Painful Lower Extremities Related to Diaphyseal Dysplasia: Genetic Diagnosis and Treatment

To the Editor:

Camurati-Engelmann disease (CED) is an autosomal-dominant condition, initially described by Cockayne in 1920[1]. Camurati was the first to suggest the hereditary component in 1922, when he reported a rare symmetrical osteitis of lower limbs in a father and son and several others in a total of 4 generations[2]. Later, Engelmann reported a case with muscular wasting and important bone involvement[3]. The disease begins in an age span between 3 months and 50 years old, with higher prevalence in males. It is characterized by progressive cortical expansion, sclerosis, and symmetrical hyperostosis affecting the diaphyses of the long bones[4,5]. We describe a case of CED in a female patient with lower limb pain with progressive worsening and difficult diagnosis.

A 37-year-old woman from Manaus, Brazil, was referred for investigation of a 5-year history of fatigue, headache, and pain in both legs, worsening over the preceding year, that had not responded to a variety of analgesics. The initial investigation included the following: normal blood count, erythrocyte sedimentation rate 15 mm/h (ESR; normal 0 to 20); rheumatoid factor 47 II/ml (normal 10 IU/ml), C-reactive protein 10.3 mg/dl (normal < 8 mg/dl), a negative antinuclear factor, alkaline phosphatase 111 U/l (normal 38–126 U/l); serum calcium was 8.7 mg/dl (normal 8.4–10.6), ionized calcium 1.42 (normal 1.2–1.6), urinary calcium 421 mg/24 h (normal 200), inorganic phosphorus 2.8 mg/dl (normal 2.5–4.5), parathyroid hormone 62 pg/ml (normal 7–53); and negative Bence-Jones proteins and normal urinary sediment.

Radiographs of both lower limbs showed cortical thickening at the diaphyses, the medium third of the tibias, and distal third of the right and left middle femur causing obliteration of the medullary cavity (Figure 1); these alterations were confirmed by computed tomography (CT; Figure 2). Radiographs of the forearms were normal. Bone scintigraphy revealed asymmetrical increased uptake in the tibias, femurs, and humerals (Figure 3A, 3B). Biopsy of the tibias and right femur revealed typical osteoclasts, and osteoblasts distributed in a circle, compatible with hyperostosis and absence of malignancy. Examination revealed proximal muscle weakness in her lower limbs, with absence of muscular atrophy. Her gait was normal. The neurological and systemic examinations were normal and musculoskeletal examination confirmed pain at legs and knees, without arthritis. She had used nonsteroidal antiinflammatory drugs (NSAID), with improvement of clinical symptoms. Repeated laboratory tests were normal. Ophthalmological examination and audiometry were normal. Chest radiograph, head CT, and abdominal ultrasound scans were unremarkable. The clinical findings and characteristic radiological appearance led to the diagnosis of CED. It was decided to initiate prednisone 40 mg/day and maintain symptomatic medications. The molecular genetic investigation showed G653A; R218H mutations in exon-4 of the ß-TGF1 gene, located in chromosome 19q13, confirmed the diagnosis of CED. The symptoms improved over the next few months with the use prednisone.

CED, or progressive diaphyseal dysplasia, is a rare autosomal-dominant inherited bone disease (prevalence 1/1,000,000) with variable penetrance, typically presenting in childhood[6]; however, cases in adults have been described[7]. All races and both sexes are affected[8]. Hyperostosis is bilateral and symmetrical, usually at the diaphyses of long bones, especially the tibia, femur, fibula, humerus, radius, and ulna[8].

The pathogenic mechanism underlying the sclerosing bone phenotype in patients with CED is increased transforming growth factor-ß1 (TGF-ß1) signaling as a result of disturbed activation or secretion of the mutant protein[9,10]. The responsible gene has been identified on chromosome 19q13[11-13]. Experimental results suggest the existence of 2 mechanisms of increased TGF-ß1 activity in CED, depending on the underlying mutation. In the first, illustrated by the R218C, H222D, and C225R mutations in exon 4 of TGF-ß1, secretion is normal, but the percentage of active TGF-ß1 is elevated[9]. In the second mechanism, illustrated by the LLL12-13ins and Y81H mutations, secretion is disturbed, leading to intracellular accumulation of TGF-ß1[9]. In our patient we found G653A and R218H mutations in exon 4 of TGF-ß1 gene, located in chromosome 19q13. However, absence of mutations in the coding region of TGF-ß1 was described, indicating the existence of at least one other form[14]. Based on the existence of mutation in the TGF-ß1 or exclusion of the TGF-ß1 gene as the site of mutation, CED is classified as type I[15] or type II[14], respectively.

Bone pain in the extremities was reported to be the most common clinical symptom (68%); other important features were waddling gait (48%), easy fatigability (44%), and generalized muscle weakness (39%), or an asymptomatic presentation[5,6]. Campos-Xavier, *et al*[10] found no obvious

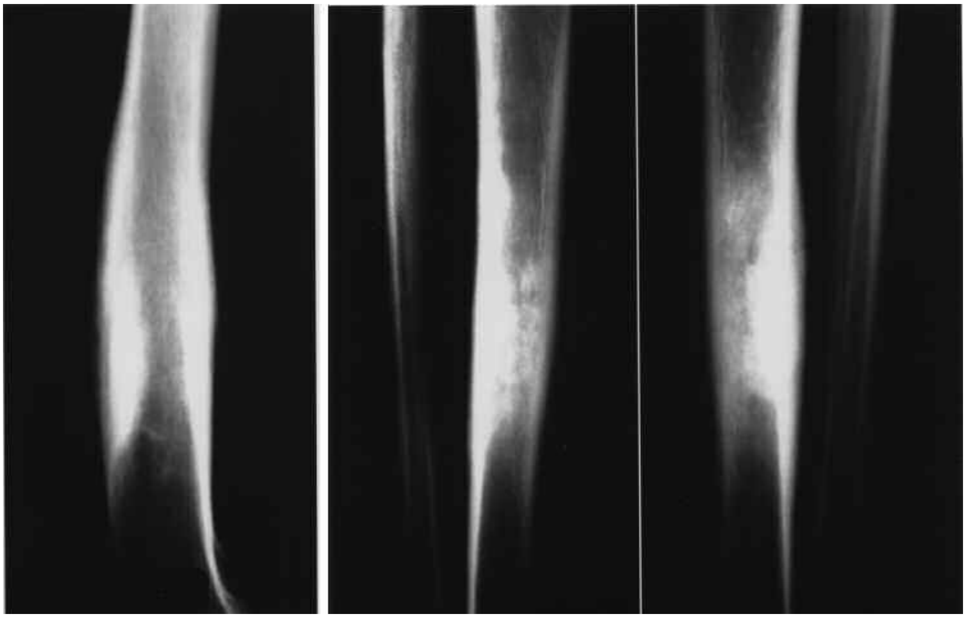

Figure 1. A and B Radiographs of both lower limbs, with cortical thickening at the diaphysis in the medium third of the tibias, medium third of the right and left femur, causing obliteration of the medullary cavity.

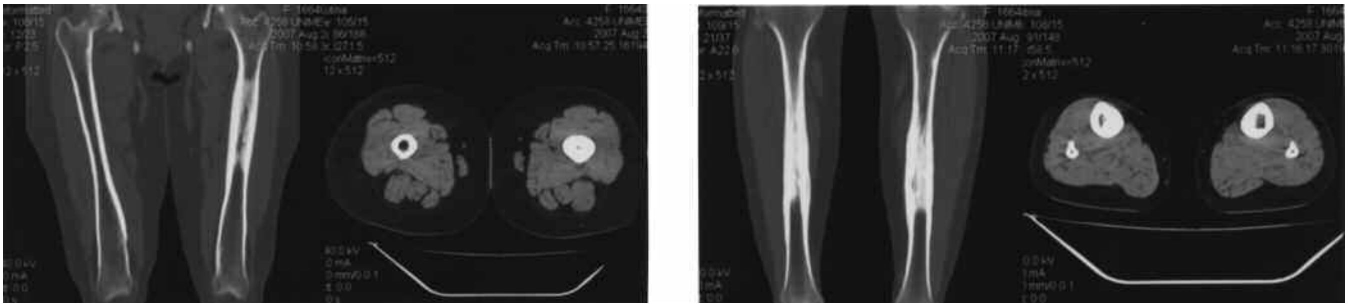

Figure 2. CT of lower limbs showing cortical thickening at the diaphysis in the medium third of the tibias, medium third of the right and left femur, causing obliteration of the medullary cavity.

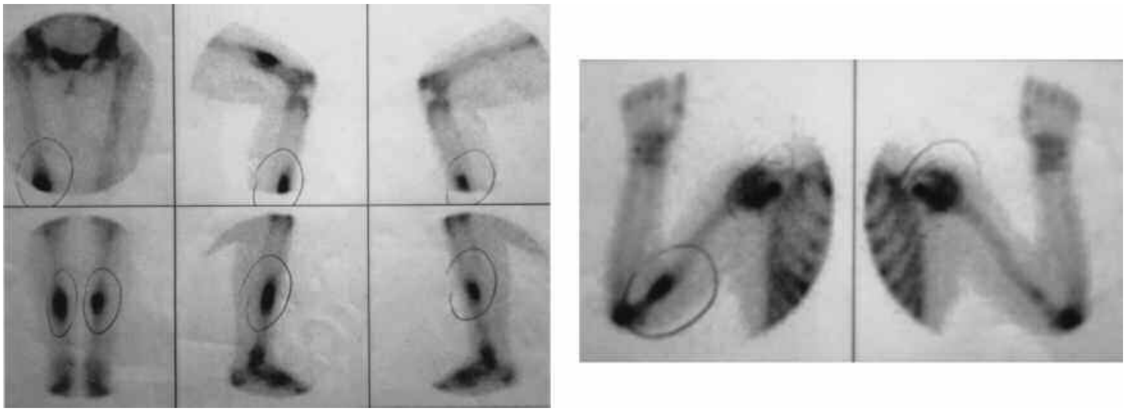

Figure 3. Bone scintigraphy revealed asymmetrical increased uptake in tibias, femurs, and humerus.

correlation between the manifestation of TGF-ß1 mutations and the severity of the clinical manifestations of CED. Laboratory findings (anemia, leukopenia, and elevated ESR) are not specific and occur occasionally[16]. Abnormal values for markers of bone resorption have been reported[17].

The radiological changes include symmetrical endosteal and subperiosteal cortical thickening, and involve primarily the diaphyses, and may extend to the metaphysis but spare the epiphyses[5,6]. Typically the long bones, especially the femur and tibia, are affected, but skull, mandible, pelvis, and vertebral involvement is recognized[5,6]. Scintigraphy examination exposed increased osteoblastic activity in the affected regions (limbs, pelvis, skull)[6].

As clinical and radiological variability is extensive, molecular analysis can provide an additional resource for a correct diagnosis[6]. Molecular genetic study was done through polymerase chain reaction and direct sequencing of the coding exons of the TGF-ß1 gene located in chromosome 19q13.

The differential diagnosis includes consideration of hereditary multiple diaphyseal sclerosis (Ribbing disease) and the group of the endosteal hyperostoses (Van Buchen, Worth, Nakamura, and Truswell-Hansen diseases)[4]. Other cranial-facial conditions resulting from osteodysplasias include Paget disease, fibrous dysplasia, especially in its pagetoid or sclerotic forms (in dysplasia there is expansion to the medullary cavity), osteogenesis imperfecta (van der Hoeve syndrome)[18], and exostosis and exuberant osteoma, among others.

There is no specific treatment for CED. NSAID such as aspirin can alleviate pain, but are ineffective at improving bone changes[6]. Corticosteroids have been reported to provide effective symptomatic improvement[16,19]. Corticosteroids are antiinflammatory and immunosuppressive agents in bone, but decrease density (1) by increasing the apoptosis rate of osteoblasts and osteocytes while suppressing osteoblast proliferation, differentiation, and bone matrix synthesis; (2) by enhancing proliferation and differentiation of osteoclast precursors; and (3) by decreasing intestinal calcium absorption. Moreover, they change the activation/expression in TGF-ß1 receptors, inhibiting the induced transcription of the gene[6]. The initial dose of prednisone is 1 mg/kg/day, with progressive tapering and maintenance at 5 to 10 mg/day. Longterm steroid therapy is not recommended due to the secondary effects, including osteoporosis. Deflazacort, a steroid with an antiinflammatory effect similar to prednisolone but with fewer adverse effects, was started in a dose of 1.2 mg/kg/day and resulted in clinical and radiological improvement within 12 months with no side effects. Deflazacort may be a safe alternative steroid therapy[20].

Biphosphonate reduced bone reabsorption, but its value in treatment of CED is disputed[6]. The use of pamidronate in CED has been reported, some reports describing worsening of bone pain[19], others describing improvement in clinical symptoms of bone pain[21].

Surgery is an alternative to drug therapy, with reaming of the medullary canal[22] or osteotomy[6]. Physiotherapy is important for increasing motor amplitudes and muscle strength[23].

In summary, CED should be considered in the differential diagnosis of nonspecific limb pain along with other musculoskeletal diseases.

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REFERENCES

1. Cockayne EA. Case for diagnosis. Proc R Soc Med 1920;13:132–6.
2. Camurati M. Di un raro caso di osteite simmetrica ereditaria degli arti inferiori. Chirurgia degli Organi di Movimento 1922;6:662–5.
3. Engelmann G. Ein fall von ostheopathia hyperostotica (sclerotisans) multiplex infantilis. Forschritte auf dem Gebiete der Röntgenstrahlen und der Nuklearmedizin 1929;39:1101–6.
4. Brat HG, Hamoir X, Matthijs P, Lambin P, Van Campenhoudt M. Camurati-Engelmann disease: a late and sporadic case with metaphyseal involvement. Eur Radiol 1999;9:159–62.
5. Vanhoenacker FM, Janssens K, Van Hul W, Gershoni-Baruch R, Brik R, De Schepper AM. Camurati-Engelmann disease. Review of radioclinical features. Acta Radiol 2003;44:430–4.
6. Janssens K, Vanhoenacker F, Bonduelle M, et al. Camurati-Engelmann disease: review of the clinical, radiological and molecular data of 24 families and implications for diagnosis and treatment. J Med Genet 2006;43:1-11.
7. Grey AC, Wallace R, Crone M. Engelmann's disease: a 45-year follow-up. J Bone Joint Surg Br 1996;78:488-91.
8. Lennon EA, Schechter MM, Hornabrook RW. Engelmann's disease. Report of a case with review of the literature. J Bone Joint Surg Br 1961;43:273-84.
9. Janssens K, Dijke P, Ralston SH, Bergmann C, Van Hul W. Transforming growth factor-1 mutations in Camurati-Engelmann disease lead to increased signaling by altering either activation or secretion of the mutant protein. J Biol Chem 2003;278:7718-24.
10. Campos-Xavier AB, Saraiva JM, Savarirayan R. Phenotypic variability at the TGF-beta-1 locus in Camurati-Engelmann disease. Hum Genet 2001;109:653-8.
11. Ghadami M, Makita Y, Yoshida K, et al. Genetic mapping of the Camurati-Engelmann disease locus to chromosome 19q13.1-q13.3. Am J Hum Genet 2000;66:143-7.
12. Janssens K, Gershoni-Baruch R, Guanabens N, et al. Mutations in the gene encoding the latency-associated peptide of TGF-beta 1 cause Camurati-Engelmann disease. Nat Genet 2000;26:273–5.
13. Vaughn SP, Broussard S, Hall CR, et al. Confirmation of the mapping of the Camurati-Engelmann locus to 19q13.2 and refinement to a 3.2-cM region. Genomics 2000;66:119-21.
14. Hecht JT, Blanton SH, Broussard S, Scott A, Hall CR, Milunsky JM. Evidence for locus heterogeneity in the Camurati-Engelmann (DPD1) syndrome. Clin Genet 2001;59:198-200.
15. Xavier ABCF, Saraiva JM, Le Merrer M, et al. Genetic homogeneity of the Camurati-Engelmann disease [letter]. Clin Genet 2000;58:150-2.
16. Crisp AJ, Brenton DP. Engelmann's disease of bone: a systemic disorder? Ann Rheum Dis 1982;41:183-8.
17. Smith R, Walton RJ, Corner BD, Gordon IR. Clinical and biochemical studies in Engelmann's disease (progressive diaphyseal dysplasia). QJM 1977;46:273–94.
18. Hamersma H. Osteopetrosis (marble bone disease) of the temporal bone. Laryngoscope 1970;80:1518-39.
19. Inaoka T, Shuke N, Sato J, et al. Scintigraphic evaluation of pamidronate and corticosteroid therapy in a patient with progressive diaphyseal dysplasia (Camurati-Engelmann disease). Clin Nucl Med 2001;26:680–2.
20. Bas F, Darendeliler F, Petorak I, et al. Deflazacort treatment in progressive diaphyseal dysplasia (Camurati-Engelmann disease). J Paediatr Child Health 1999;35:401–5.
21. Cherie-Ligniere G, Santalena G, Parafioriti A. Pamidronate in the treatment of progressive diaphyseal dysplasia (Camurati-Engelmann disease). Clin Exp Rheumatol 1999;17:264.
22. Raffaelli P, Ronzini MF. Camurati-Engelmann's disease. A case report. Ital J Orthop Traumatol 1988;14:267–71.
23. Penna V, Chung WT, Tanaka MH, Alves LA. Doença de Camurati-Engelmann. Relato de caso. Rev Bras Ortop 1998;33:239-41.

J Rheumatol 2009;36:8; doi.10.3899/jrheum.090087