Case Report

A CASE OF DISSEMINATED TYPHOID OSTEITIS

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Bone lesions have always been an uncommon complication of typhoid fever. Since 1926 only 6 cases of osteomyelitis due to *Salmonella typhi* have been reported in the literature.[1] Murphy in 1916 had estimated the incidence of this complication as 0·82% of all cases recorded at that time.[2] Although disseminated bone lesions were not infrequent in the early part of the century, the usual presentation was that of involvement of 1 or 2 bones only.

We have been unable to find a case report of *disseminated* typhoid bone involvement in the recent English literature. The purpose of this paper is to report a further case of disseminated osteomyelitis due to *S. typhi* and to stress the protean manifestations of the disease.

CASE REPORT

Symptoms and Signs

A Coloured female aged 33 years was admitted to the Somerset Hospital on 28 January 1963 with a history of pyrexia, limb pains, alopecia and weight loss.

Her past history showed that in July 1958 she had complained of a lump situated in the left posterior axillary line in the region of the 6th and 7th ribs. The lump had been present for about a year and she attended hospital because the swelling had gradually increased in size and had become painful. At no time was there any constitutional upset. The swelling was fluctuant and slightly tender and examination by X-ray showed punched out translucencies in the medulla of the 6th and 7th ribs. The cortices of the ribs were not expanded and there was no periosteal or pleural involvement (Fig. 1).

Treatment. The mass was incised and drained. *S. typhi* was cultured from the pus and the patient was transferred to the Infectious Diseases Hospital. A further pus swab taken there again grew *S. typhi.* At this stage repeated Widal agglutination tests including the Vi-agglutinin titre, blood and stool cultures were negative. Chloramphenicol administration was started and the pyrexia settled within 48 hours. After a 3-week course of chloramphenicol the patient was completely well and discharged from hospital. The wound had healed and serial radiography during the following month showed no change in the rib lesions.

Re-admission. She had remained perfectly well from August 1958 until the middle of 1962 when she experienced severe muscle pain particularly marked in the left thigh and right upper arm. She also had generalized periarticular pains: the left knee, the right elbow and shoulders being mostly affected. This was accompanied by a systemic disturbance characterized by low grade pyrexia, lethargy, and a loss of 36 lb. in weight and a progressive alopecia. These symptoms persisted for 6 months, during which time she received no antibiotic therapy. She was admitted in January 1963. Repeated questioning failed to elicit a history of typhoid fever in the past.

On examination the patient was moderately anaemic and the hair above her forehead was sparse. The temperature was 101°F, pulse 100/minute and BP 130/90 mm.Hg. A soft, smooth, non-tender hepatomegaly of 2 fingerbreadths was present and the tip of the spleen was palpable. At the apex of the heart a grade 2 systolic murmur was audible. The other systems were normal. The haemoglobin was 9·5 G/100 ml., PCV 32%, MCHC 30% and the smear showed a normochromic, normocytic picture; the reticulocyte count was 0·9% and

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the white blood cell count was 5,680/cu.mm. and differential count showed neutrophils 56%, eosinophils 2%, basophils 2% and lymphocytes 40%. The ESR (Westergren) was 105 mm. in the first hour. Urinalysis was normal.

Special Investigations

Repeated blood, urine, stool and throat cultures were negative. Acid-fast bacilli could not be detected in the urine. The Mantoux skin test (1/1,000) was positive and the blood Berger and Wassermann tests were negative. Innumerable blood examinations for LE cells and the Latex fixation test were negative. Liver-function tests were normal and the serum alkaline phosphatase was 16·8 units and 14·8 units. The serum albumin was 3·1 G/100 ml., serum globulin 3·5 G/100 ml. and the electrophoretogram showed an increased concentration of gamma globulins. Liver biopsy and bone-marrow examinations were normal.

The Paul-Bunnell, Weil-Felix, Brucella and Widal agglutination tests for *S. paratyphi* were all negative. The Widal test for *S. typhi* is shown in Table I.

TABLE I. RESULTS OF WIDAL TESTS

Agglutinin	*Before treatment*		*During treatment*			*After treatment*		
	7.1.63	14.1.63	18.3.63	9.4.63	20.4.63	1.7.63	25.4.64	25.11.64
O	1/25	1/25	1/25	1/100	1/100	1/400	1/200	1/100
H	1/200	1/200	1/1,600	1/400	1/400	1/1,000	1/200	1/400
Vi				1/5			1/10	

Cholecystogram, barium meal and X-ray examinations of the chest, skull and spine were all normal. X-ray examination of the ribs showed that the translucent areas present in the left 6th and 7th ribs in 1958 had been replaced by areas of sclerosis and the adjacent pleura was now thickened.

Course

Failure to establish a firm diagnosis after extensive investigations coupled with the past history of typhoid osteitis led to a presumptive diagnosis of typhoid infection 6 weeks after admission. Typhoid was considered despite the relatively unimpressive typhoid agglutination tests.

During the 6 weeks of investigation there was a constant pyrexia with the evening temperature usually above 100°F, and a tachycardia of 110/minute. Episodes of severe pain, attributable to muscle spasm, occurred in all her limbs and involved particularly the left thigh and right arm. Large doses of salicylates did not produce any relief from these pains.

On 11 March 1963, chloramphenicol was started in doses of 250 mg. *q.i.d.* The pyrexia subsided in 48 hours and the pain in the limbs disappeared soon thereafter. The anaemia was partly corrected by blood transfusions and then spontaneously returned to normal.

Because of the striking improvement in the limb pains, the possibility of typhoid infection of the bones was considered. This was confirmed by radiographic examination of the long bones on 25 March 1963.

There were multiple pinpoint translucencies visible at the lower end of the right humerus on its medial surface. The right tibia showed the presence of well-defined translucent areas at both ends of the shaft of the bone involving the medial wall of the cortex and the adjacent medulla; there were a number of surrounding translucent areas where the trabeculae had been destroyed (Fig. 2). Examination of the lower end of the left femur showed the presence of small translucencies.

X-ray examination of the long bones was repeated on 23 April 1963. The translucencies visible at the lower end of the humerus had coalesced to form a solitary translucent lesion which eroded the entire thickness of the medial cortex and the adjacent medullary trabeculae. Some periosteal new-bone formation was visible on the surface (Fig. 3). The lesions present in the right tibia and left femur were unchanged.

It was decided that the involved ribs should be resected and this was performed on 5 April 1963. Histological examination

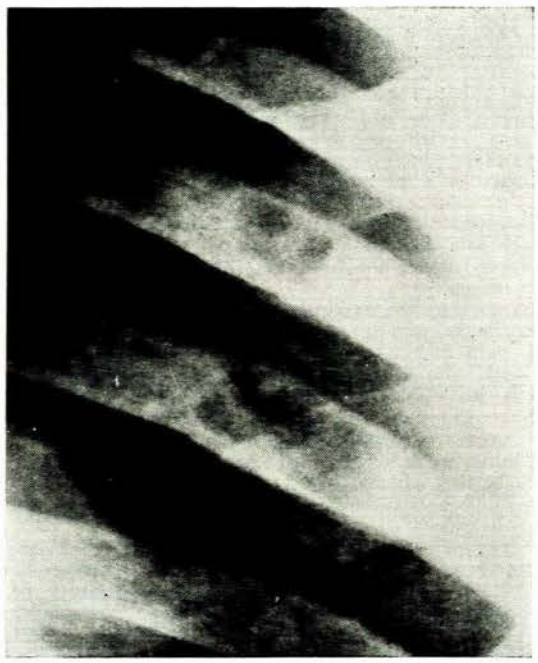

Fig. 1. Radiograph showing punched-out translucencies in the medulla of 6th and 7th ribs.

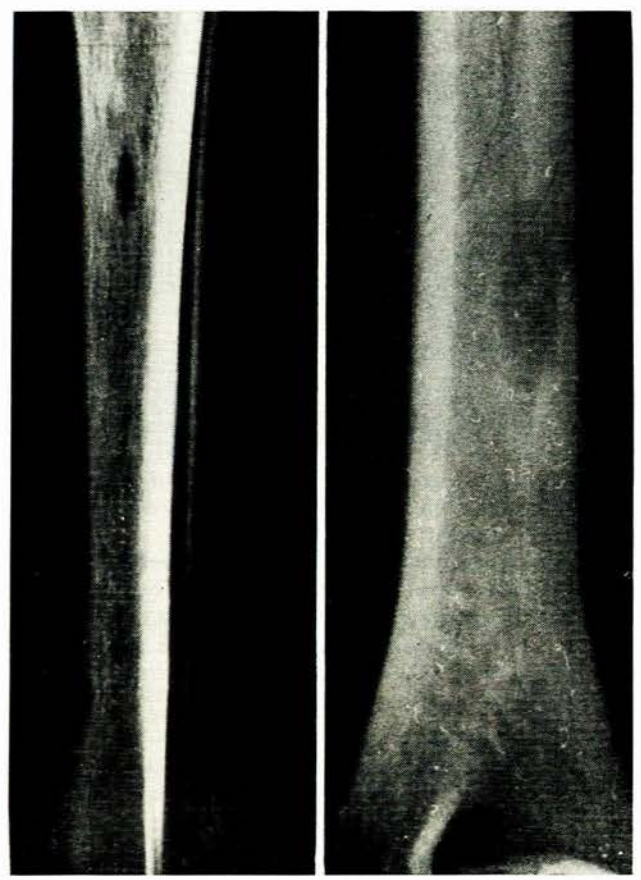

Fig. 2 *Fig. 3*

Fig. 2. The right tibia shows the presence of well-defined translucent areas at both ends of the shaft of bone; there are a number of surrounding translucencies.

Fig. 3. The lower end of right humerus shows the presence of a solitary translucent lesion eroding the entire thickness of the medial cortex and adjacent medullary trabeculae.

showed dense cortical bone and in the surrounding marrow there were a few small granulomas resembling non-caseating tubercle follicles and one area of necrosis of marrow cells with radiating epithelioid cells at the periphery. Culture of the ribs grew no organisms.

Chloramphenicol, which was given for 6 weeks, was discontinued a week before the patient's discharge on 25 April 1963. During this whole period repeated Widal tests showed a decisive increase in 'H' and 'O' agglutinin titres (Table I). There had been a marked improvement in her general condition; her weight which was 112 lb. before treatment, had increased to 128 lb., and her hair had regrown. The liver and spleen were no longer palpable. The haemoglobin was 13·5 G/100 ml. but the ESR was still 90 mm. on the Westergren scale in the first hour.

Follow-up Examination

The patient defaulted and was thus only seen again on 1 July 1963. She had remained perfectly well but the ESR was still 80 mm./1st hour. Radiographs of the right tibia and right humerus showed definite healing. The Widal test showed a further significant increase in 'H' and 'O' agglutinin titres suggestive of an active *S. typhi* infection (Table I). As a result of this finding and the persistently raised ESR she was given 250 mg. of Ampicillin *q.i.d.* which she took for 2 weeks.

She next attended the outpatient department on 25 April and 25 November 1964. At both these visits she was found to be in good health and her weight, which had increased considerably, was 150 lb. The ESR was 12 mm./1st hour. The agglutination test showed a fall in 'O' and 'H' agglutinin titres (Table I).

Radiographs of long bones were repeated at both these visits. The right humerus was almost normal in appearance except for thickening of the cortex and slight irregularity of the medullary cortex (Fig. 4). The appearance in November was unchanged. The lesions present in the right tibia were only faintly visible in April (Fig. 5) and by November there was complete resolution. The left femur, in April, contained a large translucency which had replaced the smaller translucencies (Fig. 6). The lesion was well defined and there was erosion of the inner surface of the cortical bone and slight periosteal new-bone formation was present on the outer surface. In November the translucency was slightly smaller and cortex had become thickened, although the inner surface was still irregular.

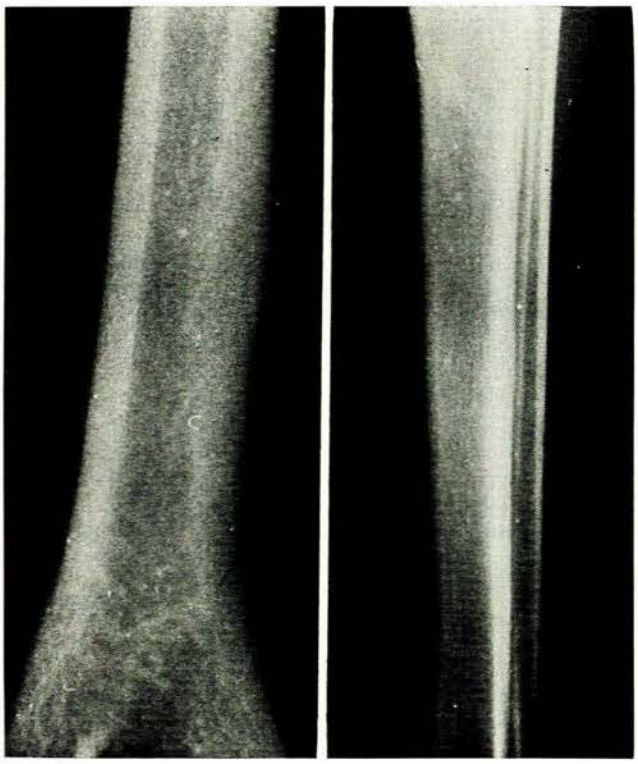

Fig. 4 *Fig. 5*

Fig. 4. The right humerus is almost normal in appearance except for thickening of the cortex and slight irregularity of the medullary cortex.
Fig. 5. There is complete resolution of lesions in the right tibia.

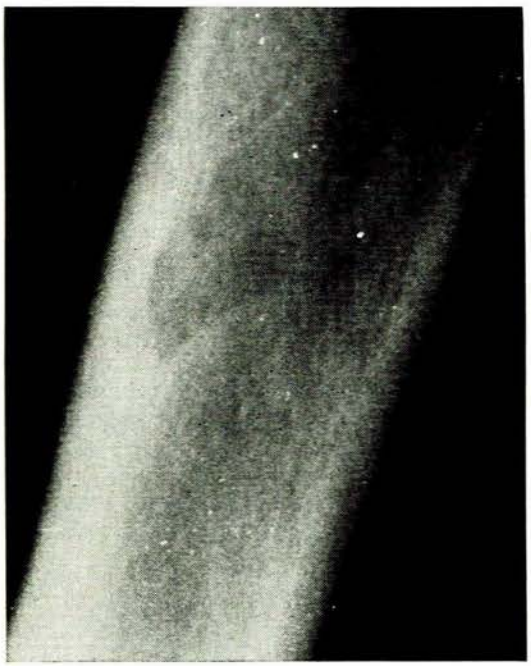

Fig. 6. The left femur shows a large, well-defined translucency with erosion of the inner surface of the cortical bone and slight periosteal new-bone formation.

DISCUSSION

A recrudescence of typhoid infection in a patient known to have had typhoid osteitis 5 years previously was, of course, initially considered in the present case. The failure, however, of the Widal agglutination tests to reflect active typhoid infection in the presence of overt systemic infection appeared to make this diagnosis untenable. Furthermore, the history of a chronic generalized disease persisting for 6 months before her admission was unlike any form of *S. typhi* infection. Despite these reasons a presumptive diagnosis of typhoid was made and chloramphenicol was started after extensive investigations had failed to elucidate the nature of the illness.

It is of interest that the diagnosis was established by the events that followed once chloramphenicol was commenced. The dramatic return of the temperature to normal indicated an excellent response to treatment. The striking alleviation of severe limb pain, a prominent feature of the illness, suggested the possibility of underlying bone infection which was confirmed by radiography of the affected area. The appearance of the lesions were in fact virtually identical to that of the rib lesions noted in 1958, strongly supporting the diagnosis of disseminated typhoid. Conclusive evidence of active typhoid infection was subsequently demonstrated by the results of serial agglutination tests which showed a gradual rise in both 'H' and 'O' aggluti-

nin titres to a diagnostic level (Table I). Short of bacteriological confirmation, the above factors coupled with the clinical and radiological remission for a follow-up period of 20 months after therapy clearly proved the diagnosis.

The pathogenesis of this patient's illness presented certain difficulties. Bone lesions occur as a sequel to acute typhoid fever but in the vast majority only manifest clinically some weeks, months or even years after the patient's recovery. Typhoid osteitis is virtually unknown in the absence of a past history of acute typhoid fever. This history could not be obtained in the present case and raises the question whether a febrile illness in the past, unrecognized as typhoid fever, was partially treated by antibiotics. This treatment may have been sufficient to prevent the features characteristic of acute typhoid fever but inadequate to eradicate widespread bone-marrow infection. The osteitis of the 6th and 7th ribs in 1958 and the subsequent disseminated osteitis 5 years later must then be attributed to reactivation of such dormant foci. Alternatively, the initial rib lesions became reactivated, resulting in a septicaemic illness with further osseous infection.

Severe limb pain, wrongly attributed to be muscular in origin, was the overriding clinical feature in the present case. Murphy[2] stated that patients with disseminating bone lesions often complained of severe pain which shifted from one region to another. The pain was almost invariably referred to the region which was subsequently the seat of an abscess. He likened this manifestation to osteoscopic pains of secondary syphilis. In our patient, X-ray examination of the limbs in which she had severe pain indeed confirmed the presence of disseminated bone lesions.

Rarity

The incidence in recent years of typhoid osteitis is extremely rare. Miller *et al.*[1] could only find 6 cases reported in the literature since 1926. We have not been able to find a single case report of disseminated typhoid osteitis in current literature and thus consider this case of interest in this respect. In 1916 Murphy[2] analysed a series of 533 typhoid bone lesions and found that the spine was involved in 20% and the ribs, tibiae and spine represented 70% of all cases. No bone in the series was exempt. When the long bones are involved the shaft rather than the metaphysis is the site of disease so well illustrated in the present case. The length of time elapsing between an attack of typhoid fever and the termination of a localized abscess is variable. Wardle (1935)[3] describes a case of typhoid abscess of the tibia occurring 10 years after an attack of typhoid fever. Lever and Barker[4] quote a case of typhoid osteitis occurring 33 years after typhoid fever and Van Dyke (1933)[5] mentions a case presenting 24 years after an original attack of typhoid fever. Murphy[2] found that 4% of cases of typhoid bone lesions manifested during the attack, 52% during convalescence and 44% months or years later. In the present case in the absence of a history of typhoid fever it is not possible to say what interval had elapsed before the commencement of the rib osteitis.

Alopecia is known to occur after severe attacks of typhoid fever or commonly to accompany typhoid fever.[6] Complete regrowth afterwards is usual. In our patient alopecia was a presenting symptom manifesting itself during the 6 months of chronic typhoid infection. Regrowth of hair was complete within a few months of discontinuing therapy.

Granulomatous lesions are commonly found in tuberculosis, sarcoidosis, Crohn's disease, brucellosis, coccidioidomycosis and histoplasmosis. Granulomas are also the result of a reaction to a foreign body such as talc or a metal such as beryllium.[7] In our case the histological picture of the resected ribs showed a few small granulomas resembling non-caseating tubercle follicles to be present in the bone marrow. Acid-fast bacilli and obvious fungi could not be demonstrated. The diagnosis of typhoid rib osteitis in 1958 was unequivocal. *S. typhi* was grown from the abscess overlying the rib osteitis. Although granulomatous lesions have not hitherto been described in typhoid infection, it is now suggested that granulomas in the marrow may be the result of chronic typhoid bone infection particularly if influenced by previous treatment. The typhoid baccillus does excite a peculiar cellular reaction which characteristically involves the large mononuclear phagocytes of the reticulo-endothelial system.

The rise in 'O' and 'H' agglutinin titres after chloramphenicol was commenced was quite unexpected and difficult to explain. Negative Widal agglutination tests were not infrequent in cases of typhoid bone disease quoted in the literature. This, in fact, was the situation in the present case until treatment was started. Widal tests done in 2 groups of patients, treated and untreated, gave supporting evidence that specific treatment of the disease with chloramphenicol inhibits the development of immunity to the causative infection.[8] It would appear that chloramphenicol, rather than inhibiting immunity, has enhanced the development of immunity or resistance in our patient.

SUMMARY

In 1958 typhoid rib osteitis was conclusively proved in a patient. There had been no past history of acute typhoid fever.

In 1963 the patient presented with a chronic illness, and the diagnosis of disseminated typhoid osteitis involving the right humerus, right tibia and left femur was established. A complete clinical remission and an almost complete radiological remission occurred after chloramphenicol therapy. The pathogenesis of the bone lesions is briefly discussed.

Negative Widal agglutination tests were found in the presence of active typhoid infection, and the Widal test only became positive after chloramphenicol was commenced.

Histology in 1963 of the old-standing rib osteitis showed several granulomatous lesions in the marrow. It is suggested that typhoid is another cause of granuloma.

We are obliged to Dr. R. Nurok, Medical Superintendent, Somerset Hospital, for permission to publish this case report: to the staff of the City Hospital, Green Point, for access to the 1958 case records; and to Dr. G. Selzer for the histological report. We wish to thank Dr. M. Horwitz for his helpful criticism and encouragement.

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