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A Case Report of a 44-Year-Old Woman With Camurati-Englemann Disease

A Case Report

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Abstract

Case: A 44-year-old woman presented with easy fatigability, diplopia, dizziness, and a 2-year history of pelvic, hip, and lower extremity aching and pain. Radiograph, magnetic resonance imaging, computed tomography, and histopathologic imaging studies were obtained. Hypersclerosis of the affected bones led to the initiation of a sclerotic bone dysplasia workup and sequencing of the transforming growth factor beta 1 gene located on chromosome 19q13 revealed a heterozygous rare missense variant in exon-4, leading to a final diagnosis of Camurati-Engelmann disease (CED). Medical treatment thus far has had a minimal effect on her symptoms, and the patient continues to be followed.

Conclusions: This specific mutation has been reported only once previously in a patient with CED. This case report expands the typical phenotype associated with CED in association with the c.667T>C, p.Cys223Arg variant.

Camurati-Engelmann disease (CED), also known as progressive diaphyseal dysplasia, is caused by mutations of the transforming growth factor beta 1 (*TGFB-1*) gene which encodes for *TGFB-1* that increases peptide activity. Dysregulation of *TGFB-1* affects its role as a mediator in bone remodeling. Although TGFB-1 is a ubiquitous peptide, manifestations of the genetic mutations are mainly skeletal. Radiographs revealed that CED most often affects the long bones of the skeleton. Periosteal bone apposition and endosteal bone removal seem to be defective, leading to long bone thickening and narrowing of the medullary canal[1-3]. Clinical features include bone pain (68%), waddling gait (48%), generalized muscle weakness (39%), and easy fatigability (44%)[1]. CED can also affect the skull base and cause cranial nerve deficits because of narrowing and sclerosis of the foramina, leading to vision problems, hearing loss, and facial paresis. Cranial symptoms are often seen during an advanced stage in the progression of the disease[2].

CED is a very rare autosomal dominant bone sclerosing condition with variable penetrance that can occur *de novo* and shows anticipation in subsequent generations[4]. The age of onset varies and has been reported as early as 3 months of age and as late as 50 years of age; however, generally, symptoms occur in adolescence[1]. Laboratory findings can include anemia, leukopenia, elevated alkaline phosphatase, and elevated erythrocyte sedimentation rate[1,5].

We describe a case of CED that presented to orthopaedic surgery with diffuse bone pain and after a diagnostic odyssey was found to have a unique variant of the *TGFB-1* gene. This mutation is extremely rare and has only been described once before in the literature[4].

Institutional review board approval was obtained, and the patient provided informed consent for the studies.

The patient was informed that data concerning the case would be submitted for publication, and she provided informed consent for the study approved by the Institutional Review Board at the University of California, Irvine.

Case Report

A 44-year-old Venezuelan woman presented to orthopaedic surgery with a 2-year history of pelvic, hip, and lower extremity aching and pain. As a child, she had persistent lower extremity pain that was interpreted as growing pains. At the age of 18 years, she was diagnosed with dermatomyositis based on a muscle biopsy and electromyographic study. She also had a rash on her face and anterior chest which had fluctuated. She was treated with 16 mg of methylprednisolone for 3 years that were tapered off over 2 years. She remained in remission until the age of 42 years when she developed fatigability and diplopia mainly on left lateral gaze and 2 months later on right lateral gaze. She was hospitalized, and extensive laboratory, acetylcholine

Disclosure: The **Disclosure of Potential Conflicts of Interest** forms are provided with the online version of the article (http://links.lww.com/JBJSCC/B152).

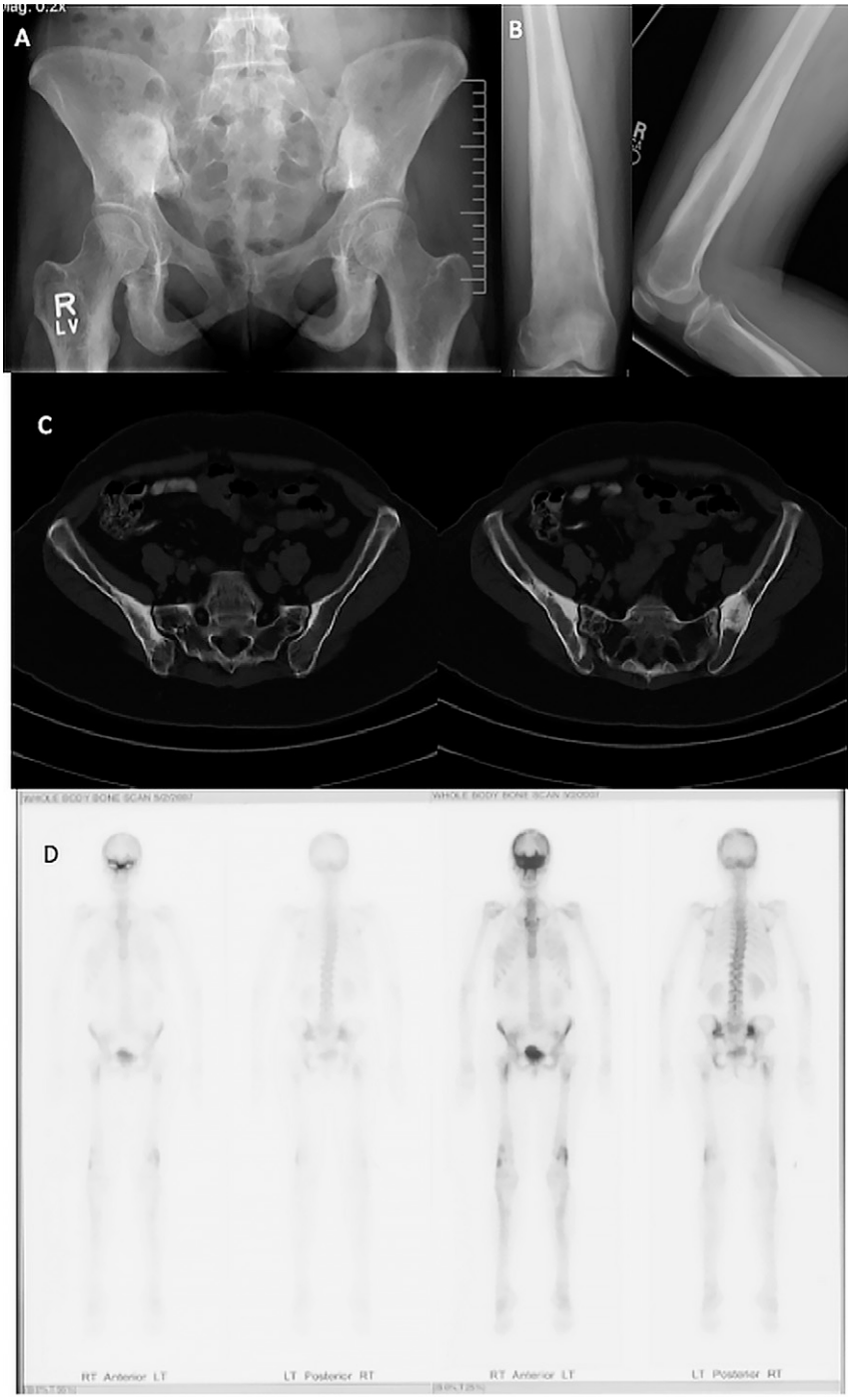

Fig. 1

Fig. 1-A AP pelvis. Sclerosis in bilateral ilium and proximal femurs. **Fig. 1-B** AP and lateral of right distal femur. There is an increased density of the cortex in the distal femur with an Erlenmeyer-Flask shape. **Fig. 1-C** CT scan pelvis. Reveals areas of trabecular irregularities and sclerosis in bilateral iliac bones. **Fig. 1-D** Bone scan. Grade III signal in anterior cranial fossa, proximal, and distal femurs. AP = anteroposterior; CT = computed tomography.

receptor antibody titers, and brain imaging (computed tomography [CT], magnetic resonance imaging [MRI] and angiogram) results were unremarkable. She continued having fatiguability, muscle stiffness, and weakness going up stairs or with any strenuous activity. Her medical history also included hypertension, hypercholesteremia, gastritis, migraines, and polymyositis. On presentation, she reported diplopia and dizziness. She denied constitutional symptoms such as fever, night sweats, or recent weight loss. She was seen by numerous specialists in rheumatology, neurology, and endocrinology before being

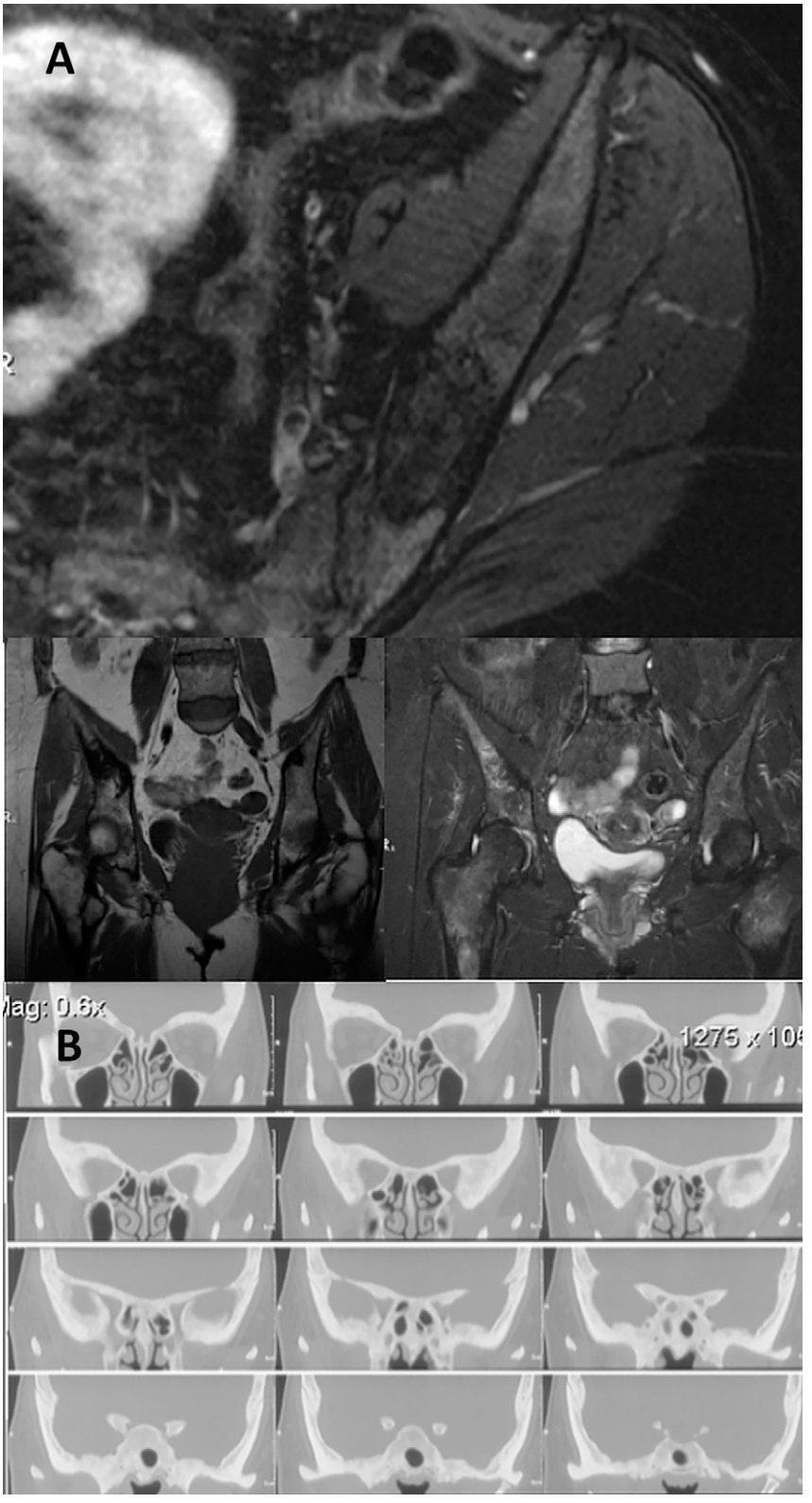

Fig. 2

Fig. 2-A MRI pelvis (axial, T2 coronal, and T1 coronal). MRI demonstrates a geographic lesion in bilateral iliac bones that does not seem locally destructive.
Fig. 2-B CT scan orbits. CT demonstrates hyperostosis of frontalis internus and cranial fossa thickening. CT = computed tomography and MRI = magnetic resonance imaging.

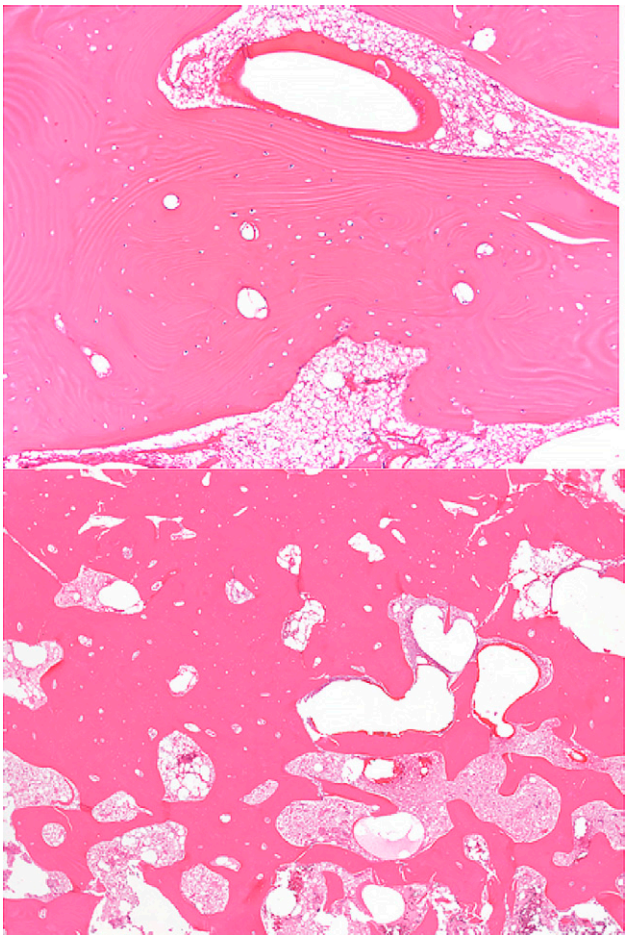

Fig. 3

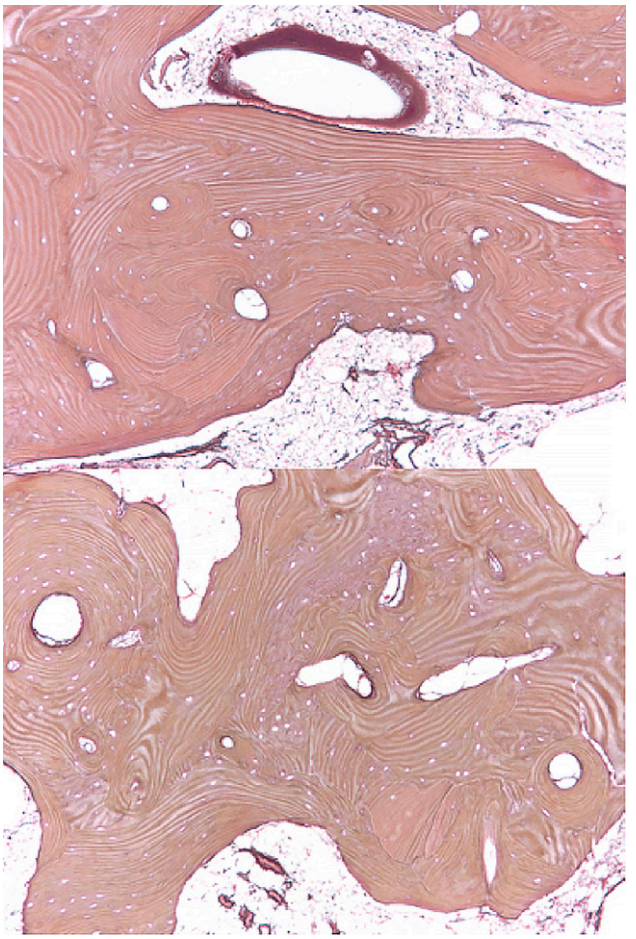

Fig. 4

Fig. 3 Biopsy hematoxylin and eosin stain. Thickened cortical and cancellous bone. The trabeculae contain haversian-like systems. **Fig. 4** Biopsy reticulin stain. This stain highlights the units of lamellar bone and small foci of woven bone.

evaluated by orthopaedic surgery. Initial diagnosis by orthopaedic surgery was polyostotic disease of uncertain etiology in the pelvis and bilateral femurs.

Family history revealed that her father had died when she was young. Her sister had similar symptoms, and 2 of her 3 children had begun to complain of bone pain. Evaluation by genetics led to their participation in our research studies.

Physical examination revealed an alert, oriented woman. Her cranial nerves were intact without nystagmus. She had full strength of all extremities with a normal gait, normal deep tendon reflexes, and no sensory deficits. Hip range of motion revealed flexion to 100° and internal rotation to 15°. Hip motion was without pain, and impingement signs were negative. Full examination of her lower extremity showed no palpable soft-tissue masses.

Imaging studies included radiographs of the pelvis and bilateral lower extremities, bone scan, scan CT of pelvis and orbits, and MRI of the pelvis and brain (Figs. 1 and 2). Radiographs revealed hyperostosis and cortical thickening in bilateral proximal and distal femurs. Both distal femurs demonstrated an Erlenmeyer-flask shape (Figs. 1-A and 1-B). Radiographs and CT revealed hyperostosis and cortical thickening in bilateral posterior ilia (Figs. 1-A and 1-C). Bone scan displayed increased activity in the anterior cranial fossa, bilateral posterior ilia, proximal, and distal femurs (Fig. 1-D). MRI of the pelvis showed marrow edema within the proximal femoral diaphysis, extending into the femoral neck at the level of the lesser trochanter with diffuse cortical thickening (Fig 2-A). Radiographs of the hands and feet revealed thickening of proximal phalanges and metatarsal cortical thickening. CT of the orbits revealed a thickened appearance of the frontal facial bone indicating hyperostosis frontalis internus and thickening of the base of the skull (Fig 2-B). Brain MRI revealed normal brain architecture except for cranial base thickening. Laboratory studies revealed elevated alkaline phosphatase, liver enzymes, and cholesterol. She was found to be anemic with decreased vitamin D levels. Thyroid hormones were normal, and analysis for heavy metals was negative.

Bilateral posterior iliac crest bone biopsies were performed using a Michel needle, and the biopsy of the posterior iliac crest lesion showed localized sclerosis of the medullary cavity with abundant lamellar and focal woven bone that had a

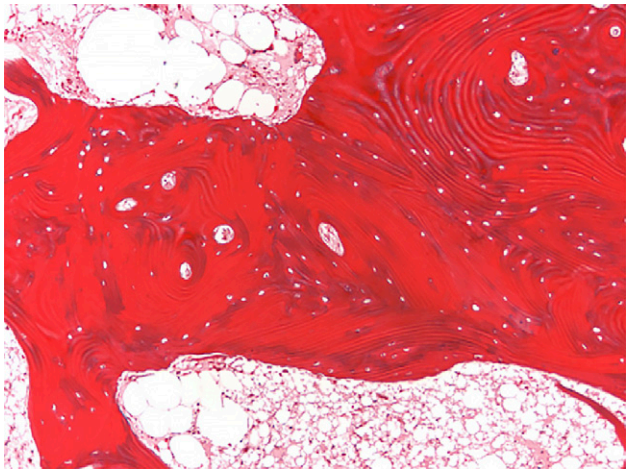

Fig. 5
Biopsy trichrome stain.

cortical-like pattern, focal marrow fibrosis, and mild chronic inflammation (Figs. 3 through 5). There was thickened cortical and cancellous bone with the trabeculae containing Haversian-like systems. Initial treatment included standard doses of nonsteroidal anti-inflammatories (NSAIDs), naproxen 500 mg 2 times daily orally as required, tramadol 50 mg once daily, and 650 mg acetaminophen, and 100 mg propoxyphene tablets sparingly for pain, sertraline 50 mg daily for depression, metoprolol 100 mg daily for hypertension, and standard bisphosphonates for presumed Paget disease of bone. Unfortunately, these did not provide significant relief. She continued to have worsening diplopia, craniocervical pain, depression, and diffuse musculoskeletal pain in her extremities.

Molecular Testing

All 7 coding exons and adjacent messenger RNA (mRNA) splice sites of the *TGFB-1* gene were amplified by polymerase chain reaction and sequenced as previously described[6]. A heterozygous missense mutation (c.667T>C, p.Cys223Arg) in exon 4 of *TGFB-1* was identified (Fig 6).

Discussion

Camurati-Engelmann disease is a rare disease associated with bone dysplasia mainly affecting the skull and the diaphyses of the long tubular bones associated with mutations in the *TGFB-1* gene. This case is unique in that the presentation was relatively late in life and the symptoms delayed.

Our case is unique also in that it reveals the heterozygous missense mutation (c.667T>C, p.Cys223Arg) in exon 4 of TGFB-1 as the cause of this patient's CED. This mutation has only been mentioned once previously in the literature[4]. Kinoshita et al. found 2 novel TGFB1 mutations in 2 Japanese families, c.667T>C (C223R) and c.667T>G (C223G) both at nt 667, these variants being associated with classic CED.

Once a diagnosis of CED is made, the initial evaluation should include full neurologic and cranial examinations, complete skeletal survey, bone scan, complete blood count (CBC), erythrocyte sedimentation rate (ESR), hearing screen, and ophthalmologic evaluation. If acute bone pain is present, ESR and a bone scan may be helpful to assess disease activity. Exacerbations in disease activity may correlate with an increase in bone scan activity.

Reflecting on this case, the patient history and the finding of bone pain for extended periods should have triggered consideration of CED. The transition from imaging studies to a genetic study should be initiated much earlier during patient care allowing for physicians to monitor the patient through regular screenings to assess disease progression on diagnosis. CED is known to be progressive and can threaten the ability to see and walk normally as the disease progresses.

Currently, there is no known cure for CED. Treatment options involve symptomatic control of pain with corticosteroids and NSAIDs[1,3,7]. Several investigators have reported

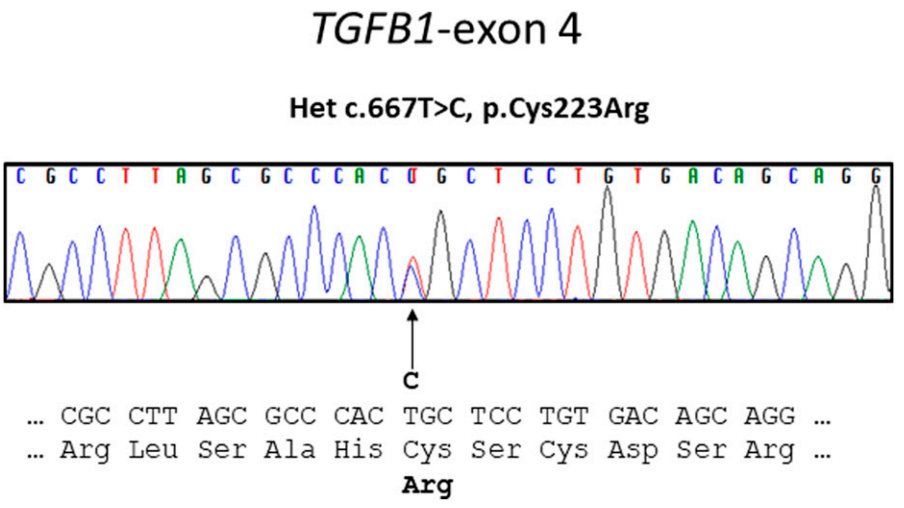

Fig. 6
GFB1 mutation as requested in Dec 2019. Chromatogram showing the c.667T>C change in the proband and carrier daughter that was not seen in unaffected relatives.

success with corticosteroids by reducing pain and weakness while improving gait, exercise tolerance, and flexion contractures in addition to correcting anemia and hepatosplenomegaly[7]. Craniectomy is a potential management technique to alleviate compressive cranial nerve symptomology, yet little research has been performed on improving diffuse skeletal pain.

Bisphosphonates have also been shown to reduce bone reabsorption; however, several authors have shown conflicting outcomes in CED from administration of bisphosphonates, ranging from subtle improvements to worsening of bone pain[1,8]. Another current treatment option is losartan, which has anti-TGFB-1 effects. It may be helpful in patients who cannot tolerate corticosteroids or as an adjunct in patients using corticosteroids who have concomitant hypertension[9,10], although as far as we know, no studies exist evaluating the effectiveness of losartan for the treatment of CED. All of the current standard treatments indicated failed to offer substantial symptom relief in our patient.

This case report offers insight into a novel *TGFB-1* gene variant associated with Camurati-Engelmann disease[2]. It details the presentation, diagnosis, current standard of care in medical practice today, and approaches to treatment and their efficacy of this rare sclerotic disease. Traditional methods of treating the symptoms of CED did not offer substantial relief in this patient, which may be attributable to her specific variant. Limitations of the study include the rarity of this disorder and the report of only 1 other case in the literature with the same variant. This case report expands the typical phenotype associated with CED in association with the c.667T>C, p.Cys223Arg variant. ■

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