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Two Cases of Malignant Lymphoma Complicated by Hemophagocytosis Resembling Orbital Cellulitis

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Abstract: Two patients with malignant lymphoma complicated by hemophagocytic syndrome (HPS) are reported. Their clinical signs at onset were similar to those of orbital cellulitis. Lymphoma complicated by hemophagocytosis is called lymphoma-associated hemophagocytic syndrome (LAHS) and its prognosis is reported to be very poor. As far as we know, this is the first report in the ophthalmological field. In our patients, we suspected that the lesions occurred from the orbit or skin of this area. The first patient was a 22-year-old man and the second patient a 16-year-old girl. The diagnosis was very difficult at the onset of disease. They died within 6 months after the first ophthalmological examination. When orbital cellulitis is suspected and antibiotic therapy is ineffective, we should suspect HPS and should examine serum ferritin, which is a good marker of HPS. Early biopsy and consultation with a hematologist are very important. **Jpn J Ophthalmol 1997;41:186–191** © 1997 Japanese Ophthalmological Society

Key Words: Ferritin, hemophagocytic syndrome (HPS), lymphoma-associated hemophagocytic syndrome (LAHS), orbital cellulitis, orbital malignant lymphoma.

Introduction

Hemophagocytic syndrome (HPS) is a clinicopathological entity characterized with the symptoms of persistent fever, pancytopenia, hepatosplenomegaly, and disseminated intravascular coagulopathy (DIC). These clinical symptoms are mainly due to hypercytokinemia produced by proliferating T cells and activated macrophages showing hemophagocytosis in the bone marrow, liver, spleen, and lymph nodes.[1,2] Lymphoma complicated by HPS is called lymphoma-associated hemophagocytic syndrome (LAHS), and its prognosis is very poor. To our knowledge, there was no report about this syndrome from the ophthalmological field.

We report herein two cases of LAHS onset with signs resembling orbital cellulitis.

Received: August 12, 1996

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Patients

Patient 1

A 22-year-old man developed swelling of his right upper eyelid at the end of June 1992. Computed tomographic (CT) scanning of the orbit and cranium demonstrated a soft tissue mass in the right eyelid and lateral portion of the head. The globe was proptosed, but the paranasal sinuses were radiolucent (Figure 1). After 1 month, he was referred to our clinic. His bilateral visual acuity was good and intraocular pressure was within normal range. His right ocular movement was restricted in all directions. The right upper eyelid swelled with redness and tenderness, showing severe chemosis of bulbar conjunctiva (Figure 2). The right preauricular and submaxillar lymph nodes were enlarged.

He was suspected to have orbital cellulitis. However, there was no improvement after several days of intravenous antibiotics. From the middle of August, swelling of his right eyelid was enlarged (Figure 3). The orbital CT scanning demonstrated increased

Jpn J Ophthalmol 41, 186–191 (1997)

Published by Elsevier Science Inc.

0021-5155/97/$17.00
PII S0021-5155(97)00036-1

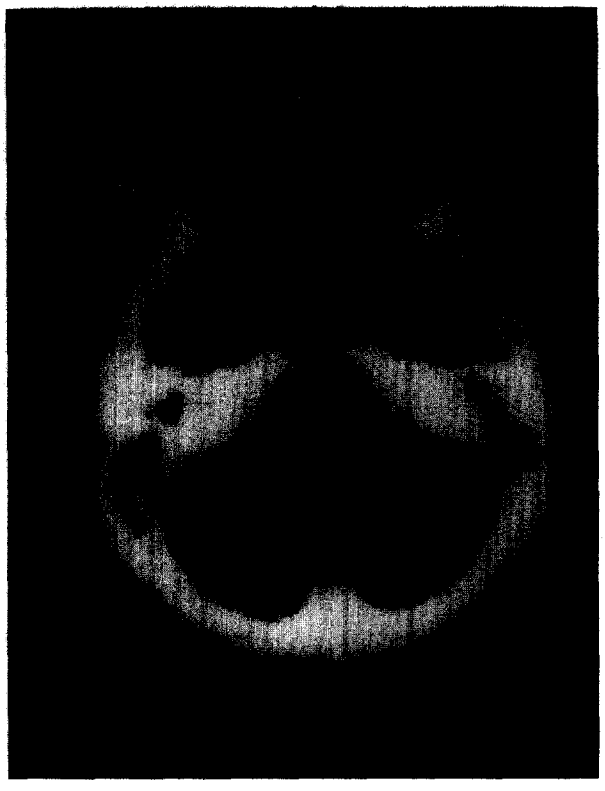

Figure 1. Patient 1: Orbital CT scan demonstrated a soft tissue mass involving the right eyelid and lateral portion of head. The globe was proptosed and paranasal sinuses were radiolucent.

swelling of subcutaneous tissue involving the right eyelid. Enhancement effect was poor and no clear tumor was demonstrated (Figure 4). He also developed high fever and hepatosplenomegaly (Figure 5).

Laboratory data revealed a white blood cell count of 2300/μL (including atypical lymphocytes value of 3%), platelet count of 82 000/μL, and hematocrit value of 34.8%. Glutamic oxaloacetic transaminase was 153 U/L (6–32), glutamic pyruvic transaminase 63 U/L (5–31), lactic dehydrogenase 1705 U/L (95–243), and C-reactive protein 4.0 mg/dL, ferritin 5500 ng/ml (19–233), and interferon-γ 11.7 U/mL. (Values within parentheses indicate normal limits in our hospital.) The titer of various kinds of virus antibodies showed nonspecific patterns.

Bone marrow biopsy showed an increase of macrophage and hemophagocytosis (Figure 6). There was no evidence of lymphomatous involvement. The high uptake in gallium scintigraphy and hypervascularity of the right side of the face suggested he had a malignancy. On September 3, biopsy of the cervical lymph node disclosed malignant lymphoma (ML; Figure 7); diffuse large T cell type. The cell surface antigen showed PanB (−), MB1 (−), CD3 (+), CD4 (+), UCHL-1 (+), lyso (−), S100 (−), and Ki-1 (−). Systemic chemotherapy was not effective. He died on October 7, 1 month after the diagnosis of ML. An autopsy was not performed.

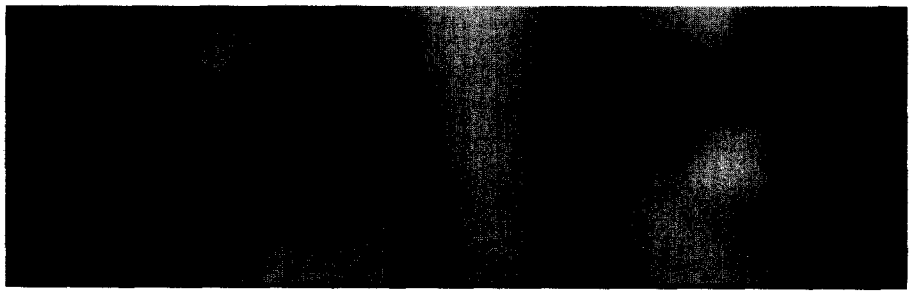

Figure 2. Patient 1: The picture at first examination showed swelling and redness of the right upper eyelid and severe chemosis. Right preauricular and submaxillar lymph nodes were markedly enlarged.

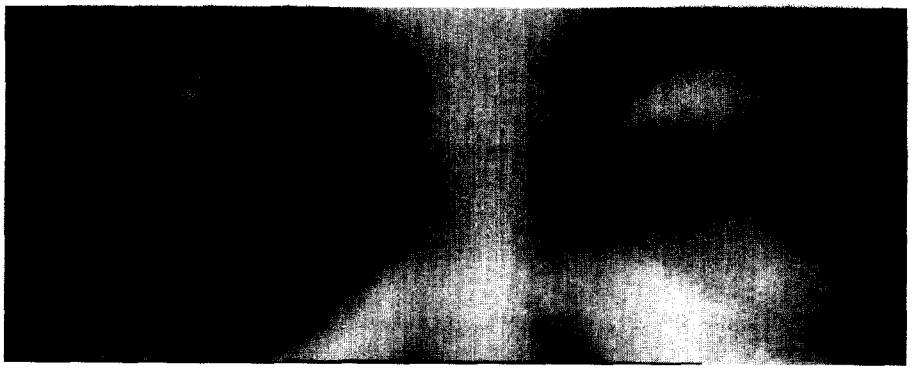

Figure 3. Patient 1: Three weeks after initial examination, swelling of right eyelid increased remarkably.

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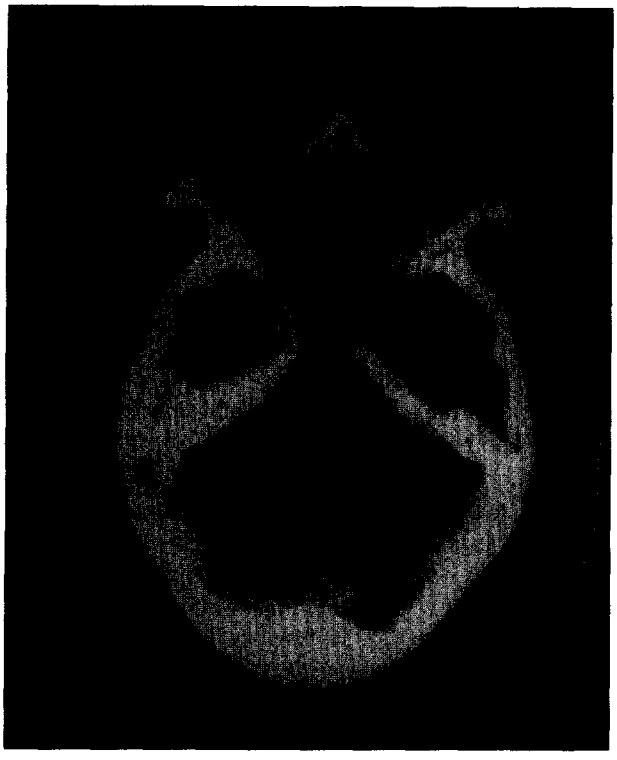

Figure 4. Patient 1: Orbital CT scan, 3 weeks after initial examination, demonstrating enlarged swelling of subcutaneous tissue invading right eyelid. Enhancement was poor and no clear tumor was demonstrated.

Patient 2

A 16-year-old girl developed swelling of her right upper eyelid and hyperemia of right conjunctiva on December 28, 1994. She was suspected to have orbital cellulitis. However, intravenous antibiotics showed no improvement. Administration of prednisone led to a reduction of her lid swelling.

Figure 5. Patient 1: Thoracoabdominal CT scan showed severe hepatosplenomegaly. There was no lymph node swelling.

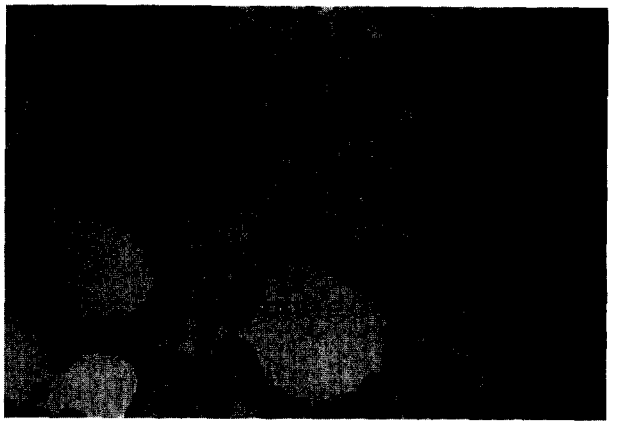

Figure 6. Patient 1: Bone marrow biopsy showed increase of macrophages and hemophagocytosis. A macrophage phagocytizing a leukocyte (arrow). There is no lymphoma cell. Bar = 5 μm.

She was admitted on January 23 to our hospital, suspected to have an orbital pseudotumor. Her bilateral visual acuity was good and intraocular pressure was within normal range. She had conjunctival hyperemia, chemosis, and proptosis of the right eye. Swelling of right eyelid was also seen. The elastic hard mass in size with 1 × 1 × 2 cm on the nasal side of the right eyelid was observed (Figure 8). The extraocular movements were not restricted, however, she had pain during her eye movement.

Despite intravenous steroid and antibiotics, a new mass was observed on the left lower eyelid. When the dosage of steroid administration was decreased, her condition deteriorated. Her left eye also showed

Figure 7. Patient 1: Biopsy of cervical lymph node disclosed malignant lymphoma. Large-sized tumor cells, often with markedly irregular nuclear contours and abundant cytoplasm, infiltrated in fat tissue. Hematoxilin-Eosin stain. Bar = 5 μm.

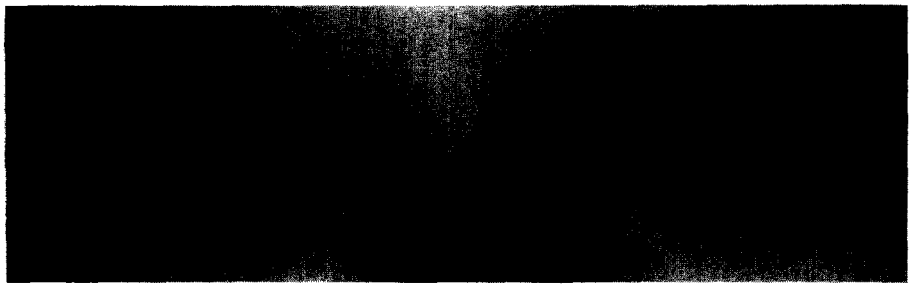

Figure 8. Patient 2: Swelling of the right eyelid. Hard mass 1 × 1 × 2 cm on nasal side of the right eyelid.

eyelid swelling, hyperemia, and chemosis of the conjunctiva. She developed a fever of 38–39° C. Increased steroid administration was effective for high fever and lid swelling, however, the mass size showed no change. The orbital CT scan showed a tumor on the nasal side of the right globe (Figure 9).

Laboratory data revealed her white blood cell count to be 1800/μL (including atypical lymphocytes value of 7%) and her platelet count to be 43 000/μL. Glutamic oxaloacetic transaminase was 188 U/L, glutamic-pyruvic transaminase 149 U/L, lactic dehydrogenase 914 U/L, triglyceride 299 mg/dL (35–212), C-reactive protein 1.4 mg/dL, and ferritin 8737.2 ng/mL. A remarkably high level of serum ferritin was shown. The titer of various kinds of virus antibodies showed nonspecific patterns.

On February 14, a bone marrow biopsy demonstrated hemophagocytosis (Figure 10). The biopsy of her right eyelid mass was disclosed to be ML (diffuse large T cell type stage IV; Figure 11). The cell surface antigen showed UCHL-1 (+), MT-1 (+), and MB-1 (−).

Chemotherapy did not change the ongoing clinical course. Tumor invasion into the brain was disclosed on April 18. She died of multiple organ failure (MOF) caused by LAHS on June 17, 6 months after the diagnosis of ML.

Discussion

HPS is a clinico-pathological entity that is caused by the proliferation of hemophagocytic macrophages in the bone marrow, liver, spleen, and lymph nodes.[1,3] This includes malignant histiocytosis (MH), familial erythrophagocytic lymphohistiocytosis (FEL), and virus-associated hemophagocytic syndrome (VAHS). Some of these are histologically benign and reactive diseases.[3] Clinically, the patients with HPS demon-

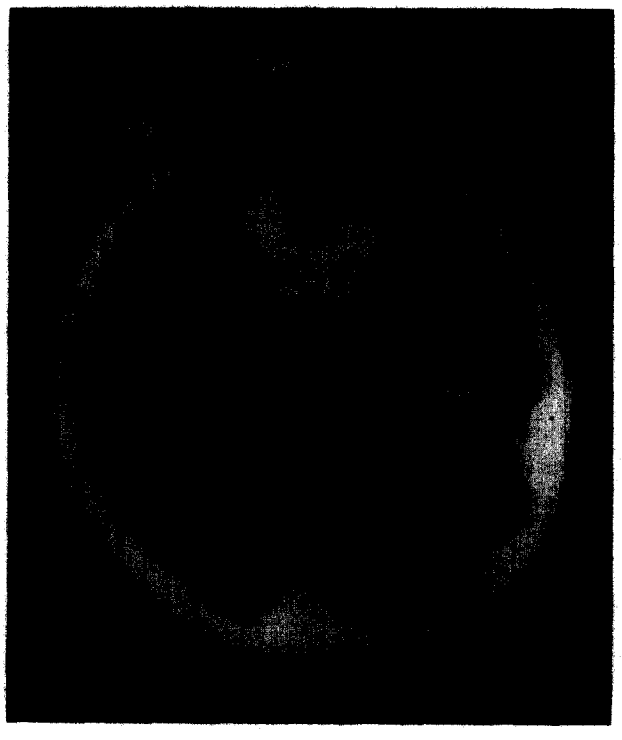

Figure 9. Patient 2: Orbital CT scan showed tumor on nasal side of the right globe.

Figure 10. Patient 2: Bone marrow biopsy demonstrated hemophagocytosis. A macrophage phagocytizes at least three erythrocytes (arrow). Bar = 5 μm.

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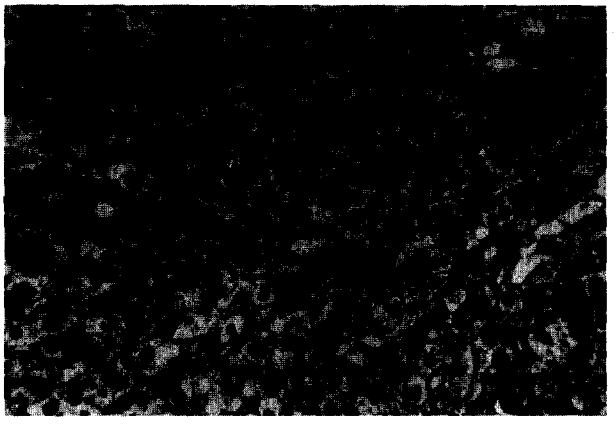

Figure 11. Patient 2: The biopsy of the right eyelid mass disclosed large-sized tumor cell to be infiltrated in fibrofatty connective tissue with inflammation. Hematoxilin-Eosin stain. Bar = 5 μm.

strate persistent high fever, weight loss, pancytopenia, hepatosplenomegaly and DIC. These symptoms are mainly due to hypercytokinemia elicited by activated T lymphocytes and macrophages in bone marrow, the liver, the spleen, and lymph nodes.[1,3] An overproduction of cytokines may be caused by either neoplastic cells in T cell lymphoma[1,4,5] and MH.[6,7] (Recent research has shown that true histiocytic malignancies are rare and that the majority of cases of MH are ML.[8]) or abnormal immunological responses to various antigenic stimuli in VAHS/FEL.[3]

HPS shows hypercytokinemia such as interferon-γ (IFN-γ),[9,10] tumor necrosis factor (TNF),[6] interleukin-2 (IL-2),[9,10] and soluble interleukin-2 receptor (sIL-2R).[9,10] Interferon-γ induces fever and pancytopenia, and is also a chemotaxic macrophage factor. Interleukin-2 induces fever, chill, anemia, thrombocytopenia, capillary leak syndrome (which lowers blood pressure and promotes edema and kidney failure). High sIL-2R serum level is observed in T cell originated diseases such as adult T cell leukemia, hairy cell luekemia and $CD4^+$ chronic lymphoid leukemia. Therefore, HPS should be regarded as one of the T cell proliferative diseases.[11] Various effects of these cytokines and prostaglandin E_2, which is promoted in its production by TNF and has various effects suppressing immunity, induce pathogenesis of HPS.[11]

Abnormalities of coagulation and fibrinolysis are major elements of HPS. These abnormalities are induced by the IL-1 and TNF cytokines. HPS is a new pathological manifestation of DIC and MOF. The tumor cells of T cell lymphoma and MH overproduce cytokines. VAHS is an immunodeficiency syndrome resulting in hypercytokinemia, which is induced as a result of immune inadequacy to bacterial or viral stimulation. HPS is suspected when the following labolatory data are obtained: (1) pancytopenia; (2) high serum ferritin level; (3) coagulation and fibrinolytic abnormalities; (4) high transaminase level; (5) hypercytokinemia (IFN-γ, IL-2); (6) high level of CD4/CD8 lymphocyte in peripheral blood (>2.0); and (7) hyperlipidemia, low cholesterolemia.[1,4]

High serum ferritin level is a particularly useful indicator of disease activity. It is considered that serum ferritin level reflects iron storage volume in vivo, and is produced and secreted by the reticuloendothelial system.[12] In isoelectric focusing, serum ferritin from HPS is different from that of the normal control. Therefore, serum ferritin in HPS is considered to be synthesized in proliferating histiocytes.[2,13] EB virus infection may have some importance in the pathogenesis of VAHS and LAHS.[1] In our two patients, the role of EB virus is unknown.

In patient 1, severe eyelid swelling and chemosis suggested that he had orbital cellulitis. However, at first he had no systemic symptom such as fever and chill. In addition, he had leukopenia, which was atypical of orbital cellulitis. His high fever was caused by HPS. Patient 2 was also suspected to have orbital cellulitis at first. Later she was suspected to have an orbital pseudotumor and steroids were administered. Administration of antibiotics was ineffective in both.

A previous paper[14] showed a patient resembling our two patients. In that report, proptosis of the eye was the first symptom of the patient. In addition, fever, severe hepatic disorder, hepatosplenomegaly, and hemorrhagic diasthesis continued.[14] He was diagnosed as having Weber-Christian disease.[14] The clinical features and laboratory findings of HPS resemble Weber-Christian disease. The hectic febrile course of HPS also prompted suspicion of infection. In our two patients, the initial diagnosis was orbital cellulitis. It is difficult to diagnose HPS in early stages of this disease.

Eyelid swelling is a common and chief complaint of orbital ML.[15,16] The 5-year survival rate of orbital ML is reported to be 58%.[16] On the other hand, the 50% survival rate of LAHS is 1 month and its prognosis is extremely poor.[1] The original region of lymphoma of LAHS is almost an extranodullar organ, which is entirely different from non-Hodgkin's lymphoma.[1] In addition, in LAHS, tumor cells infiltrate mainly into the liver, spleen, and bone marrow. Therefore, it is difficult to determine the primary or-

gan in many cases. As mentioned above, we should regard HPS as one of the T cell proliferative diseases.[11] Almost all cases of LAHS are the T cell type. The prognosis of T cell ML is poorer than B cell ML. Many orbital MLs are B cell types and their prognosis is relatively good.[16,17] However, our two patients had T cell type ML and their prognoses were poor. ML in the oculo-central nervous system often complicates uveitis and abnormality of fundi, but our two patients were free from them.[18]

As mentioned above, hyperferritinemia is a useful indicator reflecting disease activity.[2,4] IFN-γ and sIL-2R are also reported to reflect HPS activity.[9,10] When we encounter a patient experiencing the clinical features mentioned above, we should examine serum ferritin. When its level is abnormally high, we should consult a hematologist. It is reported that 90% of HPS cases have pancytopenia, coagulation and fibrinolytic abnormalities, and an increase of transaminase. These data are also useful in the diagnosis. Histological examination is also important to diagnosing LAHS. However, histological diagnosis is difficult because inflammation is dominant in LAHS tissue. The initial pathologic diagnosis of patient 2's symptoms was a pseudotumor. An experienced pathologist is necessary to diagnose LAHS correctly from histological preparations.

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