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CASE REPORT

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Dermatomyositis Associated with Hemophagocytic Syndrome: A Case Report/Review of the Literature

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Abstract: Hemophagocytic syndrome (HPS) is a disorder that might be transferred genetically due to an autosomal recessive genetic defect of the long arm of chromosome 9 and chromosome 10 (9q21.3–22 and 10q21–22), termed as primary hemophagocytic syndrome (PHPS) or familial hemophagocytic hemophagocytosis (FHPS) and it may be associated with a variety of infections, malignant neoplasms, drugs, autoimmune diseases and various immuno deficiencies, termed as secondary hemophagocytic syndrome (SHPS). For most patients with HPS, the outcome is rapid and fatal unless the diagnosis is made early and followed by prompt therapeutic intervention.

Fever, hepatosplenomegaly, cytopenia, hypertriglyceridemia and/or hypofibrinogenemia, low erythrocyte sedimentation rate, hyperferritinemia, hyponatremia and hemophagocytosis shown in bone marrow, lymph nodes or spleen biopsy specimens constitute the clinical presentations of the syndrome. In this paper, a patient diagnosed with dermatomyositis associated with HPS is reported with the clinical findings of fever, lymph node enlargement, weakness and atrophy of proximal muscles, periorbital edema, skin thickness and symmetric violet erythema of the forearms. To our knowledge only two cases of dermatomyositis associated with HPS have been published in the medical literature. In addition, periorbital edema together with dermatomyositis is a very rare condition in the literature.

Key Words: Dermatomyositis (DM), hemophagocytic syndrome (HPS), periorbital edema

Dermatomyozit Hastalığına Sekonder Hemofagositik sendrom: Olgu Sunumu ve Literatür Taraması

Özet: Hemofagositik sendrom (HPS); 9.(9q21.3-22) ve 10.(10q21-22-perforin) kromozomlarının uzun kolunda lokalize olan, otozomal resesif genetik geçiş özelliği gösteren primer HPS (PHPS) veya ailesel HPS ile enfeksiyon, ilaç, malign neoplazmlar, otoimmün hastalıklar ile değişik immün yetmezliklerden birine eşlik eden sekonder HPS (SHPS) şeklinde iki ayrı formu bulunan bir sendromdur. HPS, tanı alması ve tedavi verilmesi geciktiğinde, oldukça mortal seyredebilen bir hastalıktır. HPS; ateş, hepatosplenomegali, sitopeni, hipertrigliseridemi ve/veya hipofibrinojenemi, düşük eritrosit çökme hızı, hiperferritinemi, hiponatremi ile kemik iliği, lenf nodu ve dalak gibi dokuların biyopsisinde hemofagositozun gösterilmesi ile karakterize bir sendromdur. Olgu sunumumuz; ateş, lenfadenopati, proksimal kas güçsüzlüğü, periorbital ödem ve üst ekstremitelerde simetrik morumsu eritem ile başvuran hastada tespit ettiğimiz dermatomyozit hastalığına sekonder HPS'yi içermektedir. Literatürde, dermatomyozit hastalığına sekonder HPS olgusunun, sadece iki olgu bildirimi şeklinde yer alması, olgumuzun dikkat çekici özelliğidir. Ayrıca hastamızda görüldüğü üzere, dermatomyozit hastalığında periorbital ödem bulgusu, literatürde nadiren bildirilmiştir.

Anahtar Sözcükler: Dermatomyozit (DM), Hemofagositik sendrom (HPS), periorbital ödem

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Introduction

The following criteria are required for the diagnosis of HPS: fever ≥ 38.5°C lasting seven days or more; splenomegaly, cytopenia (at least affect two cell lines in peripheral blood), hypertriglyceridemia, and/or histopathologic criteria (hemophagocytosis without any finding of malignancy in the bone marrow, lymph nodes or spleen) (Table 1). However, all of these features are not necessary for diagnosis. In HPS, histopathological examination of affected tissue(s) is recommended to establish a diagnosis, but the findings may be difficult to interpret. For diagnosis of HPS, examination of initial bone marrow is often not diagnostic and may only show erythroid or monocytic hyperplasia at onset (1,2).

Table 1. Diagnostic criteria of HPS.

A. Diagnostic criteria for HLH proposed by Henter et al.

1. Clinical and laboratory criteria
   1. Fever (duration >=7 days, with peaks >=38.5 °C)
   2. Splenomegaly (>=3 cm below the costal arch)
   3. Cytopenia (affecting >=2 of 3 lineages in the peripheralblood and not caused by a hypocellular or dysplastic bonemarrow): ANC <=1.0 × 10^9/l, Hb <=9 g/dl, PLT <=100 × 10^9/l.
   4. Hypertriglyceridemia and/or hypofibrinogenemia
   5. Fasting TG >=2.0 mmol/l or >=3 SD of the normal value for age
   6. Fibrinogen <=1.5 g/l or <=3 SD

   Histopathologic Criteria
   7. Hemophagocytosis in bone marrow or spleen or lymph nodes.
   8. No evidence of malignancy.

B. Diagnostic criteria for HPS including secondary HPS proposed by Imashuku.

A. Clinical and laboratory criteria
   1. Fever (duration >=7 days, with peaks >=38.5 °C)
   2. Cytopenia (affecting >=2 of 3 lineages in the peripheral blood and not caused by a hypocellular or dysplastic bone marrow): ANC <=1.0 × 10^9/l, Hb <=9 g/dl, PLT <=100 × 10^9/l.
   3. Hyperferritinemia and/or Hyper-LDH-nemia Ferritin >=3 SD of the normal value for age, generally>=1,000 ng/ml, LDH >=3 SD of the normal value for age, generally >= 1,000 IU/l
   Histopathologic Criteria
   4. Hemophagocytosis in bone marrow or spleen or lymphnodes.
   5. Large granular lymphocytes, mature and immature, are
   6. often increased in number.

C. Diagnostic criteria for HPS proposed by Tsuda.

1. High fever for more than a week.
2. Unexplained progressive cytopenia affecting at least two cell lineages.
3. Bone marrow showing mature histiocytes >=3% or 2,500 cells/_l with prominent hemophagocytosis and/or hemophagocytosis in spleen or lymph nodes.

Adiagnosis of HPS requires all of the above criteria be fulfilled.

A thorough search for familial history, initiating infections, malignancies and immunosuppressive states should be performed.

D. Diagnostic criteria for FHPS proposed by Kumakura.

1. Cytopenia (affecting _2 of 3 lineages in the peripheral blood and not caused by an aplastic or dysplastic bone marrow).
2. Histiocytic hemophagocytosis in bone marrow or other reticuloendothelial systems including spleen, liver or lymph nodes.
3. Active phase of underlying autoimmune disease at the occurrence of hemophagocytosis.
4. Other reactive hemophagocytic syndromes such as virus- or malignancy-associated hemophagocytic syndrome are excludable.

Note:

Autoantibodies against hematopoietic cells sometimes develop.

High fever, hyperferritinemia and hyper-LDH-nemia are not absolutely complicated.

Case Report

An 18–year- old male patient referred to our outpatient clinic with the following symptoms: swelling of both eyelids, fever lasting for eight months, swelling of bilateral upper and lower extremities and dyspnea. Pathologic findings in physical examination were fever of 40 °C, alopecia areata in scalp, lymph node enlargement of about 3 cm in right axillary region, skin thickness and symmetric violet erythema of the forearms, bilateral pretibial edema, and decreased respiration sounds in the right lower lung area (Figures 1,2).

The complete blood count showed; white blood cells: 9x10^3/µl (4,4-11,3), neutrophil:1 × 10^3/µl (1,31-6,71), hemoglobin: 8,3 g/dl (12,3-15,3), MCV: 76 fL (80-97) and platelets:122 × 10^3/µl (150-450). Biochemical values were urea: 40 mg/dl (10-50), creatinine: 0,66 mg/dl (0,6-1,3), AST: 114I U/L (0-40), ALT: 39IU/L (0-50), ALP: 425IU/L (40-150), GGT: 88IU/L (5-64), LDH: 1607 IU/L (125-243), albumin: 28 g/L (35-54), total billirubin: 0,67 mg /dl (0,2-1,2), direct bilirubin: 0,3 mg/dl (0-0,4), Na: 122 mmol /L (135-145), K: 4,2 mmol/L (3,5-5,5), Cl: 104mmol/L (98-110), CK: 335IU/L (20-110), triglycerides: 1194 mg/dl (80-179), fibrinogen: 38 mg/dl (180-400) and ferritin>1500 ng/ml (5-148). His thyroid hormone values, PT, aPTT, INR were within the normal ranges. Complement values were C3: 0,8 g/dl (0,8-1,8) and C4: 0,39 g/dl (0,1-0,4) consecutively. Immunoglobulins were Ig G: 9,36 g/dl (7-18), Ig A: 1,81 g/dl (0,7-4,0) and Ig M: 1,81g/dl (0,4-2,3). Spot urine examination showed 25 mg of protein. Which was 103 mg/L in 24 hour urine. Markers of viral hepatitis and human immunodeficiency virus were negative. Rose –Bengal, Gruber-Widal and ELISA IgG for Trichinella were all negative. IgM examination for Toxoplasmosis, rubella, measles, mumps, cytomegalovirus, herpes virus types I

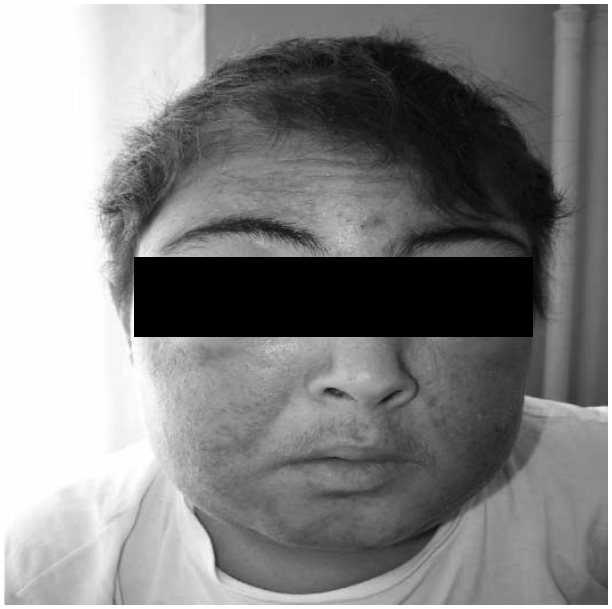

Figure 1. periorbital edema and erythema.

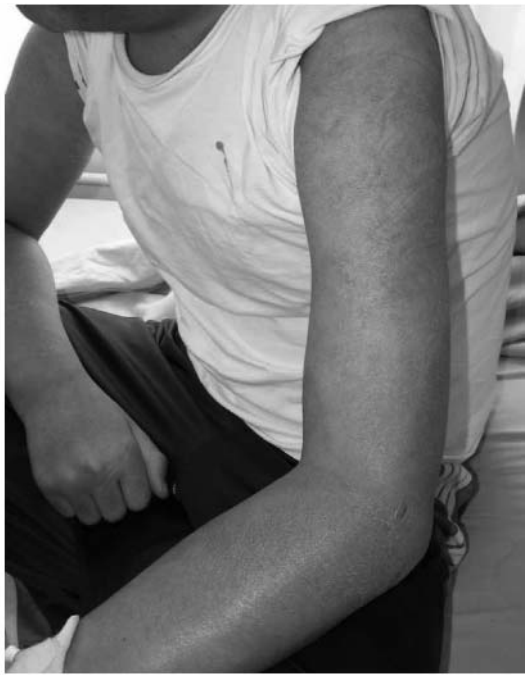

Figure 2. skin thickness in left arm.

and II and parvovirus B19 were also negative. Cultures of urine, pharynx and blood were negative at least three times. Ultrasound of the abdomen showed hepatosplenomegaly.

According to the history of the diseases and physical and laboratory findings, the patient was evaluated for viral and bacterial diseases and malignancies. Viral and bacterial diseases were excluded with bacterial cultures and immunologic markers. In the histopathological evaluation of the excisional biopsy material of the enlarged lymph node, there was no any clue for a malignant disease such as lymphoma. In lymph node biopsy, although there were histiocytes and lymphocyte proliferation in the sinus, no malignancy or granulomatous inflammation was present.

Thoracic computerized tomography was performed in order to elucidate the etiology of the clinical status of the patient. There was no pathological finding other than pleural effusion in the right hemi-thorax. Bone marrow aspiration and biopsy demonstrated, hypercellularity and increase in the activation of the three series of cells.

As the patient had cytopenia, pleural effusion, enlarged lymph nodes and alopecia, probable diagnosis included systemic lupus eryhtematosus or any other connective tissue disorder. In the evaluation of the patient, these diseases were excluded according to the values of ESR: 2 mm/h (0-12), CRP: 9,46 mg/dl (0-5), ANA: (-), anti-SM (-), anti-SS-A: (-), anti- SS-B: (-), anti-scl 70: (-), anti-centromere antibody: (-), anti- U1RNP: (-) and anti-Jo1: (-).

Atrophy and proximal muscle weakness were present, which could be associated with endocrinopathy, myotoxic drug use and neuromuscular disease, but these were excluded. İn view of the high levels of muscle associated enzymes such as AST, LDH and CK and bilateral periorbital edema, dermatomyositis had to be taken into account as a diagnostic probability. Hence, electromyography was performed and revealed polyneuropathy and myopathy of mixed type compatible with dermatomyositis. Finally, we diagnosed the patient with dermatomyositis in view of these clinical and laboratory findings.

Discussion

Familial hemophagocytic syndrome is an inherited autosomal recessive disorder, with the underlying pathophysiology of impaired natural- killer-cell and cytotoxic T-cell activity (3). In 1999, two chromosomal loci linked to the disease (9q21.3–22 and 10q21–22) were identified in families with clinical and laboratory

evidence of HPS (4,5). The two chromosomal loci defined HPS type 1 and HPS type 2, respectively. Shortlythereafter, mutations at chromosome 10q22, the locus of the perforin gene, were identified (6,7). It has also been shown that some cases of B-cell non-Hodgkin lymphoma associated with a HPS have chromosomal abnormalities at 14q32 or 19q13 (3,8).

The perforin gene includes three exons, two of which (exons 2 and 3) are translated, producing a 534-amino-acid protein. Exon 2 encodes a membrane-channel–forming domain that produces pores in the membranes of target cells. Exon 3 encodes a calcium-binding domain; when calcium is bound, this segment causes a conformational change in the membrane-channel–forming region, causing it to polymerize into the form required for membrane binding and pore formation (9,10). About %30 of the reported mutations are in exon 3, with the remainder in exon 2 (11,12). The twins had a mutation inherited from their mother in which guanine was substituted for adenine at position 665, resulting in the substitution of arginine for histidine at amino acid 222, and a polymorphism in intron 2, inherited from their father.

Familial hemophagocytic hemophagocytosis (FHPS) has an autosomal recessive mode of inheritance and consists of at least three subtypes (FHPS1,2,3). In 1999, perforin gene (PRF1) mutation was identified as a cause of 20-30% of FHPS (FHPS2) cases. In Japan, two specific mutations of PRF1 were also detected. Furthermore, in 2003, MUNC13-4 mutations were identified in some non-FHPS2 patients (FHPS3) (13) (Table 2).

Although FHPS is an autosomal recessive disorder typically occurring in infancy, it is important to clarify that the disease may also occur in older patients. It is now considered that FHPS is a disorder of T-cell function; moreover, clonal proliferation of T lymphocytes is observed in a few FHPS patients, and cytotoxicity of these T lymphocytes for target cells is usually impaired (13).

Perforin functions by perforating the membrane of the target cell, harboring microorganisms, tht allows the entry of granzymes which, in turn, initiate the apoptotic cell-death pathway. There is mutual activation and inhibition among cytotoxic T cells, natural killer cells, T helper cells, and macrophages through their cytokines: interleukin-1, interleukin-2, tumor necrosis factor

Table 2. Genetic defects in hemophagocytic syndrome.

	Chromosome Location	Associated Gene
FHPS-1	9q21.3-22	Not known
FHPS-2	10q21-22	PRF1
FHPS-3	17q25	UNC13D
FHPS-4	6q24	STX11

α(TNF-α), interferon-γ(IFN-γ), interleukin-6, interleukin-10, interleukin-12 and granulocyte–macrophage colony-stimulating factor (GM-CSF). In the absence of target-cell lysis, there is sustained activation and proliferation of cytotoxic T cells, natural killer cells, and macrophages and the generation of inflammatory cytokines, resulting in HPS (1).

In 1994, the Histiocyte Society developed a treatment strategy (HPS-94) that combines (rather than randomizes between) two previously reported regimens: chemotherapy and immunotherapy (14,15) HPS-94 is based on etoposide (VP-16), corticosteroids, cyclosporin A (CSA) and in selected patients, intrathecal methotrexate (IT MTX), prior to intended bone marrow transplantation (BMT) (16). Chemotherapy with epipodophyllotoxin derivatives, VP-16 and teniposide (VM-26), combined with corticosteroids and IT MTX, induce remission in FHPS (17,18). Remission can also be achieved with immunotherapy, antithymocyte globulin and steroids followed by cyclosporin A. Ultimately, all FHPS patients relapsed and died until Fischer (19) and coworkers showed that cure could be achieved through allogeneic BMT, which was later confirmed by others (20,21).

High mortality rates have also previously been described in infection-associated HPS (52% in a review of all patients reported in the literature between 1979-1996), in particular in Epstein Barr virus associated HPS (22). Treatment according to HPS-94, without BMT, appears beneficial also in secondary HPS (SHPS) (23). Lack of signs of disease activity during a prolonged period (longer than 12 months) after cessation of therapy, without previous BMT, will most likely suggest the diagnosis of SHPS.

It has been published that it is difficult to determine lymphohemophagocytosis in lymph node and bone

marrow biopsy specimens in early stages of the disease (1). In our case diagnosed with dermatomyositis, we found anemia, leukopenia, thrombocytopenia, hepatomegaly, splenomegaly, high levels of serum ferritin, hypertriglyceridemia, hypofibrinogenemia, low erythrocyte sedimentation rate and hyponatremia. According to this information, we considered our case as HPS secondary to dermatomyositis.

In our patient, whose clinical conditions were progressively worsening, we were able to control the disease with pulse corticosteroid (methylprednisolone 1000 mg) administration in a short time and we want to emphasize this good clinical and hematologic response in our cases. On the second day of the pulse therapy, fever resolved and body temperature was reduced to 36,8°C. Dyspnea, periorbital and edema of both upper and lower extremities ameliorated and pleural effusion began to disappear with the treatment (Figure 3). Abnormal biochemical values improved as Na: 136 mmol/L, ALP: 280 IU/L, AST: 72 IU/L, ALT: 39 IU/L, albumin:35g/L CK: 62 IU/L, LDH: 1202 IU/L and triglycerides: 851 mg/dl in sequence.

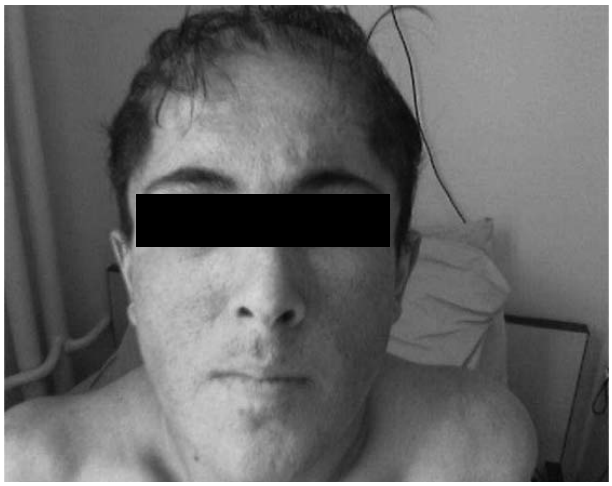

Figure 3. view of face, after diagnosis and threatment

Our case may be interesting in that, HPS is a rare complication of dermatomyositis and only two cases have been documented in the literature to date. Dermatomyositis together with periorbital edema is a very rare condition and our case is to be taken into consideration.

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