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CASE REPORT

Hemophagocytic lymphohistiocytosis in leprosy

LIV R. HØYVOLL*, YNGVAR FLØISAND**,
HILDE LANG ORREM***,
RAGNAR GUNNARSSON****, LINN LANDRØ*****,
TRINE BREVIG******, PETER GAUSTAD*******
& INGVILD NORDØY*
**Section of Clinical Immunology and Infectious Diseases, Oslo University Hospital, Rikshospitalet, Norway*
***Dept. of Haematology, Oslo University Hospital, Rikshospitalet, Norway*
****Dept. of Intensive Care Medicine, Oslo University Hospital, Rikshospitalet, Norway*
*****Section of Rheumatology, Oslo University Hospital, Rikshospitalet, Norway*
******Section of Dermatology, Oslo University Hospital, Rikshospitalet, Norway*
*******Dept. of Pathology, Oslo University Hospital, Rikshospitalet, Norway*
********Dept. of Microbiology, Oslo University Hospital, Rikshospitalet, Norway*

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Summary A patient from Southeast Asia was diagnosed with systemic lupus erythematosus. One year later, she experienced exacerbation of skin lesions and was diagnosed with erythema nodosum leprosum. Upon treatment, the patient developed hemophagocytic lymphohistiocytosis with multi-organ failure and died from invasive fungal infection. Hemophagocytic lymphohistiocytosis has to our knowledge, not previously been reported in leprosy.

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare, potentially life-threatening immunological disorder characterised by uncontrolled accumulation of activated

Correspondence to: Ingvild Nordøy, Section of Clinical Immunology and Infectious Diseases, Dept. Rheumatology, Dermatology and Infectious Diseases, Division of Cancer Medicine, Surgery and Transplantation, Oslo University Hospital, Rikshospitalet N-0424 Oslo, Norway (Tel: +47 23070000; Fax: +47 23070550; e-mail: inordoy@ous-hf.no)

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macrophages and T-lymphocytes in various organs.[1] The condition may result in multi-organ failure and left untreated can be fatal. A genetic form has been described caused by impaired natural killer cells and cytotoxic T-cells.[2,3] In adults a reactive form is more common, and may be triggered by and thus complicate malignancies, autoimmune disorders and infections.[4] We describe a patient with erythema nodosum leprosum misdiagnosed as systemic lupus erythematosus, who upon treatment for leprosy developed hemophagocytic lymphohistiocytosis.

Case report

A previously healthy patient in her late twenties, originally from Southeast Asia, was admitted to the Section of Rheumatology with erythematous skin lesions, arthritis, Raynaud's phenomenon and fever. The initial blood-samples showed anemia, leukopenia, sedimentation rate 67mm, CRP 18mg/L, slightly elevated liver-enzymes and serum ferritin 1837μg/L. Both anti-nuclear antibody titer and anti-ribonucleoprotein antibody titer were elevated. A skin biopsy showed sub-acute inflammation with edema and extravasation of erythrocytes. The immunohistochemistry assay was negative, and the findings were compatible with small-vessel vasculitis. A bone-marrow biopsy revealed signs of mild hemophagocytosis. Further investigations revealed no signs of malignancies or viral infection and a diagnosis of systemic lupus erythematosus was made. She responded successfully to therapy with prednisolone, hydroxychloroquine and azathioprine.

One year later, the patient developed fever and a generalised nodular exanthema particularly affecting her face. Erythema nodosum developed on both lower limbs. A computer tomography scan revealed mild lymphadenopathy. The symptoms and signs were perceived as a flare of systemic lupus erythematosus. The patient was treated with increased doses of corticosteroids without effect on her condition. A new skin biopsy demonstrated infiltrates of histiocytes in the dermis and subcutaneous fatty tissue. Several round to oval inclusion bodies were seen. When staining with the Auramin-Rhodamine procedure, nests of rods were seen particularly in the inclusion bodies, indicating a multi-bacillary infection. DNA extracted from the skin biopsy was amplified by polymerase chain reaction (PCR) (ABI Prism 3730 DNA analyzer, Applied Biosystems, Forster City, USA) using two primers within the 16S rDNA. The obtained sequence was compared to sequences at the National Center of Biotechnology Information database, BLAST, and demonstrated 100% homology with a sequence of Mycobacterium leprae. A bone-marrow biopsy showed large infiltrations of macrophages containing acid-fast rods, which were also identified as *M. leprae*. Based on clinical, histological and microbiological findings, the diagnosis of erythema nodosum leprosum (ENL) was made. The skin biopsy taken the previous year was re-examined with Fite-staining. A few acid-fast rods were seen.

Hydroxychloroquine and azathioprine treatment was discontinued, while Prednisolone treatment was increased. Dapsone, rifampin and clofazimine were introduced and the patient's condition improved the following weeks with discoloration of skin lesions and defervescence. Three weeks later, she developed high-grade fever, progressive generalised edema, dyspnea and bullous skin lesions on both upper arms. CT scan demonstrated bilateral infiltrates on her lungs, hepato-splenomegaly and enlarged lymph nodes. Cytopenia and multi-organ failure developed. The patient received respiratory support and continuous renal replacement therapy. Broad-spectrum antibiotics and liposomal amfotericin B were added to her treatment.

HLH was suspected. A repeat bone-marrow biopsy demonstrated hemophagocytosis and cytopenia. Though not every criterion for the diagnosis of HLH was present, she had clinical, biochemical and histopathological findings compatible with the syndrome (Table 1).[1]

Acid-fast rods were still demonstrated in large numbers in the bone marrow. No other underlying cause of HLH was unmasked. Treatment with intravenous immunoglobulin, dexamethasone, cyclosporine A and etoposide was started as described elsewhere.[3] She initially responded with defervescence, improved heart function, liver enzymes nearly normalized and serum ferritin decreased nicely (Table 1). However, bilirubin levels steadily increased, and cytopenia persisted with a total leukocyte count $< 1 \times 10^9$/L for 22 consecutive days. Renal replacement therapy and respiratory support was continued.

After 6 weeks with intensive therapy for ENL complicated with HLH, C. lusitania and E. coli sepsis and mucosal bleeding, the patient's condition deteriorated with fever and uncontrolled mucosal bleeding from the gastrointestinal tract and vagina. At the point of deterioration, she received dexamethasone, cyclosporine, dapsone, rifabutin, clofazemine, meropenem, liposomal amphotericin B and micafungin. The patient had a circulatory collapse and she died in spite of efforts to resuscitate.

An autopsy of the patient revealed invasive infection with Aspergillus flavus and C. lusitaniae in the lungs. Hemorrhagic enterocolitis from duodenum to sigmoideum was observed, but no fungal elements were seen. The bone marrow was infiltrated with histiocytes, and showed sparse signs of normal hematopoiesis. Acid-fast rods were not observed in any organ.

Discussion

Diagnostic criteria for hemophagocytis lymphohistiocytosis were revised and published in 2007.[3] In our patient, six of eight criteria were fulfilled. Fever, splenomegaly, cytopenias in three cell lineages, increased ferritin, hypertriglyseridemia and hemophagocytosis in the bone marrow were observed. We did not find any other underlying condition that might explain her condition, and conclude that leprosy was the inducer of HLH in this particular case.

Table 1. Expected diagnostic laboratory abnormalities in Hemophagocytic lymphohistiocytosis and actual values in a patient with leprosy at day of admittance and on day 20 and 43*

Expected laboratory features (ref. Values)	Day 1	Day 20	Day 43
Cytopenia			
Hemoglobin < 9 g/l (11·7–15·3 g/L)	7·6	7·4	10·6
Neutrophils $< 1 \times 10^9$/L ($1{\cdot}5–5{\cdot}9 \times 10^9$/L)	5·0	0·8	< 0·1
Platelets $< 100 \times 10^9$/L ($165–387 \times 10^9$/L)	267	70	55
Ferritin > 500 μg/L (10–167 μg/L)	1 837	99 523	12 162
Triglycerides > 3 mmol/L (0·5–2·6 mmol/L)	0·9	4·2	2·6
Fibrinogen < 1·5 g/L (1·7–4·0 g/L)	4·9	3·8	5·1
Soluble CD25 (> 2400 U/ml)	n.d.	n.d.	n.d.
Others			
AST (15–35 U/L)	115	4 411	183
ALT (10–45 U/L)	40	357	56
Alkaline phosphatase (35–105 U/L)	49	205	100
Increased LD (105–205 U/L)	726	8 242	784

* day of death, n.d. = not done.

The association of hemophagocytic lymphohistiocytosis to various micro-organisms is well documented.[5] Virus, bacteria, fungi and parasites may trigger this abnormal and destructive immune response.[6,7] Amongst bacteria, *M. tuberculosis* is the most commonly reported species to cause HLH.[8]

To our surprise, there is only one previous report on hemophagocytic traits triggered by *M. leprae*.[9] This was in an 11 year old child with ENL and hyper-ferritinemia, but without cytopenias, which is a hallmark in hemophagocytic lymphohistiocytosis. Although this may be the first report on HLH in leprosy, we do believe this may be due to previous misdiagnosis.

A recent report described a significant morbidity and mortality in ENL compared to other forms of leprosy.[10] The diagnoses reported, such as hepatitis, sepsis or multi-organ failure, may indeed be due to HLH.

In conclusion, to the best of our knowledge, this is the first report on HLH triggered by leprosy. The infection is rarely seen in Europe, can easily be misdiagnosed and immunosuppressive therapy can aggravate the disease. Whether this leads to a higher risk of hemophagocytic lymphohistiocytosis in leprosy is unknown.

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