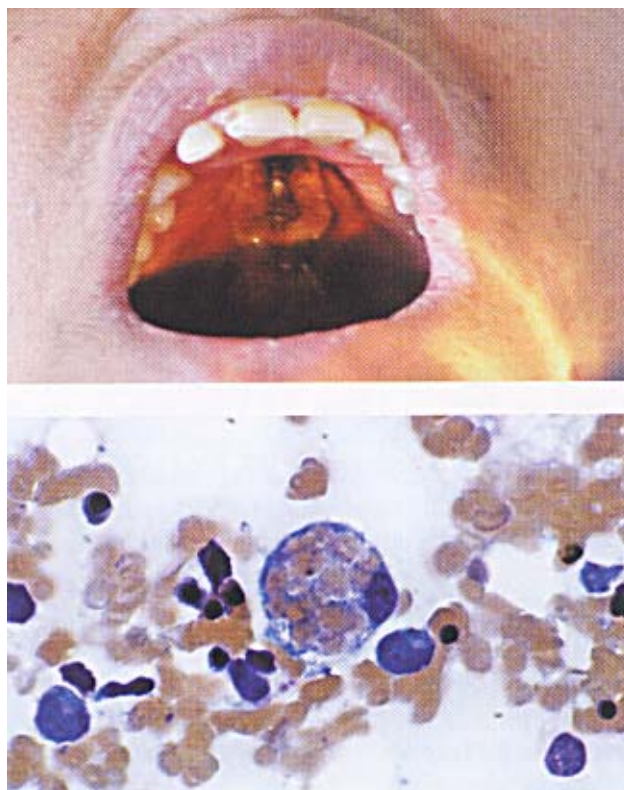


## PHOTOCLINIC



A 37-year-old woman was admitted to a hospital in Tehran, Iran, with malaise, weakness, fever, weight loss and jaundice of more than 1 month's duration. Physical examination revealed hepatosplenomegaly and an enlarged submandibular lymph node (1 × 1 cm). The laboratory findings are presented in Table 1. Biopsy results were compatible with necrotizing immunologic lymphadenitis in cervical lymph

node, and megaloblastoid maturation and normal cellularity in the bone marrow.

The patient symptoms deteriorated with time. Palatal ulceration and muscle weakness added to the clinical picture, and she sought medical attention 1 month later because of continuous fever, jaundice, hepatosplenomegaly and mid-palate necrotic ulcer, and was referred to another hospital.

**Table 1.** The patient's characteristics at first admission.

Alkaline Phosphatase = 320 IU/L	Bilirubin (T = 17.2, D = 12.9) mg / dL	Prothrombin Time = 15 s
Alkaline S Transferase = 131 IU/L	Toxoplasma, IgG = 5	Blood culture (-)
Alkaline Aminotransferase = 140 IU/L	Toxoplasma IgM = 0.7	White Blood Cell = 3,700
Lactate Deshydrogenase = 2,087 IU/L	Albumin = 3 (3.1– 4.3) g / dL	Platelets = 99,000
HBsAg (-), AntiHCV (-), AntiHIV (-), AntiCMV – IgG = 2.1	Gamma Globuline = 1.2 (0.0 – 1.6) g/ dL	Hamoglobin = 9.6 g dL
AntiCMV – IgM = 0.2	Total protein = 5.3 g/dL	Reticulocytes = 1.6%

## Photoclinic

At the time of her referral to Shariati Hospital, she was conscious and neurologic, cardiovascular and pulmonary examinations were normal. There was no evidence of ascites or peripheral lymphadenopathy. Table 2 presents the laboratory findings after her second admission.

Pathologic examination showed acute necrotizing inflammation in the palatal lesion, a megaloid reaction and mild reactive lympho-

plasmocytosis in bone marrow aspiration, and extensive steatohepatitis with a large bile duct obstruction.

Because the initial diagnostic evaluation methods did not lead to a definite diagnosis, she underwent diagnostic laparotomy. During laparotomy, a splenectomy was performed and biopsies were taken from the liver and mesenteric lymph nodes.

**Table 2.** The patient's characteristics at second admission.

---

### Culture

Blood culture (-), Urine culture (-, BMA culture (-)

### Immunology

PPD (-), VDRL (-), ANA (-), CRP (+++), ASM (-), Widal (-), Wright & Coomb's W (-), ESR = 40 mm

### CBC

Fe = 86 (15-120) ng/dL, P = 2.5 (1.7-2.3) mg dL, Ca = 9.1 (8.9-10.7) mg/dL, Cholesterol. = 150 mg/dL, TG = 645, 735, 1,032 mg/dL

### Liver Function Tests

Bilirubin? (T = 31, D = 22) mg/dL, Alkaline S Transferase=182, 256 (5-30) IU/L, Alkaline Aminotransferase= 104, 235 (5-35) IU/L, Alkaline Phosphatase = 430 IU/L,  $\gamma$ -GT= 80 ( $\rightarrow$  32)

### Other tests

Creatinine Phosphokinase=25 (25-220) IU/L, Creatinine Phosphokinase=13 ( $\rightarrow$ 24) IU/L, Aldolase = 13.2 ( $\rightarrow$ 7.6) IU/L, Lactate Deshydrogenase= 2,087 (10-250) IU/L, Creatine =0.5 mg/dL, Blood urea nitrogen = 16 mg/dL, Uric acid =4.2 mg/dL

Results were negative for:

- Peripheral blood smear (PBS) for malaria
  - Smear and culture of palatal lesion for fungus
  - Examination of liver specimen for tuberculosis
  - Serologic test for viseral leishmaniasis
- 

Your Diagnosis?

See page 208 for diagnosis

**Photoclinic Diagnosis: Hemophagocytic Syndrome — Presentation with Midline Palatal Lesion**

The pathologist reported the following:

1- In the spleen: Malignant lymphoma with erythrophagocytic syndrome (Figure).

2- In the lymph node: Hyperplasia and reactive lymph node with atypical sinus histiocytosis.

3- In the liver: Cholangiohepatitis with marked fatty changes and focal hemorrhage.

Immunohistochemistry staining of the spleen specimen using enzyme conjugation (anti-CD15 and CD30) did not show any reaction and gene rearrangement lead to the diagnosis of T-cell lymphoma (delta and gamma chain). Unfortunately, the patient did not respond to a course of 2-week chemotherapy using a high dose of etoposide and dexamethazone, and she died as a result of respiratory distress and coagulopathy. The midline lesion of the palate seen in our case is more frequently encountered in other pathologic backgrounds. The most common differential diagnosis of such a lesion is Wegener's granulomatosis and angiocentric lymphoma.

Hemophagocytic syndrome (HPS) is a rare fulminant disease characterized by generalized histiocytic proliferation associated with phagocytosis of erythrocytes, platelets and, to a lesser extent, white blood cells.<sup>1,2</sup>

To our knowledge, there have been no reports of this condition in Iran. HPS has been reported as a condition associated with certain diseases, but not as an independent entity. Review of the literature suggests that HPS is a very rare disease in Western countries, but is more common in Southeast Asia. It is reported that children and young adults are involved more frequently than older people.<sup>3-5</sup> The majority of reported cases, including ours, are female, but no sex predominance was mentioned in published series.<sup>3,4</sup> High numbers of female case reports may suggest autoimmunity as a contributory factor in the etiology of HPS.

HPS manifestations result from the overproduction of cytokines including interferon- $\gamma$ , interleukin-2 and tumor necrosis factor- $\alpha$ -(TNF- $\alpha$ ) by activated T-cells (Th<sub>1</sub> cells) and macrophages. The exact mechanisms by which abnormal cytokine production is induced by T lymphocytes remains unclear but there have been some

associations with malignant or nonmalignant have been mentioned.<sup>2-6</sup>

Clinical, laboratory and histopathologic features of HPS are shown in Table 3.<sup>7</sup> Fever and splenomegaly are the most frequent clinical signs, and hepatomegaly, lymphadenopathy, jaundice and rash are less common findings.<sup>8</sup> Encephalopathy, meningismus, and seizures are the most frequent neurologic manifestations.<sup>9,10</sup> These clinical findings may suggest an acute viral infection, such as infection with Epstein-Barr virus (EBV) or cytomegalovirus (CMV), viral hepatitis, or acute HIV seroconversion. When these conditions actually coexist with HPS, the situation is more complicated.

Among laboratory abnormalities, cytopenia is the most frequent and may be profound. Serum chemistry profile may suggest hemolysis, with hyperbilirubinemia and elevation of lactate dehydrogenase (LDH) as well as hypertriglyceridemia and marked elevation of ferritin.<sup>11,12</sup> Serum fibrinogen is typically low if disseminated intravascular coagulation has occurred.<sup>13</sup> Increases in circulating fibrin degradation products and serum ferritin are reported to be associated with an elevated risk of death in patients with HPS.<sup>14</sup>

**Table 3.** Clinical and laboratory abnormalities associated with HPS

Clinical sign <sup>(Reference)</sup>	% Of patients affected
Fever <sup>13</sup>	60–100
Splenomegaly <sup>7</sup>	35–100
Hepatomegaly <sup>7</sup>	39–97
Lymphadenopathy <sup>13</sup>	17–52
Rash <sup>13</sup>	3–65
Neurologic signs <sup>7</sup>	7–47
<b>Laboratory abnormality</b>	<b>%</b>
Anemia <sup>7</sup>	89–100
Thrombocytopenia <sup>7</sup>	82–100
Neutropenia <sup>7</sup>	58–87
Hypertriglyceridemia <sup>7</sup>	59–100
Hypofibrinogenemia <sup>7</sup>	19–85
Hyperbilirubinemia <sup>7</sup>	74

## Photoclinic

Hemophagocytosis can be found in bone marrow, spleen and lymph nodes,<sup>15,16</sup> and less frequently in the central nervous system<sup>9,17</sup> and skin<sup>8</sup>. Activated macrophages are able to ingest erythrocytes, leukocytes and platelets, their precursors, and cellular fragments. Hemophagocytosis may be present in the liver, and infiltration of the hepatic portal tracts with lymphocytes is also common.<sup>15,16</sup>

Rare occurrence of HPS, especially in Western countries may explain the lack of sufficient knowledge about this condition.

## References

- 1 Yamaguchi H, Hashimoto M, Mizuki T, et al. Skeletal muscle T-cell lymphoma following hemophagocytic syndrome [in Japanese]. *Rinsho Ketsueki*. 2000; **41**: 712–7.
- 2 Tsuda H. Hemophagocytic syndrome: problems in diagnosis [in Japanese]. *Rinsho Byori*. 2000; **48**: 741–5.
- 3 Matsuo S. Cases of hemophagocytic syndrome in Tenri Hospital [in Japanese]. *Rinsho Byori*. 2000; **48**: 734–40.
- 4 Ishikawa J, Maeda T, Miyazaki T, et al. Early onset of hemophagocytic syndrome following allogeneic bone marrow transplantation. *Int J Hematol*. 2000; **72**: 243–6.
- 5 Gagnaire MH, Galambrun C, Stephan JL. Hemophagocytic syndrome: a misleading complication of visceral leishmaniasis in children — a series of 12 cases. *Pediatrics*. 2000; **106**: E58.
- 6 Gauvin F, Toledano B, Champagne J, et al. Reactive hemophagocytic syndrome presenting as a component of multiple organ dysfunction syndrome. *Crit Care Med*. 2000; **28**: 3341–5.
- 7 Henter JI, Elinder G, Soder O, et al. Incidence and clinical features of familial hemophagocytic lymphohistiocytosis in Sweden. *Acta Paediatr Scand*. 1991; **80**: 428–35.
- 8 Smith K, Skelton H, Yeager J, et al. Cutaneous histopathologic, immunohistochemical and clinical manifestations in patients with hemophagocytic syndrome. Military Medical Consortium for Applied Retroviral Research (MMCARR). *Arch Dermatol*. 1992; **128**: 193–200.
- 9 Henter J, Nennesmo I. Neuropathologic findings and neurologic symptoms in twenty-three children with hemophagocytic lymphohistiocytosis. *J Pediatr*. 1997; **130**: 358–65.
- 10 Haddad E, Sulis ML, Jabado N, et al. Frequency and severity of central nervous system lesions in hemophagocytic lymphohistiocytosis. *Blood*. 1997; **89**: 794–800.
- 11 Koduri PR, Carandang G, DeMarais P, et al. Hyperferritinemia in reactive hemophagocytic syndrome: report of four adult cases. *Am J Hematol*. 1995; **49**: 247–9.
- 12 Esumi N, Ikiushima S, Hibi S, et al. High serum ferritin level as a marker of malignant histiocytosis and virus-associated hemophagocytic syndrome. *Cancer*. 1988; **61**: 2071–6.
- 13 Wong KF, Chan JK. Reactive hemophagocytic syndrome — a clinicopathological study of 40 patients in an Oriental population. *Am J Med*. 1992; **93**: 177–80.
- 14 Kaito K, Kobayashi M, Katayama T, et al. Prognostic factors in hemophagocytic syndrome in adults: analysis of 34 cases. *Eur J Haematol*. 1997; **59**: 247–53.
- 15 Favara B. Hemophagocytic lymphohistiocytosis: a hemophagocytic syndrome. *Semin Diagn Pathol*. 1992; **9**: 63–74.
- 16 Ost A, Nilsson-Ardnor S, Henter JI. Autopsy findings in 27 children with hemophagocytic lymphohistiocytosis. *Histopathology*. 1998; **32**: 310–6.
- 17 Martin JJ, Cras P. Familial erythrophagocytic lymphohistiocytosis: a neuropathological study. *Acta Neuropathol*. 1985; **66**: 140–4.

---

Akram Pourshams MD, Assistant Professor, Mohammad Yaghoobi MD, Research Fellow, Ahmad-Reza Soroush MD, Associate Professor, Bahram Mohebbi MD, Resident of Internal Medicine, Masoud Sotoudeh MD, Associate Professor, Rasoul Sotoudeh MD, Assistant Professor, Digestive Disease Research Center, Tehran University of Medical Sciences.