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ORIGINAL PAPER

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The syndrome of chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anaemia. Report of a new family and a review

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Abstract A new autosomal recessive syndrome of chronic recurrent multifocal osteomyelitis (CRMO) and congenital dyserythropoietic anaemia (CDA) with microcytosis has recently been described in four children (two sibships) of one consangineous Arab family. In this report, we describe the clinical features and course of the syndrome of CRMO and CDA in two additional patients (one sibship) from another consanguineous Arab family and review the literature. The two patients (brother and sister), the products of a consanguineous marriage, developed the syndrome at an early age of 3 weeks and 2 months respectively. The diagnosis of CRMO was confirmed by radiological and technetium isotope bone scans. Bone marrow studies confirmed the diagnosis of CDA. Peripheral blood films showed hypochromia and microcytosis. The sites involved by CRMO were periarticular, mainly around the elbow, knee, wrist and small joints of the hand. The brother is now 21 years old and the sister 3.5 years old and CRMO is still active with frequent relapses. The brother developed flexion deformities at the age of 13 years. Both patients failed to thrive; weight and height were below the 5th percentile. *Conclusion*: this is the second report of the syndrome of chronic recurrent multifocal osteomyelitis and microcytic congenital dyserythropoietic anaemia, confirming it as a clinical entity, inherited as an autosomal recessive trait. The disease is characterised by an early onset, long clinical course of remissions and relapses, and seems to be different from the sporadic form of chronic recurrent multifocal osteomyelitis.

Keywords Autosomal recessive syndrome · Chronic recurrent multifocal osteomyelitis · Congenital dyserythropoietic anaemia · Microcytosis

Abbreviations *CDA* congenital dyserythropoietic anaemia · *CRMO* chronic recurrent multifocal osteomyelitis

Introduction

Chronic recurrent multifocal osteomyelitis(CRMO) was first described in 1972 by Giedion et al. [12] who reported four patients with "subacute and chronic symmetrical osteomyelitis. The disease is characterised by exacerbations and remissions. The symptoms are pain and swelling usually around a joint. Isotope bone scans show a predilection for the metaphyses of tubular bones [12,15]. Bone biopsy shows non-specific subacute and chronic inflammatory changes. Blood, bone marrow and bone biopsy specimen cultures for aerobic, anaerobic bacteria, *Mycobacteria* and fungi show no growth [12,15]. Results of viral serology studies also have been negative [15] and an immunodifficiency has not been proven.

Congenital dyserythropoietic anaemia (CDA) is a term used to describe a group of inherited red blood cell disorders characterised by abnormal morphology of the normablasts in the bone marrow and ineffective erythropoiesis resulting in reduced erythrocyte output to the circulation; usually with insufficient reticulocytosis

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[14, 17,26]. Three major types have been described [14, 17,26]. Type 1 CDA is inherited as autosomal recessive and is macrocytic. Type 2 is also inherited as autosomal recessive and normocytic or macrocytic with a positive acidified serum lysis test (Ham test). Type 3 is inherited as autosomal dominant and is macrocytic. However, additional variants of CDA have been reported [3,21].

In 1989, we reported three related children with CRMO and CDA [18]. Since then, a fourth child with CRMO and CDA was born into this family. In 2000, we described the syndrome of CRMO and CDA in these four children (two sibships) and gave evidence that the syndrome was inherited as autosomal recessive [19]. In this communication, we confirm our previous report [18], and describe the syndrome of CRMO and CDA in more detail in two additional patients (brother and sister) of a new family and review the literature.

Case reports

Case 1

This Palestinian Arab girl presented to us at age 2.5 years with history of recurrent joint pain and swelling since the age of 3 weeks. The presenting complaint was fever, pain, swelling and limitation of movement of the left elbow joint. There was no history of trauma and a radiograph of the left elbow region showed no abnormal findings. The swelling resolved in few days. One month later, the child developed a similar episode involving the right elbow region which also resolved in 3 days. At the age of 4 months, she was found to be pale and her haemoglobin was 40 g/l. The periarticular lesions pursued a chronic course characterised by recurrent episodic attacks, each lasting for 2–4 days and usually associated with fever. Other sites involved were mainly around the knee and wrist joints. During each episode, one or more sites were involved. The episodes were frequent occurring once every 2–4 weeks. Parents are first cousins and a brother (Case 2) has a similar illness. She was born at full term, normal delivery with a birth weight of 3 kg, length 50 cm and a head circumference of 34 cm. There was no neonatal or past history of jaundice. Physical examination at the age of 3 years revealed a weight of 9.5 kg (< 5th percentile), height of 84 cm (< 5th percentile) and head circumference of 47 cm (< 5th percentile); mental development was normal and she had no skeletal deformities, liver span was 8 cm and the spleen was just palpable.

Investigations carried out at the age of 3 years are shown in Table1. Skeletal survey showed a single lucency in the left proximal tibial metaphysis with sclerotic margin (Fig.1). She received many courses of antibiotics, was hospitalised in many hospitals and had four blood transfusions.

Case 2

This Palestinian Arab boy (the brother of case 1) presented at the age of 2 months with recurrent episodes of high fever and irritability each lasting for 3–4 days, and recurring every 2–3 weeks. At the age of 9 months, these episodes started to be associated with periarticular swellings with hotness, tenderness and limitation of movement. The sites involved were around left elbow, right elbow, right knee and left knee and one or more sites were involved during each episode. After the age of 3 years, the episodes started involving the periarticular sites of the small joints of the hands and feet. At the age of 9 months, he was noted to be pale with a haemoglobin of 40 g/l. He sat unsupported at the age of 9 months, and could stand and walk at the age of 1.5 years. Flexion deformities of the wrists, elbows, ankles and knees were observed at the age of 13 years (Fig.2). He was born at 30 weeks gestation; birth weight was 1.5 kg, length 46 cm and head circumference 32 cm. He is now 21 years old, his weight is 19 kg (< 5th percentile) height 118 cm (< 5th percentile) and head circumference 51 cm. He could hardly stand but could not walk. His facial deformities included maxillary hyperplasia and a prominent forehead. Sexual development was absent, speech was slow but cognitive functions were normal. Investigations are shown in Table1. Ham test was negative. A skeletal survey showed a generalised increase in bone density, resorption of secondary trabeculation and prominent primary trabeculation in both femori (Fig.3). Radiograph of the skull showed vault thickening which was more prominent in the anterior plane (Fig.4). During the course of his illness, he received many courses of antibiotics, hospitalised in many hospitals and needed frequent blood transfusion.

The following tests were normal in both patients: haemoglobin electrophoresis, glucose-6-phosphate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, serum creatinine, total serum bilirubin, random blood sugar and electrolytes. Tests for antinuclear antibodies and rheumatoid factor were negative. Chromosome study showed a normal chromosomal number and structure with no unusual breakage. Abdominal ultrasound scan

Table 1 Haematological findings in cases 1 and 2

Test	Case 1 (age 3 years)	Case 2 (age 21 years)
Haemoglobin (g/l)[a]	88	40
RBC (10×10^{12}/l)	4.2	3.10
Reticulocytes	0.008	0.007
MCV (fl)	70	60
PCV (%)	35	27
MCHC (g/dl)	33	20
MCH (pg)	33	22
Blood film	Microcytic hypochromic	Microcytic hypochromic
Serum B12 (ng/l)	267	403
Serum folate (ng/l)	3.5	2.4
Serum iron (μmol/l)	14.0	10.0
Serum ferritin (μg/l)	50.8	27.0
WBC ($\times10^9$/l)	7700 Lymphocytes 68%	11 Lymphocytes 30%
ESR	68 (first hour)	127 (first hour)
Platelets ($\times10^9$/l)	396	424
Ham test	Negative	Negative
Total serum bilirubin (μmol/l)	8.55	7.2

[a]Minimal and maximal pretransfusion values in both patients were 40 g/l and 60 g/l

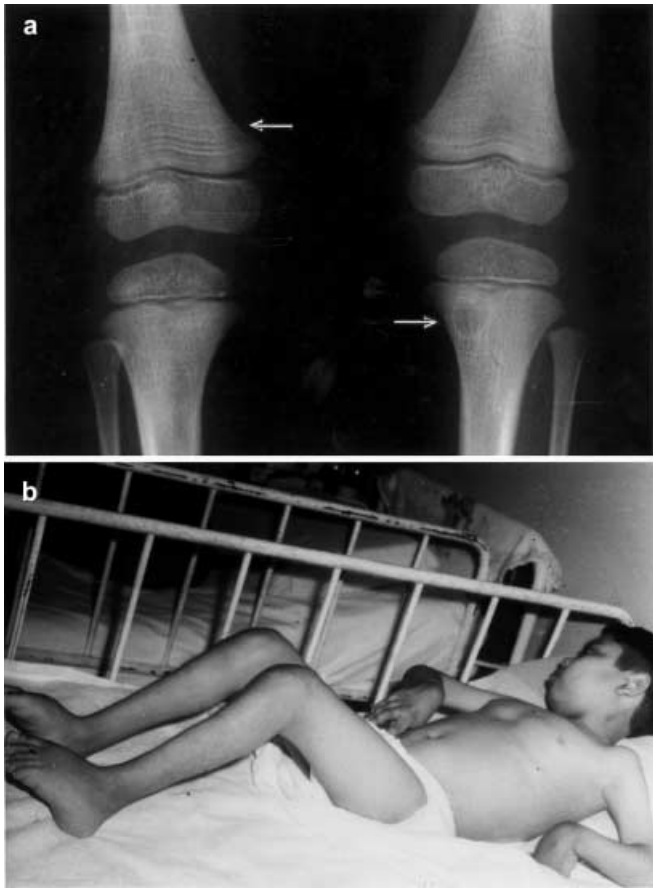

Fig. 1 a X-ray film of case 1 (3 years old) showing a lucent lesion with sclerotic outline in the upper part of left tibia. Growth lines are noted in both lower femora. **b.** Case 2 aged 13 years showing flexion deformities. Note the contractures

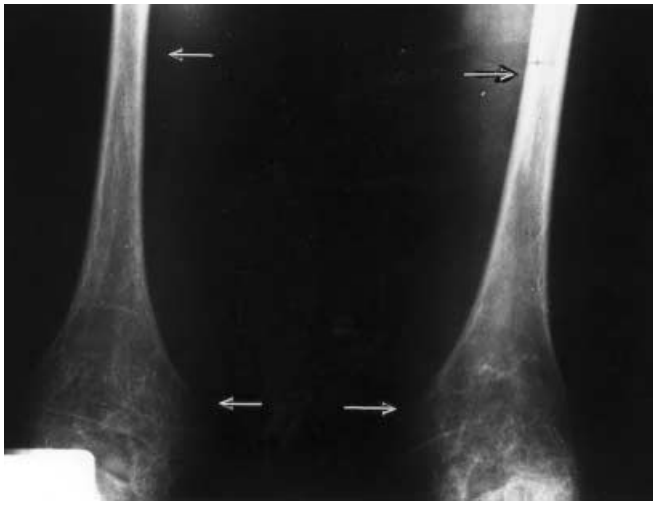

Fig. 2 X-ray film of case 2 (21 years old) showing generalised increase in bone density, resorption of secondary trabeculations and prominent primary trabeculations in both femora

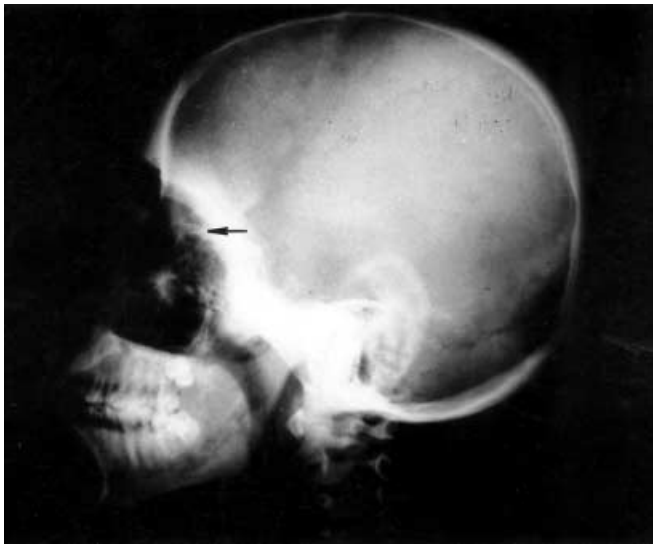

Fig. 3 X-ray film of the skull in case 2 (21 years old) showing skull vault thickening, more prominent anteriorly (*arrow*), due to the widening of the vault as a result of the hyperactive bone marrow due to the intramedullary haemolysis

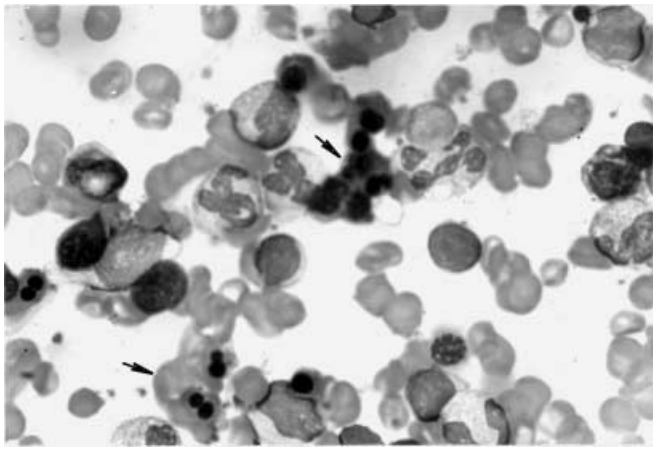

Fig. 4 Bone marrow showing hypercellular marrow with binucleated and trinuleated normoblasts (*arrows*)

gave normal findings. During diagnostic work up, technetium isotope scans showed an increased uptake in one or more sites in both patients.

Bone marrow examination of both patients showed hypercellular marrow. Erythropoiesis was markedly increased with considerable numbers of binucleated orthochromic normboblasts. In cases 1 and 2, the myeloid/ erythroid ratio was 1:1 and 0.35:1 respectively and the abnormal normoblasts constituted 24%–26% and 26%–30% of the total erythroid elements respectively. The Perl stain showed absent iron stores.

Discussion

The syndrome in our two patients is inherited as an autosomal recessive trait; the two affected siblings have the combination of two rare disorders namely CRMO

and microcytic CDA and the parents are first cousins and normal and three other siblings are normal. Together with the two sibships of the first family reported by us earlier [19], this family provides further evidence of the characteristic clinical entity of this syndrome.

Vermylen et al. [27] described a 13-year-old Belgian girl, who at the age of 5 years developed CRMO. At the age of 8 years, splenomegaly was noted for the first time and hepatomegaly appeared 5 years later. The diagnosis of CDA was established at the age of 13 years. The girl was the first and only child of healthy unrelated parents [27]. We speculate that most probably this European girl had the same syndrome we are describing.

Table 2 Comparative features of sporadic CRMO and CRMO as part of the syndrome of CRMO and CDA. (*NSAID* nonsteroidal anti-inflammatory drugs)

Feature	Sporadic CRMO	CRMO as part of CRMO and CDA syndrome
Age at onset	4–15 years	3 weeks–19 months
Frequency of episodes	1–4/month	2–4/year
Duration	1–14.5 years	4–21 years
Spontaneous remissions	Frequent	No lasting remissions
Treatment	NSAID	NSAID

Table 3 Onset and duration of sporadic CRMO and CRMO as part of the syndrome of CRMO and CDA in childhood studies

Reference	Children (*n*)	Age at onset (years)	Duration (follow-up) (years)
[23] (sporadic)	10	7–12	5
[15] (sporadic)	7	8–13	1–3
[13] (sporadic)	6	9–15	3.5
[16] (sporadic)	7	7–14.5	1–4.5
[7] (sporadic)	5	Not available	1–14.5
[11] (sporadic)	5	4–13	2–8
[19] (CRMO and CDA)	4	0.75–1.5	9–15
Present report (CRMO and CDA)	2	3–4 weeks	3.5–21

The clinical course of CRMO in this autosomal recessive syndrome seems to be different from that of the sporadic form of CRMO, first described by Geidion et al. [12] (Table2). The age at onset of the sporadic form of CRMO in the majority of the large series in childhood varied between 7–15 years, showing that CRMO is a disease of late childhood and early adolescence (Table3). However, the age at onset in our two present patients was much earlier (3–8 weeks) and is similar to the four patients of the family reported by us earlier [19] (Table4). It is interesting that the two patients (brother and sister) with CRMO described by Festen et al. [9] also had an early onset ranging between 1–2 years. Furthermore, the clinical course of CRMO in our patients seems to be far more aggressive (1–2 relapses/month) than that in reports describing the sporadic form. Of the six patients with the sporadic CRMO reported by Girschick et al. [13], three patients developed six relapses over a follow-up period of 3 years (two relapses/year). Similarly the patients described by Gallagher et al. [10] developed 11 episodes each over a follow-up period of 2.5 years (4.4 relapses/year). However, the aggressive course seen in our two present patients is similar to that described in the four patients of the family reported by us earlier [19]. Data from this study show the long duration of the disease ranging between 3.5–21 years in our two present patients and is also similar to the family reported by us earlier [19]. None of our patients had a long remission. The girl described by Festen et al. [9] had CRMO for 23 years, although she had spontaneous amelioration after puberty. However, two of the seven patients with the sporadic form of CRMO described by Leisure et al. [16] had spontaneous remission after a short follow-up period of 15 and 27 months. Of the ten patients described by Quelquejay et al. [23], four had spontaneous remissions after a follow-up period of 5 years. Unlike the sporadic form, CRMO in this syndrome is characterised by an early onset, aggressive course with frequent relapses and a long duration of activity (Table2). However, there was no correlation between the severity of anaemia and the degree of inflammatory activity.

Table 4 The demographic features of the syndrome of CRMO and CDA in six patients. Cases 1 and 2 (siblings) are the subject of the present report. Cases 3 and 4 (brothers) and 5 and 6 (siblings) are from [16]

Case (sex)	Date of birth	Present age (years)	Age at onset		No. of lesions at presentation (*n*)
			CDA	CRMO[a]	
1 (F)	05.04.1997	4	6 months	1 year	1
2 (M)	30.11.1979	21	4 months	2 months[b]	1
3 (M)	16.06.1984	16	6 months	1 month	1
4 (M)	17.11.1982	18.5	10 months	19 months	1
5 (F)	08.02.1986	15	9 months	9 months	2
6 (M)	24.10.1989	11.5	9 months	1 year	1

[a]Sites of bone lesions: right distal humerus, right distal tibia, left distal tibia, right distal ulna, left distal humerus, distal phalanx of right index figure, left proximal femur, left distal tibia, right distal femur, distal ends of proximal phalanges of both hands (during each episode one or more sites were involved; many sites were affected more than once)

[b]Started recurrent episodic fever without bone lesions at age 2 months; fever and periarticular lesions started at the age of 9 months

Both patients in this report failed to thrive; weight and height were below the 5th percentile. This was obvious and severe in case 2 seen at the age of 21 years; however it was also clear in case 1 at the age of 3 years, suggesting that these features develop early in the course of this syndrome. The four children reported by us earlier also failed to thrive; weight and height were below the 5th percentile (Table 4, cases 3, 4, 5, 6). These data strongly suggest that failure to gain weight and height is an integral part of the syndrome and develops early in the course of the disease. No solid evidence is available for the explanation of this feature, however, chronic severe anaemia and a chronic aggressive inflammatory response may be aetiological factors.

The radiological bone changes show a wide spectrum of findings; those in the skull of case 2 are due to the underlying anaemia (Fig.4) whereas those seen in the long bones of both patients are due to long standing CRMO (Figs.1, 3). It is interesting that case 1 (aged 3 years) did not develop bone changes due to CDA. In both patients, the iron stores in the bone marrow were depleted. Poverty, an underprivileged socioeconomic status and a chronic inflammatory process may be aetiological factors.

Of the three patients with CRMO and CDA reported by us in 1989, two brothers had Sweet syndrome [25]; one had spontaneous resolution without scarring [18]. A child with CRMO and Sweet syndrome was reported by Edwards et al. [8], however the child did not develop CDA and did not fit with the syndrome of CRMO and CDA. The association of CRMO with other dermatological disorders including psoriasis vulgaris and palmoplanter pustulosis has been reported in the sporadic form of CRMO and not in the syndrome described here [15]. According to the data available, Sweet syndrome does not seem to be a part of the syndrome of CRMO and CDA.

One of our patients (case 2), developed flexion deformities after a disease (CRMO) activity of 13 years (Fig.2). This has not been described before, neither in the familial nor the sporadic forms of CRMO. However, Byrd et al. [4] reported a similar disease in mice which caused deformities restricted mainly to tail kinks and limb deformities. It resembled human CRMO by having a chronic inflammatory process involving multiple osseous sites and no pathogen could be isolated. The disease causing gene was mapped to the mouse chromosome 18 [4]. However, the genetic basis of CRMO has not been established in humans, although there are scattered reports of familial cases [2, 8,20]. Similarly CDA in this report seems also to be different and is characterised by microcytosis. Type 1 CDA is macrocytic, type 2 is normocytic or macrocytic, and type 3 is macrocytic.

In our experience, non-steroidal anti-inflammatory drugs were moderately helpful. However, they did not seem to have affected the frequency of relapses, the duration of the episodes or the course of the disease. Two patients in our previous report responded remarkably to short courses of corticosteroids [18]. However, in the presence of a protracted course in some patients with CRMO, we believe that the adverse effects of long-term corticosteroid therapy, including growth retardation, are potentially dangerous. Festen et al. [9] reported a remarkable improvement in one of their two patients on 1 mg daily colchicine therapy. This is not in agreement with our experience; we tried 1.5–2 mg daily colchicine therapy for 4 months in our first three patients, initially diagnosed as familial Mediterranean fever, with no response (unpublished observation).

One of our patients (Table 4, case 2) reported earlier [18,19] had undergone a splenectomy elsewhere in 1994. Since then he did not need blood transfusions and could maintain his haemoglobin at around 110 g/l for 6.5 years thereafter. However, this did not affect the course of his CRMO which remained frequently recurrent and aggressive showing that there is no correlation between the severity of CDA and CRMO. Splenectomy was reported to be effective in CDA types 1, 2 and 3 [5,6]; nevertheless, the favourable response to splenectomy in our patient with the syndrome of CRMO and CDA has not been reported before. Recently interferons were reported as successful therapeutic measures [1, 10, 22,24]. Shamseddine et al. [24] reported two patients with CDA type 1 in whom alpha interferon therapy ''normalised their haemoglobin level which was maintained 6 months after discontinuation of treatment'' [24].

This report confirms the syndrome of CRMO and microcytic CDA as a distinct clinical entity. This is the third sibship in which at least two siblings are affected which further confirms the autosomal recessive mode of inheritance.

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References

1. Anderson R (1995) Effective treatment with interferon-alpha in chronic recurrent multifocal osteomyelitis. J Interferon Cytokine Res 15: 837–838
2. Ben Becher S, Essaddam H, Nahali N, Ben Hamadi F, Mouelhim M, Hammou A et al (1991) Recurrent multifocal periostosis in children. Report of a familial form. Ann Pediatr 38: 345–349
3. Boogaerts MA, Verwilghen RL (1982) Variants of cogenital dyserythropoietic anaemia: an update. Hematologica 15: 211–219
4. Byrd L, Grossmann M, Potter M, Chen-Ong GLC (1991) Chronic multifocal osteomyelitis, a new recessive mutation on chromosome 18 of the mouse. Genomics 11: 794–798
5. Choudry VP, Saraya AK, Kasturi J, Rath PK (1981) Congenital dyserythropoietic anemias: splenectomy as a mode of therapy. Acta Hematol 66: 195–201

6. Chrobak L, Spacek J (1997) Favourable effect of splenectomy on anaemia in 3 siblings with type II congenital dyserythropoietic anaemia (in Czechoslovakian). Vnitr Lek 43: 635–638
7. Demharter J, Bohndorf K, Michl W, Vogt H (1997) Chronic recurrent multifocal osteomyelitis: a radiological and clinical investigation of five cases. Skeletal Radiol 26: 579–588
8. Edwards TC, Stapleton FB, Bond MI, Barrett FF (1986) Sweet syndrome with multifocal sterile osteomyelitis. Am J Dis Child 140: 817–818
9. Festen JJM, Kuipers FC, Schaars AH (1985) Multifocal chronic periostitis responsive to colchicine. Scand J Rheumatol 14: 8–14
10. Gallagher KT, Roberts RL, MacFarlane JA, Stiehm ER (1997) Treatment of chronic recurrent multifocal osteomyelitis with interferon gamma. J Pediatr 131: 470–472
11. Gamble JG, Rinsky LA (1986) Chronic multifocal osteomyelitis: a distinct clinical entity. J Pediatr Orthop 6: 579–584
12. Giedion A, Holthusen W, Masel LF, Vischer D (1972) Subacute and chronic symmetrical osteomyelitis. Ann Radiol 15: 329–342
13. Girschick HJ, Krauspe R, Ischammler A, Huppertz HI (1998) Chronic recurrent osteomyelitis with clavicular involvement in children: diagnostic value of different imaging techniques and therapy with non-steroidal anti-inflammatory drugs. Eur J Pediatr 157: 28–33
14. Heimple H, Windt F (1968)Congenital dyserythropoietic anaemia with karyorrhexis and multinuclearity of erythroblasts. Helv Med Acta 34: 103–111
15. King SM, Laxer RM, Manson D, Gold R (1987) Chronic recurrent multifocal osteomyelitis: a non-infectious inflammatory process. Pediatr Infect Dis J 6: 907–911
16. Leisure Y, Kasser JR, O'Rouke E, Kozakewich H (1989) Chronic recurrent multifocal osteomyelitis: association with verbra plana. J Bone Joint Surg Am 71: 105–112
17. Lewis SM, Verwilghen RL (1984) Dyserythropoiesis and dyserythropoietic anaemia. Prog Hematol 8: 99–115
18. Majeed HA, Kalaawi M, Mohanty D, Teebi AS, Tunjekar MF, Gharbawy F, Majeed SA, Al-Gazzar AH (1989) Congenital dyserythropoietic anaemia and chronic recurrent multifocal osteomyelitis in three related children and the association with Sweet syndrome in two siblings. J Pediatr 115: 730–734
19. Majeed HA, El-Shanti H, Al-Rimawi H, El-Masri N (2000) On mice and men: an autosomal recessive syndrome of chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anaemia. J Pediatr 137: 441–442
20. Majeed SA (1994) Chronic recurrent multifocal osteomylitis associated with tumoral calcinosis. J Bone Joint Surg Br 76: 325–327
21. McBride JN, Welson WEC, Baille B (1971) Congenital dyserythropoietic anaemia type IV. Blood 38: 837–840
22. Parez N, Dommergues M, Zupan V, Chambost H, Fieschi JB, Delaunay V et al (2000) Severe congenital dyserythropoietic anaemia type 1: prenatal management, transfusion support and alpha interferon therapy. Br J Haematol 110: 420–423
23. Quelquejay C, Job-Dislandre C, Hamidou A, Benosman A, Adamsbaum C (1997) Chronic recurrent multifocal osteomyelitis in children. J Radiol 87: 115–121
24. Shamseddine A, Taher A, Jafar H, Haidar JH, Nasr R, Arzomanian V et al (2000) Interferon alpha is an effective therapy for congenital dyserythropoietic anaemia type 1. Eur J Hematol 65: 207–209
25. Sweet RD (1964) An acute febrile neutrophilic dermatosis. Br J Dermatol 76: 249–253
26. Verwilghen RL, Lewis SM, Dacia JV, Crookston JH, Crookston MC (1973) HEMPAS congenital dyserythropoietic anaemia (type 2) QJM 42: 257–278
27. Vermylen C, Scheiff JM, Zodhain J, Ninane J, Cornu G (1986) A variant of congenital dyserythropoietic anaemia type 2 with structural abnormalities in the granulocytic series. Eur J Pediatr 145: 232–235