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Imaging of chronic recurrent multifocal osteomyelitis of childhood first presenting with isolated primary spinal involvement

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Abstract *Objective:* Initial presentation with primary spinal involvement in chronic recurrent multifocal osteomyelitis of childhood (CRMO) is rare. Our objective was to review the imaging appearances of three patients who had CRMO who initially presented with isolated primary spinal involvement. *Design and patients:* The imaging, clinical, laboratory and histology findings of the three patients were retrospectively reviewed. Imaging included seven spinal MR imaging scans, one computed tomography scan, nine bone scans, two tomograms and 16 radiographs. These were reviewed by two musculoskeletal radiologists and a consensus view is reported. All three patients presented with atraumatic spinal pain and had extensive bone spinal pathology. The patients were aged 11, 13 and 12 years. There were two females and one male. *Results and conclusions:* The initial patient had thoracic T6 and T8 vertebra plana. Bone scan showed additional vertebral body involvement. Follow-up was available over a 3 year period. The second patient had partial collapse of T9 and, 2 years later, of C6. Subsequently extensive multifocal disease ensued and follow-up was available over 8 years. The third patient initially had L3 inferior partial collapse and 1 year later T8 involvement with multifocal disease. Follow-up was available over

3 years. The imaging findings of the three patients include partial and complete vertebra plana with a subchondral line adjacent to endplates associated with bone marrow MR signal alterations. Awareness of the imaging appearances may help the radiologist to include this entity in the differential diagnosis in children who present with spinal pathology and no history of trauma. Histopathological examination excludes tumor and infection but with typical imaging findings may not always be necessary.

Keywords CRMO · Chronic recurrent multifocal osteomyelitis · Spine · MR imaging · Vertebra plana

Introduction

Chronic recurrent multifocal osteomyelitis (CRMO) is often a diagnosis of exclusion in patients who present with lytic or sclerotic bone findings and periosteal reaction with serological and histological findings negative for infection and tumor [1, 2]. It is regarded by some authors as part of the spectrum of SAPHO syndrome [3]; however, others consider it to represent a distinct clinical and radiological entity [4]. More sinister pathologies such as histiocytosis X, leukemia, neuroblastoma and rhabdomyosarcoma [1, 2] and osteomyelitis or bacterial discitis need to be excluded [1]. According to King et al. [5], the following criteria should be met before a diagnosis of CRMO is made: (1) multifocal (two or more) bone lesions, clinically or radiographically diagnosed, (2) a prolonged course (over 6 months) characterized by varying activity of disease, and with most patients being healthy between recurrent attacks of pain, swelling and tenderness, (3) lack of response to antimicrobial therapy given for at least 1 month, (4) typical radiographic lytic regions surrounded by sclerosis with increased uptake on bone scan, and (5) lack of an identifiable organism. Jurik and Egund [6] added: (6) no abscess, fistula or sequestra formation, (7) atypical site for classical bacterial osteomyelitis such as clavicles and multiple sites, (8) nonspecific histopathological findings and laboratory results compatible with osteomyelitis, and (9) sometimes acne and palmoplantar pustulosis. Additionally, symmetry of the lesions has been reported as a helpful feature [7].

Spinal involvement with chronic multifocal CRMO is rare but documented [1, 5, 8, 9, 10, 11, 12, 13, 14, 15]. Initial presentation with back pain due to spinal involvement has been reported in a case study [14, 17]; however, there have been no previous series of CRMO initially presenting with isolated primary spinal involvement in the form of either partial or complete collapse with no history of significant trauma. This initial presentation with spinal disease and a lack of multifocal peripheral bony lesions made inclusion of CRMO in the initial differential diagnosis difficult and bone biopsy could not be avoided as more sinister pathology had to be excluded. This study presents three patients with vertebra plana or altered vertebral body marrow signal intensities and a subchondral fracture-like line parallel to the endplates without mass formation. This has not been previously described though this subchondral fracture-like line is evident in the images of two patients presented in the reviewed literature [16, 17].

Materials and methods

The imaging, clinical, surgical and histology notes of three patients aged 11, 13 and 12 years were reviewed. There were two females and one male. Imaging was reviewed by two musculoskeletal

radiologists by consensus and included the following: in patient 1, radiographs, spinal MR images and bone scans; in patient 2, radiographs, tomography, spinal MR images and bone scans; and in patient 3, radiographs, spinal CT and spinal MR images. MR features documented included, site, location of involvement within the vertebral body, disc status and spinal alignment. The presence or absence of marrow edema, a subchondral fracture-like line paralleling the endplates, and a focal mass of either osseous or soft tissue was also noted. The presence of lysis or sclerosis was documented from CT, tomography and radiography. Bone scintigrams were reviewed for increased activity due to multifocal and clinically occult disease. All patients underwent bone biopsy to exclude tumor and infection.

MR sequences included T1-weighted (TR: 690, TE: 12), T2-weighted (TR: 3000–3500, TE: 102–120) and STIR sequences in the sagittal plane. Axial T1-weighted sequences before (TR: 400–665, TE: 14) and after gadolinium administration (TR: 420, TE: 14), the latter with fat suppression technique, were also performed. An additional coronal T2-weighted sequence (TR: 3284, TE: 120) was performed in one patient.

Case reports

Patient 1

An 11-year-old girl presented with back pain and kyphosis following a minor fall whilst roller-blading. Initial radiographs demonstrated vertebra plana of T6 (Fig. 1A). MR studies demonstrated subtle superior endplate irregularity of T4 with increased marrow signal intensity (Fig. 1A, B) on the STIR sequence. At 6 months follow-up, the patient having been asymptomatic, vertebra plana formation had developed at the T8 level with an increased kyphosis (Fig. 1C). Initially the disc signal morphology and signal intensity remained normal, though on the follow-up MR imaging some loss of height and signal intensity of adjacent discs had occurred. Bone scintigraphy revealed additional focal spinal involvement (Fig. 1D). Two bone biopsies were performed which excluded tumor, Langerhans cell histiocytosis X and leukemia. Follow-up over 3 years showed no evidence of reconstitution of vertebral body height or of progression at other spinal levels or in the appendicular skeleton. Histopathology from T6 showed a hypercellular, partially fibrotic bone marrow with prominent neutrophils and many eosinophilic granulocytes and macrophages. There was an increased number of plasma cells, evidence of bone destruction and new bone formation, bone fibrosis and occasional foci of

Fig. 1 **A** Anteroposterior (AP) and lateral radiographs of the spine demonstrate vertebra plana formation at the T6 level (arrows). **B** Sagittal STIR image (flip angle: 180°, TR: 4000, TE: 30) at time of presentation shows T6 vertebra plana formation (white arrow) and subtle superior endplate irregularity with increased bone marrow signal in the superior subchondral bone of T4 level (white arrowhead). Adjacent discs are normal. **C** Sagittal T2-weighted image (TR: 3500, TE: 120) 5 months later shows persistent and unchanged vertebra plana formation at T6 level (arrow), and development of vertebra plana formation at T8 level (arrowhead). The kyphosis has increased. **D** Five months later bone scintigraphy shows additional levels of increased bone turnover from the mid-thoracic region to T12 level (arrows). **E** One and a half years later AP and lateral radiographs show no evidence of reconstitution of vertebral body height at T6 and T8, nor of other sites of collapse. **F** Histological examination demonstrated the features of CRMO. Hematoxylin and eosin stained image (×20) with marked cellular inflammatory infiltrate (thick arrow), bone destruction (thin arrows) and new bone formation (asterisk)

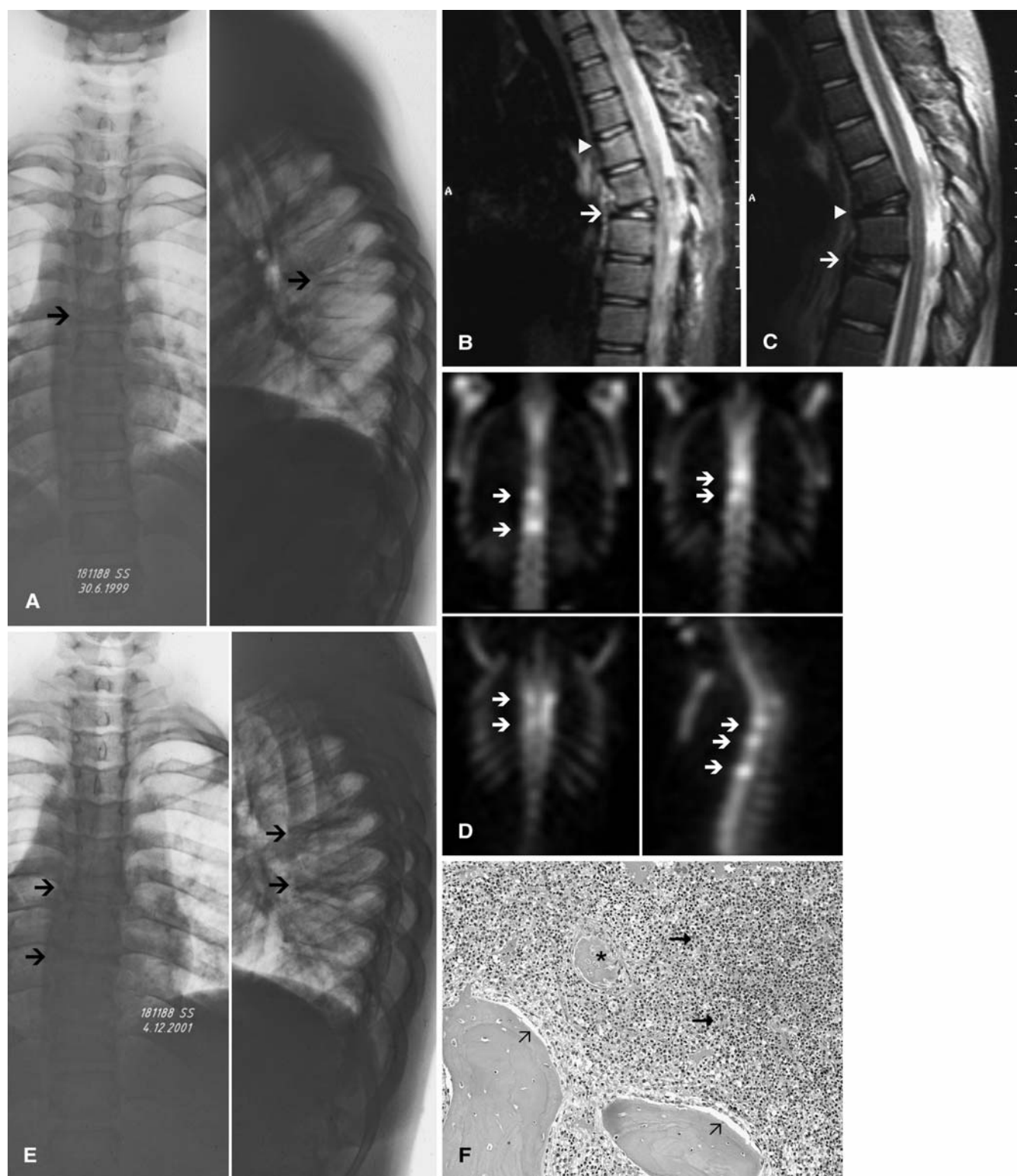


Fig. 1A-F Legends see page 329



Fig. 2 **A** AP radiograph shows partial collapse of the right side of vertebral body T9 (arrows). **B** Two months later, with persistence of pain, a sagittal T2-weighted image (TR: 3160, TE: 102) shows diffuse increase in bone marrow signal within T9 vertebral body (arrow) and a subtle low-signal line paralleling the superior endplate of T9 (arrowheads). The adjacent disc space is narrowed. Microbiological investigation showed no evidence of active bacterial infection. Histologically a chronic plasma-cell-rich infiltrate with fibrotic and ossifying osteomyelitis-like changes was seen and

considered consistent with CRMO. **C** On a T2-weighted sagittal image (TR: 3000, TE: 120) 2 years later there is involvement of C6 with partial collapse (arrowhead) and evidence of a subtle low-signal line within the vertebral body. The bone marrow signal is now normal in the T9 vertebral body with partial collapse of the body (arrow), with no evidence of reconstitution of the height of the vertebral body. **D** Three years later the partial collapse (arrow) of C6 remains unchanged in appearance

Table 1 Summary of clinical details, imaging findings, pathology, follow-up and regions of involvement

Case no.	Age (years)	Sex	History	Site of spinal involvement	Subsequent sites of multifocal disease	Biopsy for CRMO pathology	Microbiology and serology screening	Follow-up period
Case 1	11	F	Minimal fall during roller-blading	Vertebra plana of T4, T6	T4 to T10	2×	Negative for infection	3 years
Case 2	13	M	Abdominal pain after eating	T9, C6	Right hip, right mastoid, right third anterior rib, left tibial plateau, right subchondral tibia, T8, costovertebral junction of 11th rib, right first metatarsal	1×	Negative for infection	8 years
Case 3	12	F	Playing in swimming pool	L3, T8	Multiple epiphyseal and metaphyseal regions, right shoulder, left wrist, right hip, right tibia, right distal femoral condyle, left sternoclavicular joint, fourth costosternal joint, left talocalcaneal joint, T8, left T3/4 costovertebral joint, left midtarsus, right first metatarsal	1×	Negative for infection	3 years

necrotic bone. These findings were consistent with sub-acute partially osteolytic and osteoblastic osteomyelitis-like changes with bone marrow fat necrosis. Six months later a biopsy from T8 showed several plasma cells, increased lymphocytes, multiple macrophages and evidence of bone destruction consistent with chronic osteoblastic osteomyelitis-like changes. Tumor, in particular Langerhans cell histiocytosis X, was excluded with immunohistochemistry and active bacterial infection was excluded. Histopathological features were considered consistent with sub-acute CRMO.

Patient 2

An obese 13-year-old boy presented with abdominal pain after eating and was thought initially to be suffering from a psychosomatic disorder. There was no history of trauma. Screening radiography demonstrated partial collapse of T9 (Fig. 2A). MR imaging 2 months later showed diffuse increased bone marrow signal intensity within the anterior vertebral body of T9 on T2-weighted sequences, absence of an osseous or soft tissue mass and a subtle subchondral line mimicking an endplate fracture (Fig. 2B). Two years later partial collapse of C6 was demonstrated (Fig. 2C) and a similar subtle fracture-like line was evident. Radiography 3 years later showed no alteration to the morphology of the partial collapse of C6 (Fig. 2D). Biopsy was performed to exclude tumor and infection. Histopathological investigation showed a chronic fibrotic and ossifying osteomyelitis-like change rich in plasma cells, and no evidence of caseous necrosis or tuberculosis, Langerhans cell histiocytosis X or tumor cells. Microbiological tests excluded active bacterial infection. On follow-up scintigraphy over an 8 year period, multifocal extensive disease in the appendicular skeleton and thorax was evident. Multifocal peripheral disease was evident 2 years after presentation with spinal disease. The sites of involvement of the peripheral skeleton included: hip, mastoid, rib and costovertebral junction, proximal tibia, and a metatarsal bone (Table 1). The majority of lesions were intramed-

ullary in location though one had a subchondral location in the proximal tibia.

Patient 3

A 12-year-old girl complained of severe pain after twisting on a swimming pool inflatable floater. Radiographs showed subtle partial collapse of L3 (Fig. 3A) and MR imaging demonstrated focal increased signal intensity within the anterior and left lateral aspect of the anterior vertebral body on T2-weighted sequences with a subtle subchondral line mimicking a fracture (Fig. 3B). Biopsy was performed as the pain was extreme and prolonged and could not be accounted for by the imaging appearances alone. One year later there was involvement of T8 and multifocal disease was demonstrated on scintigraphy (Fig. 3C). Multifocal disease involving the metaphysis and epiphysis was evident in the following sites: shoulder, wrist, hip, tibia, distal femur, and metatarsal bones (Table 1). Joint involvement included: sternoclavicular, costosternal, talocalcaneal and mid-tarsal joints (Table 1). Follow-up was available for 3 years. Histopathological and microbiological tests showed no specific histomorphological features for tumor or active bacterial infection.

Results of the three patients are summarized in Table 1.

Discussion

Spinal involvement with CRMO is rare as is shown by the scarcity of reported cases in the literature [1, 6, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19]. In a review of 35 cases of chronic multifocal CRMO involving 157 lesions only 3% were present in vertebral bodies [15].

There have been two separate case reports of patients with CRMO presenting with primary spinal disease [14,

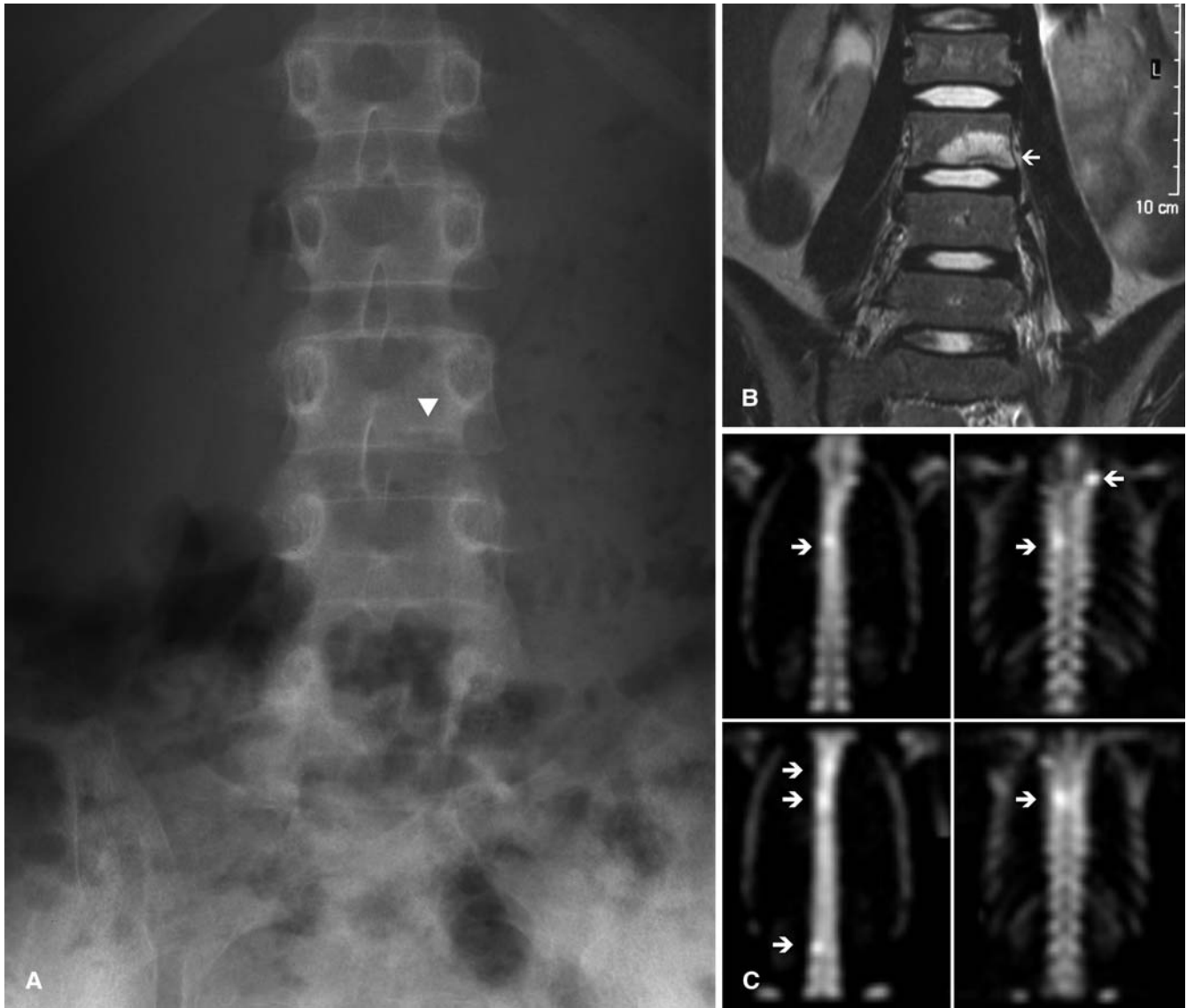


Fig. 3 **A** AP radiograph of the lumbar spine shows minimal collapse in the inferior aspect of L3 with a subtle sclerotic line (*arrowhead*). Histopathological and microbiological investigations showed no evidence of active bacterial infection or of tumor. **B** Coronal T2-weighted image (TR: 3284, TE: 120) shows marked increase in signal (*arrow*) in the vertebral marrow with a subtle low-signal line paralleling the inferior endplate. The disc signal is normal. **C** Four months later bone scintigraphy shows multiple spinal sites of involvement (*white arrows*)

17]. To our knowledge this is the first MR imaging documentation of a series of patients with initial presentation of isolated primary CRMO and with presentation of vertebra plana or of the finding of a subchondral endplate fracture-like line associated with vertebral body marrow altered signal intensity and partial collapse. Awareness of these imaging appearances in patients who present

with spinal pathology in the absence of a history of trauma should alert the radiologist and histopathologist to include CRMO in the differential diagnosis.

The term most widely accepted to describe this entity, CRMO, was first coined by Probst in 1978 [20]. It is an unusual inflammatory process occurring in children and adolescents. It remains contentious as to whether this entity is separate from the SAPHO (Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis) syndrome which occurs in adults or whether these two entities are part of a continuum [1, 3, 15]. In CRMO multiple osseous sites are usually involved and there is a fluctuating clinical course. Characteristically there are exacerbations and remissions typically lasting years. Clinically there is pain, swelling, erythema, increased over the affected region, and skin lesions may be present such as marked acne, psoriasis and palmoplantar pustulosis. No causative

agent has yet been identified. Proposed theories include a post-inflammatory reaction, as some authors report prior throat infections and elevated antistreptolysin O titers [15, 22]. There is no definite evidence of an autoimmune disorder, as serological tests for rheumatoid factor and antinuclear antibodies and HLA-B27 are usually negative [15]. Occasionally there are mildly elevated immunoglobulin levels of questionable significance [15]. The radiological differential diagnosis includes Langerhans cell histiocytosis X and lymphoma, malignant metastatic diseases (such as leukemia, neuroblastoma, Ewing's sarcoma), bacterial infection, benign bone tumors (such as osteoid osteoma, osteoblastoma), trauma, Gorham's vanishing bone disease and avascular necrosis [1, 16, 21, 22]. Langerhans cell histiocytosis X is known to be more commonly associated with vertebra plana and there is usually some percentage of vertebral body height reconstitution with time [2]. The diagnosis of CRMO is generally one of exclusion by means of laboratory, microbiology and pathology investigations which permit the exclusion of infection, tumor and systemic diseases. Due to the varied clinical and radiological appearances, it is generally recommended that two biopsies be performed from two different sites [1]. Repeated surgery and prolonged use of antibiotic therapy should be avoided [1].

Yu et al. [1] first described the association of vertebra plana and chronic multifocal CRMO in 1989, which appears to be quite rare. In their series of seven children with disease at various sites, there were 11 lesions involving the spine including three cases of vertebra plana. One case of vertebra plana resulting in spinal cord compression and neurological deficit has been described [12]. The patient described by Yu et al. [1] also had no evidence of reconstitution of the vertebral body height, which is similar to our case and is supported by other reports [4]. Since the initial report in 1989 there have been different reports of vertebra plana in association with CRMO involving five vertebral bodies [6, 9, 19]. Cyrlak and Pais [18] reported a 9-year-old girl initially presenting with back pain after a trivial fall with T5 compression fracture; however, bone scan and biopsy showed multifocal disease of CRMO. Martin et al. [16] described a 14-year-old boy with a 3 month history of lower back pain and MR imaging documenting T11 vertebral body and left pedicle involvement and unsuspected foci in L5, S1, S2 and subsequently foci in T8, T9 and T10. However, in this case report, 1 year previously, right foot pain in the second, third and fourth metatarsals was documented in the presence of widespread skin lesions, thus most likely representing CRMO disease. Only two case reports, by Dawson et al. [17] and by Tyrrell et al. [14], clearly document an initial presentation of isolated spinal involvement with CRMO. Dawson et al. [17] described a 13-year-old girl with spontaneous onset of a 7 month history of intermittent lumbar back pain with L2 vertebral and L1/2 disc space involvement. Two biopsies

were negative for infection and highly suggestive for CRMO. Seven months later repeat MR imaging showed additional involvement of L1, T12 and L2, and subsequently further foci in C5, C6 vertebral bodies and C6/7 disc space. Tyrrell et al. [14] described a 9-year-old girl presenting with L2 inferior endplate collapse and slight anterior bulging of the L2 anterior margin with diffuse osteopenia. Bone scintigraphy, lumbar and cervico-thoracic MR imaging depicted multifocal spinal disease at levels T12, C5, T2, T8 and L3. Spontaneous fractures have been described in association with pustular psoriasis and CRMO [23].

Patients with features similar to spondylodiscitis or minor partial collapse undergo gradual healing of the lesion with minor sequelae apart from minimal kyphosis [1]. This was also evident in two of our cases. In contrast, patients with vertebra plana or more extensive collapse usually have more marked kyphoses [4], as was evident in one of our cases. Intervertebral discs adjacent to the vertebra plana in CRMO have been described as either uninvolved [1, 9], herniated into the involved vertebral body involved [13, 16], or decreased in height and signal intensity [6, 14, 16, 19]. The pathology is not described as crossing the intervertebral disc [6, 13]. Table 2 summarizes the published findings on CRMO vertebral locations and vertebra plana.

Published reports concentrate on anterior vertebral body involvement, as was the case in our series. Only one published report describes involvement of the vertebral body and left pedicle [16]. Though evident in the images of two patients published [16, 17], the presence of a subchondral fracture-like line paralleling the vertebral body endplate associated with altered bone marrow signal intensity has not been described. This MR feature was present in two of our patients (Figs. 2B, C, 3B) at three sites. The exact etiology of this line is unknown but it is possible that it relates to local bony weakness of the vertebral body and possible insufficiency fracture or relative focal avascular necrosis.

MR imaging has been described as being useful in detecting disease activity [6, 13, 15]. The lytic phase is represented by decreased signal intensity on T1-weighted images and increased signal intensity on T2-weighted images and decreasing signal intensity on both T1- and T2-weighted images with a more chronic sclerotic phase [13]. Marked contrast enhancement occurs in the active lesion, decreasing with decreasing activity [13], as was the case in our patients. In contrast to pyogenic osteomyelitis and spondylodiscitis, there is an absence of abscess formation and soft tissue involvement [6, 13] and multifocal involvement usually skips vertebral bodies [18]. No focal spinal osseous masses have been described. Soft tissue masses involving the peripheral skeleton are exceedingly rare [24].

There is varied opinion in the literature regarding the use of MR imaging and bone scintigraphy in spinal in-

Table 2 Summary of published reports of chronic multifocal disease with CRMO in vertebral locations and vertebra plana

Reference	Case no.	Location of vertebral lesions	Vertebra plana	Neurological involvement	Surgery
Bjorksten et al. 1978 [8]	1	L3–L5	–	–	–
Cyrlak and Pais 1986 [18]	1	T5	–	–	–
Mortensson et al. 1988 [10]	4	11 lesions, all thoracic apart from 1 cervical and 1 lumbar	–but 3 wedge-like compressions	–	–
Brown and Wilkinson 1988 [9]	1	T4–T5–L1	3, T4, T5	–	–
	2	T4–T5–T7	–	–	–
	3+4	L1	–	–	–
Yu et al. 1989 [1]	1	T5–T6–T7	+, T5	–	–
	2	T4–L1	+, T4	–	–
	3	T8–L1–L2	+, L1	–	–
	4	T4–T5–T7	–	–	–
Carr et al. 1993 [11]	1	T5	+	–	–
	2	T8–T10	+	–	–
	3	T11–T12	–	–	–
Dawson et al. 1994 [17] ^a	1	L2–L1–T12, C5C6C6/C7 disc	–	–	–
Martin et al. 1996 [16]	1	T11–L5–S1–S2–T8–T9	–	–	–
Tyrrell et al. 1996 [14] ^a	1	L2, L3, T12, C5, T2, T8, T7/T8 disc	–	+	–
Demharter et al. 1997 [19]	3	T9, T7, T3	+, (one)	–	–
Jurik and Eglund 1997 [6]	5	T4, T6, T6, T7, T8, T9	+, T6	–	–
Baulot et al. 1998 [12]	1	T2	–	+	+
Vanhoenacker et al. 1998 [13]	1	T10	–	–	–

^a Case report, primary solitary presentation with spinal involvement

involvement. Some authors state that MR imaging is preferable to bone scanning as it detected additional and occult spinal involvement [6, 16, 17], while others maintain bone scans are more useful than MR imaging for detecting occult spinal disease (which was the case in one of our patients) or where there are subtle and questionable radiographic findings [10, 19].

As described in published cases, radiography in patients 1 and 2 showed subtle evidence of bone lysis with eventual development of a sclerotic rim adjacent to an endplate [6, 10, 12].

The pathological appearances of CRMO depend on the disease phase [1, 19, 21]. The histological appearance is practically indistinguishable from acute and chronic conventional bacterial osteomyelitis, accepting that no organisms are found. Early, more acute lesions contain polymorphonuclear (neutrophilic) leukocyte marrow infiltration [19, 21]. Neutrophils may collect in groups surrounded by a lymphocytic infiltrate forming pseudoabscesses [21]. Osteoclasts with marked osteolysis are a common feature. More chronic lesions show fibrosis and lymphocytic infiltrates with new reactive

bone in later phases [19, 21]. There may be granuloma formation consisting of collections of neutrophils surrounded by epithelioid histiocytes [21]. Bacterial, viral and fungal cultures and stains are negative. Specific immunoperoxidase tests (T6 and S-100) can confirm that any histiocytes present are not of the type strongly implicated in Langerhans cell histiocytosis X [1]. In CRMO these tests are negative.

Pain relief and supportive therapy is required if there is minimal and partial vertebral body collapse. Severe vertebra plana may be associated with marked kyphosis rarely requiring surgical fusion [11]. Only one case with cord compression requiring anterior decompression and fusion has been documented [12]. Many medications have been tried but no single medication has proven to be optimal.

In conclusion, CRMO may initially present with isolated primary spinal involvement. Awareness of the imaging appearances may help the radiologist include this entity in the differential diagnosis in children who present with spinal pathology and an inadequate history of trauma. The histopathological findings exclude tumor and infection.

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