Malignant Histiocytosis
A Clinico-pathological Study of three Autopsied Cases

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Clinicopathological features of three male cases with malignant histiocytosis (MH) are described. Case 1, aged 27, had an indurated swelling of the left mandibular region, histologically being chronic lymphocytic inflammation, with ebb and flow for 4 years prior to the onset of MH, with low grade fever, lymphadenopathy and pulmonary infiltration. Histology of the lymph node was compatible with MH, and only a temporary improvement was obtained by COP therapy. Case 2, aged 32, showed acute febrile onset with severe anemia and splenomegaly. Diagnosis of MH was determined by bone marrow histology. COP therapy appeared effective, but caused severe leukopenia and thrombocytopenia resulting in fatal gastrointestinal bleeding. Case 3, aged 16, had high fever and cutaneous mass of the left chest wall, histology of which suggested MH. Bone marrow biopsy was also diagnostic. Severe pancytopenia allowed only a limited therapy. Morphology of the histiocytes was variable in each case. Diffuse infiltration of neoplastic histiocytes in many organs and erythrophagocytosis in the bone marrow were commonly found in all the cases. The present cases suggested a diagnostic value of bone marrow biopsy and possible effect of antineoplastic combination therapy on earlier stage of MH.

Key Words: Malignant histiocytosis, Histiocyte, Erythrophagocytosis.

Histiocytic medullary reticulosis, a disorder of neoplastic proliferation of the histiocytic cell, was first described by Scott and Robb-Smith in 1939. Rappaport introduced a term malignant histiocytosis (MH) into a similar condition as defined clinically by fever, lymphadenopathy, hepatosplenomegaly and death within six months, and histologically by a systemic neoplastic proliferations of histiocytes and their precursors with frequent erythrophagocytosis. Since the two conditions have been considered synonym, the latter term is used more commonly. Before the Rappaport's definition, malignant histiocytosis and the related disorders had been reported under a variety of different terms, which makes difficulties in recognizing the cases of malignant histiocytosis in the literature. In Japan, however, at least 130 cases described as malignant reticulosis, 42 cases as histiocytic medullary reticulosis, and 4 cases as MH for last 10 years were found.

We report three autopsied cases with malignant histiocytosis all fulfilling the Rappaport's criteria, and discuss in the clinical and pathological aspects.

CASE REPORT

Case 1
A 27-year-old man was admitted on February 4, 1977 to our hospital because of indurated swelling of the left mandibular region. In March 1973 this episode had first
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occurred and annually relapsed with spontaneous remission. In February 1976, on the fourth relapse, he visited a hospital where a diagnosis of lymphangioma was made. In October when he was aware of hoarseness to visit another hospital, a biopsy from the buccal mucosa revealed hyperplasia of lymphoid tissues, and that from the pharynx showed chronic inflammation. Because of mandibular swelling followed by cervical lymph node enlargement with low grade fever since January 1977, he was referred to our clinic.

On physical examination he was 163 cm in height and 48 kg in weight, the temperature 37°C, the blood pressure 128/74 mmHg and the pulse 90/min. regular. The left mandibular and buccal region was diffusely swollen with induration and exfoliation (Fig. 1). The swelling was extended over the left cervical soft tissue. The lymph nodes, up to soy bean size, were palpable in the inguinal regions. The heart, lungs and abdomen were normal.

The laboratory findings, summarized in Table 1, were slight increase in the serum level of LDH, total protein, albumin, IgG and IgM, slight decrease in the white blood cell count, 2+ positive for CRP test, and negative skin tests for PPD and PHA. X-ray films of the chest and abdomen were normal.

The hospitalized course is shown in Fig. 2. The buccal and cervical swelling was progressive with fever and emaciation, while multiple biopsy specimens were taken from lymph node, buccal and pharyngeal mucosa without any favorable results. Prednisolone had been given in a daily dose of 30 mg since March 1, resulting in temporary improvement. Two weeks later the mandibular lesion, lymphadenopathy and hoarseness were again conspicuous, additionally with small patchy shadows in X-ray films of the chest. The biopsy of the cervical lymph node on this occasion revealed the histology characteristic of MH. A course of COP (cyclophosphamide, 800 mg and vincristine, 1.5 mg, i. v., on the first day, prednisolone, 60 mg, p. o., for 14 days) had been started on May 2. The remarkable clinical improvements were obtained. He discharged on July 23. Three weeks later he began to feel fatigue and dyspnea and was readmitted.

![Fig. 1. Left buccal swelling in case 1.](image-url)
Case 1
A 27 year-old male was admitted to our hospital on January 13, 1977. Fever developed on December 25 and persisted. He had a history of chronic toluene abuse. Physical examination revealed hepatomegaly and lymphadenopathy. X-ray films of the chest showed extensive pulmonary shadows. He died on August 26.

!!! ADDED TEXT !!!!

The autopsy findings were as follows; whitish tumorous lesion of walnut size with obscure border was observed in the left mandibular region and a similar lesion (7.5 x 2.5 cm) in the left cervical region. Bilateral mandibular and hilar lymph nodes were swollen in soy-bean to thumb tip size. In the lungs (right 1080 g, left 1120 g) were found multiple nodules up to thumb tip size. Microscopically, these lesions were principally composed of infiltrations of atypical histiocytes (Fig. 3). The spleen (310 g) showed marked congestion, histologically with scattered infiltrations of the atypical cells, especially in the medullary cord in the red pulp. The bone marrow was similarly involved. The liver (1640 g) showed moderate fatty change, but no tumor cells were detected.

Case 2
A 32 year-old man was admitted to our hospital because of high fever on September 5, 1977. Fatigue and dry cough developed on July, followed by high fever a month later. He was given antibiotics at another hospital without any effect and was admitted on August 23, when he had mild disturbance of consciousness, anemia and splenomegaly. He received antibiotics and blood transfusions without favorable response. Additionally abdominal pain, vomiting and diarrhea developed, then he was transferred to our hospital.

On physical examination he was 159 cm in height and 53 kg in weight. The temperature was 39.2°C, the blood pressure 108 /64 mmHg, the pulse 138/min. regular. He was disoriented, severely anemic, and icteric. No lymphadenopathy was found. A grade 2 systolic ejection murmur was heard along the apex to 2L. The breath sound was normal. The spleen was palpable 2 cm below the left costal margin, but not the liver. Neurological examination was negative.

The ESR was moderately accelerated, the urine and the stool specimens were normal. 

Fig. 2. Clinical course of case 1 (KS, 27Y, Male).

Fig. 3. Histology of the mandibular lesion of case 1, showing mixed infiltrations of atypical histiocytes, lymphocytes and plasma cells (HE, x100).
The blood chemical examination disclosed slight elevation of LDH, alkaline phosphatase, total bilirubin, and BUN, and severely decreased level of total protein, albumin, and γ-globulin. CRP test was strongly positive. The blood count showed severe anemia (hemoglobin 3.6g/dl) and thrombocytopenia (0.8×10^4/mm^3). Immunoglobulins of all the classes were decreased, severely for IgG and IgM. PPD and PHA skin tests were negative (Table 1).

Clinical course is shown in Fig. 4. On the day of admission, after routine cultures, antibiotics were started and later a large amount of blood transfusions. Prednisolone in 100mg daily dose was added, resulting in a temporary fall in temperature. The bone marrow aspiration on September 5 demonstrated atypical histiocytes with occasional erythrophagocytosis, by which the diagnosis of MH was almost confirmed. On September 16, a course of COP (cyclophosphamide, 800 mg, and vincristine, 1 mg, i.v. both on the first day, prednisolone, 100 mg, p.o. up to the 14th day) was started. Transient improvement was obtained, which was, however, followed by rapid fall in white cell count with severe thrombocytopenia, and high fever over 40°C. The patient was deteriorated and died on September 28.

The autopsy findings were as follows;

![Fig. 5. Histology of the lymph node of case 2, showing marked proliferations of histiocytes mainly in the sinus (HE, ×100).](image)

macroscopically systemic lymph nodes were swollen, up to thumb-tip size. The lungs (right 390 g, left 300 g) showed bronchopneumonia and pleural effusion was found bilaterally (500 ml, bloody in the right and 300 ml, yellow and clear in the left). The liver was slightly enlarged (1910 g). The spleen showed marked enlargement (690 g) with congestion and obscure lymph follicle. The kidneys (both 180 g) were slightly swollen with hemorrhagic foci in the pelvic mucosa. The severe esophagitis with hemorrhagic necrosis, scattered erosion of the stomach, and segmental focal hemorrhage of the colon were noted.

Histologically, the lymph nodes showed marked proliferation of histiocytes mainly in the sinus, including occasional atypical cells and frequent erythrophagocytosis, with fairly preserved basic architecture (Fig. 5). The spleen showed principally the same change. The bone marrow showed proliferation of swollen histiocytes with phagocytic activity.

**Case 3**

A 16 year-old boy was admitted to our hospital because of high fever and fatigue. Early in August 1980, he became febrile, and noticed a reddish, indurated cutaneous mass at the left chest wall and enlarged lymph nodes at the left axilla. He went to a hospital and received excision of the cutaneous mass, which was histologically suggestive of MH. However he left there to visit another hospital, where pancytopenia and liver dys-
function were noted, and antibiotics were given without effect. On September 19, he was transferred to our hospital.

On physical examination he was well developed young man (180 cm and 64 kg) in acute distress. The temperature was 38.4°C, the blood pressure 130/50 mmHg, the pulse 100/min. regular. The pharynx was hyperemic, and the tonsils were red and swollen. The superficial lymph nodes were palpable in the neck and the inguinal regions bilaterally, and in the left axilla. The grade 2 systolic ejection murmur was heard along the apex to 2L. The lungs were normal. The liver was palpable 2 cm below the right costal margin, but not the spleen.

The ESR was slightly accelerated. The urine and the stool specimens showed positive occult blood. Marked elevation of the serum enzyme activity and hyperbilirubinemia suggested liver involvement. Slight increase of BUN and creatinine was found as well. The CRP test was 3+ positive and ASO titer was normal. The hematological data showed severe pancytopenia and atypical lymphocytes on a smear. PPD and PHA skin tests were negative (Table 1). Chest X-ray films revealed reticular shadows in the right middle lung field. The electrocardiogram showed myocardial injury. The aspiration of the bone marrow revealed scattered infiltration of histiocytes, occasionally atypical, with the erythrophagocytosis by which the diagnosis of MH was confirmed.

Soon after admission he was given antibiotics and transfusion of red cells and platelets. Then a modest therapy with vincristine (1 mg, i.v. once a week) and prednisolone (30 mg, p. o. daily) was started, considering severe pancytopenia. All the treatment, however, was unsuccessful and he died on September 30 (Fig. 6).

The autopsy revealed systemic involvement of the disease. Macroscopically the lymph nodes showed systemic enlargement, up to thumb-tip size, mainly in the neck, axillae, and the paratracheal and perigastric regions. The lungs had multiple miliary abscesses with hemorrhage, which were histologically determined as aspergillosis. There were several nodules, up to small-finger-tip size, in the liver (2100 g). The spleen (350 g) had several anemic infarctions. Mucosal hemorrhage was scattered in the gastrointestinal tract. The heart (300 g) appeared slightly atrophic and the kidneys (right, 200 g; left, 210 g) were congested with mucosal bleeding of the pelvis.

Histologically the cutaneous mass excised at the onset, showed extensive proliferations of large histiocytes without cohesive tendency in the dermis and subcutaneous fat tissues, where slight to moderate cellular atypism, frequent mitosis, and phagocytosis were noticed (Fig. 7). The lymph nodes were

![Clinical course of case 3 (MU, 16Y, Male).](image-url)
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infiltrated by atypical histiocytes, mainly in the sinus and medullary cord. In the red pulp of the spleen the sparse infiltrations of atypical histiocytes were observed without the destruction of the cordal structure (Fig. 8). The nodules of the liver were revealed to be necrotic foci of the tumor cells, and also occasional atypical histiocytes were found in the sinusoid and portal area. Sparse infiltration of the histiocytes was found in the various organs and tissues such as gastrointestinal wall, subarachnoid space of the spinal cord, urinary bladder, testis, heart, and perirenal fat tissue. There were a few fungal colonies at the trachea, duodenum, and liver.

**Cytological study** (Table 2)

The morphological characteristics of the histiocytes were as follows; the cells in case 1 and 2 were 10–15 μm in diameter and oval round with diverse amount of cytoplasm, occasionally foamy in the latter, and irregular nuclear chromatin, while those in case 3 were 20–30 μm in diameter with foamy abundant cytoplasm and irregular chromatin as well. The nuclei were of distinct nuclear membrane, bi- or multi-nucleated, lobulated, and indented in case 1, and of various size in case 2. The cells showed atypism, without cohesive tendency, frequent erythrophagocytosis and intracytoplasmic hemosiderin accumulation. In the lymph nodes these histiocytes infiltrated mainly in the medullary cord and as well in the sinus in cases 1 and 3, but not in the capsule, without destruction of the basic architecture.

**Table 2. Cytological feature of histiocytes in 3 cases.**

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Fig. 7. Histology of the cutaneous mass of case 3, showing extensive proliferations of large histiocytes. The erythrophagocytosis was noticed (HE, ×200).

Fig. 8. Histology of the spleen of case 3, showing sparse infiltrations of histiocytes in the red pulp (HE, ×200).

Fig. 9. The smear of bone marrow of case 3, showing histiocyte with erythrophagocytosis (Wright, ×1000).

The cytochemical study disclosed positive reaction to α-naphthyl acetate esterase, naphthol AS acetate esterase, and acid phosphatase in all the cases, and to PAS in 1 case examined, and questionable reaction to naphthol AS-D chloroacetate in 2 cases examined. The reaction to naphthol AS acetate esterase was inhibited by NaF in all cases. The electron-microscopic examination performed in case 1 demonstrated that the histiocytes had irregular nucleus with clear nucleoli, and a large number of ribosome and mitochondria in the cytoplasm.

DISCUSSION

Three cases with malignant histiocytosis, including one with atypical clinical course, were reported. As for diagnosis the autopsy findings fulfilled the definition of Rapaport in the following points; 1) morphologically and cytochemically identified histiocytes including atypical cells infiltrated in the medullary cord and sinuses of the lymph nodes but not in the capsules, 2) phagocytic activity such as erythrophagocytosis, 3) no formation of cohesive cell masses, and 4) the presence of plasma cells. The clinical course was typical in cases 2 and 3, while case 1 showed unusual course that the localized mucocutaneous lesion in the left mandibular portion, histologically composed of chronic inflammation with lymphoid proliferation, had been observed four years prior to the systemic manifestations.

Vardiman suggested possible chronic form of malignant histiocytosis by studies of their atypical cases where neoplastic histiocytic proliferation was limited in some lymph nodes for months to years. In the present case 1, however, such histiocytic proliferation could not be disclosed in the multiple biopsy specimens during the limited stage of the disease, so that the onset of the disease in this case remains obscure. We could not relate the earlier mandibular lesion to the later malignant histiocytosis. There remains a question, however, that the previous inflammatory lesion may play a possible role in occurrence of the disease.

In the two typical cases, severe anemia and thrombocytopenia in case 2 and pancytopenia in case 3 were highly suggestive of hematological diseases. A bone marrow aspiration biopsy was greatly contributable for diagnosis in these cases. It disclosed histiocytes which phagocyte erythrocytes in its foamy cytoplasm (Fig. 8). The diagnosis of malignant histiocytosis is principally made by lymph node biopsy, but bone marrow aspiration is of diagnostic values. Lampert et al. noted liver biopsy may also be available.

Monocytic origin of the tissue macrophages is commonly accepted, and as well for macrophage origin of the histiocytes. Then it may be in question how to differentiate MH from acute monocytic leukemia. The latter is characterized by uniform proliferation of monoblastic cells without erythrophagocytic activity in the bone marrow and peripheral blood. In the present cases the neoplastic cells could be considered to have histiocytic nature by the results of morphological and cytochemical studies, and additional phagocytic activity may be a great evidence for the cells of macrophage-mono- cytic cell line.

No characteristic findings were found in the laboratory data. Abnormal serum immunoglobulin levels and negative test for delayed hypersensitivity skin reaction may be suggestive of immunological disorders in this disease. Considering important role of macrophages on the immune response, the disease should be studied precisely from immunological aspects. In this respect we could not obtain any more data from our cases.

No favorable therapy has yet been established for MH. In recent years chemotherapy according to non-Hodgkin's malignant lymphoma has been tried with some effect. Alexander et al. described that two of five patients responded to COP therapy (cyclophosphamide, vincristine, and prednisolone) and five of seven to CHOP (COP plus Adriamycin), and that the mean survival of
the responders was 17 months. As mentioned above, we also attempted such a therapy on the present cases with a temporary improvement in case 1. Case 3, a critical case with severe pancytopenia was given a combination of vincristine and prednisolone, which was effective in some cases\textsuperscript{15}, with unsuccessful result. Further supportive cares such as antibiotic therapy and blood transfusion may be important to keep better condition for the specific therapy. We emphasize, 'the earlier diagnosis, the better prognosis.'

REFERENCES
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