[原著]An Autopsy Case of Histiocytic Medullary Reticulosis

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An Autopsy Case of Histiocytic Medullary Reticulosis

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Pathological conditions with marked proliferation of reticulum cells in general reticuloendothelial systems are designated as reticulosis. However, definite classification of the reticulosis is not precisely established up to the present, with the exception of a few provisional attemption.[3,5,8,17]

The reasons of difficulty concerning the classification of the reticulosis are based on existence of rather many exceptional cases having an obscure nature with unknown etiology.

Besides the certain reticuloses with obvious nature, like reactive or neoplastic, there is a series of peculiar reticulosis which is interpreted as one differing from those two reticuloses and or situating in the middle position between above two reticuloses. This unknown natured reticulosis has been precisely represented with the term of "cataplastic reticulosis" by some investigators, and the report of the cases belonging to this category increased recently.[8]

Among the cases of those unknown natured reticulosis there is a group of reticuloses named idiomatically as "malignant reticulohistiocytosis" which is characterized as an acute progressive invariably fatal disease of adult. The terms of malignant reticulosis,[17] malignant histiocytosis[13] or histiocytic medullary reticulosis which was firstly described by Scott & Robb-Smith[15] in 1939, are commonly used as the synonymes of this disorder. Some investigators interprete that the histiocytic medullary reticulosis is nothing but a subgroup of so-called malignant reticulohistiocytosis which has some subtypes in it.[17]

Clinically, the histiocytic medullary reticulosis is characterized usually by weakness, malaise and weight loss, high fever, hepatosplenomegaly, anemia, granulocytopenia and rather less often jaundice. Histological investigation shows a diffuse proliferation of large abnormal histiocytes in lymph nodes, spleen, liver and bone marrows.[6,7,10,19]

Regard to the nature of this abnormal histiocytes, many investigators interpreted that

the histiocytes are belonging to that of malignant neoplasma which proliferate progressively and systematically.[2,15,16,19] However, the microscopic features of this histiocytes show some resemblance to that of common inflammatory or 'reactive' conditions of reticuloendothelial systems which often encountered in sepsis.

Purpose of this paper is to report an autopsied case resembled closely to the features of the histiocytic medullary reticulosis and to discuss the nature of this abnormal histiocytes, as neoplastic or not, from the basis of the histological findings of the histiocytes impregnated in general reticuloendothelial systems systematically.

Case Report

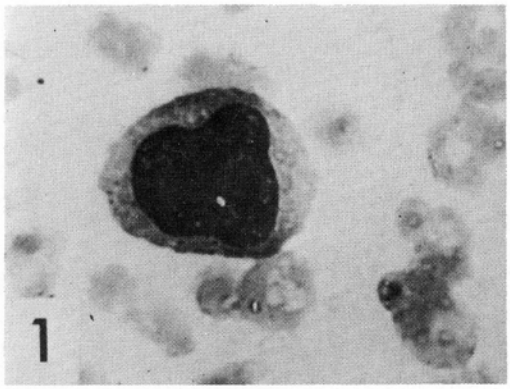
Clinical Data

A twenty-six-year-old married woman was admitted to Tottori University School of Medicine on June 25, 1966, complaining of fever, chills, dizziness, headache and upper abdominal discomfort. She had been healthy until about 20 days before admission, except appendectomy at age of 14. When she first felt headache, chills and dizziness, she was treated for common cold by a doctor.

Three days before admission, she visited the practitioner again because of increasing in severity of dizziness, headache, loss of appetite, and weakness, and was pointed out the enlargement of the liver and spleen. The doctor advised her to consult a specialist.

Family history was noncontributory.

On admission, the patient's temperature was 38.3℃, pulse frequency 100 per minute. The patient was normally developed and well nourished. No lymphadenopathy was discerned. The eye lids were anemic and the pharynx was not red. The sclera and the skin were not jaundiced. The limit of cardiac dullness was normal. At the examination of the heart sound, systolic murmur was noted at the apex, however, the breathing sound was normal. The liver was palpable five fingerbreadths below the right costal margin, and tender on pressure. The spleen was also palpable five fingerbreadths below the left costal margin. Ascites and edema were not marked. The blood pressure was 94/44 mmHg. There were none of the pathologic reflexes. As a hemorrhagic manifestation, some suggillations of the skin were noted at the chin, right forearm, and left pelvic limb. Roentgenogram of the chest was normal. In the electrocardiogram, there was no evidence of abnormal finding. Hemoglobin was 5.4 to 7.6g/dl, and the platelet count 8,000 per cu. mm. (direct method); the erythrocyte count was 1,950,000 to 2,490,000 per cu. mm. with 16% reticulocytes. The white blood cell count varied between 1,000 and 1,200 per cu. mm. with 20% segmented cells, 30% band forms, 2% myelocytes, 28% lymphocytes and 20% unclassified abnormal cells. Those abnormal cells were almost round or irregular in shape,



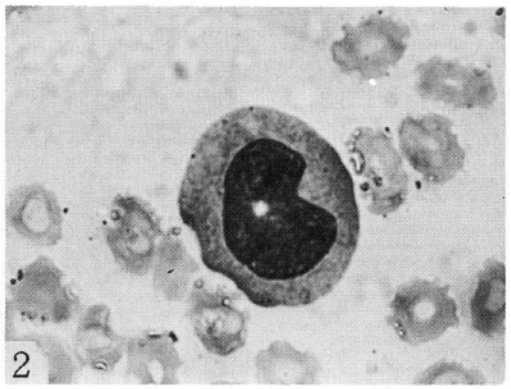


Fig. 1-2. Peripheral blood. Large lymphocytic abnormal cells. ×1200.

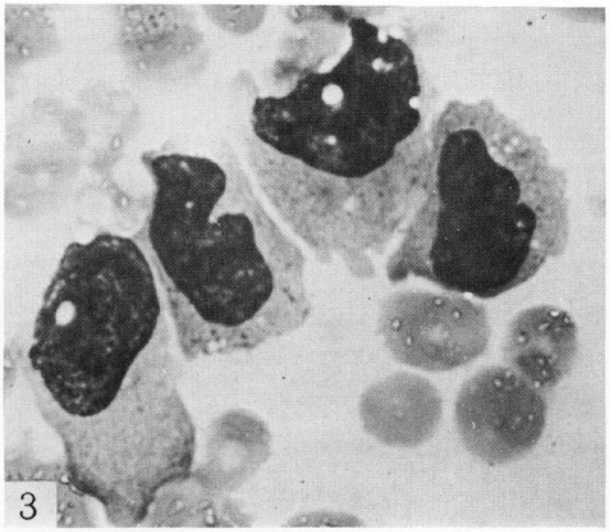


Fig. 3. Peripheral blood. Monocytoid polymorph mononuclear cells. ×1200.

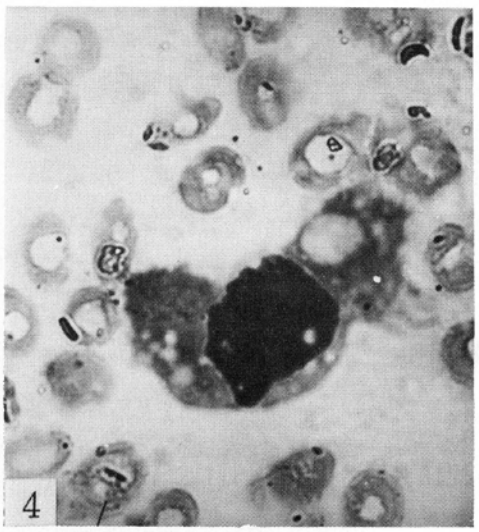


Fig. 4. Peripheral blood. Irregular shaped endothelial cell with coarsely vacuolated large cytoplasm. ×1200.

having a large pale staining homogenous cytoplasm and an almost round, occasionally indented, hyperchromatic nucleus. The cytoplasm of some such abnormal cells revealed small clear vacuoles in it. They were diagnosed as the one classified in the reticulum cell series.

Bone marrow aspiration was performed from the sternum, 5 days after admission. The marrow aspirates revealed a marked increase in polychromatic erythroblasts and a decrease of the neutrophilic leukocyte series. A few percent of abnormal cells, similar to those in the peripheral blood stream, were observed in that aspirate. The bleeding time was 6 min. and the coagulation time was 8 min. The serum proteins were 5.6 gm. per 100 ml.

Wasserman reaction, Widal reaction and Weil-Felix reaction were all negative. The blood sedimentation rates were 27 mm/one hour, and 56 mm/two hours. The examination of urine and stool was almost normal. Liver function tests revealed a marked increase of Meulengracht's icterus index from 5.8 to 63.3, S-GOT (Karmen) from 45.0 to 525.0, S-GPT

(Karmen) from 18 to 150.0, thymol turbidity test 2.9 units, zinc sulfate test 8.4 units, and alkaline phosphatase 6.3 to 57.2 (King-Armstrong).

The patient was found to be septic and was diagnosed as leukemic reticulosis. Under that diagnosis, she was treated with antibiotics and predonisolone. The treatments were not effective, and the patient died approximately 7 weeks after the onset of her illness.

Autopsy Findings

The body exhibited a generalized jaundice and scleral icterus. The organs were all pale and edematous, especially the gastrointestinal wall was markedly edematous and thickened. The pericardial sac contained 100 ml. of a clear, straw-colored fluid. The peritoneal cavity contained only a little quantity of yellow fluid. The pleural surfaces of the lower lobes of both lungs and the mucosa of the stomach and the kidney pelvises showed congestive hyperaemia and numerous petechiae. Cut surfaces of both lungs revealed congestion in the lower lobes. There were abundant superficial erosions in the mucosa of the esophagus. The lumen of the small intestine included bloody material. The liver weighed 1,100 gm., and it had a smooth surface and a firm consistency. Cut surfaces of the liver revealed the obscure architecture. Tumor formation and bleeding in the liver were not observed. The spleen weighed 750 gm., and had a smooth expanded capsule and a relatively soft consistency. Cut surfaces of the spleen revealed a dull red color and obscure Malpighian follicles. There were no tumor formations or anemic infarctions in the spleen. The lymph nodes were not prominent, but several peripancreatic and periaortic nodes were slightly enlarged measuring up to 1.5 cm in diameter. They were gray-yellow in color and soft in consistency. Bone marrow of the sternum, ribs, and vertebrae revealed a dull red color. The right ovarium had a blood cyst measured 2.0 cm in diameter. The kidneys revealed the cloudy swelling (right 195gm., left 225gm.). The heart, pancreas, thyroid and adrenal glands revealed no prominent abnormal findings.

Microscopic Findings

A prominent proliferation of large histiocytic cells was observed in the liver, spleen, lymph nodes, bone marrow, and ovaries. The greater part of the histiocytic cells proliferated in those organs had a pale irregular cytoplasm and showed pronounced vacuolation or erythrophagocytosis. Besides this, somewhat small round cells having a homogenous cytoplasm and slightly enlarged hyperchromatic nucleus are observed simultaneously. They were closely resembled to the abnormal cells appeared in the circulating blood.

The liver sinusoids were markedly distended and filled with large irregular cells which showed many vacuoles or erythrophagocytosis in the cytoplasm. The Kupffer's cells were also enlarged and increased in number. There existed in the liver, abundant small necrotic

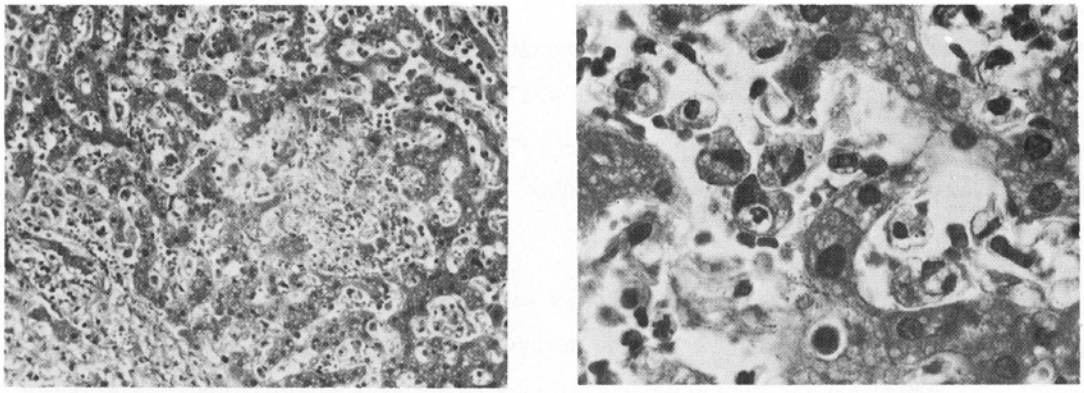


Fig. 5-6. Postmortem tissue of the liver, showing a small focal necrosis and numerous large abnormal histiocytic cells impregnated in the sinusoid. H & E. ×100, ×400.

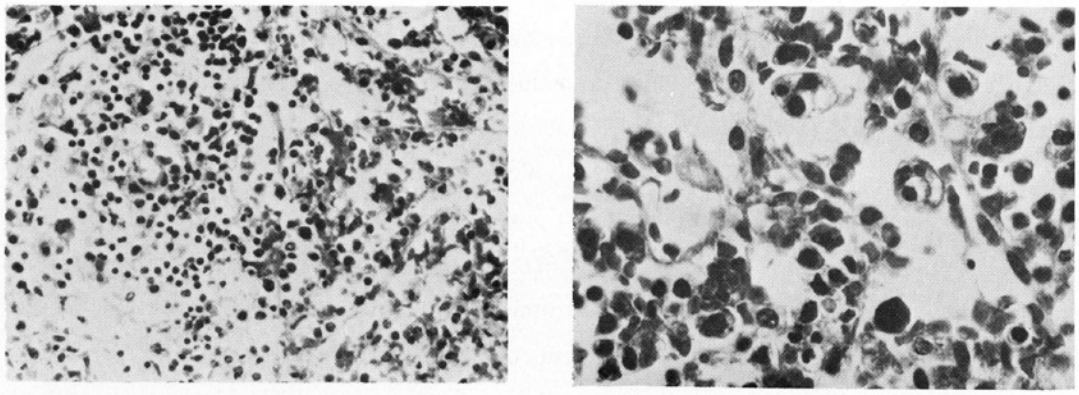


Fig. 7-8. Spleen with atrophic Malpighian follicle and large abnormal histiocytic cells containing ingested cells in the cytoplasm. H & E. ×100, ×400.

foci, and the liver cells revealed an atrophic or degenerative change with vacuoles in the cytoplasm.(Fig. 5,6) The spleen revealed marked congestion and marked proliferation of large abnormal histiocytes with phagocytized many red cells and other degenerated cells in the red pulp. The normal archtecture of the spleen was preserved approximately but the medullary cords were distended by the impregnation of the polygonal enlarged histiocytes. The sinuses of the spleen were dilated with congested red cells but scarce abnormal histiocytes. Greater part of the abnormal enlarged histiocytes were thought as original reticulum cell of the spleen. Malpighian follicles were atrophic and diminished in size with scarce lymphocytes.(Fig. 7,8)

All lymph nodes, whether enlarged or not, showed marked dilatation of subcapsular and medullary sinuses, filling the abnormal large histiocytes with vacuolation or erythrophagocytosis. Besides this abnormal histiocytes, proper reticulum cells in the lymph sinuses also enlarged with vacuolation. However, the general architecture of the nodes was well

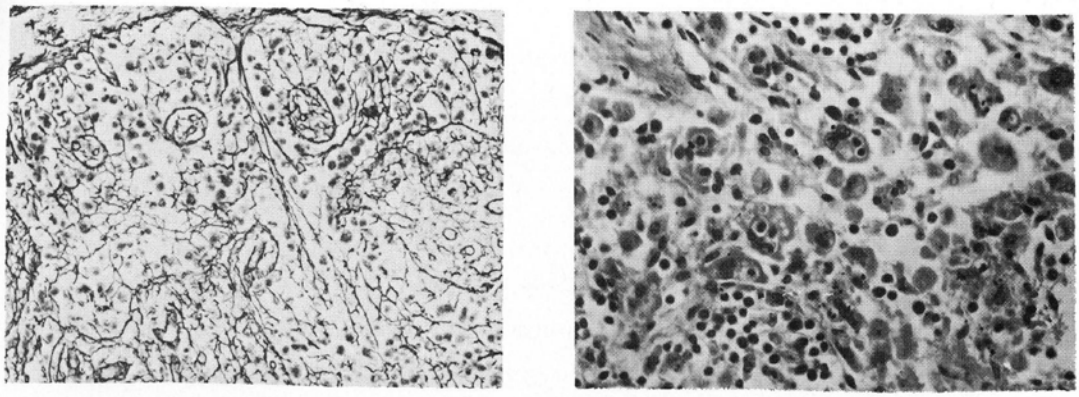


Fig. 9-10. Lymph node. Sinuses are dilated and filled with large abnormal histiocytic cells. Silver impregnation(left) ×100. H & E. ×200.

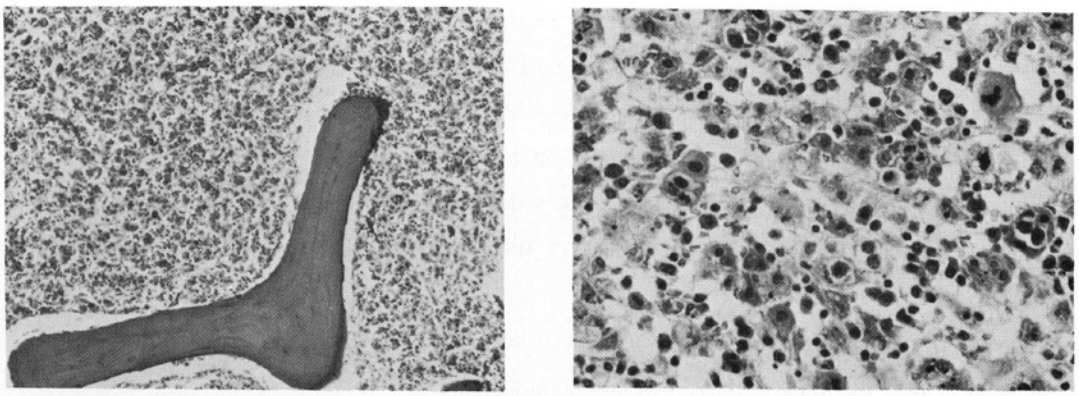


Fig. 11-12. Bone marrow. Normal hematopoietic cells are markedly reduced and replaced with large polygonal histiocytes. ×40, ×200.

preserved, except for a slight atrophy of the lymphoid tissue and lymph follicles due to compression by the dilated sinuses.(Fig. 9,10)

The bone marrows from multiple areas were almost replased by the polygonal histiocytes with prominent phagocytosis similar to those found in other organs. But the majority of those enlarged histiocytes were thought as originating from the proper fixed reticulum cells of the bone marrow. The normal hematopoiesis of the bone marrow was reduced markedly.(Fig. 11,12)

Discussion

The findings of this case were those of histiocytic medullary reticulosis, which was proposed by Scott and Robb-Smith as disease having a rapid clinical course, fever, enlargement of spleen and liver, lymphadenopathy, hemorrhagic manifestation, jaundice, pancytopenia, and marked proliferation of reticulo-histiocytes in the reticuloendothelial systems.

As mentioned above, reticulosis and reticuloendotheliosis are accepted by pathologists as a series of pathologic phenomenon but not an independent disease. And there is much confusion concerning classification of reticulosis. They may be roughly divided into three groups according to their clinical and pathological characteristics as follows:

1) Reactive reticulosis; accompanied by an infectious disease or metabolic disturbances.

2) Neoplastic reticulosis; having an obvious neoplastic characteristics.

3) Cataplastic reticulosis (Kojima); situating intermediately between the above two types of reticulosis.

However, this classification is not clear nor distinct. There are boundaries among these reticuloses. Histiocytic medullary reticulosis is thought as a disease which belongs to the category of cataplastic reticulosis. To be regarded as having a independent entity, this disease must have peculiar characteristics differentiating from other similar disorders.

Scott and Robb-Smith proposed the name of histiocytic medullary reticulosis, because of the existence of the peculiar characteristic where the proliferation and active phagocytosis of the cells are predominantly observed in the medullary portion of the nodes.

Clinical and autopsy findings of this case were closely similar to that of the histiocytic medullary reticulosis. Cosequently, it had no difficulty in diagnosing about this case as histiocytic medullary reticulosis.

Some findings in this case were thought to be similar to findings in reactive reticulosis; showing proliferation, hypertrophy, erythrophagocytosis of the reticulohistiocyte and a stimulated state of all reticuloendothelial cell, including the Kupffer's cells in the liver.
However, not only this case had no distinct inflammatory disease regarded as the cause of the disorder clinically, but also no inflammatory findings except histiocytosis in the reticuloendothelial organs and tissues histopathologically. The patient was not reactive to treatment with antibiotics or cortico-steroids.

As the systemic and diffuse infiltration of the abnormal and immature histiocytes in the hematopoietic organs, and the abnormal cells in the peripheral blood stream, which appeared only few percent, were observed, this disease could be thought as an allied disease to leukemia.

However, the leukemia and a disease called as leukemic reticuloendotheliosis differ from the cataplastic reticulohistiocytosis, because neoplastic undifferentiated cells in the blood stream prominently appear. And the abnormal cells of cataplastic reticulosis did not show marked cellular atypism, and they did not make any destruction of tissues by its infiltration and tumor formation based on its proliferation.

The cause of the fever, and hydrops was not clear. The genesis of jaundice was not

clear too. But some reports explained the cause of jaundice as a result of obturation icterus based on the microscopic intrahepatic biliary obstruction by the severe infiltration of abnormal histiocytic cells. The focal necrosis of the liver parenchymal cells was seemed to be a inflammatory manifestation, but the genesis was not clear. The cause of the pancytopenia was considered as due to the replacement of bone marrow tissues by marked proliferation of reticulohistiocytes.

Scott and Robb-Smith thought these abnormal cells belong to the histiocytic series. According to their explanation, almost all the abnormal cells were prohistiocytes which were regarded as the precursors of histiocytes. Vaithianathan emphasized the appearance of three types of abnormal cells, which are 1) the prohistiocyte having a relatively small amount of pale staining homogenous cytoplasm and almost round hyperchromatic nucleus, 2) the large histiocytic cell with irregular margins and foamy cytoplasm containing ingested red cells and cell debrises within the cytoplasmic vacuoles, 3) the large bizarre giant cells occasionally simulating the Reed-Sternberg cells of Hodgkin's disease.

In Japan, only 22 or so cases were reported under the heading of the histiocytic medullary reticulosis. And some other cases exhibiting the similar findings as those of histiocytic medullary reticulosis seemed to be reported with the name as malignant reticulosis, cataplastic reticulohistiocytosis or leukemic reticuloendotheliosis. But the differencial diagnosis of those similar reticulosis has a great difficulty because those disorders have much confusions in the conception. For that reason, it is thought difficult that making a decision about independence of the entity of the histiocytic medullary reticulosis. Henceforward, we must study this disease and must fix its position exactly by comparing the variation of the findings. At the same time, some similar reticulosis like familial hemophagocytic reticulosis,[1,9] reticulum-celled medullary reticulosis,[4] leukemic reticuloendotheliosis,[3,5] and Letterer-Siwe disease must be investigated, because these disorders are believed to have cases overlapping each other.

From the fact that the greater part of clinical and histological findings of this case was corresponded with that of histiocytic medullary reticulosis, it was easily concluded that the case is a disease which have to be diagnosed as histiocytic medullary reticulosis. On the other hand, the following controversial points which had not been discussed in the previous reports, were made apparant by this investigation.

They are: 1) In spite of the typical histopathological findings were noted, liver did not show hepatomegaly, weighing only 1,100 gr., and this gave rise to a question that the increasing of the liver weight is necessary or not? 2) Nevertheless the typical histopathological features were noted, the lymphadenopathia was not prominent also. 3) The liver showed a kind of an inflammatory reaction with necrosis histologically. 4) Almost all of the

enlarged abnormal histiocytes, observed in general reticuloendothelial systems, were thought as originating from the fixed proper reticulum cells of each organs, including a small number of rather small histiocytes which were thought to belong to precursors of histiocyte. As to the origin of the abnormal cells, it may possibly be interpreted that the almost all of the abnormal histiocytes impregnated in those organs, are not which were infiltrated and transported to those organs from other sites neoplastically proliferated. Those hypothesis could be ensured by the peculiar findings that the Kupffer's cells in the liver

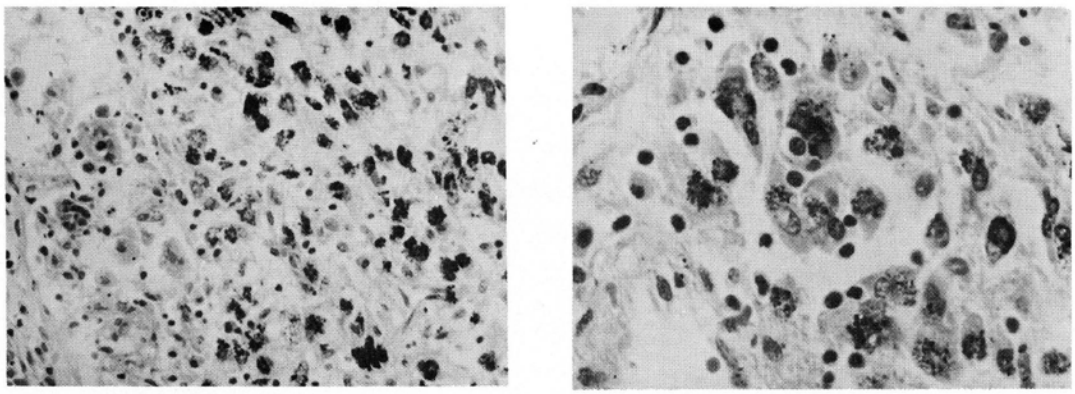


Fig. 13-14. Bronchopulmonary lymph gland. The fibrous histiocytes containing carbon pigment, are enlarged and plumply transformed. Some of them showed phagocytized red cells or lymphocytes in the cytoplasm. H & E. ×200, ×400.

sinusoids were abnormalily enlarged and the fibrous histiocytes in the bronchopulmonary lymph glands were also enlarged and plumply transformed with containing a great amount of carbon pigments.(Fig. 13,14)

From those findings, the nature of the abnormal cells representing a distinctive entity of this disease, the neoplastic nature was contradictive and the condition with impregnation of the abnormal histiocytes is thought as not neoplastic proliferation nor infiltration.

The possible character of the abnormal cells is a transformation of the original reticulum cells to the enlarged phagocyting histiocytes, in a short period, by an unknown cause which might irritate the generalized reticulum cells in reticuloendothelial systems. For the consummation of the characteristic lesions of this disorder, it might require a preceeded nonspecific inflammatory reactive reticulosis and additional other unknown factor which could transform the reticulum cells to the abnormal histiocytes.

As to the cause of fatal short clinical course, most probable interpretation is the blockage and loss of metabolic function of the reticulum cells in the general reticuloendothelial systems resulted by this transformation.

As some investigators have stated, to perform an antemortem diagnosis, an increase of the knowledge concerning this disease is necessary.

An increase of opportunities for antemortem examination of this disease will make more detailed research possible.

Summary

A twenty-six-year-old woman died with an illness characterized by splenomegaly, leukopenia, anemia, appearance of abnormal histiocytes in the peripheral blood and bone marrow, and short clinical course. Antemortem diagnosis could not be established. The findings of post-mortem examination were that of typical histiocytic medullary reticulosis. There are only small number of cases in Japan. However, an increase of antemortem diagnosis of this disease could be presumed to aid the progress of knowledge concerning this kind of disease.

(This reported case was presented at the 30th Annual Meetings of the Japan Haematological Society.)

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