GENERALIZED CRYPTOCOCCOSIS WITH OSSEOUS INVOLVEMENT

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Cryptococcosis or torulosis has been prominent in the medical literature in recent years, and its protean manifestations have been well reviewed. The pulmonary, osseous and central nervous systems are most frequently involved. In the acute fulminating cases a meningo-encephalitis is nearly always present, and the outcome is almost invariably fatal. Miliary involvement of the lungs may occur in the disseminated disease. In the more chronic cases pulmonary involvement is frequent. Pulmonary lesions may be indistinguishable from tuberculosis, or may be present as solid masses resembling tumours. Tumours of the lung due to *Cryptococcus histolyticus* (*neoformans*) were reported by Dormer and his collaborators in 1945[1] and 1947.[2] Osseous lesions tend to occur when the infection is generalized. Prior to a report of 3 cases by Collins[3] in 1950, there had been 17 instances of bone involvement in a review of over 200 cases reported in the literature. Multiple bone lesions were present in a case report by Wiener[4] in 1951. In an analysis of 21 cases by Wolfe and Jacobson[5] in 1958, there were 3 cases of osseous involvement. In 1958 Hilbish[6] stated that bone involvement occurs in approximately 10% of patients with the disseminated disease.

The lesions are characteristically osteolytic. Progression and regression are slow. Comparison with bone lesions in other mycoses,[3] notably blastomycosis and coccidioidomycosis, stresses that periosteal proliferation is a frequent finding in the latter. All the mycotic lesions are destructive, with little reactive sclerosis. Predilection for bony prominences is a feature of mycotic lesions, as opposed to other infections with multiple bone involvement. Abscess formation is frequent at the site of bone lesions. The pus is characteristically mucoid or gelatinous.

Association of cryptococcosis with sarcoidosis and Hodgkin's disease is mentioned by Collins.[3] Coexistent tuberculosis is uncommon.

Up to the time of the discovery of amphotericin B, no satisfactory treatment was known, and cases of generalized infection were very frequently fatal.

CASE REPORT

P.S., Bantu male aged 14 years, was admitted to King George V Hospital on 5 January 1959. He was transferred from McCord's Zulu Hospital, Durban, where he had been treated for typhoid fever since 25 September 1958. The diagnosis of typhoid fever was confirmed by positive stool culture. He was persistently febrile on subsidence of the typhoid fever. X-ray of the chest on 29 October 1958 (Fig. 1) showed miliary nodulation, which was regarded as tuberculous and treated with izoniazid, 200 mg. *t.d.s.* and streptomycin, 1 g., twice weekly. Chest X-ray on admission to King George V Hospital showed clearing of the nodulation. Antituberculous treatment was continued.

On 9 January 1959 he developed a swelling of the left upper eyelid, which appeared to be a sebaceous or meibomian cyst. On 20 January he complained of pain in the left ankle and gave an erroneous history of trauma. The ankle became swollen. X-ray on 11 February showed an erosion in the os calcis, which was regarded as a tuberculous osteitis. A plaster cast with walking sandal was fitted. The swelling in the left orbit gradually increased in size, became fluctuant, and discharged muco-pus spontaneously on 20 March. At this time he was found to have a cervical adenitis.

On 11 April a foul-smelling discharge from the left ankle was observed. On removal of the plaster there were 2 large erosions of the skin with a sloughing base and a watery discharge. Repeat X-ray on 15 April (Fig. 3) showed increase in extent of erosion of the os calcis.

At this time a painful swelling of the left side of the chest developed, and X-rays on 15 April showed an osteitis of the 9th rib at the site of the swelling. Shortly after this a swelling over the xiphisternum appeared. Swabs taken from this yielded no organisms on culture. Swabs taken from the heel showed haemolytic *Staphylococcus albus*, sensitive to streptomycin, achromycin, chloromycetin, ilotycin, furadantin and aureomycin.

X-ray of the cervical spine on 23 April revealed lesions of the 4th and 5th vertebrae, consistent with tuberculosis. A Mantoux test at this stage was positive.

The patient had been on continuous antituberculous treatment since admission. The progression of the erosion of the os calcis and the development of other foci of bone infection threw grave doubt on the tuberculous aetiology of the disease. As he had had typhoid before transfer to King George V Hospital, the possibility that the bone infections might be caused by *Eberthella typhosa* was considered. Blood culture, however, was sterile. Chloromycetin therapy was commenced empirically, but resulted in no improvement.

On 11 May pain over the left ilium developed. X-ray showed an erosion in the anterior superior iliac spine.

In smears from the discharging heel, mycelial elements were seen on staining. The patient was put on potassium iodide in increasing doses up to 90 gr. daily and mycostatin, 2 tabs 4 times a day.

Repeat X-ray on 27 May showed further erosion of the os calcis, with decalcification of the foot bones. The eroded area in the left ilium appeared slightly larger. The clear-cut focus of infection in the 9th rib had not changed, but periosteal reaction was evident (Fig. 2). In the cervical spine (Fig. 4) there was progression of the infective process, but less prevertebral swelling.

The first laboratory reports (culture) indicated the growth of a fungus of candida type, but as the colonies grew it became evident that they resembled *Cryptococcus neoformans*. A rich growth of

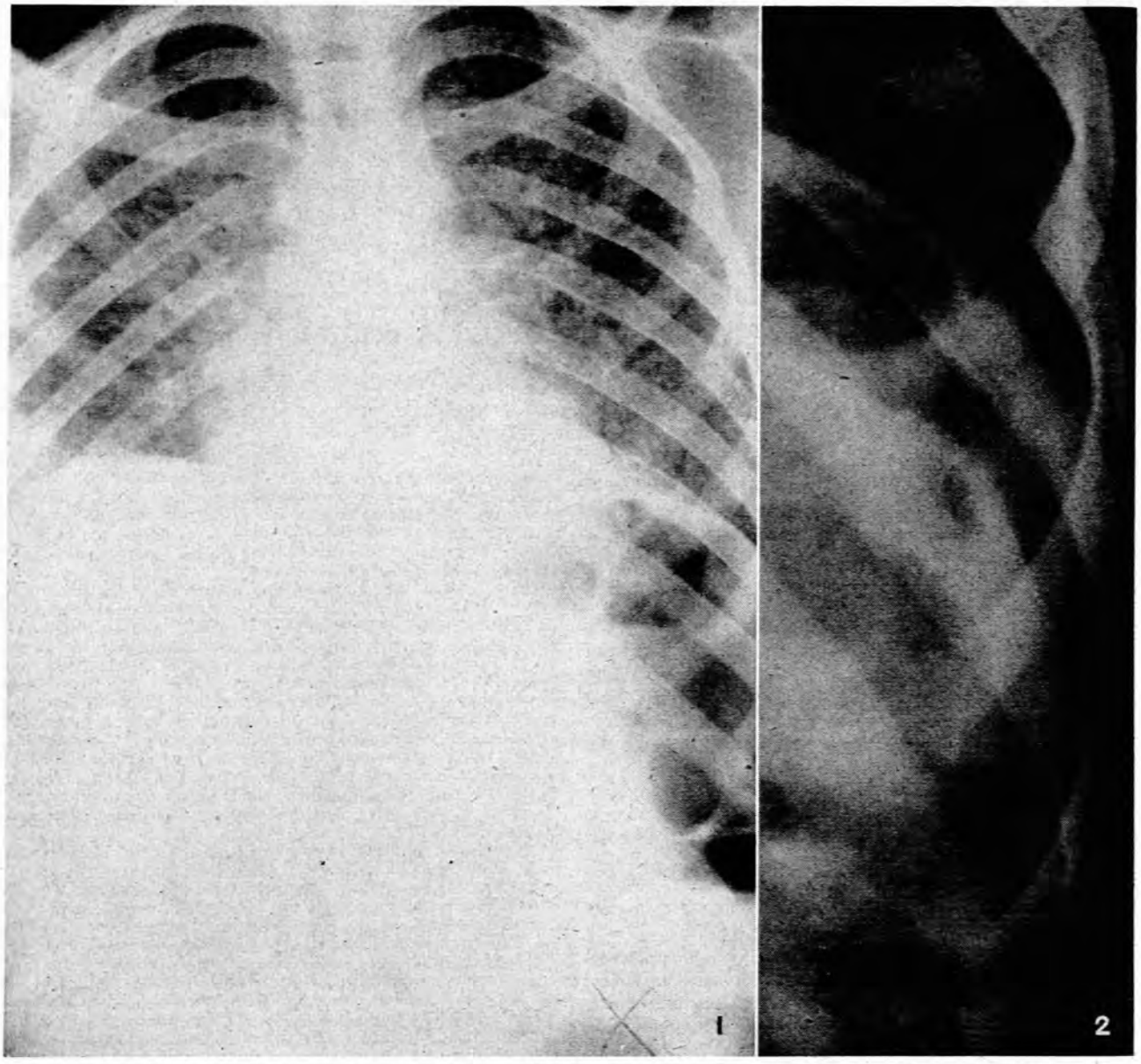

Fig. 1. Chest, 29 October 1958, showing miliary nodulations in lungs. *Fig.* 2. Ribs, 27 May 1959, showing clear-cut erosion in 9th rib, with periosteal reaction.

this organism in pure culture was obtained. Mice were inoculated and positive growth was obtained. In view of this finding, therapy with amphotericin B was commenced on 3 June. A polythene catheter was inserted into the inferior vena cava, *via* the right saphenous vein, and a continuous drip containing amphotericin B was started with a concentration of 0·25 mg. per kg. for the first day, increased to 0·5 mg. the next day, and then up to 0·75 mg. per kg. It was kept at this level. There were no reactions for the first 6 days. Then a steady pyrexia commenced and became persistent, and the dosage had to be reduced to 0·25 mg. per kg. At this level there was practically no reaction, and the dosage was maintained until 19 June.

A blood count on 13 June was as follows: Hb. 11 g.%; wbc. 15,000 per c.mm.; rbc. showed hypochromia and anisocytosis; platelets appeared slightly increased; polymorphs showed a marked shift to the left; two metamyelocytes were seen; differential count—neutrophils 93%, lymphocytes 6%, mononuclears 0, eosinophils 1%.

The blood culture for fungi was reported as negative on 27 June.

A great improvement followed clinically on this treatment. On 18 June repeat X-ray of cervical spine, ribs and ankle showed a healing process. Follow-up X-rays on 18 August of cervical spine and on 16 September of ankle and ribs showed progression of healing. X-ray of chest showed practically clear lung fields.

The patient was discharged on 26 October 1959.

DISCUSSION

There were several factors which contributed to the difficulty in making a diagnosis in this case.

The diagnosis of typhoid fever before admission to this hospital seems to be established. The miliary lung infection was indistinguishable from miliary tuberculosis, and had to a large extent resolved on admission, apparently in response to anti-tuberculous treatment. In retrospect it appears probable

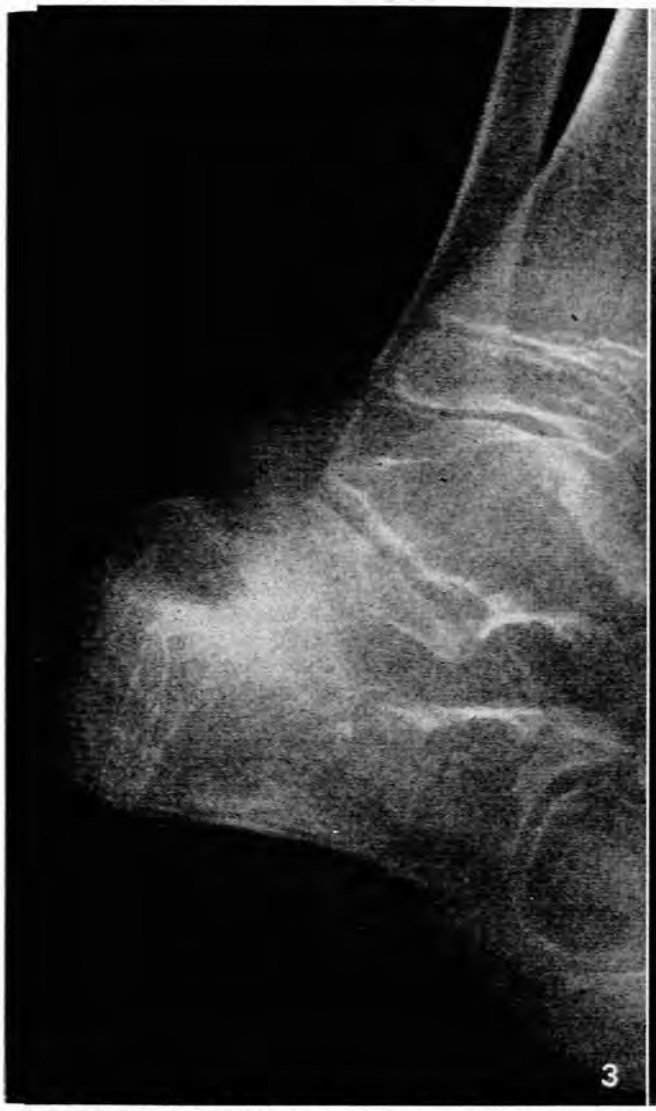

Fig. 3. Left ankle, 15 April 1959, showing erosion in os calcis.

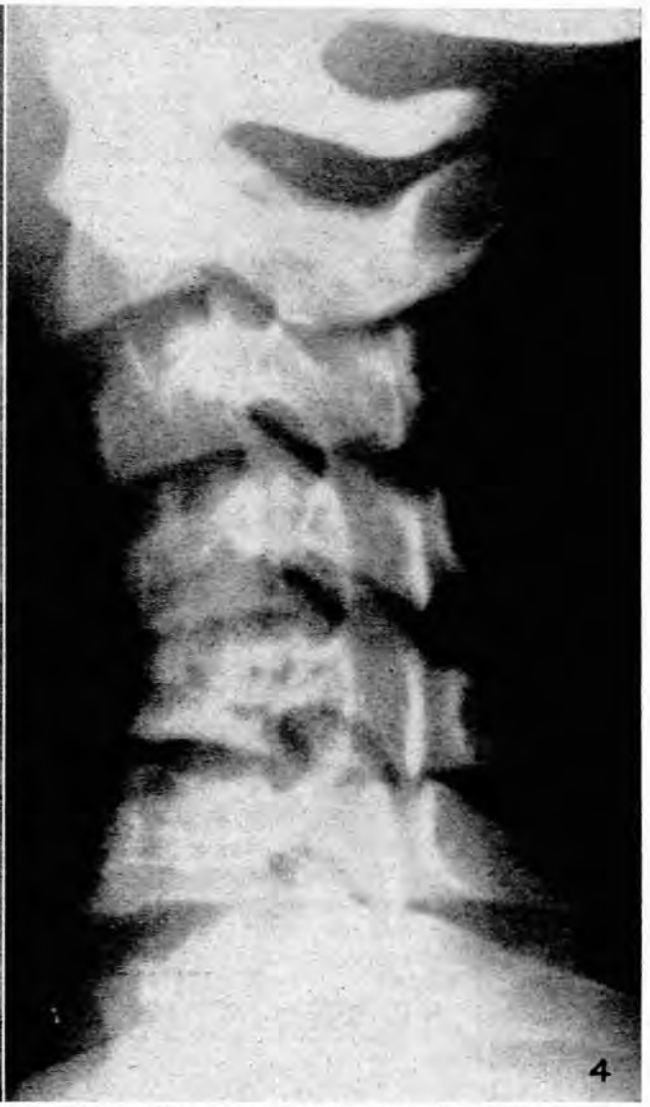

Fig. 4. Cervical spine, 27 May 9159, showing erosion of anterior surfaces of C4, 5 and 6 on adjacent surfaces of C4 and 5.

that the miliary lung involvement was not tuberculous, but an early manifestation of systemic cryptococcus infection. The subcutaneous lesion of the left orbit was apparently another manifestation of generalized infection.

The bone lesions which followed the lung and subcutaneous infections in no way differed from those of tuberculous aetiology. It was the successive development of these, and their progression while on antituberculous treatment which made it appear unlikely that tuberculosis was the infective agent. The Mantoux test, however, was positive.

The subsequent behaviour of the ankle infection was not like tuberculosis. It was from the swabs of this lesion that the diagnosis of *Cryptococcus neoformans* infection was established.

The patient's condition deteriorated until specific anti-fungus treatment was initiated and, from then onwards, a steady improvement was manifest, and maintained until he was fit for discharge.

SUMMARY

The manifestations of systemic cryptococcus infection are briefly reviewed, particularly in relation to pulmonary and osseous involvement.

A case is reported in which the initial features of generalized infection were pulmonary and subcutaneous.

Multiple osseous lesions followed. These were all osteolytic in nature, and resembled tuberculous infection radiologically.

The development of successive lesions while the patient was on anti-tuberculous treatment led to the investigations which eventually established the diagnosis.

A satisfactory response to treatment by amphotericin B is described.

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