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Case Report

Camurati-Engelmann Disease Complicated by Hypopituitarism: Management Challenges and Literature Review of Outcomes With Bisphosphonates

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ABSTRACT

Background: Camurati-Engelmann disease (CED) is a rare bone dysplasia characterized by diffuse diaphyseal osteosclerosis. Skull base involvement in CED can result in hypopituitarism but is seldom reported. Our objective was to report a patient with acquired hypopituitarism due to CED and assess the management challenges.

Case Report: A 20-year-old boy presented with lower limb pain. He had walking difficulty in childhood, which was diagnosed as CED and managed with prednisolone. He later discontinued treatment and was lost to follow-up. Current re-evaluation showed short stature (−3.6 standard deviation), low weight (−4.3 standard deviation), and delayed puberty with delayed bone age (13 years). He was found to have secondary hypogonadism (luteinizing hormone level, 0.1 mIU/mL [1.7-8.6 mIU/mL]; follicle-stimulating hormone level, 1.0 mIU/mL [1.5-12.4 mIU/mL]; and testosterone level, 0.087 nmol/L [9-27 nmol/L]), growth hormone deficiency (low insulin-like growth factor I level, 120 ng/mL [226-903 ng/mL] and peak growth hormone level of 7 ng/mL on insulin-induced hypoglycemia), and secondary hypocortisolism (cortisol level, 105 nmol/L [170-550 nmol/L] and adrenocorticotropic hormone level, 6 pg/mL [5-65 pg/mL]). Serum prolactin level was normal (8.3 ng/mL [5-20 ng/mL]), and he was euthyroid on levothyroxine replacement. Magnetic resonance imaging revealed a partially empty sella. Sanger sequencing revealed a missense mutation (p.R218C/c.652C>T) in exon 4 of the *TGFβ1* gene. The patient was treated with zoledronate, losartan, and oral prednisolone and continued on levothyroxine and testosterone replacement, which resulted in symptomatic improvement.

Discussion: The index case manifested severe CED requiring multimodality therapy. Later, he developed combined pituitary hormone deficiencies, which were managed with thyroid and gonadal hormone replacement with the continuation of glucocorticoids. The partial efficacy of bisphosphonates in CED has been reported in the literature.

Conclusion: Skull base involvement in CED can lead to structural and functional hypopituitarism as a result of intracranial hypertension.

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Abbreviations: CED, Camurati-Engelmann disease; SD, standard deviation; TGFβ1, transforming growth factor β1.

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Introduction

Camurati-Engelmann disease (CED) is a rare sclerosing bone dysplasia characterized by increased osteoblast function due to a gain-of-function mutation in the *TGFβ1* gene.[1] The hallmark of this disease is a symmetrical diaphyseal involvement of the long and flat bones. Progressive disease may cause compressive cranial neuropathies and result in visual or auditory compromise, and rarely, brainstem herniation due to the skull base involvement.[2] Hypopituitarism has seldom been described in CED but warrants recognition as it has management implications.[2]

The optimum treatment of CED is not clear. Glucocorticoids, nonsteroidal anti-inflammatory drugs, bisphosphonates, and transforming growth factor β1 (*TGFβ1*) inhibitors (losartan) have been used for its treatment.[3-6] However, evidence with each of these agents is equivocal.[4-6] Glucocorticoids and nonsteroidal anti-inflammatory drugs can offer transient clinical relief. Bisphosphonates have been used in these patients but with conflicting results. However, due to their long retention in the bone matrix and potential dual action in suppressing the accelerated bone turnover and as anti-osteoporotic therapy in cases managed with long-term glucocorticoids, they deserve more attention.

Herein, we describe a case of genetically confirmed CED, with complications including hypopituitarism, papilledema, and hypoacusis due to the skull base involvement. We also review the outcomes with the use of bisphosphonates hitherto available in the literature.

Case report

The patient was a 20-year-old boy who was seen in the endocrinology clinic for bony pain in the lower limbs. His first medical consultation was at the age of 3 years when he was evaluated for complaints of difficulty in walking and getting up from a seated position. On examination, proximal myopathy and waddling gait were present, whereas anemia, hepatosplenomegaly, bony deformities, and dentition abnormalities were absent. Family history was significant for treated acromegaly in his father and diabetes in his mother, but no similar complaints as seen in the boy were reported. Initial investigations showed normal hemogram, calcium, inorganic phosphate, and alkaline phosphatase. Radiographs showed diffuse osteosclerotic lesions in the long bones and skull base (Fig. 1). A presumptive diagnosis of CED was made, and the boy was initiated on oral prednisolone (1 mg/k.), calcium, and cholecalciferol, resulting in clinical (improved gait and reduced pain) and scintigraphic improvement. The patient was then lost to follow-up for 8 years. During this period, he reported intermittent intake of nonsteroidal anti-inflammatory drugs and/or glucocorticoids. At the age of 12 years, he was initiated on thyroid hormone replacement for hypothyroidism elsewhere (thyroxine level, 9.6 μg/dL [4-12 μg/dL], thyroid-stimulating hormone level, 18 μIU/mL [0.2-4.2 μIU/mL], and thyroid peroxidase negative [<34 IU/mL]). On assessment at 16 years of age, he had a short stature (−3.6 standard deviation [SD]), low weight (−4.3 SD), delayed puberty (axillary and pubic hair absent with bilateral testicular volume of 3 mL), and delayed bone age (13 years). He also had a Marfanoid habitus, frontal bossing, bilateral proptosis, dilated veins over the forehead, and generalized wasting. Visual acuity, fields, and fundi were normal. Body composition analysis by dual-energy x-ray absorptiometry showed a low overall fat mass (16.3%), specifically in the trunk and lower limbs. Dual-energy x-ray absorptiometry for bone mineral density showed a Z-score of +1.6 SD at the femoral neck, −0.7 SD at the lumbar spine, and −0.4 SD for the whole body (headless). He was euthyroid on levothyroxine replacement (75 μg/day) but was found to have secondary hypogonadism (luteinizing hormone level, 0.1 mIU/mL [1.7-8.6 mIU/mL]; follicle-stimulating hormone level, 1.0 mIU/mL [1.5-12.4 mIU/mL]; and testosterone level, 0.087 nmol/L [9-27 nmol/L]), growth hormone deficiency (low insulin-like growth factor I level, 120 ng/mL [226-903 ng/mL]) and peak growth hormone level of 7 ng/mL on insulin-induced hypoglycemia), and secondary hypocortisolism (cortisol level, 105 nmol/L [170-550 nmol/L] and adrenocorticotropic hormone level, 6 pg/mL [5-65 pg/mL]). Serum prolactin level was normal (8.3 ng/mL [5-20 ng/mL]). Contrast-enhanced magnetic resonance imaging revealed a partially empty sella with the flattening of the anterior pituitary (Fig. 1). The patient was treated with zoledronate and initiated on losartan 25 mg, followed by oral prednisolone (1 mg/kg/day) 6 weeks later. This led to a significant reduction in limb pain over the next 6 months. Glucocorticoid tapering was attempted, but the patient was unable to tolerate it because of the re-emergence of lower limb aches and pains. He was also prescribed testosterone at a monthly dose of 100 mg administered intramuscularly. On re-evaluation at 18 years of age, ophthalmologic assessment showed papilledema, and pure tone audiometry showed a mixed pattern of bilateral hearing loss. Contrast-enhanced computed tomography of the head showed significant calvarial thickening and expanded craniofacial bones with narrowed bilateral optic and auditory canals (Fig. 1). Bisphosphonate therapy (pamidronate 90 mg over 3 days) was re-administered with calcium supplementation. On follow-up at 20 years of age, his only complaint was mild heaviness in the legs, which was relieved with prednisolone 2.5 mg daily. He did not have headache, visual, or hearing deficits. Repeat calcium profile was normal, but accelerated bone turnover was persistent (Supplementary Fig. 1) as was the extensive disease on scintigraphy (Fig. 2). Details of follow-up are summarized in Supplementary Table 1. This was managed by repeat bisphosphonate therapy (zoledronate 4 mg infusion) without any adverse effects.

Genetic analysis involved polymerase chain reaction amplification followed by Sanger sequencing, which revealed a mutation p.R218C/c.652C>T in exon 4, a hotspot of the *TGFβ1* gene, on chromosome 19q13 (Fig. 3). The parents of the index patient were not his biologic parents.

Discussion

The index case represents a severe form of a rare sclerosing bone dysplasia complicated by skull base involvement and intracranial hypertension, resulting in hypopituitarism. The patient had multiple anterior pituitary hormone deficiencies that required replacement. Imaging revealed a partially empty sella, consistent with the diagnosis of hypopituitarism. Hypoacusis, headache, and rarely, cranial neuropathies are described in CED, especially in those with skull base osteosclerosis, but hypopituitarism is seldom reported. Nevertheless, this must be borne in mind while dealing with these patients to optimize the management of hormone deficiency.

CED or progressive diaphyseal dysplasia is an eponymous disorder characterized by bilateral symmetrical hyperostosis involving the appendicular skeleton. Limb pain is the usual presenting symptom, whereas progression can result in skull base thickening and cranial neuropathies affecting vision, hearing, and rarely, deglutition. Other osteosclerotic diseases include juvenile Paget disease, Kenny-Caffey syndrome, and osteopetrosis. Juvenile Paget disease results from a genetic defect in the osteoprotegerin gene (*TNFRSF11B*) and is characterized by diffuse initial resorption followed by compensatory bone formation. Kenny-Caffey syndrome (infantile cortical hyperostosis) occurs due to genetic defects in the collagen gene (*COL1A1*) and manifests as hyperostosis in the mandible, clavicle, scapula, skull, ilium, or long bones.

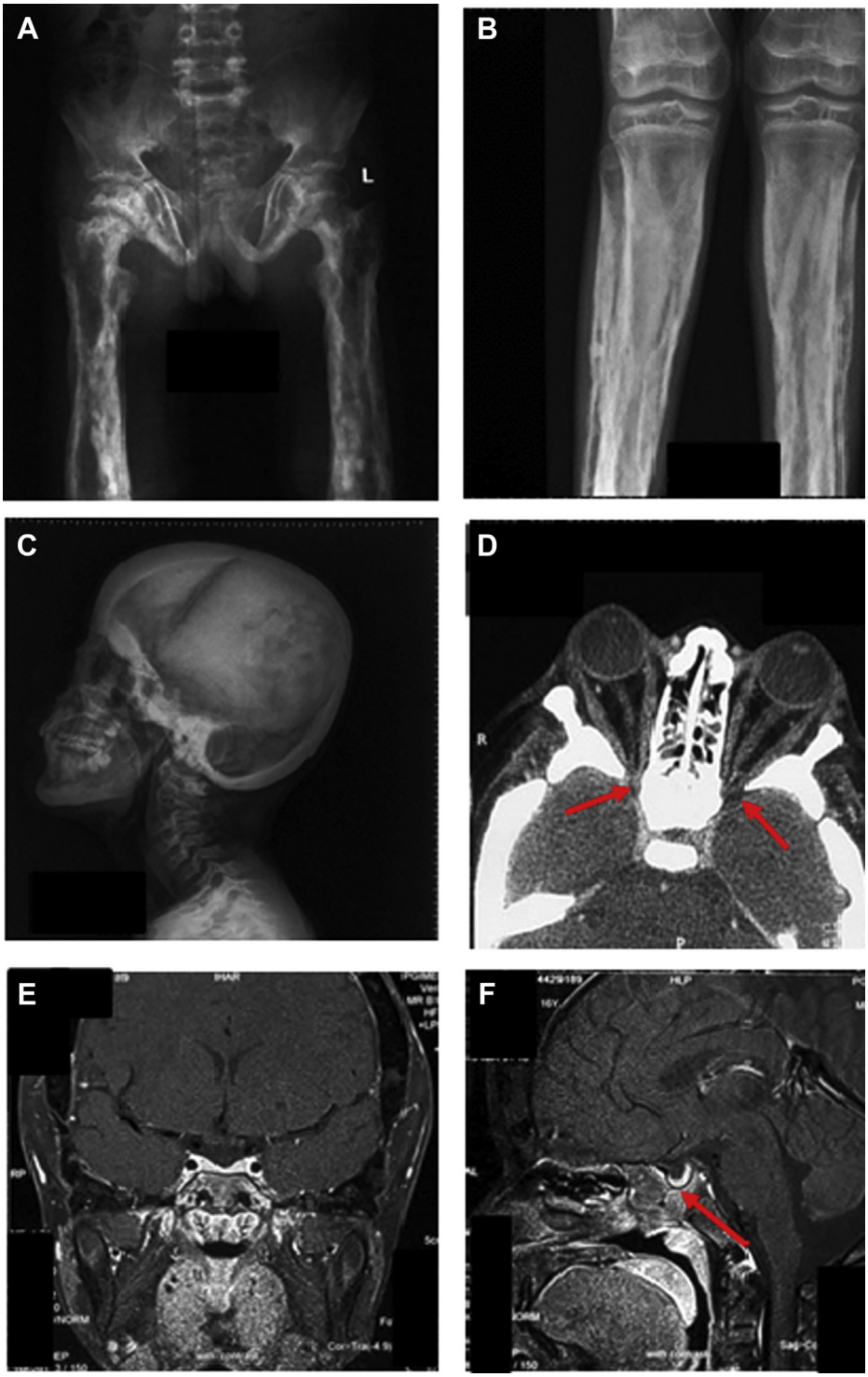

Fig. 1. Panel of photographs. The top panel depicts the thickening and cortical sclerosis of the diaphysis of the long bones of the lower limbs on x-ray (*A* and *B*). The middle panel shows diffuse calvarial thickening and skull base osteosclerosis on lateral x-ray of the skull (*C*), and computed tomography head axial sections depict contracted optic canals bilaterally (red arrows) (*D*). The bottom panel shows typical flattening of the pituitary gland with partially empty sella on coronal (*E*) and sagittal (*F*) sections (red arrow) of gadolinium-enhanced magnetic resonance imaging as a consequence of intracranial hypertension due to skull base involvement.

Osteopetrosis is caused by defective osteoclastic resorption, leading to sclerotic, brittle bones. These disorders lack the preferential diaphyseal involvement of the long bones as well as the skull base involvement seen in CED.

Hypopituitarism is an exquisitely rare complication of CED, with very few reports describing hypothalamo-pituitary hormone deficiencies.[7-9] Hypothalamic amenorrhea in a young female, secondary hypogonadism with hyperprolactinemia, and primary hypothyroidism have been described earlier.[7-9] In a review by the Mayo clinic (n = 306), skull base involvement was reported in 56.5% of patients radiologically, but less than half of these were symptomatic.[2] Hypoacusis, headache, exophthalmos, and frontal bossing were the

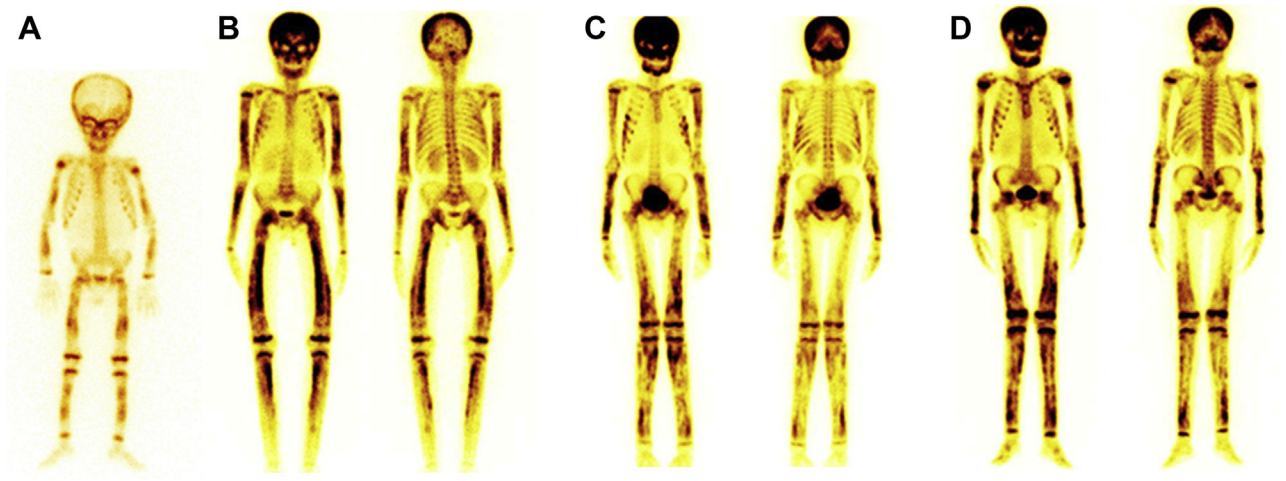

Fig. 2. Panel of photographs showing sequential technetium-99m methyl diphosphonate–labeled triple-phase bone scans of the index patient. *A*, Increased uptake bilaterally in the long bones, including the humerus, femur, tibia, forearm bones, and skull, including the supraorbital ridges and frontal regions; the left parietal region of skull; and the metacarpals, and irregular uptake in the lumbar spine at baseline (at the age of 3 years). *B, C, D,* Subsequent scans performed at 16, 18, and 20 years of age showing reduced, diffuse, and bilateral symmetric uptake in long bones and skull.

most common manifestations. Our patient had skull base osteosclerosis, causing optic and auditory canal stenosis. However, the hearing loss was subclinical, diagnosed only by pure tone audiometry, with a mixed (both conductive and sensorineural) pattern. Cranial neuropathies and brainstem compression were uncommon. However, hypopituitarism was sparingly described in the study.[2]

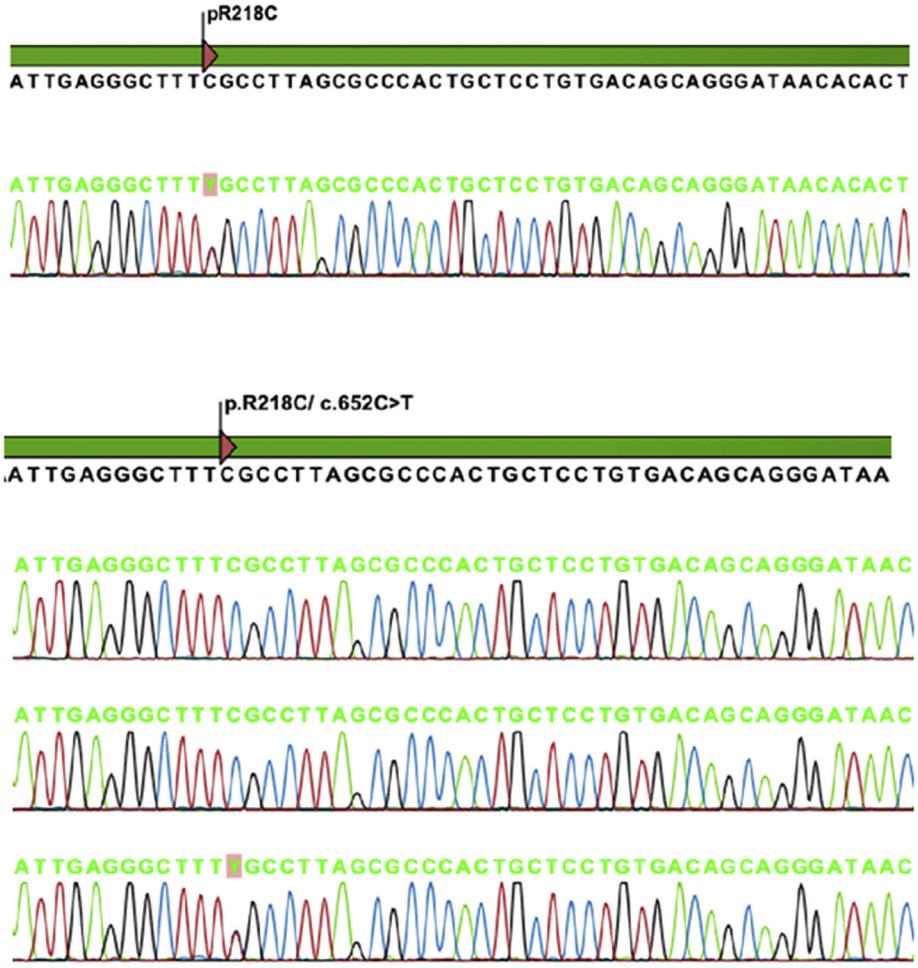

Fig. 3. Chromatogram of the patient. The top panel depicts a missense mutation showing p.R218C/c.652C>T in exon 4, a mutational hotspot of the *TGF-β* gene on chromosome 19q13 detected on PCR amplification, followed by direct whole-exome sequencing.

Table
Review of Literature of Various Bisphosphonates Used in the Management of CED with Assessment of Clinical, Biochemical, Radiologic, and Scintigraphic Efficacy

Author/year	Age (years)/sex	Agent used, dose	Clinical improvement	Radiological improvement	Scintigraphic improvement	BTMs	Comments
Di Carlo et al/2016[13] (TGFβ1 mutation -ve)	45/F	Neridronate, 100 mg every 3 months Given 5 doses	No (VAS) Tolerable pain	No (persistent bone marrow edema on MRI)	Not assessed	Not assessed	Multiple diaphyseal sclerosis Positive response to corticosteroids but stopped due to hyperglycemia
Savoie et al/2013[14] Heterozygous missense mutation c.466C>T; NP 000651.3: p.R156C	52/F (age at symptom onset—33 years)	Pamidronate 90 mg every 2 months, 5 doses Zoledronate 5 mg every year, 3 doses	No	Not assessed	Not assessed	Not assessed	Initially reaming of the tibia done Better clinical response to methylprednisolone boluses Partial relief with NSAIDs
Savoie et al/2013[14] Heterozygous missense mutation c.466C>T; NP 000651.3: p.R156C	47/F (age at symptom onset—43 years)	Zoledronic acid 5 mg	No	Unchanged	Unchanged	Not assessed	No response to methylprednisolone infusions No response to Anakinra
Iba et al/2008[15] (LAP domain of TGFβ1)	17/F (age at symptom onset—6 years)	Oral alendronate 5 mg daily, 1 month	Yes (significant)	Increase in BMD, No other structural change assessed	Not available after treatment	Increased serum OC, BSALP, serum, and urine NTX at baseline Reduction in VAS correlated with a reduction in BTMs	Early (within 1 month) and sustained (within 2 years) response
Iba et al/2008[15] (LAP domain of TGFβ1)	23/M (age at symptom onset—19 years)	Alendronate 5 mg daily, 3 months	Yes (significant)	Not assessed	Not assessed	Raised urine NTX, BSALP	Elder brother of the previous case
Castro et al/2005[6] (genetic analysis NA)	33/F (symptomatic since 5 years of age)	Alendronate 40 mg daily + prednisolone 20 mg daily started simultaneously, 6 months Clodronate 1800 mg every 6 months	No	No change with clodronate	Increased uptake at baseline No reduction in disease activity following 6 months of alendronate	Increased ALP Normalized following alendronate	Tibia bone biopsy-apposition, no inflammatory changes Failed 2 bisphosphonates Offered NSAIDs, opioids
Castro et al/2005[6] (genetic analysis NA)	24/F (symptomatic since childhood)	Deflazacort 12 mg daily + Risedronate 20mg daily Changed to oral alendronate 40 mg daily Changed again to clodronate 600 mg daily for 3 consecutive days 2 months later, alendronate was reintroduced and continued for other reasons (osteopenia and continuation of steroids)	Transient clinical improvement followed by worsening of pain	Not assessed	Increased uptake at the same/ previously involved sites	Not assessed	Unsatisfactory response to NSAIDs, analgesics No response to 3 different bisphosphonates attributed to severe and extensive disease by the authors
Inaoka et al/2001[16] (genetic analysis not done)	27/F (diagnosed at the age of 11 years)	Pamidronate 60 mg every alternate week, 5 doses (already on prednisolone 25 mg for 16 years) Restarted on corticosteroids (dexamethasone 2.5 mg daily for 2 weeks, followed by prednisolone)	Increase in pain	Not assessed	Increased tracer uptake at involved regions	Increased BSALP	No response to pamidronate Improvement (clinical and scintigraphic) with corticosteroids
Rubin et al/1995[17] (genetic analysis not done)	17/F	Pamidronate 100 mg daily	Reduction in pain, improved gait and strength	Not assessed	No changes in scintigraphy	High BTMs at baseline Reduction	-

Table (*continued*)

Author/year	Age (years)/sex	Agent used, dose	Clinical improvement	Radiological improvement	Scintigraphic improvement	BTMs	Comments
Bondestam et al/2007[18] (652C > T in exon 4 resulting in R218C)	10/M (symptomatic since the age of 4 years)	Prednisolone (tapered over 7 months) Pamidronate 1 mg/kg on 3 consecutive days every 4 months) For osteoporosis and ongoing steroid therapy	Not assessed as not used for the disease but for the side effects of therapy	Not assessed	Not assessed	Not assessed	Performed bone histology and histomorphometry showing reduced trabecular volume
Baroncelli et al/2017[4]	19/F	Prednisolone Zoledronic acid (at 0.02 mg/kg) every 4 months for 7 doses	Almost complete resolution of pain, improvement in gait	Improvement in diaphyseal thickening and cortical sclerosis	Not assessed	Reduced osteocalcin, BSALP, P1NP, CTX	Marfanoid habitus
Baroncelli et al/2017[4]	4/M	Neridronic acid 1 mg/kg every 4 months for 4 doses, stopped due to no response and started on Zoledronic acid (0.015-0.018 mg/kg), 4 cycles for 18 months	No improvement with neridronate, improvement with zoledronic acid	Improvement in bone lesions 2 years after the discontinuation of zoledronic acid	Not assessed	Reduced osteocalcin, BSALP, P1NP, CTX	Marfanoid habitus
Uehara et al/2020[19]	66/F (diagnosed previously [exact duration NA])	Alendronate for 3 years Denosumab 60 mg once every 6 months	Not assessed	Not assessed	Not assessed	Reduced BAP, NTX, Trap5b	Denosumab given for osteoporosis in CED and fragility fractures Improvement in BMD No hypocalcemia
Current study/2021 (TGFβ1 mutation p.R218C/c.652C>T in exon 4)	20/M (diagnosed since childhood but under regular follow-up since the age of 16 years)	Zoledronate 4 mg Discontinued due to symptomatic hypocalcemia Given 5 mg dose a year later Pamidronate 90 mg over 3 days Zoledronate 5 mg dose	Not significant Could not taper steroids Relief with steroids Concurrent Losartan	No	Increased uptake at same sites Additional sites also involved	Increased P1NP, CTX	Additionally assessed other aspects of disease activity including fat and muscle mass Continued on testosterone and thyroid replacement and prednisolone 10mg for disease

Abbreviations: ALP = alkaline phosphatase; BMD = bone mineral density; BSALP = bone specific alkaline phosphatase; BTM = bone turnover markers; CED = Camurati-Engelmann disease; CTX = cross-linked telopeptide of type I collagen; LAP = latency associated peptide; MRI = magnetic resonance imaging; NA = not applicable; NSAID = nonsteroidal anti-inflammatory drug; NTX = N-terminal cross linked telopeptide of type I collagen; OC = osteocalcin; P1NP = procollagen type 1 N-terminal propeptide; VAS = visual analogue scale.

The reasons for hypopituitarism are multiple and include skull base osteosclerosis causing small sella, intracranial hypertension leading to pituitary compression, the putative effect of *TGFβ1* on multiple endocrine organs (the pituitary, thyroid, and gonads), or low body mass index and fat mass that leads to hypogonadism. TGFβ1 is a multifunctional cytokine with an inhibitory role in germ cell proliferation and Leydig cell steroidogenesis, besides inhibiting human chorionic gonadotropin–mediated testosterone production at high concentrations.[7-9] The other possible reason is the proximity of the *LH* gene to the *TGFβ1* gene (both on chromosome 19q). Interestingly, the more common pattern of hypogonadism that has been described is of pituitary origin (secondary), irrespective of glucocorticoid use. Similarly, *TGFβ1* has been associated with the development of primary autoimmune hypothyroidism and is a regulator of prolactin. However, the index patient demonstrated secondary hypothyroidism with negative thyroid peroxidase antibody titers, thereby favoring intracranial hypertension as the cause for secondary hypogonadism, hypocortisolism and normal prolactin levels. Our patient had low fat mass (average, 17.4% [20%-25%]) but not as low as previously described in association with hypogonadism (<10%). The most plausible reason for his hypopituitarism was skull base osteosclerosis and intracranial hypertension (as proven by the radiology and papilledema).

CED is the result of gain-of-function mutations in *TGFβ1*, most commonly affecting the latency-associated peptide, which results in the overactivation of *TGFβ1*.[10] Our patient harbored a missense mutation in the *TGFβ1* gene on exon 4 p.R218C/c.652C>T of chromosome 19. This mutation is previously described in another Indian family.[5] However, these individuals were not related, and this observation reflects the high frequency of this particular mutation.[1] *TGFβ1* is released from the matrix after osteoclastic resorption and stimulates the proliferation and differentiation of osteoblast precursors besides inhibiting osteoclast differentiation. This makes CED an osteosclerotic bone remodeling disease. Bone turnover markers procollagen type 1 N-terminal propeptide and cross-linked C-telopeptide of type I collagen are elevated, as documented in our patient and in prior studies.[11] Observations of low body fat (globally as well as in lower limbs) and muscle mass in our patient can be attributed to the inhibitory effect of *TGFβ1* on adipogenesis and myogenesis.[1]

Our patient had nonremitting disease, requiring multiple drugs including prednisolone (steroid-dependent), losartan, and bisphosphonates. The management of CED is highly variable, ranging from the use of glucocorticoids, *TGFβ1* inhibitors (losartan), and bisphosphonates to anti-TNFα therapy, denosumab, and bone-targeted delivery of TGFβ1 receptor inhibitors more recently.[3-6,12] The creation of a surgical window is marred by a high chance of failure due to persistent bony overgrowth. Our patient was unwilling for surgical reaming. Anti–TNFα therapy was planned, but a positive Mantoux test dismissed its use. There are no randomized controlled trials comparing the efficacy and safety of bisphosphonates and glucocorticoids. These are the 2 most frequently used therapies in the management of CED, despite contrasting effects on the skeleton. Glucocorticoids cause *TGFβ1* resistance by inhibiting

its intracellular signaling, whereas bisphosphonates target the accelerated bone turnover.[4,5,8] Available evidence is equivocal regarding bisphosphonates, with some studies showing benefit while others not replicating these results (Table).[4,6,19,13-19]

Conclusion

CED complicated by hypopituitarism is a rare entity. Both structural and functional hypopituitarism can occur in CED due to multiple reasons, especially in those with skull base osteosclerosis. This is an under-reported complication and must be borne in mind while dealing with these patients.

Ethical Approval and Informed Consent

All procedures performed involving human participants/patients were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Author Contributions

L.D. drafted the manuscript and performed clinical assessment as well as the follow-up of the patient. V.D. recorded and retrieved the data. P.D. oversaw patient management and edited the manuscript. A.S. provided the scintigraphic expertise. M.P. provided the radiological expertise. W.V.H. performed the genetic analysis and edited the manuscript. S.K.B. conceived the study, performed clinical assessment, supervised patient management, and edited the manuscript. All authors have reviewed and accepted the final version of the manuscript.

Disclosure

The authors have no multiplicity of interest to disclose.

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