รายงานผู้ป่วย

Disseminated phycomycosis: Complication of hypoplastic anemia*

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A case of hypoplastic anemia and disseminated phycomycosis in a 58-year-old woman is reported. For 6 weeks prior to death, she had intermittent fever with bleeding tendency. Two weeks before death, tenderness occurred at the right upper quadrant of the anterior abdominal wall accompanied by abnormal liver function tests. Throughout the course of illness, there was persistent infiltration of the upper portion of her right lung. She eventually died with bleeding per gum, nose, and digestive tract. Moreover, the clinically unsuspected phycomycosis was found to involve the lungs, mural endocardium of the cardiac ventricles, and right lobe of the liver, It produced multiple infarcts of the lungs and one infarct of the right lobe of the liver, Awareness and suspicion should be given for complicated fungal infection in handling a debilitated patient.

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สำรวย ช่วงโชติ. ฟันโคมัยโคซิสชนิดแพร่กระจาย : โรคแทรกของอาการโลหิตจางชนิดไขกระดูกไม่ทำงาน. จุฬาลงกรณ์เวชสาร 2531 กรกฎาคม : 32(7) : 661-669

ผู้ป่วยหญิงอายุ 58 ปี มีอาการโลหิตจางอันเนื่องมาจากไขกระดูกไม่ทำงานโดยไม่ทราบสาเหตุและตายภายใน 6 สัปดาห์ ระหว่างที่ป่วยอยู่นั้นผู้ป่วยมีไข้ ภาวะเลือดออกง่ายและมีรอยโรคในปอดขวาตอนบนให้เห็นได้ในเอกซเรย์ของทรวงอกตลอดเวลา 2 สัปดาห์ก่อนตาย มีบริเวณเจ็บที่บริเวณหน้าท้องชีกขวาตอนบน ร่วมไปกับความผิดปกติในหน้าที่ของตับ ผลการตรวจศพพบเนื้อเยื่อไขมันแทรกแซงไขกระดูกเป็นอย่างมาก เหลือเซลล์ที่ผลิตเม็ดเลือดเพียงเล็กน้อย ยิ่งกว่านั้นยังพบฟันโคมัยซิสในปอดทั้งสองข้าง ที่เวนตริเคิลทั้งสองของหัวใจ และที่กลีบขวาของตับ เชื้อราแทรกแซงผนังหลอดเลือดและจับกันเป็นกลุ่มอุดรูหลอดเลือด ก่อให้เกิดหย่อมเนื้อตายหลายหย่อมในปอดทั้งสองข้าง และหนึ่งหย่อมใหญ่ในกลีบขวาของตับ โรคราน้ำไม่ได้สงสัยขณะที่ผู้ป่วยยังมีชีวิตอยู่ จึงควรที่จะพึงระมัดระวังเกี่ยวกับโรคราแทรกซ้อนไว้เสมอเมื่อพบผู้ป่วยที่เจ็บป่วยเรื้อรังและมีภูมิต้านทานโรคต่ำ

Phycomycosis is the term given to a group of infections caused by fungi belonging to the class Phycomycetes. In the past, the term mucormycosis was widely used because it was believed that the malady was caused by genera of the family Mucoraceae such as Mucor, Rhizopus, Absidia, Basidiobolus and so on. Subsequently, it was found that these fungi were within the class Phycomycetes. When fungal culture is not done, the term phycomycosis should be employed because it has broader meaning than the term mucormycosis.[1,2]

Phycomyceteous fungi are ubiquitous and nonpathogenic but opportunistic. They live in soil, dung, fertilizer, and decayed vegetatbles. They produce air-borne spores. Man becomes infected mainly in relation to debilitating ailments such as diabetes mellitus especially in uncontrolled and acidotic states, acidosis of various causes, hematologic disorders, cancers, chronic renal and hepatic diseases, malnutrition, severe diarrhea, tuberculosis, and prolonged or careless administration of antibiotics, corticosteroids, and cytotoxic or immune suppressing agents.[3-7] The author describes herein a patient who had disseminated opportunistic phycomycosis involving the lungs, heart, and liver in association with hypoplastic anemia.

Case Report

Six weeks before death, a 58-year-old woman was admitted to a hospital because of severe pallor, general weakness, palpitation, bleeding per gum, and fever. Examination disclosed a body temperature of 39°C. A platelet count showed 25,000 thrombocytes/mm^3. A chest X-ray revealed an area of infiltration in the upper field of the right lung. A biopsy of the bone marrow exhibited fatty infiltration; hypoplastic anemia, then, was diagnosed.

Two weeks prior to death, she was transfered to Chulalongkorn Hospital. Her body temperature was 40.5°C, pulse rate 130 beats/min, respiratory rate 26/min, and blood pressure 130/90 mm Hg. Petechiae and ecchymoses of the skin were noted throughout her body as well as bleeding per gum and nose. Cardiac murmur was not detected. Coarse crepitations were noted in the upper field of the right lung. There was tenderness at the right upper quadrant of the anterior abdominal wall.

Hematocrit ranged form 22 to 27 volume%, leucocyte counts 700 to 5,000 cells/mm^3, and platelet counts 8,000 to 89,000 thrombocytes/mm^3. Total bilirubin ranged from 2.8 to 5.1 mg/100 ml, direct bilirubin 1.45 to 2.85 mg/100 ml, alkaline phosphatase 16.5 to 80.0 IU/l, SGOT 47 to 240 IU/l, SGPT 133 to 404 IU/l, serum albumin 1.95 to 2.25 gm/100 ml, and globulin 2.35 to 2.60 gm/100 ml. Serum sodium ranged from 119 to 134 mEq/L, potassium 2.3 to 7.2 mEq/L, chloride 92 to 95 mEq/L, and carbon dioxide 10 to 23 mEq/L. Fasting blood sugar was 110 mg/100 ml, BUN 9 to 21 mg/100 ml, and creatinine 0.4 to 0.7 mg/100 ml. A repeated biopsy of the bone marrow showed severe hypoplasia of all cellular constituents in association with increased adipose tissue component. Pseudomonas aeruginosa was isolated in a hemoculture.

Antibiotic drugs, testosterone, blood transfusion, and other supportive treatments were given. However, the patient continued to have intermittent fever (37.5° to 40°C). Bleeding per gum and nose could not be controlled. The pulmonary infiltration remained unchanged in repeated chest X-rays. The patient died 2 weeks after hospitalization or 6 weeks of her illness.

Postmortem examination (A-30-57). Numerous petechiae and ecchymoses of the skin were scattered throughout. The gum was hemorrhagic. Films of blood coated the wall of the nostrils. The sclerae, lips, buccal mucosa, and skin were remarkably pale. The vertebral marrow was yellow. About 50 ml of thin serosanguinous fluid filled the pericardial sac. A 420-gm heart showed extensive hemorrhage of the epicardium and mural endocardium of the right atrium with extension into the base of all leaflets of the tricuspid valve. Hemorrhagic vegetations 2.0 and 3.0 cm in greatest dimension were adherent to the mural endocardium of the left and right ventricles respectively (Fig. 1). Atrial and ventricular septal defects were not observed. The right and left lungs (600 and 500 gm respectively) contained many firm nodules, 1 to 3 cm in diameter, in all lobes. Some nodules were hemorrhagic. Others lay against the visceral pleura. A 1,400-gm liver had a roughly wedge-shaped, focally hemorrhagic, and necrotic area of 5 cm.in diameter in the right lobe (Fig. 2). It lay against the surface of the right lobe. The remaining part of the liver was gray and rubbery. The mucosa of the entire digestive tract was congested and focally hemorrhagic. About 600 of altered blood filled the lumen of the stomach and small bowel. A 1,160-gm, congested, and edematous brain showed focal subarachnoid hemorrhage at the occipital regions. Many petechiae and echymoses, 1 to 5 mm across, were scattered within the substance of the brain.

Microscopically, the vertebral marrow was severely replaced by mature adipose tissue cells.

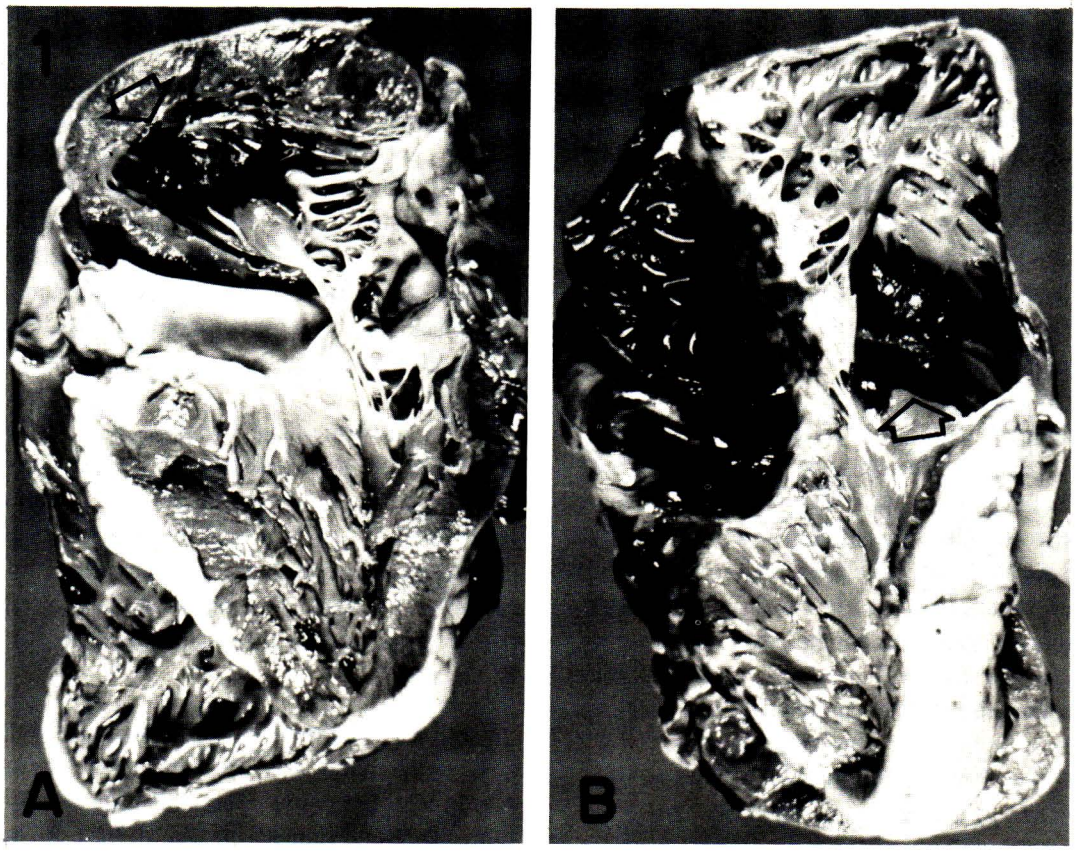

Figure 1 Bilateral ventricular mural vegetations of the heart.

(A). The arrow points toward a hemorrhagic vegetation attaching to the mural endocardium of the anterior wall of the left ventricle.

(B). The arrow points toward a hemorrhagic vegetation attaching to the wall of the right ventricle and partly covering by a tricuspid leaflet. There is extensive hemorrhage of the mural endocardium of the right atrium with extension into the base of all tricuspid leaflets.

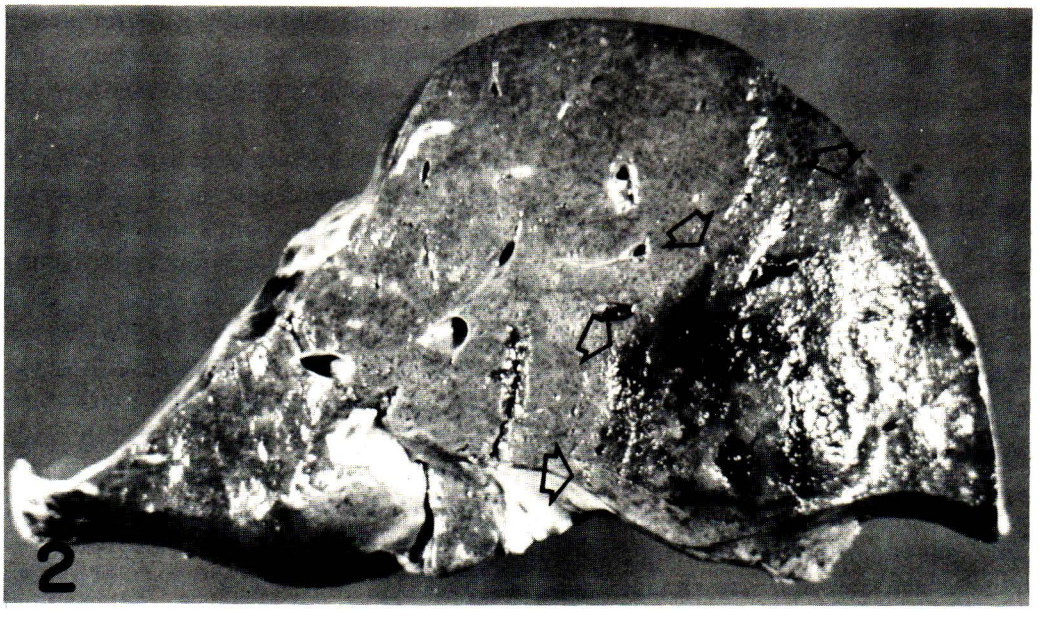

Figure 2 Liver showing a roughly wedge-shaped zone of recent infarct as outlined by the arrows.

Only a small number of the erythroid and myeloid cells remained (Fig. 3). Multiple sections of the lungs, heart, and liver showed similar fungal infection. The lesions in various places were composed of fungal hyphae which were broad, branching, and mostly nonseptate. They were best seen in Gomori's methenamine-silver (GMS) stain (Figs. 4 to 6). The branch tended to be at obtuse or at right angle to the main hypha (Figs. 5B and 6C). Only a few fungal mycelia were septate (Fig. 6C). The fungal hyphae often invaded the vascular walls and occluded their lumens (Figs. 4 and 6) which resulted in infarction of the lungs and liver. Free fungal mycelia were slso scattered within the sebstance of the lungs and liver. There were hypertrophy of the myocardium and advanced centrilobular hemorrhagic necrosis of the liver. The brain showed only edema and foci of recent hemorrhage; no fungi were seen.

The pathologic diagnoses were hypoplasia of bone marrow with considerable fatty infiltration; hypertrophy of heart; petechiae and ecchymoses of skin, gum, heart, mucosa of digestive tract, and brain; altered blood in gastrointestinal tract; phycomycosis involving lungs, mural endocardium of cardiac ventricles, and liver; fungal vasculitides and thromboses of pulmonary blood vessels and intrahepatic branches of hepatic artery; multiple recent infarcts of lungs; and single recent infarct of right lobe of liver.

Discussion

Although the culture was not done the broad and nonseptate features of most fungal mycelia with branching at obtuse or at right angle to the main hypha were morphologically diagnostic of phycomycosis in tissue sections.[8,9] However, the presence of septa in some hyphae, as shown in the figure 6C, suggests that the fungi may not be phycomyceteous. Nevertheless, Chandler and Watts[10] clearly demonstrated that, on rare occasion, septate hyphae are present in phycomyceteous fungi. Therefore, the author is certain concerning the pathologic diagnosis of the phycomycosis in this case.

The following forms of phycomycosis have been described in the medical literature eg rhinofaciocranial (rhinooculocerebral, faciocerebral, or cerebral), pulmonary (thoracic), gastrointestinal, disseminated (systemic), cutaneous, subcutaneous, and miscellaneous ones.[3,6,8] The current author has reported four cases of cerebral phycomycosis[5,11,12] and an example of gastrointestinal phycomycosis.[3] In the latter instance, combined moniliasis and phycomycosis involved the stomach of a diabetic patient who, in addition, has as well candidiasis of the urinary bladder.[3] In the current patient, phycomycosis widely affected the lungs, heart, and liver. Hence it should be categorized as disseminated form.

Pulmonary phycomycosis has been frequently

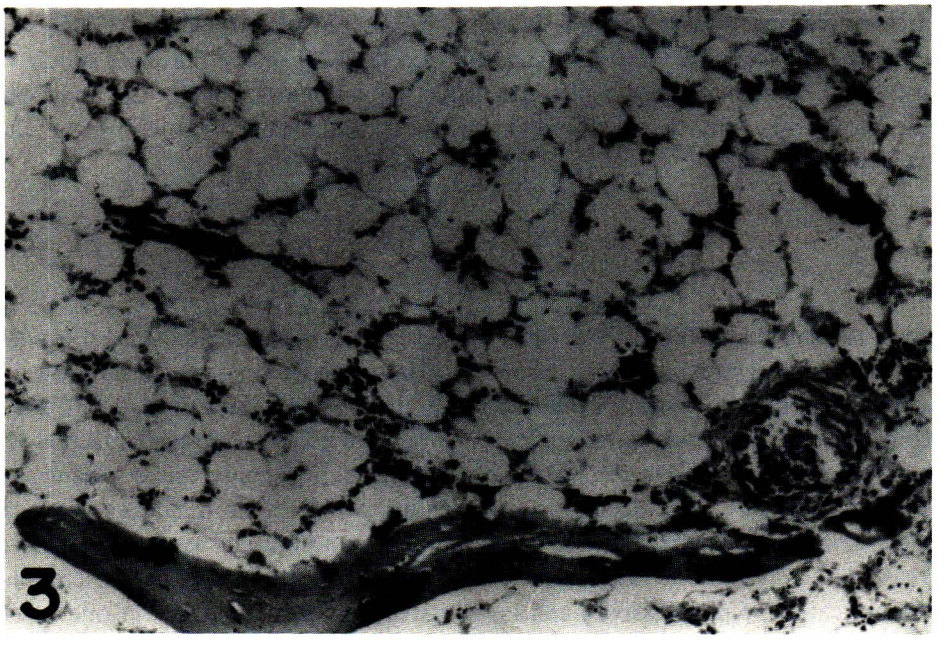

Figure 3 Extensive fatty infiltration of the vertebral marrow is shown. Only a small number of hematopotietic cells remain. A curvilinear bony trabecula lies below. (Hematoxylin and eosin, × 50).

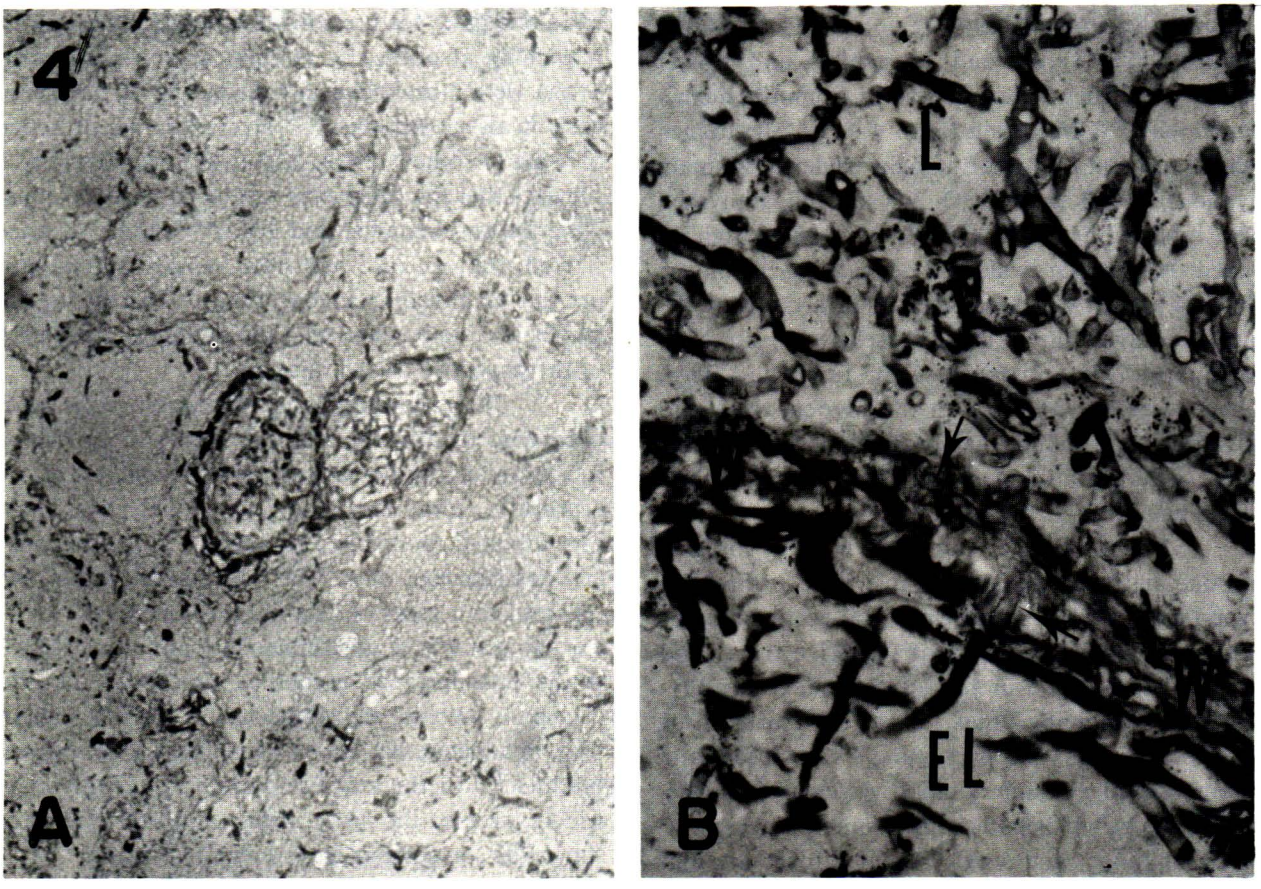

Figure 4 Phycomycosis of lung.

(A). Two blood vessels with clumps of funfal mucelia within lumens lie in the recently infarcted pulmonary tissue which also contains scattered fungal hyphae. (GMS, × 100).

(B). Invasion of the fungal mycelia into the wall of a pulmonary blood vessel is demonstrated. Numerous fungal hyphae are within the vascular lumen (L). Others lie extraluminally (EL). The arrows point toward fungal mycelia that are embedded within the vascular wall (WW). (GMS, × 400).

observed in relation to diabetes mellitus,[14-16] renal failure,[17] burn,[18] leukemia, lymphoma, and severe neutropenia,[4] as well as in healthy person.[19] On the other hand, phycomyceteous endocarditis is rare.[7,20,21] Even rarer is the phycomycosis of the liver.[4,7] Meyer and Rosen[4] presented phycomycosis occurring in a woman who had promyelocytic leukemia and disseminated intravascular coagulation. Terminally, her illness was complicated by progressive hepatic failure with severe jaundice. Postmortem examination disclosed thrombosis of the entire hepatic artery and its major intrahepatic branches due to intraluminal growth of nonseptate fungal mycelia; broad area of ischemic necrosis and infarction were present in the liver. This patient also had massive cerebral infarction because of fungal infection. To the author's knowledge, phycomycosis involving the lungs, mural endocardium of both cardiac ventricales, and liver in the same patient as described herewith has not been reported. Although Parichatikanond et al[7] stated that phycomycosis in one of eleven cases of their autopsied series involved many organs they did not specify the organs that were affected.

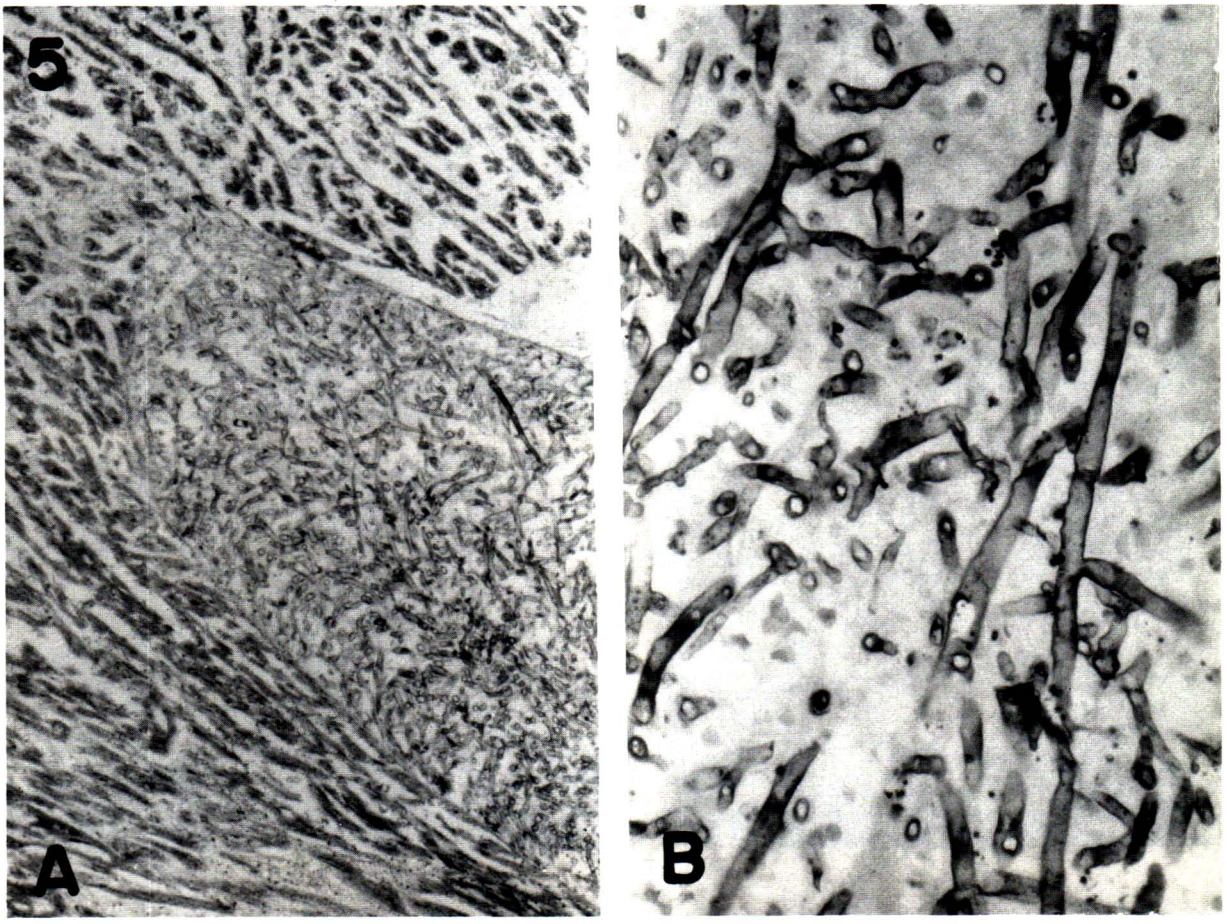

Figure 5 Phycomycosis of heart.

(A). A large fungal colony is partly surrounded by bundles of the myocardial fibers. (GMS, × 100).

(B). Individual fungal mycelia are shown. Note broad hyphae with occasional branches at obtuse angle to the main hyphae. (GMS, × 400).

Progressive debility of the current patient from hypoplastic anemia is undoubtedly the main underlying condition that predisposed her to the opportunistic phycomycosis. The author does not know about the route of entry of the fungi into her body. Nevertheless, the respiratory tract is suggested as the most likely route of entry of the organism, based on the persistence of the infiltrative shadow in the upper part of the right lung as seen roentgenographically throughout the patient's course of illness. Form the lung, the fungi could enter the left side of the heart because of their invasive nature through the pulmonary vascular walls.[3,10,14] A vegetation, then, could be formed upon the mural endocardium of the left cardiac ventricle. Form this vegetation, fungal emboli could be dislodged to the liver by the way of the hepatic artery to cause infarction of the right lobe of the liver. Within the liver, the fungi could pass into the hepatic sinusoids, hepatic vein, inferior vena cava, and right side of the heart. A vegetation, then, could be developed upon the mural endocardium on the right cardiac ventricle. Form this vegetation, infected emboli could be thrown again into the lungs.

Clinically, phycomycosis in this patient has not been recognized. It is suggested that awareness

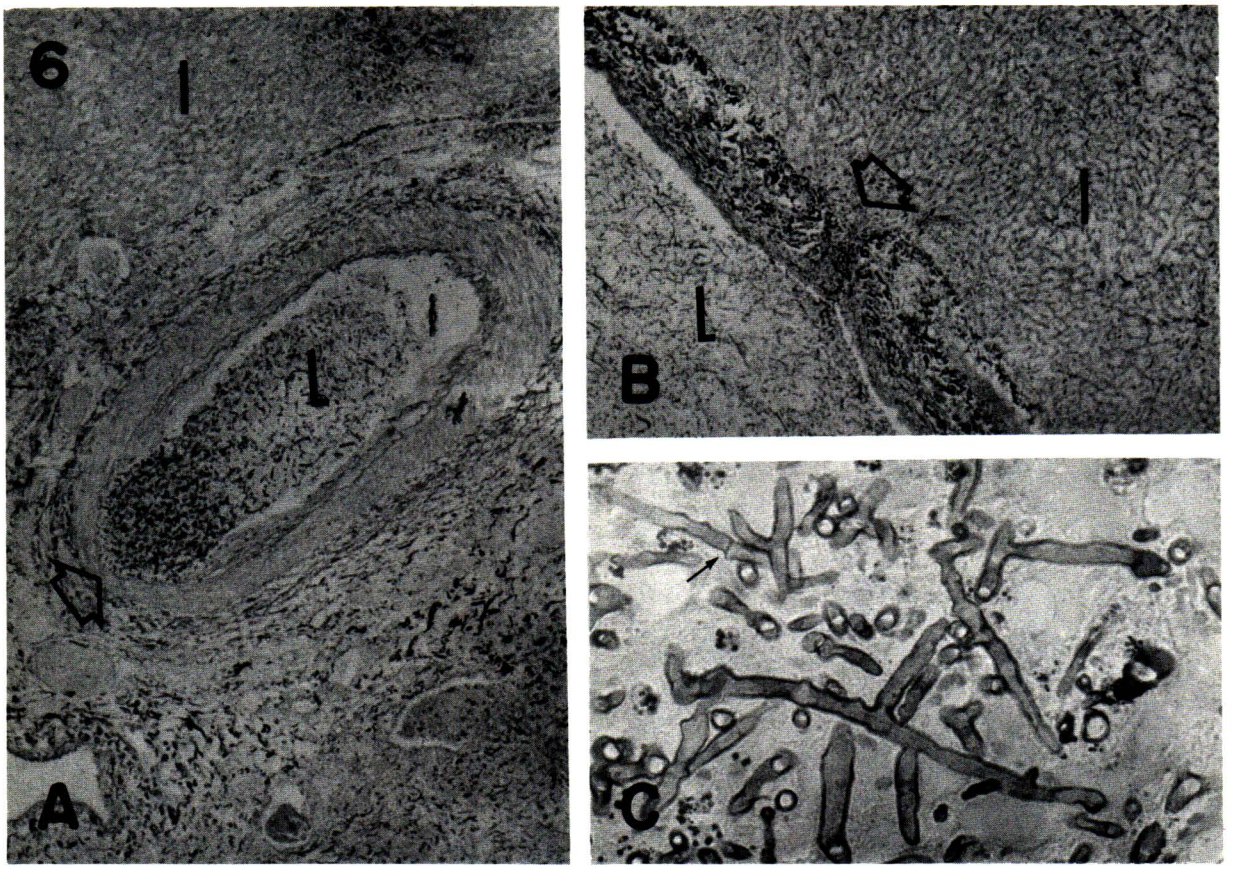

Figure 6 Phycomycosis of liver.

(A) and (B). Branches of the hepatic artery contain clumps of fungal hyphae within the lumens (L). The arrows points toward regions of the arterial walls that are invaded by the fungi. The hepatic tissue (l) is adjacent to the arterial walls. (GMS, × 50 each).

(C). Most fungal mycelia are nonseptate and branched at obtuse angles. Only a hypha has septum (arrow). (GMS, × 400).

and suspicion of any fungal infection should be given in handling debilitated patient. If the fungal infection is recognized when patient is still alive in may be treatable. Amphotericin B has been known to be effective in treating phycomycosis.[6,11] For instance, Shuangshoti[11] reported a 42-year-old diabetic man who had had a large mass in the left frontal lobe of the brain which was surgically removed and proven pathologically to be phycomyceteous granulomas. The patient was fully treated postoperatively with amphotericin B and was discharged from the hospital in satisfactory condition. He died 8 years later at 50 years of age. A postmortem examination (A-29-47) disclosed calculi in the pancreatic duct, advanced fibrosis and atrophy of the parenchyma and islets of Langerhans of the pancreas, diabetic glomerulosclerosis, thrombosis of the superior mesenteric artery, gangrene of the small and large bowels, and advanced bronchophneumonia with abscesses. The left frontal lobe of the brain became cystic and gliotic from the previous surgical intervention but phycomycosis was absent. Nevertheless, it might be predictable that such benefit with amphotericin B therapy would not be gained in the current patient because of an underlying fatal hypoplastic anemia.

References

1. Joe LK, Eng N-IT, Tjokronegoro S, Schaafma SJ, Emmons CW. Phycomycosis of the central nervous system associated with diabetes mellitus in Indonesia. Am J Clin Pathol 1959 Jul; 32(1): 62-70
2. Joe LK, Eng N-IT. Subcutaneous phycomycosis: a new disease found in Indonesia. Ann N Y Acad Sci 1960 Aug; 89: 4-16
3. Straatsma BR, Zimmerman LE, Gass JDM. Phycomycosis: a clinicopathologic study of fifty-one cases. Lab Invest 1962 Nov; 11 (11): 963-985
4. Meyer RD, Rosen P, Armstrong D. Phycomycsosis complicating leukemia and lymphoma. Ann Intern Med 1972 Dec; 77(6): 871-879
5. Shuangshoti S, Pongsabutra S. Phycomycosis of the brain. J Med Assoc Thai 1979 Mar; 62(3): 146-152
6. Lehrer RI, Howard DH, Sypherd PS, Edwards JE, Segal GP, Winston DJ. Mucormycosis. Ann Intern Med 1980 Jul; 93(1): 93-108
7. Parichatikanond P, Manonukul J, Chantarakul N. Systemic fungal infection: a study of 165 autopsies. Siriraj Hosp Gaz 1983 Oct; 35 (10): 867-872
8. Baker RD. Fungus infections. In: Anderson WAD ed. Pathology. Vol 1. 5th ed.St Louis: CV Mosby, 1966. 301-323
9. Fetter BF, Klinworth GK, Hendry WS. Mycoses of the Central Nervous System. Baltimore: Williams & Wilkins, 1967. 25-37
10. Chandler FW, Watts JC. Mycotic, actinomycotic, and algal infections. In: Kissane JM ed. Anderson's Pathology. Vol 1. 8th ed. St Louis: CV Mosby, 1985. 371-400
11. Shuangshoti S. Neuropathology in Thailand. Chula Med J 1982; 26 (Suppl): A48-A119
12. Kasantikul V, Shuangshoti S, Taecholarn C. Primary phycomycosis of the brain in heroine addicts. Surg Neurol 1987 Dec; 28(6): 468-472
13. Shuangshoti S. Diabetic polyneuropathy with systemic moniliasis and phycomycosis. J Med Assoc Thai 1980 Nov; 63(11): 630-636
14. Murray HW. Pulmonary mucormycosis with massive fatal hemoptysis. Chest 1975 Jul; 68(11): 65-68
15. Bragg GD, Janis B. The roentgenographic manifestations of pulmonary opportunistic infections. AJR 1973 Apr; 117(4): 798-809
16. Miller JW, Calenoff L. Cavity lung lesions in a diabetic. Chest 1977 Jul; 72(1): 79-80
17. Stevens KM, Newell RC, Bergstrom L. Mucormycosis in a patient receiving azathioprine. Arch Otolaryngol 1972 Sep; 96(3): 250-251
18. Bruck HM, Nash G, Foley FD, Pruitt AB Jr. Opportunistic fungal infection of the burn wound with Phycomycetes and Aspergillus: a clinical-pathologic review. Arch Surg 1971 May; 102(5): 476-482
19. Record NB Jr, Ginder DR. Pulmonary phycomycosis without obvious predisposing factors. JAMA 1976 Mar 22, 235(12) : 1256-1257
20. Torack RM. Fungus infections associated with antibiotic and steroid therapy. Am J Med 1957 Jun; 22(6): 872-882
21. Khica GJ, Berroya, RB, Escano FB, Lee CS. Mucormycosis in a mitral prosthesis. J Thorac Cardiovasc Surg 1972 Jun; 63(6): 903-905