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SHORT REPORT

Hemophagocytic syndrome in a child with severe Crohn's disease and familial Mediterranean fever☆

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a rare, potentially fatal, severe condition of hyperinflammation caused by the uncontrolled proliferation of activated lymphocytes and histiocytes secreting high amounts of inflammatory cytokines. Here we report a fatal hemophagocytic syndrome in a 11-year-old boy with a diagnosis of both Crohn's disease receiving immunosuppressive therapy and familial Mediterranean fever. It is important to evaluate the patients with inflammatory bowel disease receiving immunosuppressive therapy presenting with unexplained fever, cytopenia, progression of organomegaly and biochemical changes for the investigation of HLH for diagnosis and treatment.

1. Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare, potentially fatal, severe condition of hyperinflammation caused by the uncontrolled proliferation of activated lymphocytes and histiocytes secreting high amounts of inflammatory cytokines.[1] HLH comprises two different conditions that may be difficult to distinguish from one another: 1—the primary or genetic HLH, which occurs in familial forms (FHLH), in which HLH is the primary and only manifestation, and in association with immune deficiencies, and 2—secondary (acquired) (s)HLH.[2] We herein report an 11-year-old boy with Crohn's disease (CD) and familial Mediterranean fever (FMF) who developed fatal hemophagocytic syndrome during the course of disease.

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2. Case report

The patient, whose parents were first cousins, first presented to the hospital at the age of 9 years with complaints of mucous bloody diarrhea, abdominal pain, vomiting, and fever since the age of 1. He had three living and three deceased siblings, who died before 1 year of age. Malnutrition and clubbing were noted on his physical examination. Laboratory evaluation revealed anemia and elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels. Endoscopic examination with biopsy of the upper gastrointestinal tract showed chronic inflammation without granuloma. Colonoscopy revealed widespread aphtoid ulcers with normal appearing mucosa between them. Histology was consistent with areas of ulcerations, active colitis with severe mixed inflammatory cell components, few crypt abscesses, few crypt distortion and without granuloma. Mild to moderate inflammation of terminal ileum was observed with mixed inflammatory cell components. He was diagnosed as CD at the age of 9 years. Treatment with mesalamine, prednisolone, and azathioprine was started. During the follow-up, he was also hospitalized for recurrent abdominal pain, and swelling, pain and tenderness of joints. After further investigations, he was also diagnosed as FMF as he had clinical features of FMF and had been identified as carrying compound heterozygote MEFV mutations (M694V/E148Q); colchicine was started at the age of 10. During the follow-up, he experienced severe exacerbations of CD as prednisolone was tapered, resulting in treatment with increased prednisolone doses. Despite intensive therapy, complete remission could not be achieved.

Two years after the diagnosis of CD, he was hospitalized again with persistent fever, bloody diarrhea, vomiting, abdominal pain, weight loss, and fatigue. He was pale and cachectic. His weight and height were below the 3rd percentiles for age. Abdominal examination revealed hepatosplenomegaly and diffuse tenderness especially localized at the right lower quadrant. The laboratory data at the time of presentation showed anemia (hemoglobin 6.6 g/dl), leukopenia (1000/mm^3), neutropenia (absolute neutrophil count: 160/mm^3), increased ESR (90 mm/h), positive CRP (15 mg/dl), and hypoalbuminemia (2.0 g/dl). Ultrasound examination of the abdomen revealed diffuse thickening of walls of the small bowel and right colon and mesenteric lymphadenopathies. The patient was placed on bowel rest with total parenteral nutrition. Elevated ferritin (672 ng/ml) and fasting triglyceride (261 mg/dl) were also observed. A bone marrow examination showed an increase in the number of histiocytes and intense hemophagocytosis (Fig. 1). No sign of malignancy was evident. Based on these findings, a diagnosis of hemophagocytic syndrome was made and intensive immunosuppressive therapy was started. He was then treated with methylprednisolone (2 mg/kg), intravenous immunoglobulin (0.5 g/day for 3 consecutive days), and cyclosporine. Azathioprine use was discontinued and oral mesalamine therapy was continued. A blood transfusion of both erythrocytes and platelets was frequently performed. Granulocyte colony-stimulating factor was given because of severe neutropenia, but the neutropenia persisted against therapy. He also received broad-spectrum antibiotics for neutropenic fever.

The family was first analyzed by homozygosity testing for the three genes known to be responsible for the pathologies observed in FHLH patients. Blood samples were taken from the patient and family members after obtaining written informed consent. DNA was extracted using standard protocols. Linkage analysis was performed by using at least 5 microsatellite markers flanking each of the genes, and no homozygosity was observed for PRF1, UNC13D and STX11 genes. This study was approved by the Hacettepe University Ethical Board (approval number: TBK 05/19-25).

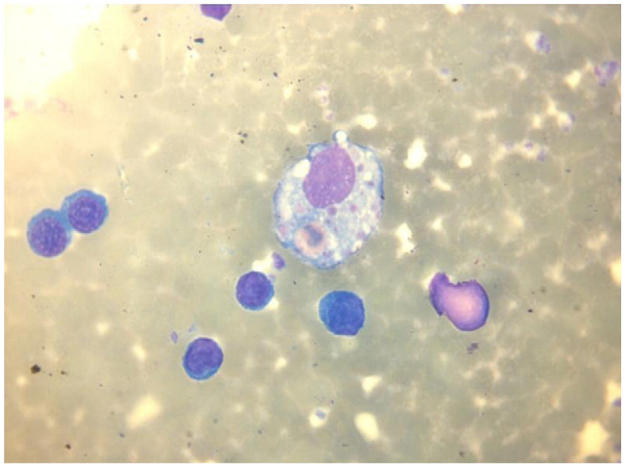

Figure 1 Bone marrow aspirate of the patient showing phagocytosis of eryhtrocyte and platelets (Wright stain ×400).

The causes that may lead to sHLH were investigated by performing virologic and bacterial studies. Serum immunoglobulin G antibodies against Epstein–Barr virus (EBV) virus capsid antigen (VCA) were present, but IgM antibodies against VCA were negative. Polymerase chain reaction of blood was negative for EBV, cytomegalovirus and parvovirus B19. Other viral studies including human immunodeficiency virus (HIV), herpes simplex virus, hepatitis A–B–C viruses, and varicella zoster virus were also negative. Tuberculin skin test was nonreactive. Multiple induced sputum samples were also negative for acid-fast organism. One of the blood cultures was positive for *Acinetobacter baumannii* on the 10th day of admission to the hospital, but other multiple cultures of blood, urine and stool were negative for diagnostic bacterial, fungal, mycobacterial, or parasitic organisms. During the course, despite this intensive treatment, his condition deteriorated; fever persisted, pancytopenia worsened (hemoglobin: 5.4 mg/dl, leukocyte: 800/mm^3, thrombocyte: 11000/mm^3) and massive hematochezia developed. Because the patient's bleeding continued despite medical interventions, he underwent emergency exploratory laparotomy. Multiple bleeding sites were diffuse throughout the small bowel and colon, and there were fistulas and dense adhesions between the small bowel and colon. No surgical resection was possible and he died 41 days after admission.

3. Discussion

This case describes a pediatric patient with concurrent CD and FMF who developed hemophagocytic syndrome. HLH is diagnosed based on the presence of five of the following eight disease criteria of the HLH Histiocyte Society: persistent fever, splenomegaly, cytopenias involving two or more cell lines,