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CASE REPORT

Treatment of refractory bone pain with intravenous lidocaine, ketamine and magnesium sulfate in a patient with Camurati-Engelmann Disease. Case report

Tratamento de dor óssea refratária com lidocaína, cetamina e sulfato de magnésio por via venosa em paciente portadora da Doença de Camurati-Engelmann. Relato de caso

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ABSTRACT

BACKGROUND AND OBJECTIVES: Camurati-Engelmann Disease (CED) or Progressive Diaphyseal Dysplasia is a rare genetic syndrome, characterized by progressive periosteal and endostal hyperostosis mainly in bone diaphysis. CED can presents intense pain that is difficult to control with conventional treatment using corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs), which may be secondary to diaphyseal hyperostosis and narrowed medullary canal, and in most severe cases, there is a need surgical decompression. The aim of this study was to report the case of a patient diagnosed with CED, in whom sympathetic venous blockade (SVB) was performed by intravenous infusion of lidocaine, ketamine and magnesium sulfate associated with opioids to treat severe chronic pain refractory to several usual treatment methods, bringing to light new therapeutic proposals for pain in this rare disease.

CASE REPORT: A female patient, 38 years old, diagnosed with CED at 16 years old, with intense chronic widespread pain, functional limitation and previous unsuccessful treatments. She underwent a serial intravenous infusion of lidocaine, ketamine, and magnesium sulfate associated with opioid use, resulting in a significant reduction in pain intensity, improvement in physical limitation and increasing the interval between pain attacks. This report is unprecedented, with no previous description of this therapeutic approach to control pain in this disease.

CONCLUSION: Treatment with intravenous infusion of lidocaine, ketamine and magnesium sulfate associated with opioid can be a safe option for treating refractory pain related to CED.

KEYWORDS: Carmurati-Engelmann syndrome, Chronic pain, Lidocaine, Opioid analgesics, Rare diseases.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A Doença de Camurati-Engelmann (DCE), ou Displasia Diafisária Progressiva, é uma síndrome genética rara, caracterizada por hiperostose progressiva periostal e endostal, principalmente nas diáfises dos ossos. A doença pode cursar com quadro álgico de difícil controle, mesmo em vigência de tratamento convencional com corticosteroides e anti-inflamatórios não esteroides (AINES), secundariamente à hiperostose diafisária e redução do canal medular, sendo necessária, nos casos mais graves, a descompressão cirúrgica. O objetivo deste estudo foi descrever o caso de uma paciente com diagnóstico de DCE, tendo sido realizado o bloqueio simpático venoso (BSV) através de infusão por via venosa de lidocaína, cetamina e sulfato de magnésio associado ao uso de opioide para tratar o quadro de dor crônica intensa e refratária aos diversos tratamentos experimentados, trazendo à tona novas propostas terapêuticas álgicas para essa doença rara.

RELATO DO CASO: Trata-se de uma paciente do sexo feminino, 38 anos, com diagnóstico de DCE aos 16 anos de idade, portadora de quadro álgico crônico intenso generalizado, limitação funcional e tratamentos anteriores sem sucesso. Foi submetida a BSV seriado semanal, associado ao uso de opioide, resultando em importante redução na intensidade da dor, melhora da limitação física e aumento do intervalo entre as crises. Este relato é inédito, não havendo descrição anterior dessa associação terapêutica para o controle da dor.

CONCLUSÃO: A associação do bloqueio simpático venoso ao uso de opioide pode ser uma opção segura de tratamento da dor refratária causada pela DCE.

DESCRITORES: Analgésicos opioides, Doenças raras, Dor crônica, Lidocaína, Síndrome de Camurati-Engelmann.

HIGHLIGHTS

- Patient with Camurati-Engelmann disease, a rare syndrome with severe pain in the upper limbs, lower limbs, spine, face and headache, with no response to conventional treatment with corticosteroids and non-steroidal anti-inflammatory drugs
- Pain relief with weekly sympathetic venous blockade associated with opioid
- A new perspective on pain relief

INTRODUCTION

Camurati-Engelmann disease (CED), or Progressive Diaphyseal Dysplasia, is a rare bone metabolism disorder of autosomal dominant genetic inheritance. This syndrome belongs to the craniotubular hyperostosis group and is characterized by progressive and symmetrical endosteal and periosteal bone formation, mainly in the diaphysis of the long bones, determining cortical thickening, diaphyseal widening and narrowing of the medullary canal[1-5]. This disease has variable penetrance and can affect several members of a family or be an isolated case[1,2]. The most frequent clinical manifestations are pain in the affected limbs, sometimes disabling, a wobbly (myopathic) gait, proximal muscle weakness and easy fatigue.

CED is caused by a mutation in the gene encoding the ß1 subunit of Transforming Growth Factor -TGF ß1, located on chromosome 19, an important mediator of bone remodeling, leading to an increase in the activity of this molecule and an imbalance in bone turnover. Diagnosis is based on the patient history, through characteristic clinical and radiological findings with bilateral and symmetrical diaphyseal cortical thickening. There is no specific laboratory test, and the diagnosis is complemented by genetic testing of the TGF ß1[2,4]. It is very important to include bone dysplasia as a differential diagnosis in cases of non-specific limb pain. There is no specific treatment, in general corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) are used to control the disease and pain[1-5].

The aim of this study was to report the case of a young woman diagnosed with CED when she was a teenager, faced with the challenges of treating the pain caused by the disease. SVB was performed using intravenous infusion of lidocaine, ketamine and magnesium sulfate[6-13], combined with the use of opioids[4], in the management of severe bone pain that was refractory to conventional treatment, an unprecedented therapeutic combination that had not been described before, bringing to light new therapeutic proposals against pain for this rare disease.

CASE REPORT

Initially, all clinical information was collected after authorization from the Clinical Board and obtaining the Free and Informed Consent Term (FICT). All personal data was preserved.

She is a 38-year-old female patient, cleaning assistant, daughter of non-consanguineous parents, who underwent bariatric surgery at the age of 33, body mass index (BMI): 41, with hypertension, bronchial asthma, depressive disorder, panic disorder, former alcoholic, who was diagnosed with CED at the age of 16, 11 years after the onset of pain, based on clinical and imaging findings.

The patient reported that at the age of 5 she began to suffer from intense pain in her knees and heels, described as deep, which worsened with movement, with walking being limited by the pain, requiring hospitalization for a week. She was given painkillers and later discharged without investigation.

At the age of 7, she had another episode of intense pain in her knees and ankles, making it impossible for her to walk. The diagnostic hypothesis was rheumatic fever (RF), and she was given prophylactic benzathine penicillin until the age of 14. At that time, she also began to suffer from continuous, non-articular pain in her left tibia, forearms and right hand, referred to as bone and muscle pain, which worsened with movement and exposure to cold.

At the age of 15, the hypothesis of RF was ruled out by a rheumatologist, after 2 bone biopsies were carried out on the tibia with the result of cortical bone sclerosis, and she was then referred to the Hereditary Diseases Clinic, which issued the following report:

Physical examination: good general condition, no cognitive impairment, obesity and asymmetry of the right lower limb, with a smaller diameter than the left lower limb (secondary to walking). Echocardiogram: concentric hypertrophy of the right ventricle. Abdominal ultrasound: normal. X-ray of lower limbs: periosteal/cortical thickening in tibial diaphyses, greater on the right, bilateral distal femoral diaphyseal widening. X-ray of the spine: scoliosis. Tibial biopsy: cortical bone sclerosis. Bone scintigraphy: showed marked heterogeneous radiopharmaceutical hyperuptake in the long bones of the upper limbs, lower limbs and left foot. Serum Ca^{+2}, inorganic phosphorus, alkaline phosphatase, blood count, TSH, T3 and T4, urine 1 with normal results. ASLO = normal. IGE = 992 UI/mL (normal up to 128 UI/mL), ESR = 20 mm/h (children up to 10 mm/h, women up to 20 mm/h), C Reactive Protein = 120 mg/dL (normal below 1mg/dL) and Mucoproteins = increased. Rheumatoid factor = negative, ANF = non-reactive.

After an exhaustive review, it was concluded that the most plausible hypothesis was diaphyseal dysplasia of the Camurati-Engelmann type.

The clinical history, clinical and radiological findings and bone scintigraphy led to the diagnosis of CED in 2002. Although she was assessed by the Hereditary Diseases Clinic, the genetic test was not carried out. The patient reported two other similar cases in her family, with clinical-radiological diagnoses of CED (maternal aunt and maternal grandmother's brother). The patient was followed up by Rheumatology and Orthopedics over the years.

After all this clinical history, the patient was referred to the Pain Service at the age of 38. The main complaint was chronic widespread diffuse pain, which had been difficult to manage for 12 years, with psychiatric follow-up. The patient reported constant frontal and occipital headaches, pain in the face and ear on the left, as well as intense bone and muscle pain in the arms, forearms, hands, hips, right knee, legs, ankles, back of the feet and the entire spine, which worsened with movement and exposure to cold, with no improvement factor, muscle weakness and fatigue, and severe limitations in carrying out daily and professional activities.

On physical examination, she was normotensive, with heart rate = 76bpm, Sat O_2= 96%; in a regular general state, eupneic, morbidly obese, with slow speech and no cognitive impairment. Cardiovascular auscultation was normal; pulmonary auscultation showed sparse wheezing bilaterally; abdomen was globose and painless; osteotendinous reflexes were normal; proximal strength of upper limbs and lower limbs was reduced; there was slight edema in the legs; supine feet; spine with slight scoliosis and significant limitation of extension; pain on palpation in the face, humerus, distal tibiae and spine; gait was slow and wobbly.

The patient reported a pain score on the verbal numerical scale (VNS) = 8. She was taking dipyrone, paracetamol, gabapentin

600 mg/day, cyclobenzaprine 10 mg/day, topiramate 100 mg/day, risperidone 4 mg/day, amplictil 50 mg/day, clonazepam 2 mg/day, venlafaxine OD 225 mg/day, hydrochlorothiazide 25 mg/day, oral and injectable NSAIDs and betamethasone 3 mg intramuscularly during crises.

Nuclear magnetic resonance of the lumbar spine: degenerative hypertrophy of the lumbar interapophyses, diffuse disc bulging with dural impression and foraminal bases at the L3-L4 level. Recent bone scintigraphy: heterogeneous increase in the concentration of the radiopharmaceutical to a moderate degree in the tibial diaphyses, and to a lesser degree in the skullcap, shoulders, humerus, radius, ulna, spine, sacroiliac joints, hip joints, femurs, knees and tarsal bones, bilaterally, interpreted as a diffuse increase in osteogenic activity in the segments described (Figure 1).

Recent X-rays of the upper limbs and lower limbs: cortical thickening and sclerosis in the diaphyses of the long bones, with stenosis of the medullary canal (Figures 2 and 3).

The skull X-ray was unchanged, although the scintigraphy showed that the skullcap was affected (Figure 4).

As a treatment for the relevant pain, SVB was proposed, consisting of lidocaine 2 mg/kg, ketamine 0.1 to 0.3 mg/kg, MgSO4 10% 1-2 g, weekly, without limiting the number of sessions, administered on an outpatient basis with an infusion pump for two hours, under multiparametric monitoring.

In addition to the sessions, she was prescribed buprenorphine patch 10 mg, the dose of gabapentin increased to 900 mg/day, and she was referred to physiotherapy and hydrotherapy when she came out of the acute phase. There was a significant improvement in diffuse pain in the first cycle with 3 sessions. The VNS went from 8 to 4, with moderate pain remaining under control for 3 months. The 2nd cycle was followed by 10 sessions, with a reduction in VNS from 8 to 3 for 5 months. The patient is currently in the 3rd cycle. At the end of each session, she obtained a VNS of 0 to 2. Buprenorphine was replaced by 100 mg tramadol every 8 hours, after 6 months of use, due to the lack of distribution of the drug in the institution. With the reduction in pain, there was an improvement in the patient's mobility, who began to take short 10-minute walks (5 times a week) and started hydrotherapy sessions twice a week.

DISCUSSION

This study describes a case of a 38-year-old patient diagnosed with CED in adolescence, with clinical presentation, radiological

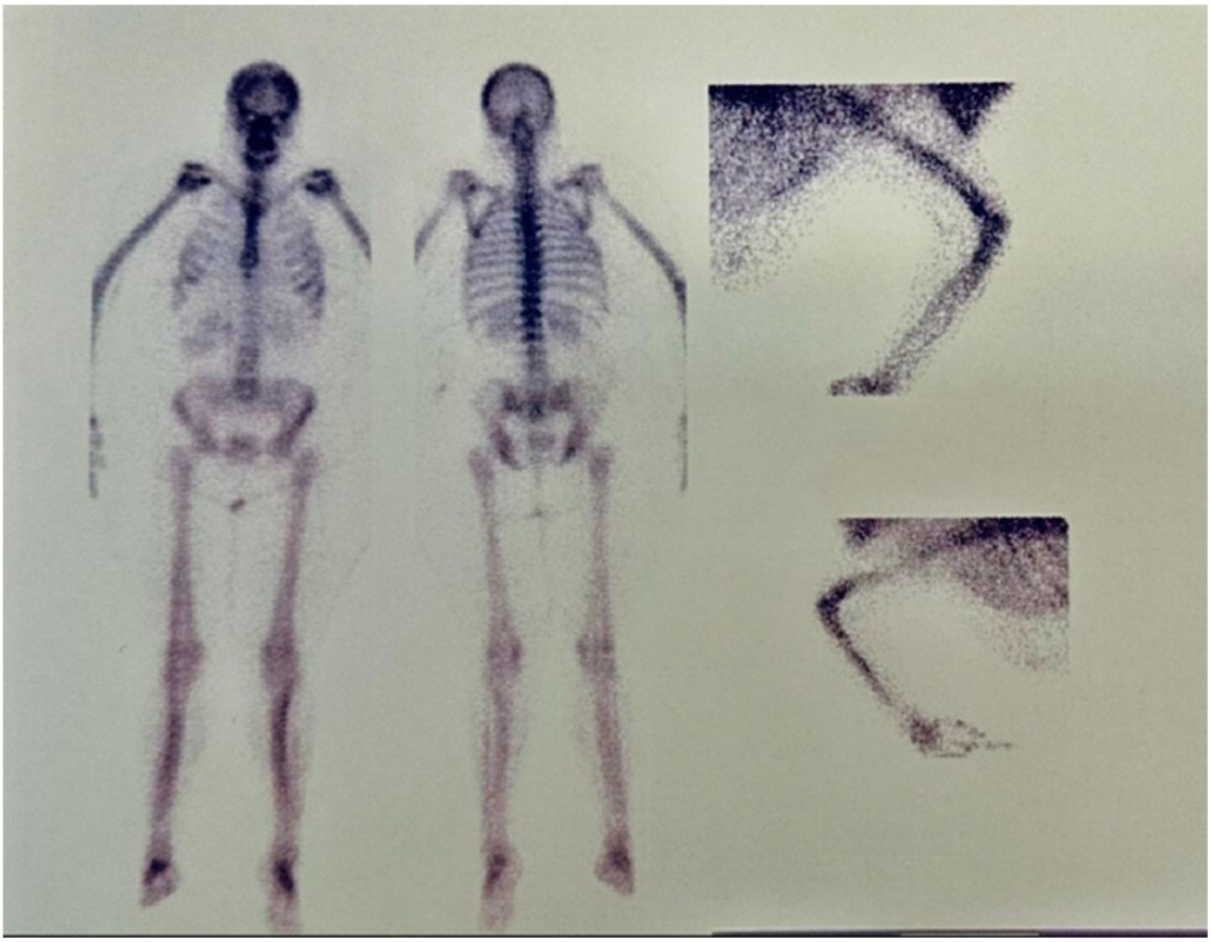

Figure 1. Bone Scintigraphic: heterogeneous and moderate increased tracer uptake in tibiae diaphyses, and lesser degree in skull, shoulders, humerus, radius, ulnae, spine, sacroiliac and coxofemoral joints, femurs, knees, and tarsal bones bilaterally. The figure detail shows the lateral side of the right and the left arm.

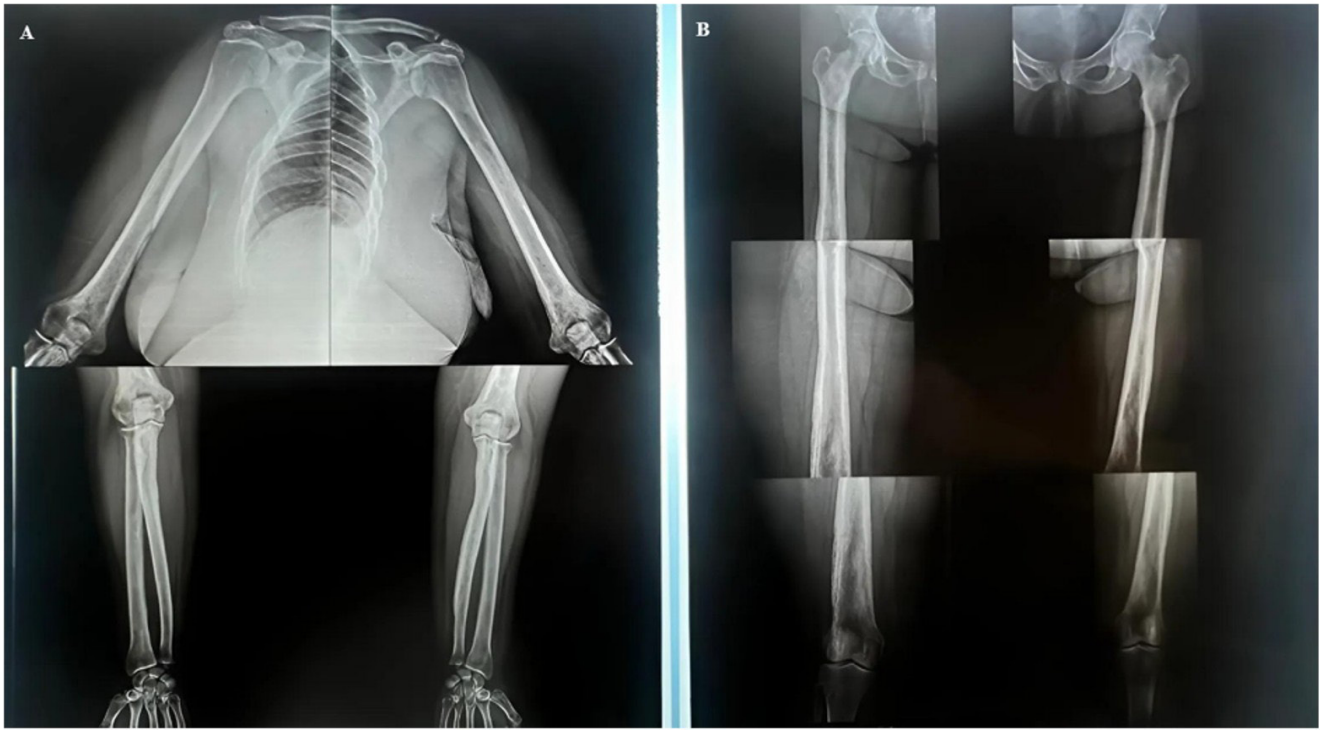

Figure 2. (A) Radiological image of upper limbs right/left (AP view) with cortical thickening and sclerosis humerus, radius and ulnae; (B) Radiological image of femora right/left (AP view) with symmetrical distribution at the cortical thickening and narrowing of femoral medullary canal.

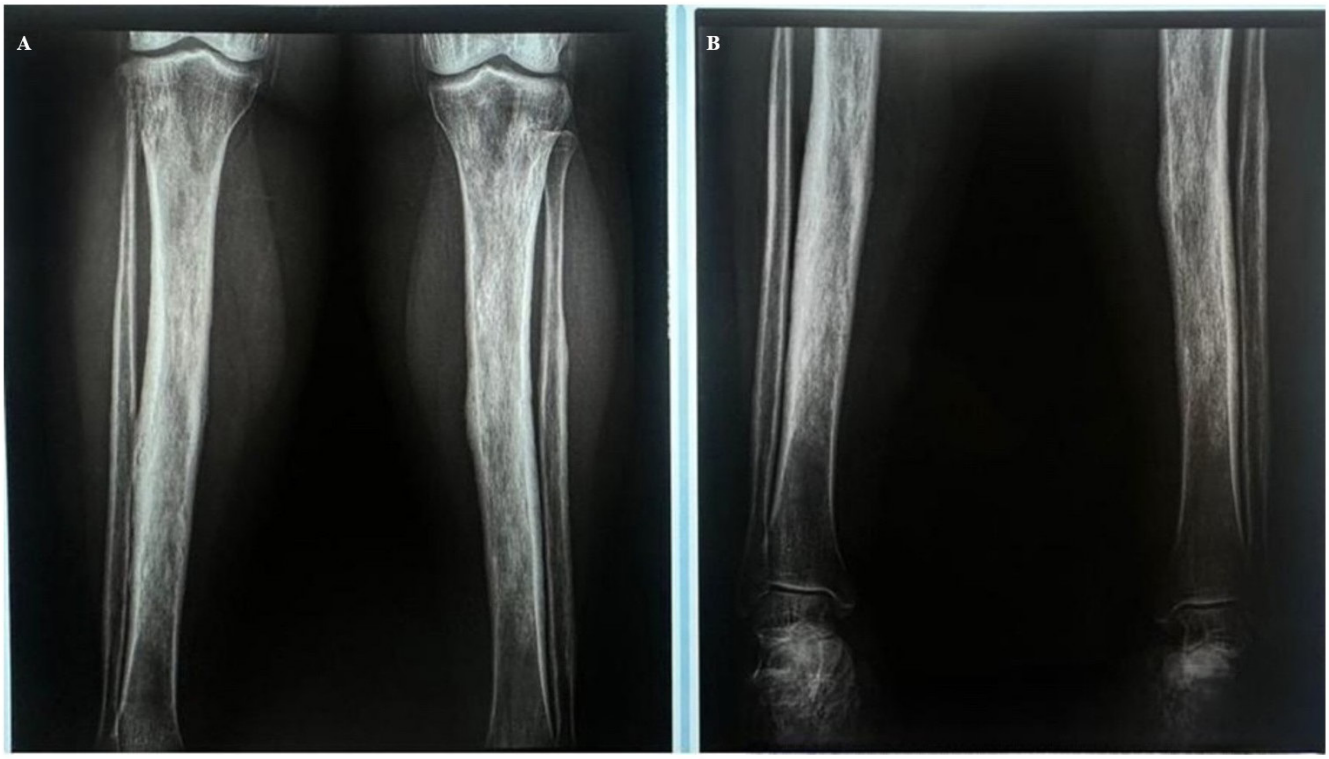

Figure 3. (A) Radiological image of tibiae and fibulae, there is cortical thickening, sclerosis and modeling defect at the tibiae diaphysis; (B) Radiological image of tibiae and fibulae, sparing distal metaphysis and epiphyses.

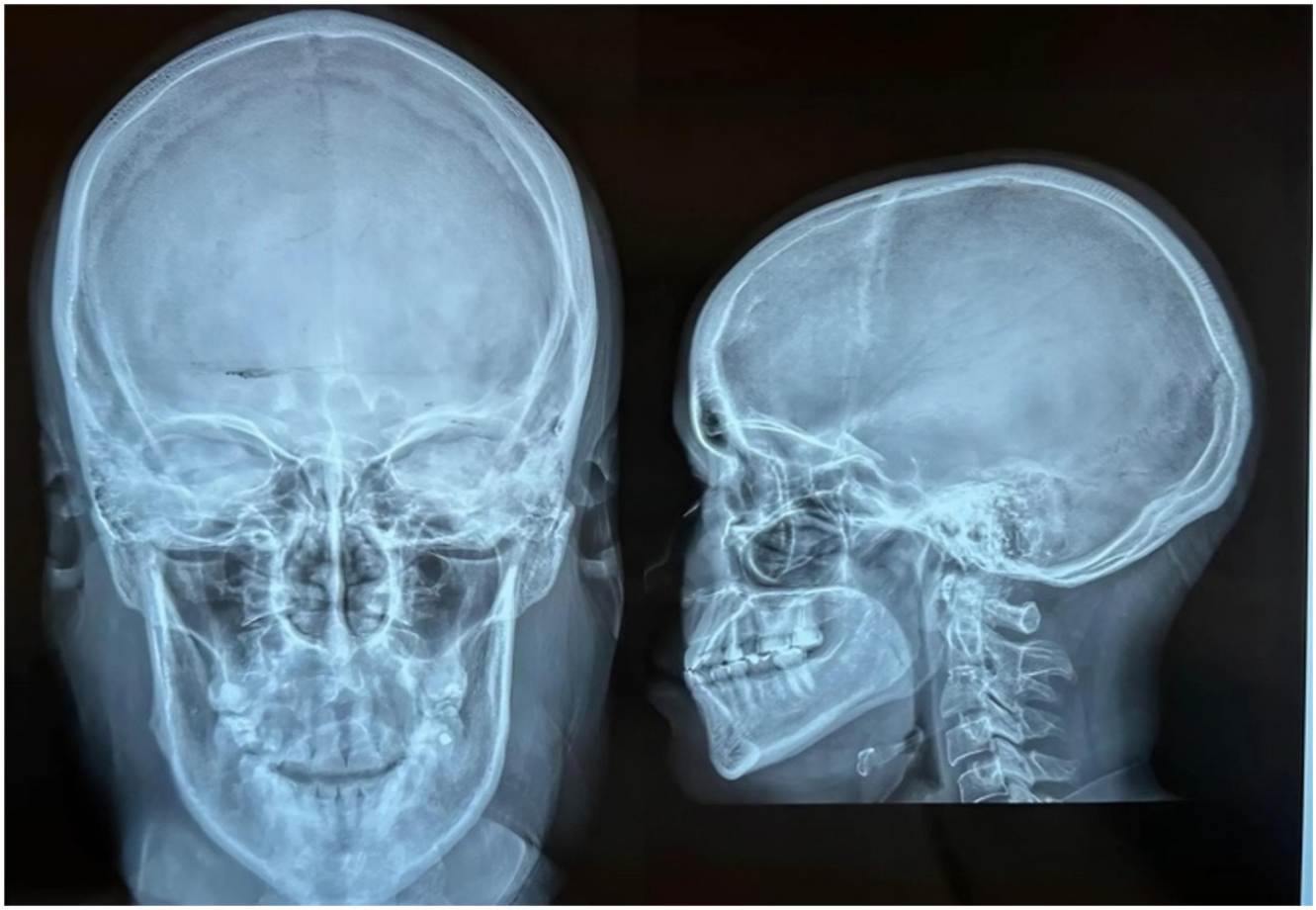

Figure 4. Radiological image of normal skull (AP view and Lateral view); although scintigraphy detected increased osteoblastic activity in the skullcap. This increase can be noticed even before sclerosis becomes visible radiologically.

and scintigraphic characteristics and difficulty in controlling the pain caused by the disease. The diagnosis was based on characteristic and specific clinical and radiological findings, according to a reference study[2,4]. She underwent a genetic evaluation which concluded that she was compatible with the disease, but without a genetic test for TGF ß1, although genetic analysis is an additional tool for confirming the diagnosis[5].

CED is a rare genetic syndrome with a heterozygous mutation, with very varied phenotypic expression, producing different clinical pictures, with just over 300 reports in worldwide literature[1,4].

CED is radiologically marked by a sclerosing bone dysplasia resulting from a mutation in a gene located on chromosome 19 that encodes TGF ß1, an important mediator of bone remodeling, producing an erroneous expression of this molecule, leading to a reduction in osteoclastic activity and an increase in osteoblastic activity, with a predominance of intramembranous bone deposition[2].

The patients have skull bones, and the diaphysis of long bones affected, sparing the metaphyses and epiphyses which are endochondral bone formation as observed in the patient of this study. The bone scintigraphy findings were useful, showing increased uptake of the radiopharmaceutical in various areas of the body, including the skull, which had a normal radiological image. Bone scintigraphy is an important method for monitoring the progression of the disease, as hyperuptake of the radioactive marker can be seen even before the sclerosis is visible radiologically[1-4].

Symptoms can begin in childhood or at any stage of life; the patient presents with bone pain often involving bilateral long bones and the skull, secondary to specific characteristic diaphyseal hyperostosis, accompanied by proximal muscle weakness, headache, altered gait and easy fatigue. The progression of the disease can also affect the metaphyses, sparing the epiphyses; there can be sclerosis of the skull base, involvement of bones such as the hip, face, jaw, rib cage, vertebrae and nerve compression[1-5]. Laboratory tests may be altered, such as alkaline phosphatase, hypocalcemia, hyperphosphatemia and increased erythrocyte sedimentation rate[3].

There is great difficulty in making the diagnosis, often leading to misunderstandings, as shown in this case, in which the patient was diagnosed and treated for RF.

It is important to make a differential diagnosis with other dysplasias who follow the course of osteosclerosis and/or hyperostosis[2-4], such as Ribbing-Fairbank disease (multiple epiphyseal dysplasia), Van Buchem disease (generalized cortical hyperostosis, mainly affecting the skull, the mandible with characteristic enlargement, clavicle, ribs and less frequently long bones), craniodiaphyseal dysplasia (generalized sclerosis, mainly of the bones of the skull and face, with facial abnormalities), polyostotic fibrous dysplasia

(replacement of bone by fibrous tissue), Paget's disease of bone and osteopetrosis (diffuse increase in bone density, affecting the epiphysis, metaphysis and diaphysis).

There is no specific treatment and pain is usually controlled with the use of corticosteroids (prednisolone at a dose of 0.5-1 mg/kg/day) and NSAIDs, and in very severe cases, surgery to decompress the medullary canal can be chosen[3,4]. Corticosteroids have a certain role in reducing bone density by reducing the proliferation, differentiation and bone formation of osteoblasts and promoting the proliferation and differentiation of osteoclast precursors[3,4], but the risks of the side effects of these drugs at long-term use should be taken into account.

There are reports in the literature on the efficacy of different drugs combined with conventional therapy in relieving bone pain, such as calcitonin as an analgesic and losartan as a TGF ß antagonist[1]. One study used a single dose of zoledronic acid 5 mg intravenously, resulting in immediate pain relief, managing to withdraw the steroid after 6 months and achieving pain remission with etoricoxib 60 mg/day[1]. Another study achieved adequate control of somatic pain persistent to conventional treatments with the use of an opioid, hydrocodone 500mg every 8 hours, in a patient with CED[4]. Pain management and physical training are essential aspects of the approach to patients with CED.

For the patient in the present study, it was decided to intervene with SVB consisting of lidocaine, ketamine and magnesium sulfate on a weekly basis, and to use opioids due to her severe chronic pain, which was intractable and physically limiting with the treatments previously tried.

SVB is a therapy used for refractory pain of various natures, nociceptive, somatic/visceral, neuropathic and nociplastic, with no previous description for the treatment of pain caused by CED[6-10]. A retrospective study investigated the effect of intravenous infusion of lidocaine with ketamine in 319 patients, with a total of 2995 infusions in patients with various types of refractory chronic pain: neuropathic pain, chronic post-surgical or chronic post-traumatic pain, primary chronic pain, cancer pain and complex regional pain syndrome, concluding that it is a safe combination, showing benefits in reducing pain in the short term and moderate reduction in the long term[10]. According to another study, ketamine and magnesium are two main antagonists of the N-methyl-D-Aspartate (NMDA) receptor, used in the treatment of post-operative pain and various acute and chronic pain conditions[13]. There are numerous theories about the mechanisms of antinociceptive action of the drugs used in SVB, as well as a broad evidence base supporting their use.

Lidocaine is a local anesthetic widely used for various purposes, such as regional anesthesia, antidysrhythmics and analgesics for peripheral and central neuropathic pain. The administration of intravenous lidocaine reflects its multifactorial mechanism, resulting from interaction with Na^+ channels and direct and indirect interaction with different receptors and nociceptive transmission pathways, although the pharmacological mechanism is still not well understood, resulting in its potential effects[6-9]. Its anti-inflammatory effects include inhibiting the production and migration of pro-inflammatory cytokines, granulocytes and the release of lysosomal enzymes. The anti-hyperalgesic effects include the modulation of NMDA receptors through an effect similar to that of glycine and a reduction in the increase in calcium-mediated excitability of central nociceptive neurons.

The inhibition of nociceptive transmission is mediated by monoethylglycinexylidide, an active metabolite of lidocaine that inhibits glycine transporter 1, leading to an increase in extracellular concentrations of glycine, an inhibitory neurotransmitter, which can reduce nociceptive transmission.

Stimulation of the descending inhibitory pathways can increase acetylcholine in the cerebrospinal fluid via muscarinic (M3) and nicotinic receptors, which can increase the activity of the descending inhibitory pathway.

In summary, lidocaine has the following characteristics: muscarinic agonist, reduced production of excitatory amino acids, reduced production of thromboxane A2, release of endorphins, reduction of neurokinins, release of adenosine triphosphate. As for central sensitization, it is suggested that lidocaine has a peripheral anti-hyperalgesic action in somatic pain and a central action in neuropathic pain, with a resulting blockade of central hyperexcitability[6-8].

Ketamine is a derivative of phencyclidine, described as a dissociative anesthetic, whose supraspinal blockade of the NR2B subunit of NMDA is considered the most important antinociceptive effect. However, the immediate analgesic effects are probably mediated by a combination of sensitization of the opioid system and antinociception through aminergic action (inhibition of serotonin and noradrenaline reuptake and their activation). The antineuropathic effects may depend on a combination of immediate action mediated by an NMDA receptor and hyperpolarization-activated cyclic nucleotide channels (HCN1), and may have anti-inflammatory effects by inhibiting the recruitment of inflammatory cells, the production of cytokines and negatively regulating inflammatory mediators[9-11].

Magnesium is the fourth most common cation in the body and the second most common intracellular ion. Magnesium is considered a non-competitive antagonist of NMDA receptors in the spinal cord, playing an important role in preventing central sensitization and attenuating established pain hypersensitivity. Magnesium has anti-inflammatory effects, reducing plasma levels of interleukin -6 (IL -6) and tumor necrosis factor alpha in the postoperative period. Magnesium has an alpha-adrenergic antagonist effect and inhibits neuroendocrine calcium secretion, which may have an impact on the nociceptive process[12,13].

The combination of intravenous lidocaine and opioids has been used to control severe pain in various cases, including cancer pain[8]. Its use in the case of this study proved to be a safe and effective option for controlling somatic nociceptive pain, offering some comfort to the patient by improving functionality and quality of life.

The drugs explained above, corroborating all the current literature on the treatment of different pain syndromes, have been properly used to treat pain in CED.

CONCLUSION

The pain of CED can be difficult to manage with the use of NSAIDs and corticosteroids. Intervention with BSV and opioids

associated with physical rehabilitation has proved to be a safe alternative for controlling somatic and mixed nociceptive pain that is refractory to conventional treatments, reducing the use and effects of these drugs, improving the patient's quality of life, prolonging pain-free intervals and preventing future painful recurrences.

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AUTHORS' CONTRIBUTIONS

Emica Shimozono: Data Collection, Conceptualization, Methodology, Writing - Preparation of the Original, Writing - Review and Editing
Vanessa Henriques Carvalho: Writing - Review and Editing, Validation