Congenital dyserythropoietic anemia and chronic recurrent multifocal osteomyelitis in three related children and the association with Sweet syndrome in two siblings

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Congenital dyserythropoietic anemia and chronic recurrent multifocal osteomyelitis, uncommon childhood diseases of unknown cause, occurred in three children (two brothers and a female cousin). Their parents are consanguineous, and the clinical course of their illness was similar. The two brothers also had Sweet syndrome. The association of Sweet syndrome with chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anemia in this family suggests that these rare conditions may be interrelated. (J PEDIATR 1989;115:730-4)

Congenital dyserythropoietic anemia is a heterogeneous group of rare refractory anemias characterized by ineffective erythropoiesis and multinucleated erythroblasts in the bone marrow. On the basis of the morphologic abnormalities of the erythroblasts and positive acidified serum test results, CDA has been classified into types I, II, and III. An additional type IV variant and a few cases with overlapping hematologic features also have been reported. Despite the heterogeneity of the clinical and hematologic findings, these conditions share many common features, and are all characterized by an autosomal recessive mode of inheritance. Some patients have had an associated mental subnormality.

Chronic recurrent multifocal osteomyelitis is characterized by exacerbations and remissions consistent with osteomyelitis at multiple sites. Bone biopsy specimens show nonspecific acute and chronic inflammatory changes. The cause of this recurrent inflammatory process is unknown. Blood and bone biopsy specimens have been cultured for aerobic and anaerobic bacteria, mycobacteria, and fungi, and have showed no growth. Results of viral serologic studies also have been negative. Infection by a fastidious organism of low virulence or an immunodeficiency has not been proved. The disease has been reported in association with palmo-plantar pustulosis, less commonly with pso-


Table. Essential clinical information

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Date of birth</th>
<th>Age at onset</th>
<th>No. of bone lesions at presentation</th>
<th>Site of bone lesions</th>
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<tr>
<td></td>
<td></td>
<td>CDA</td>
<td>Sweet syndrome</td>
<td>CRMO</td>
</tr>
<tr>
<td>1</td>
<td>6/16/84</td>
<td>6 mo</td>
<td>19 mo</td>
<td>1</td>
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<td>L distal humerus*R</td>
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<td>19 mo</td>
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<td>R distal tibia*</td>
</tr>
</tbody>
</table>

*R Affected more than once.

Dyserythropoietic anemia, osteomyelitis, and Sweet syndrome

Fig. 1. Family pedigree.

Table.

- Sweet syndrome is characterized by multiple painful cutaneous plaques ranging from 0.5 to 4 cm in diameter. The plaques appear dull red and raised; in the majority of cases, their surfaces become studded with vesicles and pustules. The characteristic pathologic feature is a dense dermal polymorphonuclear leukocytic infiltrate without leukocytoclastic vasculitis. The eruption may last for 2 to 6 months, but the duration and severity show considerable variation. No pathogenic organism has been identified and there is no response to antibiotic therapy, but the response to corticosteroid therapy is dramatic.

In this communication, we report three related children with CDA and CRMO; two of them are brothers, and their illness is also associated with Sweet syndrome (Fig. 1).

METHODS

Onset of CDA. The three children had pallor, without jaundice, between the ages of 6 months and 1 year (Table). They were failing to thrive and had hepatosplenomegaly. Their hemoglobin level ranged between 5.2 and 7.9 gm/dl,
with hypochromia and microcytosis. The complete hemogram of patient 1 was similar to those of the other two children, and showed an erythrocyte count of $3.47 \times 10^{12}/L$, hemoglobin level 7.7 gm/dl (77 gm/L), hematocrit 29%, mean corpuscular volume 65.5 fl, mean corpuscular hemoglobin 22.9 pg, mean corpuscular hemoglobin concentration 34.9 gm hemoglobin/dl, erythrocytes and reticulocytes 2%. The smear showed hypochromia, microcytosis, and anisopoikilocytosis. Results of the following tests were normal: white blood cell and platelet counts, hemoglobin electrophoresis, osmotic fragility test, glucose-6-phosphate dehydrogenase level, and determinations of serum iron and total iron binding capacity. Bone marrow examination was carried out in the three patients and showed a hypercellular marrow and normoblastic erythropoiesis with mild megaloblastic changes; erythroid cells showed nuclear fragmentation, karyorrhexis, and binucleated, trinucleated, and multinucleated erythroblasts, as well as internuclear bridging (Fig. 2). The Perl stain showed normal iron stores. Results of the Ham lysis test were negative. A therapeutic trial of vitamins B12 and B6, B12, and folic acid gave no response. Patient 2 needed five blood transfusions.

**Onset of CRMO.** The bone pains started between the ages of 9 and 19 months (Table). In two children the condition started at one site with pain, tenderness, and swelling around a joint, associated with mild fever; the third patient (No. 3) had pain at two sites simultaneously (Table). Tenderness was maximal above the joint. Eventually other sites were involved, mostly at one site but sometimes at two or three sites simultaneously. "Mirror image" lesions were not seen. The duration of each clinical episode lasted between 1 and 2 weeks; the pain and tenderness were severe in the first 48 hours but mild and tolerable thereafter. Technetium scan showed increased uptake at the metaphyseal ends of the bones that were clinically involved. The radiologic findings included dense metaphyseal borders, mild periosteal reaction, remodeling of the bone, and lucent areas. During the attacks, the erythrocyte sedimentation rate was always high, ranging between 80 and 100 mm/hr. The leukocyte and platelet counts were also high. Blood and bone marrow specimens cultured for aerobic and anaerobic bacteria, mycobacteria, and fungi revealed no growth. Results of agglutination tests, a tuberculin test, viral serologic studies of hepatitis A and B, Epstein-Barr, rubella, and cytomegalic viruses, and studies of rheumatoid factor, antinuclear antibodies, complements C3 and C4, and quantitative immunoglobulins were normal. Bone biopsy was carried out in the three children. The findings included mild chronic inflammatory changes, fibrosis of marrow spaces (indicating healed inflammation), and excessive resorption of bony trabeculae. All children were treated with antibiotics at the time of the initial presentation. The duration of symptoms before a diagnosis of CRMO was made ranged between 1 and 3 years. Aspirin therapy was tried with no response.
Fig. 3. Skin biopsy specimen from patient 1. Note edema and predominantly neutrophilic perivascular infiltrations with no leukocytoclasis in dermis. (Hematoxylin-eosin stain; × 140; inset at higher magnification.)

However, naproxen, 100 mg twice daily, resulted in good therapeutic response; the attacks, which had ranged between 1 and 3 months in duration, were much reduced in frequency and severity.

**Onset of Sweet syndrome** (Table). When patient 1 was 19 months of age, erythematous palques with small vesicles developed on the surface of the left arm. The lesions soon spread to involve the face, trunk, and extremities; the palms and soles were spared. The lesions ranged in size between 0.5 and 4 cm, were itchy, and had a serosanguineous discharge. The surface of the large lesions was studded with vesicles. Systemic and topical antibiotic and topical corticosteroid applications gave no response. A skin biopsy specimen (Fig. 3) showed a patchy, predominantly perivascular inflammation in the papillary and mid portions of the dermis. The majority of cells were neutrophils, with few lymphocytes and occasional eosinophils. No leukocytoclasis and no features of vasculitis, such as extravasation of erythrocytes or fibrinoid changes, were detected. The epidermis showed a small subcorneal pustule and focal spongiosis.

Dexamethasone, 0.5 mg given orally twice daily, resulted in great improvement of the skin lesions within 1 week. The dose was tapered after 1 month. It was then realized that during the dexamethasone therapy, the painful bone episodes had become less frequent; the patient had only five episodes over a period of 6 months, and all were less severe (mild pain for 12 hours). However, there was no change in the hematologic findings. The patient’s brother (patient 2) had similar skin lesions at the age of 3 years, also sparing the palms and soles. The mother believed that they were indistinguishable from those present in patient 1). The skin lesions showed no response to antibiotics and topical steroid applications. Patient 2 had a spontaneous remission after 1 year, and the lesions have not appeared since.

**DISCUSSION**

The diagnosis of CDA type I in our patients was established by the presence of chronic mild anemia, typical bone marrow findings, and lack of response to hematonic drugs. The diagnosis of CRMO was confirmed by the chronic clinical course of exacerbations and remissions, the demonstration of increased uptake of technetium at multiple metaphyseal sites, radiologic evidence of chronic inflammatory bone changes, the bone histopathologic findings, and the failure to incriminate an etiologic pathogen. However, the clinical course of CRMO in these children seems to have been far more aggressive than that previously described, with a frequency of one to three relapses a month. Furthermore, the age at onset was also earlier than that previously described, except that the two patients reported by Meller et al. were first examined at the age of 18 months. The diagnosis of Sweet syndrome in patient 1 was confirmed by the fulfillment of the two major and two of the four minor criteria proposed for the diagnosis of Sweet syndrome. Although we have not seen the skin le-
sions of patient 2, who is the brother of patient 1, we have little doubt about the diagnosis; the mother believed that the skin lesions were indistinguishable. The lack of response to the same treatment given to patients 1 and 2, the sparing of the palms and soles, and the spontaneous disappearance of the lesions without scarring after a year also support the diagnosis.

The association of CRMO with Sweet syndrome tempted Edwards et al. to speculate that CRMO may represent another clinical manifestation of Sweet syndrome. Similarly, the association of CRMO with other skin disorders, including psoriasis vulgaris and palmoplantar pustulosis, suggested to King et al. that CRMO may be a seronegative spondyloarthropathy similar to Reiter disease and psoriatic arthropathy, in which skin lesions and periostial lesions occur. Both CRMO and Sweet syndrome have been reported to follow acute infections after a latent period. The association of CRMO and Sweet syndrome in this family strongly suggests that CRMO and Sweet syndrome may be interrelated. The response of CRMO to systemic corticosteroids in one of our patients is in agreement with another report. However, the response to naproxen in the two other patients is not in agreement with other reports.

Congenital dyserythropoietic anemia type I is an autosomal recessive disorder, whereas CRMO and Sweet syndrome are disorders of unknown cause not known to segregate in families. In this family, the association of CDA, CRMO, and Sweet syndrome in two siblings, and of CDA and CRMO in their cousin, suggests that an inherited tendency to develop CRMO and Sweet syndrome may segregate along with CDA because of consanguinity. This may possibly account for the early onset and aggressive nature of CRMO in these three related children and for the occurrence of Sweet syndrome, which is mainly a disease of adults, in the two young brothers. Another alternative is that this inherited tendency to develop CRMO and Sweet syndrome is an integral part of the CDA. If so, it may be that CDA in this family represents a new entity hematologically similar to CDA type I. In favor of this conclusion is the finding of microcytosis in these children, instead of the macrocytosis usually seen in CDA type I.

REFERENCES