Case Reports

TREATMENT OF NORTH AMERICAN BLASTOMYCOSIS WITH AMPHOTERICIN B

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THIS PAPER records the first case of systemic blastomycosis known to have occurred in Nova Scotia: the first case in Canada to be treated by use of amphotericin B: and the complication of acute agranulocytosis occurring during therapy.

This 39-year-old white labourer was a machine operator in a salt plant. He lived on a small farm where he raised chickens, and had never journeyed outside Nova Scotia except for one winter five years before when he did construction work in the Arctic. He was transferred to the medical service of the Victoria General Hospital, Halifax, in April 1958, for investigation and treatment of pneumonia of undetermined etiology.

His symptoms began in March 1958, about two weeks after he had cleaned his chicken house. He developed acute discomfort in his left chest and consulted his physician. Radiography confirmed the clinical diagnosis of pleuropneumonitis of the left lower chest. At this time his temperature ranged between 99 and 101° F. There was a leukocytosis of 19,800 (bands 9%, neutrophils 65%, lymphocytes 21%, eosinophils 4%, monocytes 1%). The sputum was negative for ordinary pathogens and tubercle bacilli on several occasions. Fluid obtained by thoracentesis was similarly negative. Aspirates from a subcutaneous abscess which developed in the region of the left knee were negative for bacteria. Several broad-spectrum antibiotics had been administered without any clinical or radiological evidence of improvement. He was transferred from the Highland View Hospital, Amherst, N.S., for investigation and treatment.

Examination revealed an acutely ill man measuring about 5 feet 10 inches in height and weighing 130 lb. He had a cough productive of some watery sputum and accompanied by pain in his left chest. Oral temperature was 101° F. There was restricted movement of his left hemithorax and some dullness to percussion at the left base. Diminished breath sounds were present anteriorly and no breath sounds were heard over the basal segments on the left. No rales or rhonchi were heard. A draining sinus was present over the medial aspect of the left knee with induration of the surrounding tissues, but no tenderness, erythema, or fluctuation (see Fig. 1). Non-tender soft tissue swellings were noted on the right elbow and right thigh. Otherwise physical examination was noncontributory.

The urinalysis was negative; the specific gravity, 1.018. Examination of the blood revealed a hæmoglobin of 12.8 g. per 100 ml. and a white blood cell

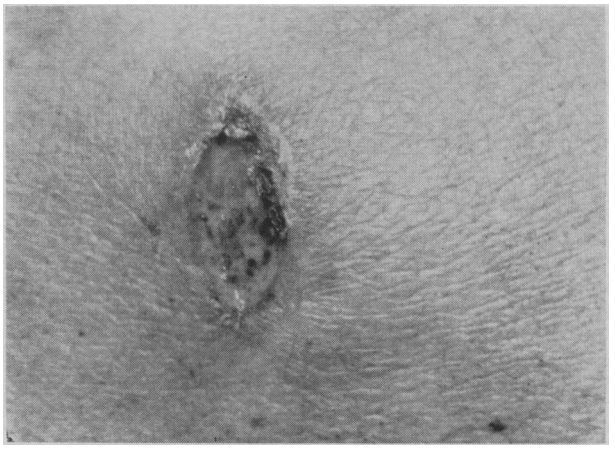

Fig. 1.—Draining sinus left knee.

count of 13,500 (81% polymorphonuclears, 19% lymphocytes). The red cells were normochromic and normocytic. The erythrocyte sedimentation rate (Wintrobe) was 27 mm. in one hour. The non-protein nitrogen was 27 mg. % and the fasting blood sugar 103 mg. %. The sputum was negative for ordinary pathogens, tubercle bacilli and fungi. The pleural fluid was similarly negative. Repeated blood cultures were sterile. Cerebrospinal fluid examination revealed a clear fluid under normal pressure with a cell count of 1, protein 39 mg. %, chlorides 710 mg. %. The colloidal gold curve was normal and the serology negative. An electroencephalogram showed low voltage and slow waves over the right temporal region. The electrocardiogram had minor non-specific T wave changes. Reaction to 0.001 mg. P.P.D. was negative. The admission chest radiograph (Fig. 2) revealed elevation of the left diaphragm, consolidation of the left lung to the level of the 4th rib anteriorly, atelectasis of the left basal segments with some consolidation of the lingular segment and a loculated basal effusion. Skeletal radiographs showed no bone lesions. Bronchoscopic examination found congestion of the left main bronchus but no other abnormality. A pleural biopsy specimen was unsuitable for examination. Smears from the draining abscess of the left knee contained organisms character-

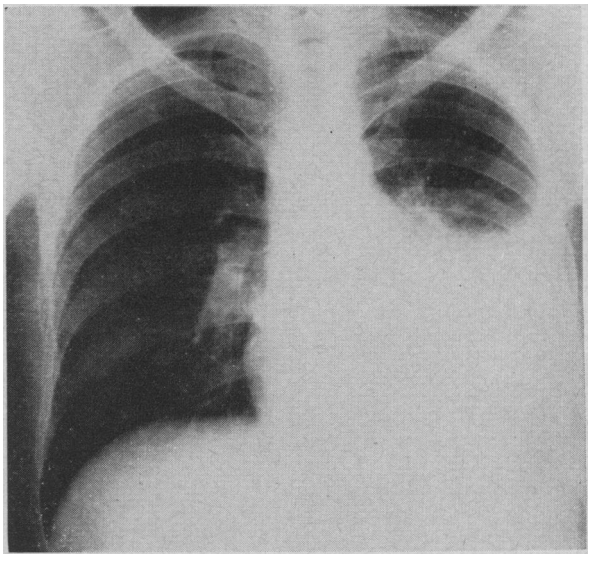

Fig. 2.—Admission chest radiograph

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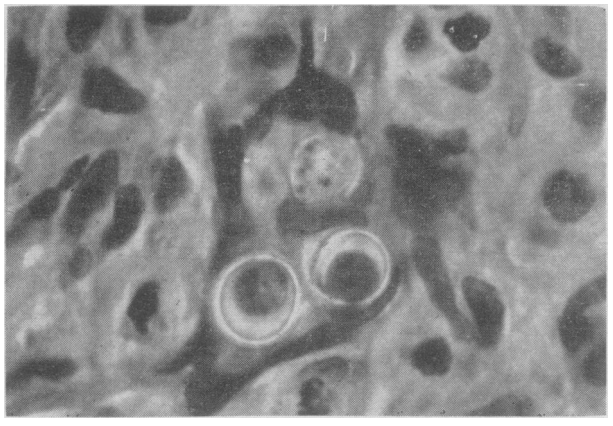

Fig. 3.—Biopsy of subcutaneous tissue showing three blastomycetes; magnification × 450.

istic of *Blastomyces dermatitidis* on direct smear, and typical cultural characteristics on Sabouraud's dextrose agar at room temperature and on blood agar at 37° C. At room temperature on Sabouraud's medium, mycelial threads with lateral conidia were seen on microscopical examination of the mould-like growth. On blood agar at 37° C. a wrinkled waxy colony developed; microscopical examination showed large, rounded thick-walled cells with budding. A biopsy specimen from the swelling of the right elbow revealed the same organisms in the subcutaneous tissues (Fig. 3). Repeated sputum examinations failed to demonstrate the fungus.

Amphotericin B (Fungizone for infusion, E. R. Squibb & Co.) was given intravenously daily, starting at 25 mg. in 250 ml. of 5% glucose and water and increasing gradually over a two-week period until a dose of 100 mg. in 1000 ml. of solution was given daily. Concurrently prednisone (5 mg. q. 8 h.) and promazine (25 mg. q. 6 h.) were administered in an attempt to minimize anticipated side effects. Frequent hæmograms, urinalyses, non-protein nitrogen determinations, and cephalin-cholesterol flocculation tests were done during the course of treatment. Improvement was apparent before the end of the first week of therapy. The temperature returned to the normal range.

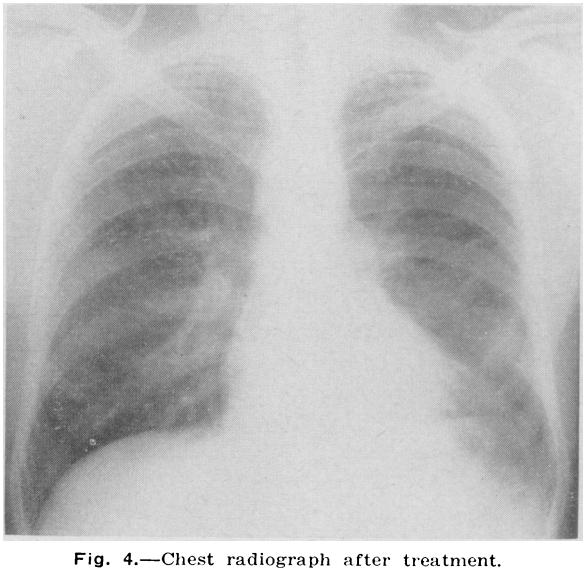

Fig. 4.—Chest radiograph after treatment.

The draining sinus, which had been present for two months, healed completely. Within two weeks there was improvement of the chest radiograph abnormalities.

Clinical improvement continued until the 32nd day of treatment when the patient developed a fever of 104° F. accompanied by chills. Before this time he had tolerated the drugs well, apart from complaining of anorexia. His laboratory tests had been within the normal range. All drugs were discontinued and within two days his temperature became normal and remained so for three days, then rose to 102.4° F. Numerous shallow ulcers of the tongue and buccal mucosa developed. The hæmoglobin was 10.7 g. %. The white cell count was 2250 (100% lymphocytes). The platelets were scanty on the smear. A sternal marrow biopsy revealed a hypoplastic marrow, with arrest of myeloid and erythroid maturation, and marked reduction of granulocytic elements. Within 48 hours the white cell count began to rise and within a week reached 7300, with a normal differential count. His mouth lesions healed rapidly and he was discharged to his home and advised to rest for a month. He has been seen at regular intervals during the last 18 months and has remained asymptomatic. He has gained 50 lb. in weight and has resumed his former occupation. Chest radiographs show some residual fibrosis and pleural thickening at the left base (Fig. 4).

DISCUSSION

Over 500 cases of North American blastomycosis have been reported in the literature. Of these over 95% have occurred in the United States.[1] In 1948 Starrs and Klotz made a critical review of reported cases of North American blastomycosis diagnosed in Canada; 16 cases were discussed: two were accepted as proved, three presumptive, and 11 unproved. To this they added one case proved at post-mortem examination.[1] No comprehensive review of cases in Canada has been published since 1948. It is interesting to note that four cases have been reported in Canada in the past two years.[2, 3]

North American blastomycosis of the systemic type has had a reported mortality of 75 to 92% within two to five years of onset of the disease.[4-7]

Amphotericin B appears to be a very effective agent in the treatment of blastomycosis in the limited number of cases reported,[8-10] and it is expected to reduce the morbidity and mortality greatly. We believe that our patient represents the first case of North American blastomycosis treated in Canada by amphotericin B.

This patient has shown a very satisfactory therapeutic result, with no evidence of relapse after 18 months. The bone marrow depression which occurred during treatment might represent a toxic effect of amphotericin B; however, prednisone and promazine were given concurrently, so no definite conclusion could be drawn. In a review of the literature we found no reported cases of agranulocytosis associated with the use of amphotericin B. In one there was some depression of the platelet count and in others some fall in hæmoglobin level associated with a rising level of blood urea nitrogen

necessitating stopping the drug for a few days. Other toxic effects were anorexia, nausea, vomiting, fever, chest pain and liver damage.[9] In one case too rapid infusion (28 mg. in 40 min.) resulted in death due to cardiac arrest.[10]

SUMMARY

The first case of systemic North American blastomycosis to be recognized in Nova Scotia has been reported. A satisfactory recovery followed use of amphotericin B; agranulocytosis developed during treatment.

REFERENCES

1. STARRS, R. A. AND KLOTZ, M. O.: *Arch. Int. Med.*, 82: 1, 1948.
2. WATSON, S. H., MOORE, S. AND BLANK, F.: *Canad. M. A. J.*, 78: 35, 1958.
3. GRANDBOIS, J.: *Ibid.*, 79: 828, 1958.
4. MARTIN, D. S. AND SMITH, D. T.: *Am. Rev. Tuberc.*, 39: 275, 1939.
5. *Idem*: *Ibid.*, 39: 488, 1939.
6. SCHWARZ, J. AND BAUM, G. L.: *Am. J. Clin. Path.*, 21: 999, 1951.
7. SNAPPER, I. AND MCVAY, L. V., JR.: *Am. J. Med.*, 15: 603, 1953.
8. HARRELL, E. R. AND CURTIS, A. C.: *A.M.A. Arch. Dermat.*, 76: 56, 1957.
9. COSTELLO, M. J., DEFEO, C. P., JR. AND LITTMAN, M. L.: *Ibid.*, 79: 184, 1959.
10. MCLEAN, W. C. AND FITZ-HUGH, G. S.: *South. M. J.*, 52: 667, 1959.

POST-TRAUMATIC HÆMOBILIA*

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POST-TRAUMATIC HÆMOBILIA is a rare complication of hepatic lesions and may be defined as the presence of blood in the biliary tract due to hepatic trauma. Although first described by Owen[11] in 1848, it was not until a hundred years later that Sandblom gave this condition the name of hæmobilia.[12] Blood in the bile may be clinically observed leaving from either end of the digestive tract. Opinions are divided on the frequency of this complication.[13, 14]

The origin of hæmobilia as such is variable. According to the few observations already published in the literature, blood in the biliary tract comes from liver parenchyma, gallbladder or the bile ducts themselves. We have noted in one instance that insertion of a T-tube caused hæmorrhage in the common duct.[1] Ruptured gallbladder with blood in the viscus itself and in the peritoneal cavity and rupture of intramural vessels of the gallbadder[5-25] have been reported to cause hæmobilia. Malignant hepatoma and hepatic metastases have also caused hæmobilia according to Rudström.[6] Benign tumours of the biliary tract,[7] hepatic angiomata, aneurysms or 'pseudo-aneurysms of the hepatic artery[4, 8-10] have been described by various authors as possible causes of bleeding in the biliary tract. However, the most frequent cause of this syndrome is hepatic trauma.

According to Sandblom, traumatic lesions of the liver fall into three groups: rupture of the capsule and the parenchyma, central rupture, and hepatic subcapsular rupture. A brief review of the sequence of events may help to clarify the pathology of such cases. With rupture of the capsule and injury to the underlying liver parenchyma, blood trickles out of the wound into the peritoneal cavity. If, however, the capsule remains intact, blood may accumulate underneath it and force its way into the biliary tract. A lesion located in the centre of the organ may have the same result. Although the presence of bile does not prevent coagulation, according to Gereben[13] when a certain amount of blood mixed with bile has accumulated in the newly formed cavity the pressure rises therein to a point equal to or above that of the bile in the canaliculi. The flow of the bile is then reversed and this viscous mixture of blood and bile eventually flows through the canaliculi, biliary vessels, hepatic ducts, common bile duct and on to the duodenum. If it gets into the gallbladder it may become inspissated and coagulate, and cause a clinical picture identical to that produced by cholecystitis with cholelithiasis. Necrosis of liver tissue may favour the progression of hæmorrhage; this in turn may start a vicious circle by increasing the pressure inside the cavity, causing further ischæmia of the surrounding tissue, leading to further necrosis. The cavity may empty every now and then, giving rise to intermittent hæmobilia. Lesions deep in the liver parenchyma tend to produce severer symptoms because the ruptured vessels are of larger calibre. Unless the ruptured vessels heal or thrombose, the process is bound to persist.

Surgery of the liver may also cause hæmobilia. Sutures may damage blood vessels, and the recently developed hæmostatic substances such as Oxycel and Gelfoam have been known to produce necrosis of the tissue, resulting in the formation of a cavity or the enlargement of an already existing one. The same process as described above then enters into play. Necrosis therefore from any cause such as infection or the presence of fragmented tissue left behind in an inadequate exploration of the wound can lead to the same results. Resorption of bilirubin will give rise to jaundice.

Hæmobilia may take place even after simple cholecystectomy. In 1950, Hart[15] reported on a patient referred to him for treatment of a central hepatic hæmatoma subsequent to cholecystectomy. The gallbladder bed had been closed by deep intrahepatic sutures by the former surgeon. At a new operation, Hart attempted to stop the hepatic hæmorrhage and was partially successful. However, the patient died at home during an attack of massive hæmobilia in the course of convalescence.

Of the various forms of treatment offered for hæmobilia, the first and most important is preven-

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