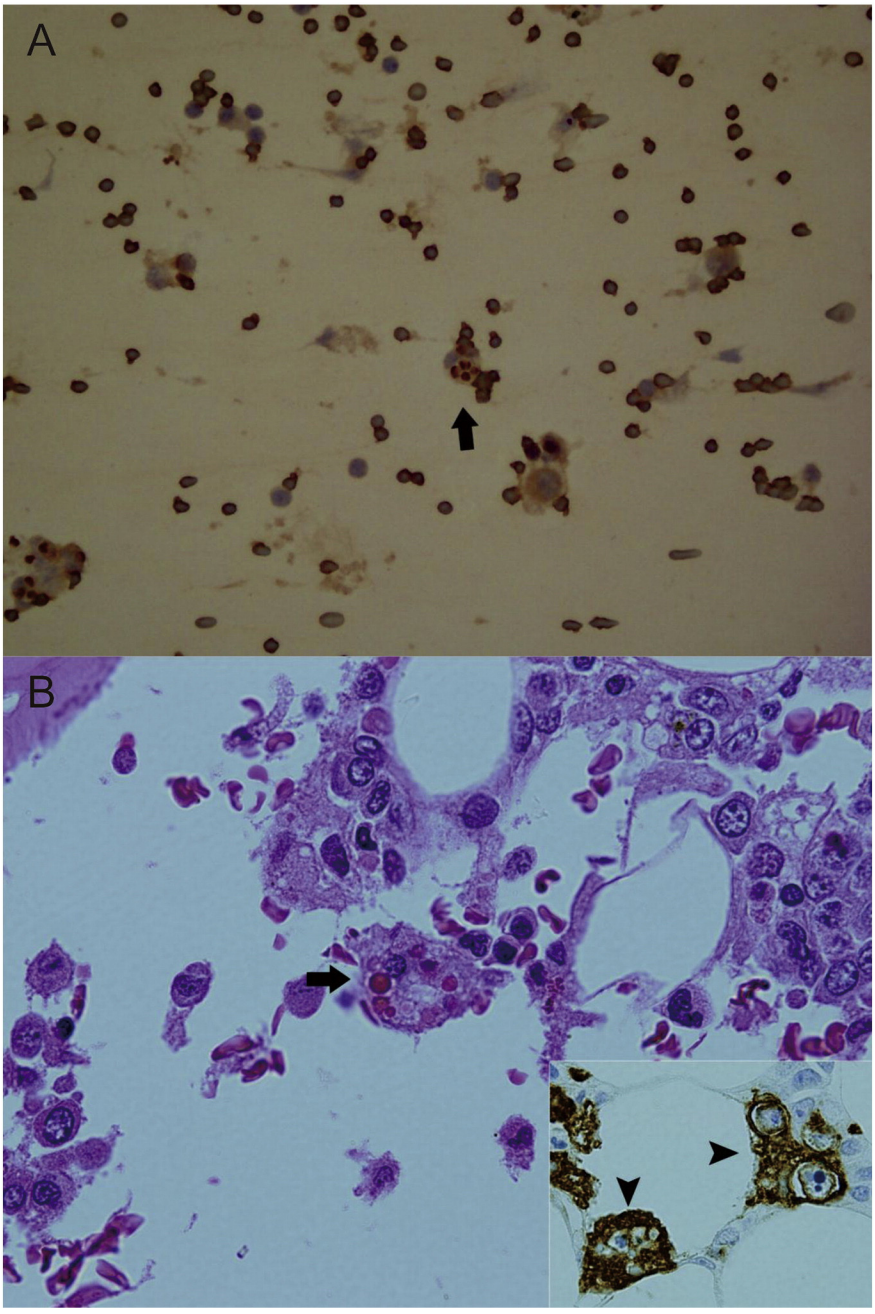

Fig. 1. Pathological findings in pleural effusion cytology and bone marrow aspiration. (A) Active macrophages (arrow) in the pleural effusion with hemophagocytosis of erythroid and other nucleated elements (Myeloperoxidase stain, ×400). (B) A bone marrow aspiration reveals active macrophages with phagocytosis of degenerated erythrocytes (arrow) and nucleated cells. The small inserted image (lower right corner) for CD68 highlights a hemophagocytic macrophage with erythroid and myeloid cells (arrowhead) within its cytoplasm (Hematoxylin and eosin stain, ×1000).