รายงานผู้ป่วย

Death occurring within 6 days after initial presentation of malignant histiocytosis.

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A 43-year-old woman is reported to have clinically undiagnosed malignant histiocytosis (MH). She died within 6 days after the initial presentation of the malady. Although the prognosis of patients with MH is generally poor death occurring within 6 days is highly unusual. Postmortem examination disclosed MH involving the porta hepatic and peri-pancreatic lymph nodes, liver, spleen, and bone marrow. Additionally, abnormal histiocytes were present intravascularly. It is suggested that attempt is made to recognize these histiocytes in routine examination of the peripheral blood in order to reach rapidly the clinical diagnosis and proper management of MH during life of the patient. Enlargement of lymph nodes, liver, and spleen is common in MH, especially during subsequent course of ailment. However, this finding may not be detectable at the initial presentation of the malady.

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สำรวย ช่วงโชติ. มรณกรรมที่เกิดขึ้นภายใน 6 วัน หลังจากฮิสติโอซิสร้าย ปรากฏอาการขึ้นครั้งแรก. จุฬาลงกรณ์เวชสาร 2531 มกราคม ; 32 (1) : 67-74

ผู้ป่วยหญิงอายุ 43 ปี ตายภายใน 6 วัน หลังจากอาการของโรคฮิสติโอซัยโตซิสร้ายปรากฏขึ้นเป็นครั้งแรกและวินิจฉัยโรคไม่ได้ก่อนผู้ป่วยสิ้นชีวิต โดยทั่ว ๆ ไปการพยากรณ์โรคมักเลวมากในโรคนี้ แต่ก็มีน้อยมากที่จะตายเร็วอย่างผู้ป่วยรายนี้ ตรวจศพพบฮิสติโอซัยโตซิสร้ายเกิดขึ้นที่ต่อมน้ำเหลืองแถวบริเวณขั้วตับและรอบ ๆ ตับอ่อน ตับ ม้าม และไขกระดูก ทั้งพบฮิสติโอซัยท์กินเม็ดเลือดแดง ทะลุทะลวงผนังหลอดเลือด และอยู่ภายในรูหลอดเลือด สิ่งตรวจพบอันหลังนี้แสดงว่ามีฮิสติโอซัยท์อยู่ในกระแสโลหิตด้วย จึงควรมองหาฮิสติโอซัยท์เหล่านี้บนแผ่นกระจกป้ายเลือดของผู้ป่วยด้วย ถ้าพบก็คงช่วยให้วินิจฉัยและรักษาโรคได้รวดเร็วขึ้น ขณะที่ผู้ป่วยยังมีชีวิตอยู่ การโตของต่อมน้ำเหลือง ตับ และม้าม พบได้บ่อยในโรคนี้ โดยเฉพาะอย่างยิ่งในระยะท้าย ๆ ของโรค แต่อาจตรวจไม่พบทางคลินิกเมื่อโรคเริ่มปรากฏอาการดังในผู้ป่วยที่นำมารายงาน ณ ที่นี้

Malignant histiocytosis (MH) or histiocytic medullary reticulosis (HMR), a highly malignant systemic disease relating to primary (idiopathic) proliferation of the histiocytes and their precursors,[1,2] usually cause death of patients within a year. Pileri et al,[3] in their clinicopathologic study of 25 patients with MH noted the mean survival time to be 12 months. However, fatality may come as early as a few months[4] or even a few weeks.[5] In such cases, the clinical diagnosis of MH is frequently missed because of insufficient time for investigation to reach a proper diagnosis and management during life. The febrile episode often directs our attention toward the infectious disease. The true nature of MH may only be discovered postmortem. The purpose of this communication is to present a woman who died within 6 days after onset of the clinically unrecognized MH in order to warn us that such unusually rapid fatality may occur with this malady.

Case Report

A 43-year-old woman was admitted to hospital because of fever, cough, nausea, and loss of appetite for 3 days. Prior to hospitalization, a private physician gave her some drugs which did not alleviate these symptoms. Her past history was noncontributory to the present illness.

On hospitalization, the patient's body temperature was 39.7° C, pulse rate 100 beats/min, respiratory rate 40/min, and blood pressure 100/60 mmHg. She was generally weak and mildly restless, with injected pharynx and tender anterior abdominal wall. The heart and lungs were unremarkable. The superficial lymph nodes, liver, and spleen were not palpable. Pelvic examination disclosed a cystic mass on the left side of the pelvic cavity.

Hemoglobin was 12 gm/100 ml. A leucocyte count revealed 9,900 cells/mm.^{3} with 71% neutrophils, 26% lymphocytes, and 3% monocytes. However, a repeated blood examination 38 hours after hospitalization exhibited 2,300 leucocytes/mm.^{3} with 49% neutrophils, 50% lymphocytes, and 1% monocytes. Blood platelet count disclosed 20,000 thrombocytes/mm.^{3} Urinalysis demonstrated 1 plus protein, plentiful erythrocytes/high power microscopic field, and leucocytic clumps.

The patient's blood pressure fluctuated within the range of 80/50 to 100/70 mmHg. The presence of a pelvic mass and tender anterior abdominal wall led to the clinical impression that the patient might have a rupture pelvic abscess with generalized acute peritonitis and septic shock. Dopamine was administered to maintain constant blood pressure but was fruitless. Antibiotic drugs, fluid, and electrolytes were also given but the patient deteriorated rapidly. She died with bleeding per gum, 57 hours after hospitalization or about 6 days of ailment.

Postmortem Examination. An autopsy was done 40 minutes after death. The gum was focally hemorrhagic. The anterior abdominal wall was bulging. The right and left pleural cavities contained about 500 and 200 ml of straw colored serous fluid respectively. About 500 ml of thin serosanguinous fluid filled the peritoneal sac. There was severe edema of the mesentery and peritoneum. The porta hepatic and peripancreatic lymph nodes were enlarged; they ranged from $1.0\times1.5\times1.5$ to $2.0\times2.5\times2.5$ cm. The gray cut surface was bulging and focally hemorrhagic. The liver (1030 gm) showed focally reddish cut surfaces. The spleen (170 gm) exhibited dark-red and bulging cut surfaces. The vertebral marrow was gray and friable. The right and left kidneys (110 and 140 gm respectively) showed hemorrhagic mucosa of the pelves and calyces. The gastric mucosa was focally hemorrhagic; about 500 ml of coffee-ground material filled the gastric lumen. The left ovary became a cystic tumor (40 gm) which contained sebum and hairs. Abundant mucus plugged the bronchial lumens and the lungs (470 gm right, and 430 gm leff) were severely collapsed. The heart (200 gm) appeared normally.

Tissues were fixed in 10% formalin, embedded in paraffin, and stained with hematoxylin and eosin (H & E). Mallory's phosphotungstic acid hematoxylin (PTAH) stain was used to detect disseminated intravascular coagulation (DIC). Moreover, paraffin sections of lymph nodes, spleen, and bone marrow were processed by peroxidase-anti-peroxidase (PAP) indirect immunohistochemical method for localization of lysozyme and alpha-1-antitrypsin in the cytoplasm of histiocytes.

Microscopically, the substance of enlarged porta hepatic and peripancreatic lymph nodes was severely altered because of infiltration of many atypical histiocytes, both mature and immature ones (Fig. 1A), particularly in the sinuses (Fig. 1B). The histiocytes were also seen in the lumen of blood vessels within the lymph nodal capsule (Fig. 1A). The latter was additionally invaded by histiocytes. Some histiocytes were multinucleated and others showed erythrophagocytosis (Fig. 1C). A few portal triads of the liver were as well infiltrated by histiocytes. However, such histiocytic infiltration

was not observed in the hepatic parenchyma and sinusoids. There was advanced centrilobular hemorrhagic necrosis of the liver. The spleen was also infiltrated by plentiful histiocytes. Some blood vessels such as those in a few splenic trabeculae contained intraluminal histiocytes and the walls were as well invaded by them (Fig. 2). The vertebral marrow was hypercellular because of histiocytic infiltration. The adipose tissue content of the marrow was considerably diminished (Fig. 3). Megakaryocytes were adequate in number. Erythrophagocytosis by histiocytes, as in the lymph node, was also noted in the spleen and bone marrow. DIC was not perceived in tissue sections stained with PTAH. PAP studies disclosed localization of lysozyme and alpha-1-antitrypsin within the cytoplasm of cells that had been interpreted as histiocytes. Hence, their histiocytic nature was further confirmed immunohistochemically. The left ovarian lesion was verified microscopically as benign cystic teratoma.

The pathologic diagnosis was MH involving lymph nodes (porta hepatic and peripancreatic nodes), liver, spleen, and bone marrow.

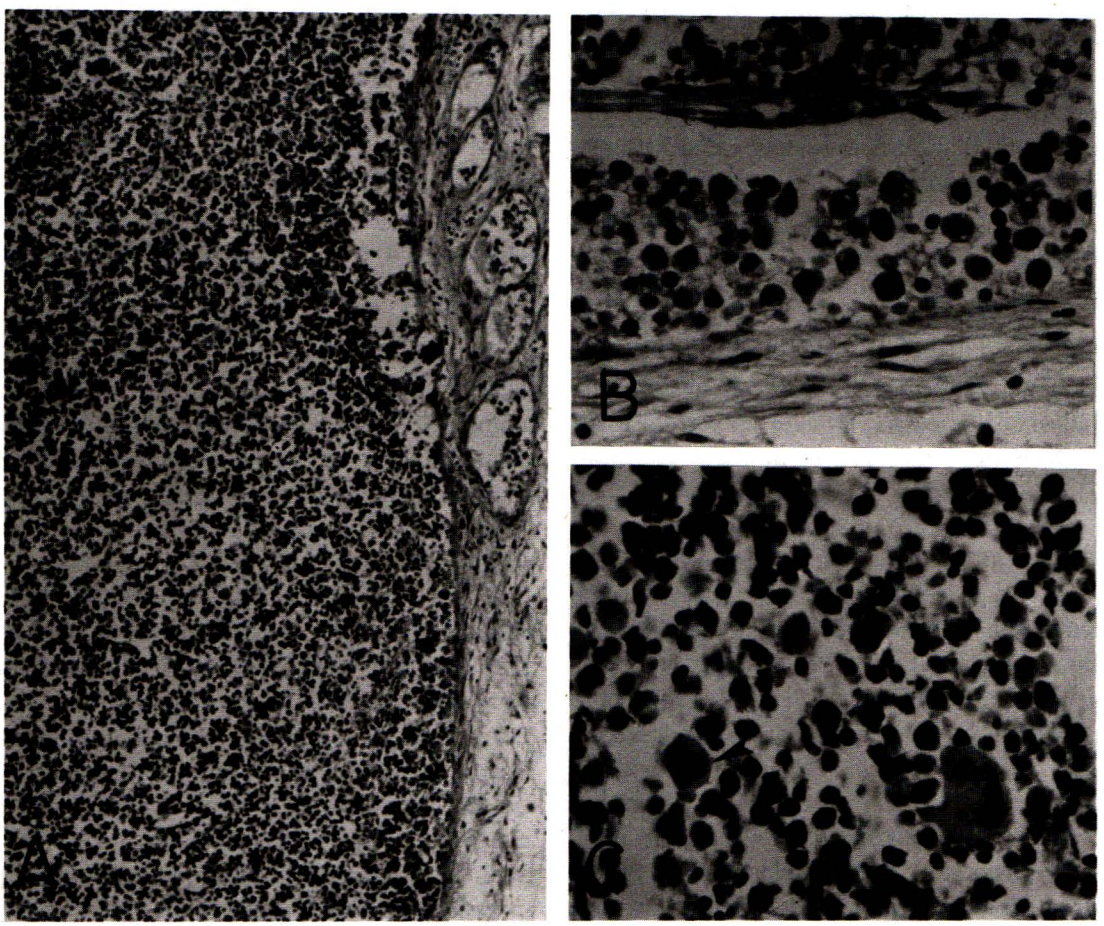

Figure 1 Histopathology of lymph node in MH.

(A). The lymph nodal architecture is severely disturbed because of infiltration by histiocytes. The latter are not clearly recognized at this magnification. Multiple blood vessels within the lymp nodal capsule on the right margin of the photomicrograph contain histiocytes in lumens. (H & E, × 50).

(B). A subcapsular lymph sinus is filled by many histiocytes. (H & E, × 100).

(C). Histiocytes within the lymph nodes are clearly recognized. They have pale ample cytoplasm and vesicular nuclei. A large histiocyte is multinucleated. An arrowed histiocyte shows cytoplasmic phagocytosed erythrocyte in juxtaposition to the lobar uncleus. (H & E, × 100).

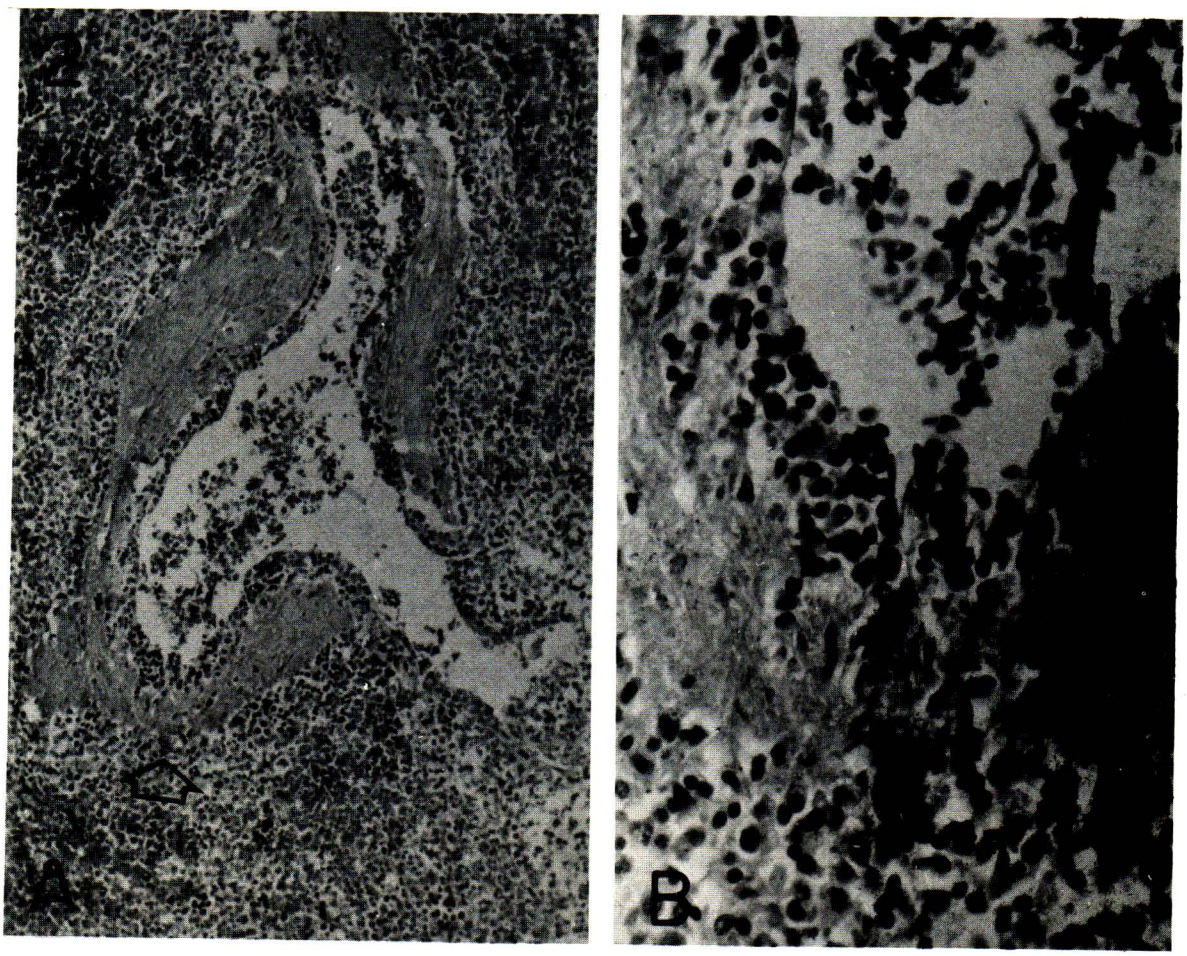

Figure 2 Vascular change in spleen.

(A). A splenic fibrous trabecula lies within the substance of the spleen which is infiltrated by many histiocytes. A trabecula vessel interpreted as vein contains histiocytes in its lumen. Its wall is invaded by histiocytes. Portion of the vascular wall corresponding to the arrow is further shown in B. (H & E, × 50).

(B). Infiltration of histiocytes into the vascular wall is clearly noted. Some histiocytes and erythorcytes lie within the lumen. (H & E, × 100).

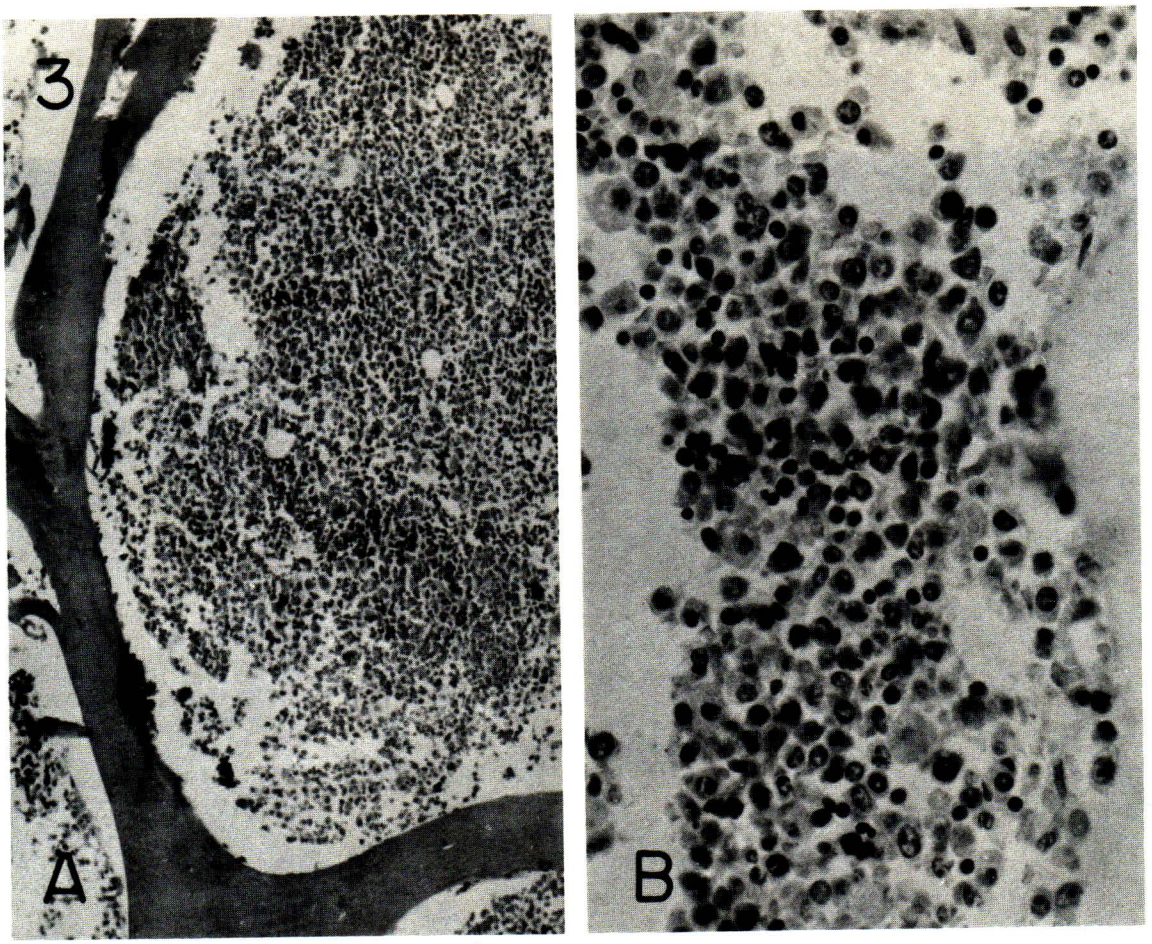

Figure 3 Bone marrow in MH.

(A). Hypercellularity and severe depletion of adipose tissue content of the vertebral marrow in relation to histiocytic infiltration is exhibited. Also note a curvilinear bony trabecula. (H & E, × 50).

(B). Many histiocytes in bone marrow are clearly recognized at higher magnification. (H & E, × 100).

Discussion

The presence of plentiful abnormal histiocytes within lymph nodes, spleen, and bone marrow, invasion of these histiocytes into the lymph nodal capsule and vascular wall, histiocytic erythrophagocytosis, and systemic manisfestations such as fever and hematologic disorders (leucopenia, thrombocytopenia, and bleeding episode) support the author's diagnosis of MH in this patient. Lymphadenopathy, hepatomegaly, and splenomegaly have been regarded as important findings in making the clinical diagnosis of MH. However, these findings may not be observed at the initial presentation of MH. Warnke et al,[6] in thier clinicopathologic study of 29 patients with MH, noted lymphadenopathy in 21 cases, hepatomegaly in 12 instances, and splenomegaly in 11 examples. Similarly Pileri et al,[3] in their clinicopathologic study of 25 patients with MH, observed lymphadenopathy in 21 cases, hepatomegaly in 3, and splenomegaly in another 3 examples. Both observations were made at the initial presentation of the disease. Thus, the clinical absence of lymphadenopathy and hepatosplenomegaly at onset of the malady should not be regarded as negative finding to exclude MH. Slight enlargement of the deep lymph nodes may not be detected and infiltration of histiocytes limited to a few portal triads may not cause notable hepatomegaly as in the current patient. However, lymphadenopathy and hepato-

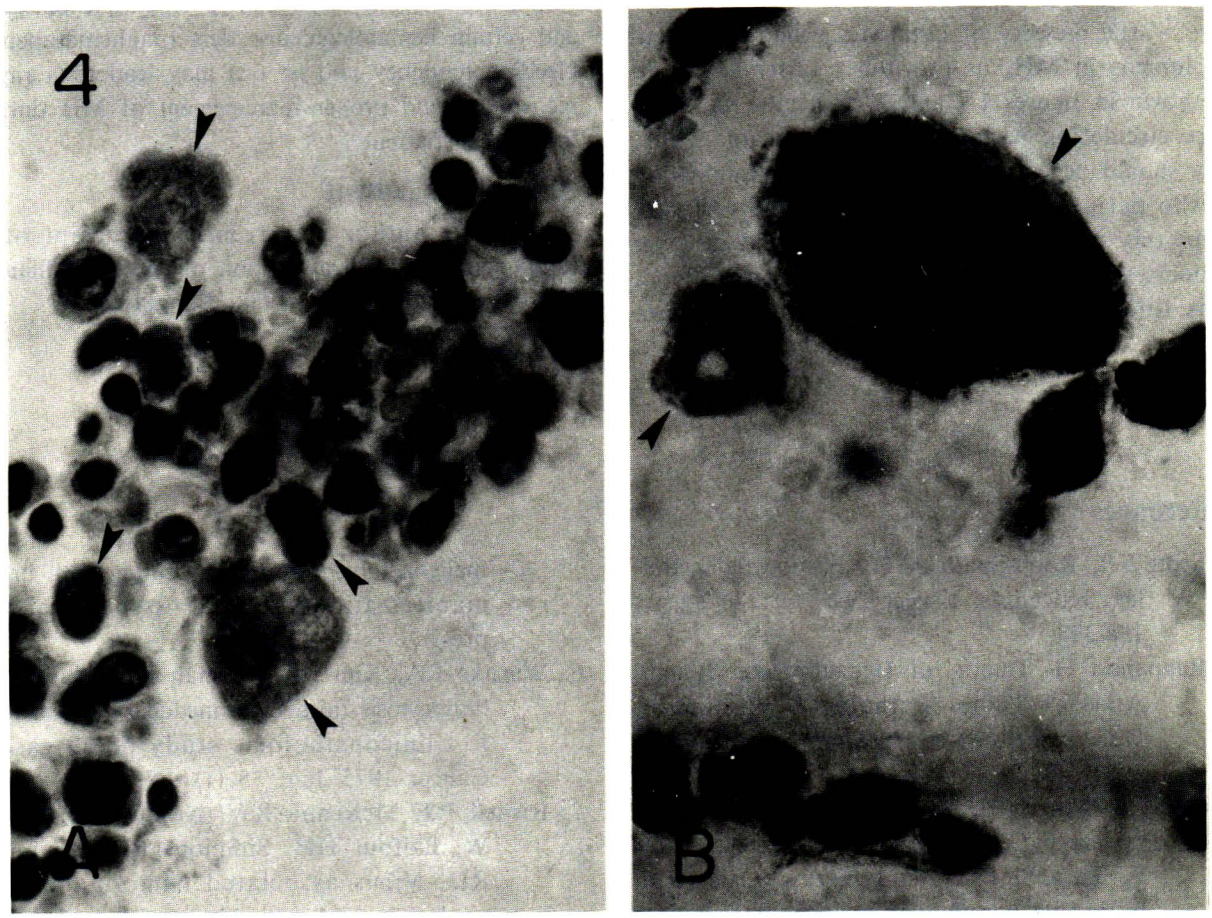

Figure 4 Result of PAP immunohistochemical study of bone marrow in MH.

(A). Dark cytoplasm of the arrowed cells is related to localization of lysozyme. (PAP stain for lysozyme, × 400).

(B). Dark perikaryon of these two arrowed cells is associated with localization of alpha-1-antitrypsin. (PAP stain for alpha-1-antitrypsin, × 1000).

Because of positive lysozyme and alpha-1-antitrypsin in the cytoplasm, all arrowed cells are interpreted as histiocytes.

splenomegaly are quite common during subsequent clinical course or at postmortem examination of patients with MH.

The author does not consider this patient to have virus associated hemophagocytic syndrome[7] or histiocytosis with massive lymphadenopathy.[8] Histiocytic invasion of the lymph nodal capsule and vascular wall in this case supports the author's contention upon the malignant neoplastic nature of these histiocytes. By contrast, histiocytes in those two conditions are benign and the disorders regress spontaneously. However, the author concurs with Pileri et al[3] that MH and histiocytic lymphoma are the same disease.

The immediate cause of death of the current patient is considered as related to shock with tissue hypoxia. The latter is partly reflected by severe centrilobular hemorrhagic necrosis of the liver. Shock also induced edema of the mesentery and peritoneum, serosanguinous ascites, and hydrothorax. However, the pathogenesis of shock in this case remained unclear. Edema of the mesentery and peritoneum is suggested to produce tender anterior abdominal wall which inappropriately directed the clinical consideration toward acute peritonitis. A benign cystic teratoma of the left ovary is an accidental postmortem finding. It is less likely to produce sign of acute peritonitis

when it was not ruptured.

The presence of histiocytes within the vascular lumens in MH, as previously observed[5] and as shown in figures 1A and 2, indicates that they were circulating within the blood stream. Thus, they should be encountered in routine examination of the peripheral blood of the patient. If one keeps this suggestion in mind one should discover histiocytes in routine smear of the patient's blood. This finding combined with other clinical data such as fever, lymphadenopathy, hepatosplenomegaly, and certain hematologic disorders (panhematopenia, bleeding tendency and so on) may lead to a rapid recognition and proper management of MH during life of the patient.

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