รายงานผู้ป่วย

Malignant histiocytosis with clinical presentations simulating meningitis*

Samruay Shuangshoti**

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A 25-year-old woman presented clinically with fever, nuchal rigidity, and abnormal findings in the cerebrospinal fluid (CSF) that resemble those seen in meningitis. However, repeated attempts to identify the microorganism within the CSF yielded negative results. The patient died 16 days after the onset of illness. Postmortem examination disclosed malignant histiocytosis (MH) involving some deep groups of lymph nodes (porta hepatic, para-aortic, peripancreatic, and hilar), liver, spleen, bone marrow, and leptomeninges of the brain. It is suggested that meningeal and/or cerebral neoplasia should be also suspected in a patient who presents with clinical manifestations of meningitis, especially when the CSF is sterile.

Reprint request : Shuangshoti S. Department of Pathology, Faculty of medicine, Chulalongkorn University, Bangkok 10330, Thailand.

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** Department of Pathology, Faculty of Medicine, Chulalongkorn University.

สำรวย ช่วงโชติ. ฮิสติโอซัยโตซิสชนิดร้ายแรงที่ให้อาการและอาการแสดงทางคลินิกคล้ายเยื่อหุ้มสมองอักเสบ. จุฬาลงกรณ์เวชสาร 2532 พฤษภาคม; 33(5) : 381-389

ผู้ป่วยหญิงอายุ 25 ปี มีอาการไข้ คอแข็ง และน้ำหล่อสมองและไขสันหลังผิดปกติ คล้ายกับมีโรคเยื่อหุ้มสมองอักเสบ แต่ไม่พบเชื้อโรคใด ๆ จากการตรวจน้ำหล่อสมองและไขสันหลังด้วยกล้องจุลทรรศน์และการเพาะเชื้อ ผู้ป่วยเสียชีวิต 16 วันหลังจากอาการไข้ปรากฏขึ้น ตรวจศพพบโรคฮิสติโอซัยโตซิสชนิดร้ายแรงที่ต่อมน้ำเหลืองบางแห่ง (บริเวณขั้วตับรอบ ๆ หลอดเลือดเอออร์ตา รอบ ๆ ตับอ่อน และที่ขั้วปอด) ตับ ม้าม ไขกระดูก และเยื่อหุ้มสมอง ฉะนั้นควรนึกถึงเนื้องอกของเยื่อหุ้มสมอง และ/หรือ สมองไว้บ้าง เมื่อพบผู้ป่วยที่ให้อาการและอาการแสดงทางคลินิกประหนึ่งเป็นโรคเยื่อหุ้มสมองอักเสบ โดยเฉพาะอย่างยิ่งในรายที่น้ำหล่อสมองและไขสันหลังปลอดเชื้อโรค

Malignant histiocytosis (MH) or histiocytic medullary reticulosis (HMR) or true histiocytic lymphoma, an uncommon malignant systemic disease associating with primary (idiopathic) proliferation of the histiocytes and their precursors, usually persents clinically with fever, lymphadenopathy, hepatosplenomegaly, physical wasting, and hematologic abnormalities such as leucopenia, thrombocytopenia, and bleeding tendency.[1-9] Cutaneous or subcutaneous lesions may occur such as papules, nodules, or plaques which may be early manifestations of the disease.[3] Neurologic manifestations are uncommon although encephalopathy[10] and paresis due to compression of the cauda equina[11] have been reported. In this communication, an instructive case of MH with clinical manifestations simulating meningitis is reported.

Case Report

Sixteen days before death, a 25-year-old woman had fever with chill, headache, and mild sore throat. Nevertheless, she could go to work as usual. Nine days later, she experienced nausea and vomiting. She was hospitalized 10 days after ailment with body temperature of 39°C, pulse rate 120 beats/min, respiratory rate 20/min, and blood pressure 130/90 mmHg. Her neck was stiff. The eye ground was normal. The liver was 2 finger-breadths below the costal margin. The spleen was not palpable. The superficial lymph nodes were not enlarged. The heart and lungs were normal under auscultation.

Examination of her blood revealed 10 gm/100 ml of hemoglobin and 10,050 leucocytes/mm^3, with 74% neutrophils and 26% lymphocytes. Fasting blood sugar was 91 mg/100 ml, BUN 12 mg/100 ml, sodium 139 mEq/L, potassium 4.5 mEq/L, and carbon dioxide 19.5 mEq/L. Serum albumin was 2.25 gm/100 ml, globulin 4.35 gm/100 ml, SGOT 44 IU/L, SGPT 15 IU/L, alkaline phosphatase 12.5 IU/L, and prothrombin time 11.9 seconds (control 12.1 seconds).

Three consecutive lumbar punctures were made. The first, 1 day after hospitalization, had an opening pressure of 230 mm of water. The clear cerebrospinal fluid (CSF) contained 50 mononuclear cells/mm^3, 110 mg/100 ml of protein, and 61 mg/100 ml of sugar (Blood sugar at the time was 131 mg/100 ml). The second puncture, 5 days after hospitalization, had an opening pressure of 270 mm of water. The clear CSF had 88 mononuclear cells/mm^3, 1 plus Pandy's test, and 39 mg/100 ml of sugar (Blood sugar was 119 mg/100 ml). The third puncture, 6 days after hospitalization, was turbid, had an opening pressure of 190 mm of water, 370 atypical mononuclear cells/mm^3, 2 plus Pandy's test, and 76 mg/100 ml of sugar (Blood sugar was 434 mg/100 ml due to intravenous infusion of glucose solution). Gram's stain, India ink preparation, and culture of the CSF from each lumbar puncture revealed no microorganism. There was no document of cytologic examination of the CSF.

The clinical impression was that of meningitis. The temperature fluctuated between 37.5° to 41°C. She died of severe dyspnea on the sixth day of hospitalization or 16 days after the onset of ailment.

Postmortem examination. An autopsy was done 22 1/2 hours after death. The lungs (1,040 gm) were wet. The porta hepatic, para-aortic, peripancreatic, and hilar lymph nodes were enlarged up to 2.5 cm in diameter (Fig. 1). The cut surfaces were homogeneous, gray-white and bulging. The liver (1,450 gm) showed congested and bulging cut surfaces. The spleen (140 gm) exhibited dark-red and bulging cut surfaces. The vertebral bone marrow was gray and friable. The congested and edematous brain (1,140 gm) showed flat gyri, narrowed sulci, and prominent groove on the cerebellar tonsils to indicate herniation of the latter in association with increased intracranial pressure. The leptomeninges were cloudy at the dorsal convexity of the cererbral hemispheres resembling acute purulent meningitis (Fig. 2). Horizontal sections of the brain disclosed no remarkable changes within the brain subtance.

Tissues were fixed in 10% formalin, embedded in paraffin, and stained with hematoxylin and eosin (H&E). Moreover, paraffin sections of lymph nodes, bone marrow, and brain were processed by peroxidase-anti-peroxidase (PAP) indirect immunohistochemical method for localization of alpha-1-antitrypsin and lysozyme in the cytoplasm of histiocytes.

Microscopically, the lungs showed advanced congestion and edema. A large number of alveoli were filled with edema fluid. The substance of the enlarged lymph nodes was severely infiltrated with atypical histiocytes, both mature and immature ones (Fig. 3). Histiocytic infiltration was noted in the capsule and surrounding fibroadipose tissue of lymph nodes. Similar histiocytic infiltration was observed in the liver (Fig. 4), spleen, and vertebral bone marrow (Fig. 5). Within the liver, they often appeared in sinusoids, vascular lumens (Fig. 4), and in the portal triads. Erythrophagocytosis by histiocytes was detected (Fig. 5). The brain showed infiltratrion of histiocytes in the leptomeninges and in the subarachnoid space (Fig. 6 and 7). Invasion of the vascular walls and superficial part of the cerebral cortex by histiocytes was observed.

Immunohistochemically, alpha-1-antitrypsin and lysozyme were localized in the cytoplasm of the tumor cells in lymph nodes, bone marrow, and brain (Fig. 7). The finding supported histiocytic nature of these neoplastic cells.

The pathologic diagnosis was MH involving lymph nodes, liver, spleen, bone marrow, and brain especially the leptomeninges over the dorsal surface of the cerebral hemispheres.

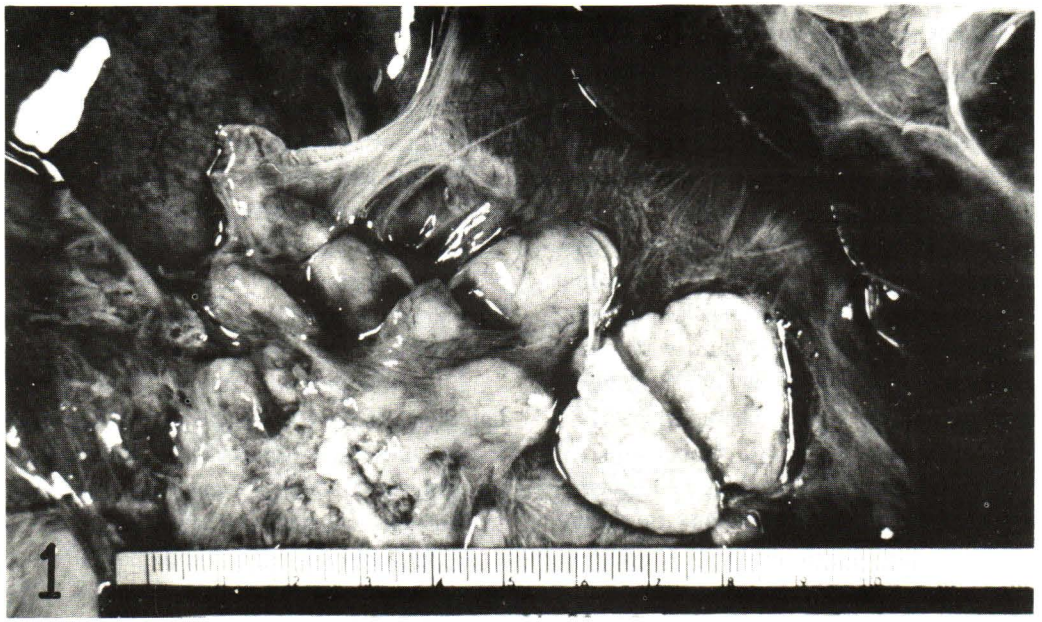

Figure 1. Gross appearance of lymph nodes in MH. Enlarged porta hepatic lymph nodes are shown. Note bulging and homogeneous cut surfaces of one node.

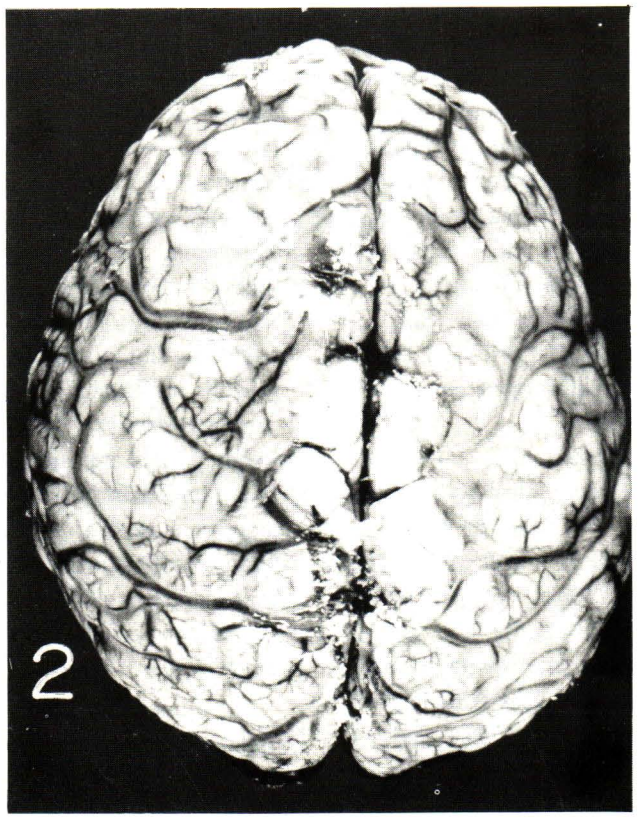

Figure 2. Brain in MH. Note opacity of the leptomeninges and congested blood vessels on the dorsal aspect of the cerebral hemispheres to resemble acute purulent meningitis.

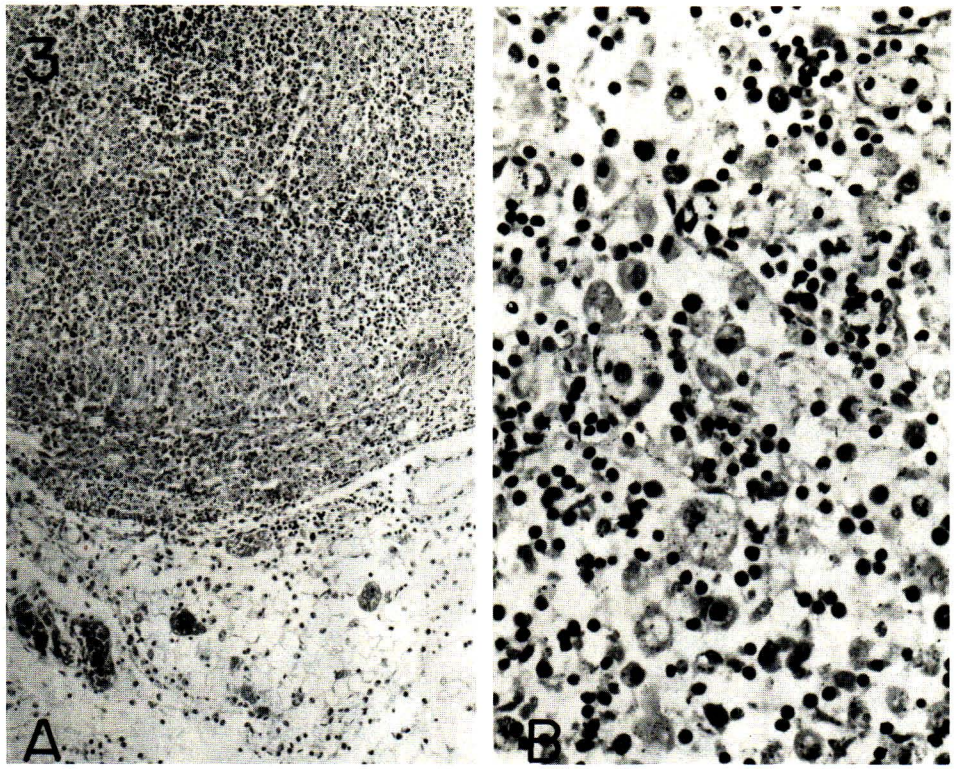

Figure 3. Histopathology of lymph node in MH.

(A) The architecture of a lymph from the porta hepatic region is severely altered by infiltration of many histiocytes which also invade the capsule of the lymph node and perinodal soft tissues. (H & E, × 50).

(B) Histiocytes within the lymph node are further illustrated at higher magnification. They are large and have vesicular nuclei surrounded by pale ample cytoplasm which is occasionally vacuolated. (H & E, × 400).

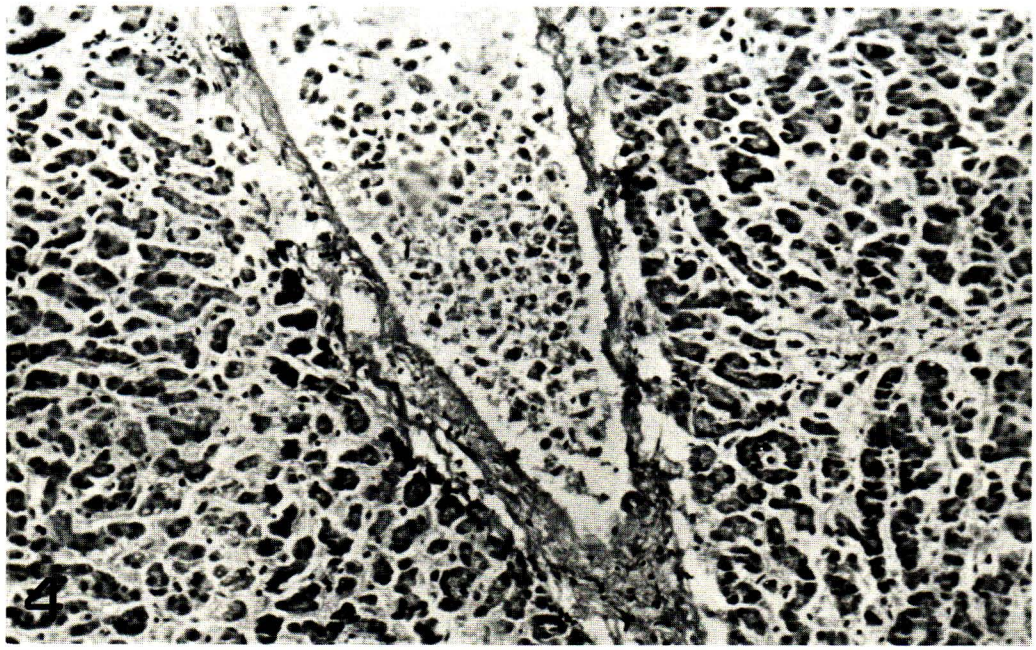

Figure 4. Liver in MH. A blood vessel filled with histiocytes is exhibited. (H & E, × 100).

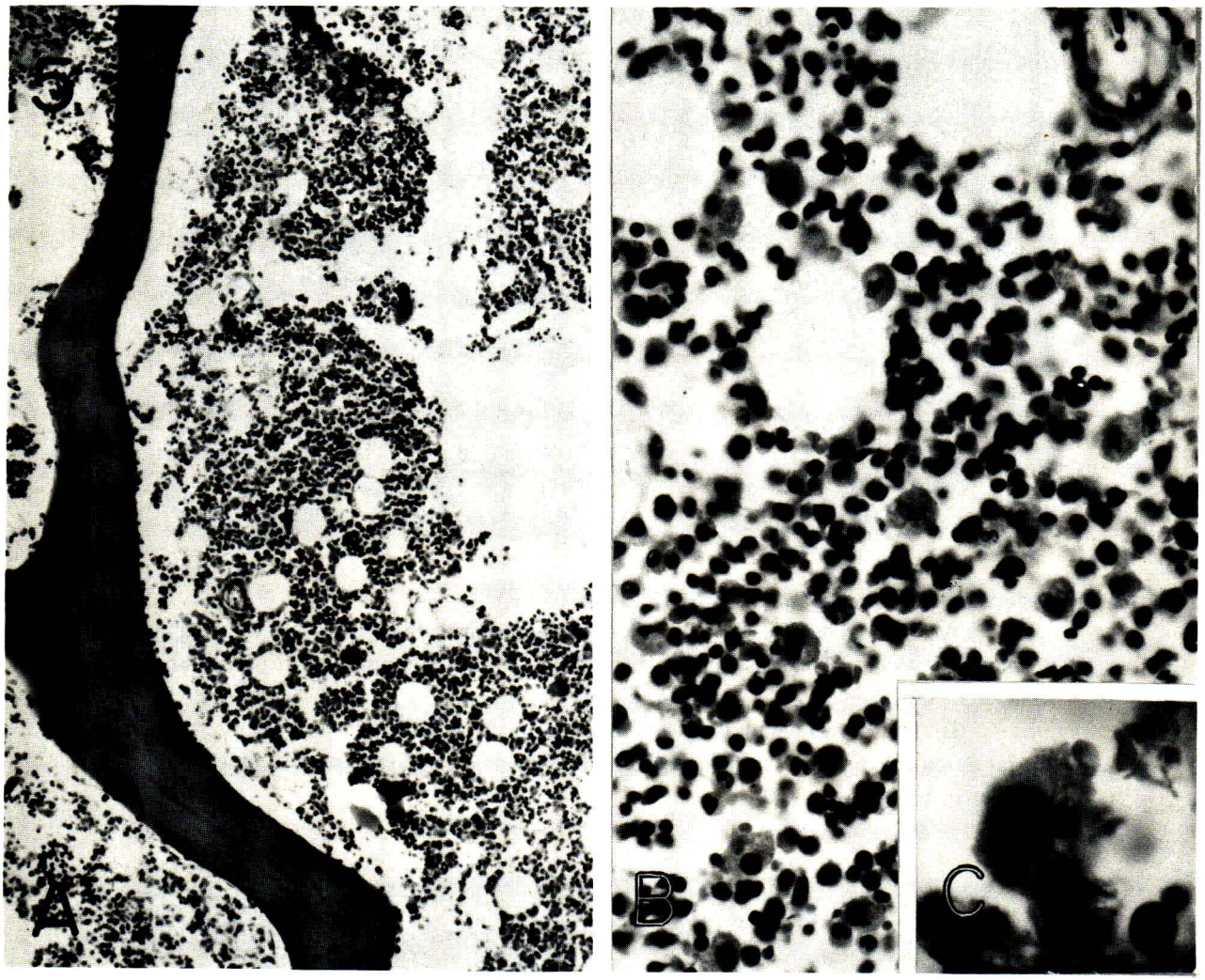

Figure 5. Bone marrow in MH.

(A) Hypercellularity of bone marrow from a vertebral body is demonstrated. A curvilinear bone trabecula lies on the left side of the photomicrograph. (H & E, × 50).

(B) Many histiocytes are clearly recognized within the bone marrow. (H & E, × 400).

(C) A histiocyte with phagocytosed erythrocytes within its cytoplasm is demonstrated. (H & E, × 1000).

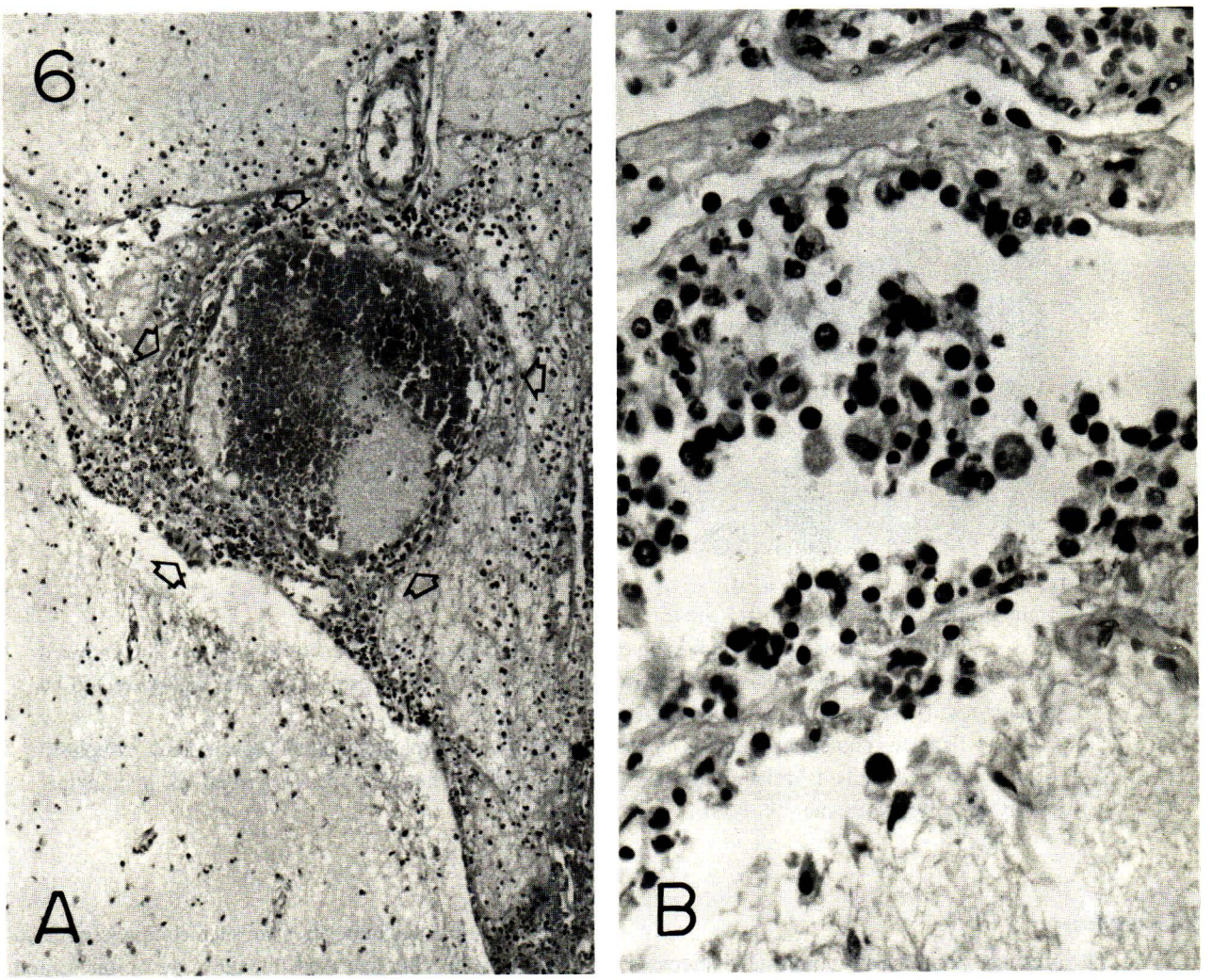

Figure 6. Brain in MH.

(A) A few blood vessels within the subarachnoid space are shown; one is outlined by arrows. Cells in the subarachnoid space are mostly histiocytes. Note infiltration of cells, particularly histiocytes, within the vascular wall outlined by arrows. (H & E, × 50).

(B) Histiocytes within the subarachnoid space are clearly perceived; some of them invade the lephomeninges. Part of the brain is seen at the right lower corner of the photomicrograph. (H & E, × 100).

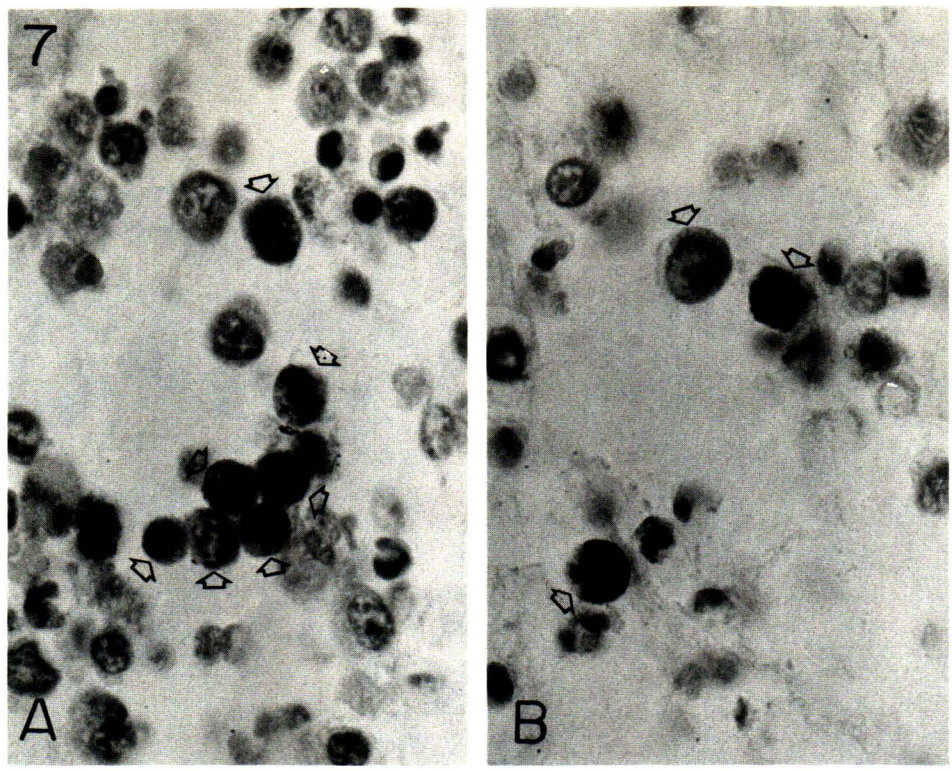

Figure 7. Immunohistochemistry of histiocytes.

(A) This photomicrograph is taken from the subarachnoid space of the brain. The arrowed cells have dark cytoplasm because of postitivity to alpha-1-antitrypsin. They are interpreted to be histiocytes. (PAP stain for alpha-1-antitrypsin, × 1000).

(B) This photomicrograph is also taken from the cerebral subarachnoid space. Dark cytoplasm of the arrowed cells is related to lysezyme positivity. They are also regarded as histiocytes. (PAP stain for lysezyme, × 1000).

Discussion

The presence of numerous abnormal histiocytes in the enlarged lymph nodes, liver, spleen, bone marrow, and brain as well as the invasion of the histiocytes into the capsule of lymph nodes and perinodal soft tissues, and vascular walls in the subarachnoid space, histiocytic erythrophagocytosis, and systemic manifestation such as fever support the diagnosis of MH in this patient.[1-9] Nuchal rigidity and abnormal CSF findings such as increased cellular and protein contents and occasionally low sugar content suggest bacterial or fungal meningitis. However, such CSF findings can be related as well to the neoplasia of the meninges and/or brain which should be considered until proven otherwise, particularly when the CSF is sterile,[12,13] and the cytologic study of the CSF should be done in such case. The immediate cause of death of the current patient was considered to be related to compression of the medulla oblongata by the herniated cerebellar tonsils. The respiratory failure may occur in association with disturbance of the respiratory center within the medulla oblongata from such compresion. Such event may be characterized clinically as dyspnea, and pathologically as the collection of fluid within the alveoli (pulmonary edema).

The differential diagnoses of MH include virus associated hemophagocytic syndrome,[14] histiocytosis with massive lymphadenopathy,[15] and leukemia. The histiocytes in the former two conditions are benign and the disorders regress apontaneously. In the current patient, the histiocytes may look benign but their invasive nature as characterized by their infiltration of the capsule of lymph nodes, perinodal soft tissues, and vascular walls in the subarachnoid space aupport their malignant behavior. Rappaport[2] characterized MH as a systemic progressive, and invasive proliferation of morphologically atypical histiocytes and their precursors. The current author, therefore, regards the invasive nature as a significant finding in diagnosing MH when the cytologic malignancy is equivocal. The presence of abnormal histiocytes intravascularly as shown in figure 4 suggests

leukemia. However, there is no distinctive leucocytosis in this patient to support such diagnosis. Moreover, intravascular MH has been reported.[10]

The diagnosis of MH should be made when the patient is still alive. A satisfactory survival was reported in some individuals with MH who were treated with chemotherapeutic agents.[5] Recognition of histiocytes, such as in the CSF sediment, may be difficult because they may be similar to other mononuclear cells. Nevertheless, when atypical mononucelar cells are observed, as in the third lumbar puncture of the current patient, a neoplastic process rather than an inflammatory condition, should be suspected and the cytologic study of the CSF should be done. Such atypical mononuclear cells may be atypical histiocytes as previously reported.[10]

Generally, the patient with MH dies within 1 year.[6,7] Rapid fatality within 16 days in the current patient is an unusual course for MH. Nevertheless, there have been cases reported to have died within 1 to 3 week (s) after the initial onset of MH.[9,10]

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