HISTOPATHOLOGICAL ASPECTS OF CHRONIC RECURRENT MULTIFOCAL OSTEOMYELITIS

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Chronic recurrent multifocal osteomyelitis (CRMO) is characterised by an insidious onset of fever, local swelling and pain in affected bones, and radiological abnormalities suggestive of osteomyelitis. The histopathological features in 14 patients are described. Morphologically CRMO begins as an acute inflammatory process with a predominance of polymorphonuclear leucocytes, which occasionally form an abscess and osteoclastic bone resorption. At a later stage the predominant features are lymphocytes in the inflammatory infiltrates and occasional granulomatous foci and signs of bone formation. The clinical course may be prolonged for many years.

In previous publications we have reported a variety of osteomyelitis which we have designated chronic recurrent multifocal osteomyelitis (CRMO) and have described the clinical (Björkstén et al. 1978) and radiological (Probst, Björkstén and Gustavson 1978) features. This disorder is characterised by an insidious onset of fever, pain and swelling over affected bones, and a radiological picture suggestive of osteomyelitis. The lesions are predominantly localised in the metaphyses of the tubular bones and in the clavicles. The clinical course is characterised by unpredictable periods of exacerbation and improvement over several years. A relationship has been observed between palmoplantar pustulosis and CRMO (Bergdahl et al. 1979). A similar disorder has been reported in four patients by Giedion et al. (1972) and in one patient by Gustavson and Wilbrand (1974).

The microscopic appearance of the bone lesions have only briefly been described (Giedion et al. 1972; Gustavson and Wilbrand 1974; Björkstén et al. 1978). Since we believe that CRMO represents a distinct clinical entity of unknown aetiology, and since problems of differential diagnosis may arise, we set out to define the histopathological basis of this disorder.

CLINICAL MATERIAL
Fourteen patients were studied: seven of these have previously been described by us (Björkstén et al. 1978) and one by Gustavson and Wilbrand (1974). The age at onset of bone symptoms ranged from 4 to 27 years, except for one woman who was 55 years old. Table I summarises certain clinical details of these patients and those reported by other authors.

The diagnosis of CRMO was based on the presence of osteomyelitis in 14 patients. The figure shows the number of patients with one or more lesions in the various bones (and the number of lesions).

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of multifocal bone lesions, the 20 patients reported in Table I having a total of 95 lesions (Fig. 1); on the typically prolonged clinical course over several years, characterised by varying activity of the disease, most patients being healthy between the recurrent periods of local pain, swelling and tenderness; and on the lack of response to antimicrobial therapy given, over a period of several months, because the symptoms suggested the presence of an acute infection. Radiological examination in the acute stages of the disease showed osteomyelitis (Figs 2 and 3). The lesions were often surrounded by sclerosis and showed healing over a period of about six months until an exacerbation occurred or new lesions developed elsewhere.

**ILLUSTRATIVE CASE HISTORIES**

**Case 1.** This girl was born in 1964 (Björkstén et al. 1978). In 1972 she developed pain in her ankles and recurrent fever up to 40 degrees Celsius; her erythrocyte sedimentation rate (ESR) was 53 millimetres.

<table>
<thead>
<tr>
<th>Source</th>
<th>Number of patients</th>
<th>Sex</th>
<th>Age at onset of bone lesions (years)</th>
<th>Number of lesions</th>
<th>Duration of symptoms (years)</th>
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<td>3 F, 1 M</td>
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<td>2-6</td>
<td>1-5</td>
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<td>Present study</td>
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<tr>
<td>Gustavson and Wilbrand (1974)</td>
<td>1</td>
<td>F</td>
<td>5</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Björkstén et al. (1978)</td>
<td>9*</td>
<td>5 F, 4 M</td>
<td>4-26</td>
<td>2-12</td>
<td>2-15†</td>
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<td>Previously unpublished</td>
<td>6</td>
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<tr>
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<td>F</td>
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<td>8</td>
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<tr>
<td>Case 3</td>
<td>F</td>
<td>55</td>
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<td>F</td>
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<td>Case 7</td>
<td>F</td>
<td>14</td>
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</table>

*Seven of these patients are included in this study, one of whom is described in Case 1 (see text).
†One girl developed acute lymphocytic leukaemia 3 years after onset of bone lesions.
in the first hour. Radiological investigation revealed osteolytic lesions in the distal tibial metaphyses. She was treated with oral lincomycin and fusidic acid for seven months. Her symptoms improved but she continued to have slight pain in the ankles.

In January 1973, three months after the antibiotic treatment was discontinued, she developed pusular lesions on the soles of both feet, fever of about 38 degrees Celsius, and pain in the ankles and the left clavicle. The ESR rose from 20 to 60 millimetres in the first hour. Radiological examination showed osteolytic lesions around the ankles and in midshaft of the left clavicle (Fig. 2). Biopsy of the clavicle revealed infiltration of inflammatory cells suggesting osteomyelitis (Fig. 4). She was given another course of lincomycin for 10 months. During this treatment she suffered from recurrent periods of pain and swelling over the affected regions, pusular skin lesions developed on the palms and there was exacerbation of those on the soles.

In March 1974, an extensive radiological investigation revealed, in addition to previous findings, osteolytic lesions in the metaphyses of the right radius and the left third metacarpal bone (Probst et al. 1978). A second biopsy taken from the left clavicle showed non-specific inflammatory lesions suggesting chronic osteomyelitis (see Fig. 8). A culture prepared from a biopsy specimen showed neither aerobic nor anaerobic bacteria.

During the next two years the girl had recurrent periods of clavicular pain accompanied by low-grade fever and occasional palmar plantar pustulosis, despite continuous antibiotic treatment with lincomycin or clindamycin. Since her symptoms did not appear to be influenced by antibiotic treatment a therapeutic trial with prednisolone, 15 milligrams daily, was instituted. She responded very well, so the dosage was gradually lowered to five milligrams every other day. When the treatment was stopped the pain recurred. She was therefore given 2.5 to 5 milligrams prednisolone daily or every other day and, except for a short period of clavicular pain, she then remained free from symptoms for two years.

In April 1978, a biopsy from the left clavicle showed fibrotic cancellous bone without any inflammatory changes.

Case 2. This girl was born in 1948. In May 1967, she developed a painful swelling over the eighth rib and radiological investigation revealed an osteolytic lesion involving the costovertebral joint. The ESR, haemoglobin, white blood cell counts and protein electrophoresis test were all normal. Since tuberculosis was suspected, the enlarged portion of the rib and adjacent part of the vertebra were resected. Histological examination revealed inflammatory cells suggestive of osteomyelitis but no signs of tuberculosis (see Fig. 6). The pain subsided gradually over one month but recurred. This time she had an elevated ESR (55 millimetres in the first hour) and a radiograph revealed a second osteolytic lesion in the seventh rib. She was treated with oral penicillin for two months, but with no obvious clinical effect.

Over the next six years she had several episodes of pain, local swelling and redness over various ribs. She also complained of recurrent toothache. Histological examination of extracted teeth showed chronic unspecific inflammation. She was treated continuously with flucloxacillin or Erythacin for 22 months without effect on the symptoms. Intense search for an infectious agent, including culture of blood and biopsy specimens obtained in 1967, 1970 and 1973 for *Mycobacterium tuberculosis*, anaerobic bacteria and L forms gave negative results.

In September 1973, when antibiotic treatment was stopped she had no clinical or laboratory signs of infection. However, six months later she again developed thoracic pain and had a raised ESR and C-reactive protein. Although not proven, infection with an anaerobic bacterium was suspected and she was treated with oral clindamycin for 11 months. Her condition slowly improved during this time although she had recurrent periods of pain.

Over the next three years she did not receive any antimicrobial treatment and had only short periods of local pain. Radiological examination in August 1978 did not show any abnormalities.

**HISTOPATHOLOGICAL STUDY**

Bone biopsies were done during various stages of the disease. The specimens were fixed in 10 per cent formalin. The original slides were re-examined and new sections were cut from the blocks. These were stained with haematoxylin and eosin, van Gieson's stain, periodic acid-Schiff, Laidlaw's stain, Ladiev's stain, Gram's stain and the Ziehl-Neelsen stain for *Mycobacterium tuberculosis*.

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Fig. 4
Early lesions. Figure 4—Infiltration of inflammatory cells, mainly polymorphonuclear leucocytes. (Haematoxylin and eosin, ×230.)

Fig. 5
Fig. 6
Figure 5—Abscess formation (A) and osteoclasts (O). (Haematoxylin and eosin, ×180.) Figure 6—Abscess (A) surrounded by lymphocytes (L). (Haematoxylin and eosin, ×205.)
RESULTS
The early lesions were characterised by an accumulation of polymorphonuclear leucocytes in the marrow (Fig. 4). They were mainly of neutrophilic type. Only a few eosinophils were observed. An abscess was occasionally seen (Fig. 5). Collections of lymphocytes could be found around small abscesses (Fig. 6). An increased occurrence of osteoclasts (Fig. 5), and signs of bone resorption (Fig. 7) were also observed in early lesions.

In long-standing lesions there was often a predominance of lymphocytes (Fig. 8). In addition, plasma cells, histiocytes and some polymorphonuclear leucocytes were observed. In a few cases granulomatous foci were found in the marrow (Fig. 9). Their centre exhibited a rich number of neutrophils. There was no caseous necrosis. Staining for Mycobacterium tuberculosis, other bacilli and fungi gave negative results in these foci, as well as in other portions of the marrow. Multinucleated giant cells, possibly of foreign-body type, were also observed diffusely in the inflammatory infiltrates. These cells varied in shape, in staining affinity, and in the number and appearance of nuclei (Fig. 10). Cystic cavities were occasionally found in areas of inflammation; they were lined by loose connective tissue containing inflammatory cells.

Necrotic bone fragments were observed in the lesions (Fig. 11). In long-standing lesions, fibrosis was seen around foci of inflammation (Fig. 12) and irregularly in the marrow (Fig. 13). An increased occurrence of osteoblasts and signs of new bone formation were also observed (Fig. 14). The blood vessels were dilated in areas of inflammation. Their walls were normal.

DISCUSSION
We have previously described the clinical findings in nine patients with CRMO (Björkstén et al. 1978). In the present study we report six new cases of CRMO, and the microscopic findings in biopsies from 14 patients during various stages of the disease. No other underlying disease was present. Bacteria or fungi were not isolated or suggested by serological investigations. Previous studies indicated that recurrent osteomyelitis secondary to immune deficiency was unlikely (Björkstén et al. 1978).

Study of the biopsy specimens with the light
microscope disclosed in all cases an inflammatory process, which at least in some cases was of granulomatous type. Microscopic signs suggestive of tuberculosis—caseous necrosis, epithelioid cells and multinucleated giant cells of Langhans type—were not observed, nor were any fungi or other micro-organisms identified in the biopsy specimens. Thus, the microscopic findings gave no indication of a possible aetiological basis for the development of CRMO. Correlation of the microscopic findings and the clinical duration of the disease indicated that CRMO morphologically begins as an acute inflammatory process with a predominance of polymorphonuclear leucocytes, and occasional abscess formation. In the early stage there is also osteoclastic bone resorption. At a later stage there is a predominance of lymphocytes in the inflammatory infiltrates, and in some cases also granulomatous foci. The formation of new bone, seemingly of a reactive nature is also observed. The structural signs of new bone formation are consistent with the radiological observation of osteosclerosis around inflammatory foci (Probst et al. 1978). Biopsies obtained when the disease had improved clinically disclosed only slight inflammatory changes, with a predominance of lymphocytes. No biopsies were obtained during symptom-free periods, thus we do not know if there is a complete disappearance of the microscopic signs of inflammation. Signs of collagen disease or any other systemic disease were not found. The long-term prognosis appears to be good.

REFERENCES


