CASE REPORT

Pain improvement in Camurati-Engelmann disease after anti-TNF α therapy

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SUMMARY

Camurati-Engelmann disease (CED) is a rare disorder included in the group of craniotubular hyperostosis diseases. Corticosteroids are used for pain management in CED, but in refractory or corticosteroid-non-tolerant patients, pain management is limited. We report the case of a woman with CED diagnosed in early infancy whose initial complaints included persistent bone pain associated with progressive functional disability. She was treated with steroids but over time became dependent on higher doses with only mild pain relief. In her third decade, she was diagnosed with ulcerative colitis (UC) and was treated with mesalazine, azathioprine and prednisolone. Due to recurrent exacerbations of UC, treatment was changed to infliximab, an antitumour necrosis factor-alpha (TNF α). Remission of UC was achieved and CED-associated pain also improved with infliximab. This is the first report showing a possible role of anti-TNF α in pain management in CED with unsatisfactory response to steroids.

BACKGROUND

Camurati-Engelmann disease (CED) or progressive diaphyseal dysplasia (MIM#131300) belongs to the group of craniotubular hyperostosis diseases. It is a rare autosomal dominant condition with described mutations in the transforming growth factor-beta-1 (TGF- β 1) gene on chromosome 19q13.¹ TGF- β 1 is secreted as an inactive form, consisting of three subunits: the signal peptide, the latency-associated peptide (LAP) and the mature peptide. The activation procedure includes the cleavage of the signal peptide followed by cleavage of LAP from the mature peptide. Missense mutations located in exon 4 of LAP are the most common mutations in CED.² CED is characterised by bilateral hyperostosis, involving the diaphyses of the femur and tibia with progression to the fibula, humerus, ulna and radius. Metaphyses may become affected but the epiphyses are spared.³ Osteosclerosis is also commonly observed in the skull and pelvis.² Bone scintigraphy reveals increased radionuclide uptake within active lesions, due to increased osteoblastic activity, and is therefore used for early stage diagnosis and patient follow-up.²⁻⁴ Disease onset, penetrance, rate of progression and clinical course are highly variable.²⁻⁵ Main presentation symptoms include pain in the extremities, a staggering gait, easy fatigability and muscle weakness. Systemic manifestations are occasionally observed, including anaemia, leucopenia, hepatosplenomegaly and Raynaud phenomenon.⁶

No disease-modifying treatment is known for CED. Corticosteroids are reported to relieve symptoms, with reduction of bone pain and mild correction of its histological abnormalities. Losartan has been reported in patients as a corticosteroid sparing agent. Use of bisphosphonates is controversial, with some reports showing bone pain exacerbation and others pain relief.⁷⁻⁸ More satisfactory treatment approaches are needed for CED. We report here the case of a patient with CED who experienced pain relief with an antitumour necrosis factor-alpha (anti-TNF α).

CASE PRESENTATION

We report a case of a 46-year-old Caucasian woman with CED bearing the mutation p.R218H at exon 4 of the TGF- β 1 gene, located on chromosome 19q13.2. Although her symptoms started in early infancy, diagnosis of CED was only established at 24 years of age. She had persistent bone pain in the upper and lower limbs. On physical examination, we observed a staggering gait, painful palpation of upper and lower limbs and functional disability. Radiologically, she presented with diffuse osteosclerosis, bilateral patchy thickening of the cortical diaphysis of the forearm bones, tibia and fibula (figure 1A,B). She was initially treated with low doses of steroids and achieved satisfactory pain control. However, over the years she needed higher doses of steroids, reaching 30mg prednisolone/day and only mild pain relief. Further increase in doses of prednisolone did not result in further pain management. In her third decade, she presented with recurrent diarrhoea, associated with blood and mucus, colicky abdominal pain and urgency. She was diagnosed with ulcerative colitis (UC). She also developed polyarthralgias involving mainly the hip, knee and tibiotarsal articulations associated to joint swelling. These extraintestinal symptoms aggravated her previous functional disability. She was initially treated with mesalazine 3g/day without response and subsequently with prednisolone 20–40mg/day and azathioprine 100mg/day. Nevertheless, she presented with several acute exacerbation of UC and was started on infliximab, an anti-TNF α intravenously administered at a standard dose of 5 mg/kg at weeks 0, 2 and 6 and then every 8 weeks.

OUTCOME AND FOLLOW-UP

Over the last 24 months, she had only two exacerbations of UC. Regarding CED-associated bone pain, she experienced progressive pain reduction until complete relief. Radiological evolution, which is difficult to analyse due to irregular hyperostosis,

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Figure 1 Diffuse osteosclerosis, bilateral patchy thickening of the cortical diaphysis of the forearm bones, tibia and fibula, before (A,B) and after (C,D) antitumour necrosis factor- α treatment.

showed no evidence of disease progression (figure 1C,D). Bone densitometry (dual-energy X-ray absorptiometry, performed 2 years after starting treatment with infliximab, showed lumbar osteopenia (L1-L4: T score -1.8 and Z score -1.7) and increased bone density of femur (T score 3.6 and Z score 6.7). Prior to the treatment, the T scores were -2.9 for the lumbar region and 4.2 for femur. These results indicated an increase in bone density at the lumbar level and decrease in density in femur after anti-TNF α therapy. Osteoblastic activity was still observed in diaphysis of long bones in bone scintigraphy after anti-TNF α (figure 2).

DISCUSSION

This is the first report where complete pain relief in a patient with CED was achieved with anti-TNF α therapy. The role of TNF α and TNF α blockade in pain modulation has gained increasing interest in several pain disorders. TNF α blockade

was successfully used for pain management in conditions like acute sciatica and SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis and osteitis).^{9,10} In this report, infliximab, a chimeric monoclonal antibody against TNF α , was used to achieve remission of UC disease. Nevertheless, the patients not only reported improvement in UC-associated symptoms but also in CED-associated bone pain. Several studies have described a local effect of TNF α by induction of extracellular matrix degrading enzymes and pain-related molecule expression, a process regulated by transforming growth factor- β -activated kinase 1 (TAK-1), a member of the mitogen-activated protein kinase family.¹¹ TNF α also seems to trigger hypernociception through changed pain processing in the central nervous system.¹² TNF α blockade can rapidly reverse this pain sensitisation effects.¹² TGF- β 1 has also been implicated in pain modulation through activation of TAK-1, namely in peripheral inflammation-induced hyperalgesia and bone cancer.^{13,14}

Our patient had the p.R218C mutation in exon 4 of LAP. This mutation results in higher instability of precursor protein facilitating activation of TGF- β 1, despite minor variations in total TGF- β 1 levels.^{15,16} The presence of activating mutations results in high levels of active TGF- β 1, leading to decreased bone resorption and increased bone formation. TNF α also plays an important role in the regulation of bone homeostasis via activation of complex signalling pathways leading to gene transcription of several regulators of bone homeostasis, including the expression of TGF- β 1. Upregulation of TGF- β 1 by TNF α was shown in different cell types including microglial cells, mature adipocytes and rat pulmonary artery endothelial cells and seems to involve a combination of transcriptional and post-transcriptional events.¹⁷⁻²⁰ TNF α blockade could interfere with TGF- β 1 upregulation, reducing TGF- β 1 levels. We were not able to show that infliximab is a disease-modifying agent in CED since differences in radiographies are difficult to analyse, TGF- β 1 levels before and after treatment were not measured and osteoblastic activity was still observed in diaphysis of long bones after anti-TNF α treatment. Long-term follow-up of the patient will be important to clarify its efficacy as a possible disease-modifying agent.

We conclude that anti-TNF α therapy might be a promising treatment in CED with unsatisfactory pain relief with steroids.

Figure 2 Bone scintigraphy with radionuclide uptake 1 year after antitumour necrosis factor- α treatment.

In vivo and vitro studies will be important to further elucidate the effect of TNF α and anti-TNF α on TGF- β 1 levels, bone metabolism and pain management.

Learning points

- ▶ No disease-modifying treatment is known for Camurati-Engelmann disease and pain management is limited.
- ▶ Antitumour necrosis factor-alpha (TNF) therapy might be promising for pain relief in patient with limited response to steroids or important steroid-related side effects.
- ▶ TNF has been shown to regulate the expression of transforming growth factor-beta-1 in different cell types through transcriptional and post-transcriptional events, but the use of anti-TNF as a disease-modifying agent in Camurati-Engelmann disease has not been proved.

Contributors SM and BC conceived the case report. SM was a major contributor in writing the manuscript. NPJ treated the patient and also interpreted the patient data. NPJ and LS were involved in the review. All authors read and approved the final manuscript.

Competing interests None declared.

Patient consent Obtained.

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REFERENCES

- 1 Janssens K, Gershoni-Baruch R, Van Hul E, *et al.* Localisation of the gene causing diaphyseal dysplasia Camurati-Engelmann to chromosome 19q13. *J Med Genet* 2000;37:245–9.
- 2 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.
- 3 Sparkes RS, Graham CB. Camurati-Engelmann disease. Genetics and clinical manifestations with a review of the literature. *J Med Genet* 1972;9:73–85.
- 4 Kumar B, Murphy WA, Whyte MP. Progressive diaphyseal dysplasia (Engelmann disease): scintigraphic-radiographic-clinical correlations. *Radiology* 1981;140:87–92.
- 5 Makita Y, Nishimura G, Ikegawa S, *et al.* Intrafamilial phenotypic variability in Engelmann disease (ED): are ED and Ribbing disease the same entity? *Am J Med Genet* 2000;91:153–6.
- 6 Crisp AJ, Brenton DP, Shaw DG. Case report 202. Engelmann disease of bone (diaphyseal dysplasia) with bilateral shortened fibulae. *Skeletal Radiol* 1982;8:239–40.
- 7 Iba K, Takada J, Kamasaki H, *et al.* A significant improvement in lower limb pain after treatment with alendronate in two cases of Camurati-Engelmann disease. *J Bone Miner Metab* 2008;26:107–9.
- 8 Castro GR, Appenzeller S, Marques-Neto JF, *et al.* Camurati-Engelmann disease: failure of response to bisphosphonates: report of two cases. *Clin Rheumatol* 2005;24:398–401.
- 9 Genevay S, Finckh A, Zufferey P, *et al.* Adalimumab in acute sciatica reduces the long-term need for surgery: a 3-year follow-up of a randomised double-blind placebo-controlled trial. *Ann Rheum Dis* 2012;71:560–2.
- 10 Hampton SL, Youssef H. Successful treatment of resistant SAPHO syndrome with anti-TNF therapy. *BMJ Case Rep* 2013;2013:bcr2012007161.
- 11 Uchida K, Takano S, Matsumoto T, *et al.* Transforming growth factor activating kinase 1 regulates extracellular matrix degrading enzymes and pain-related molecule expression following tumor necrosis factor- α stimulation of synovial cells: an in vitro study. *BMC Musculoskelet Disord* 2017;18:283.
- 12 Hess A, Axmann R, Rech J, *et al.* Blockade of TNF- α rapidly inhibits pain responses in the central nervous system. *Proc Natl Acad Sci U S A* 2011;108:3731–6.
- 13 Utreras E, Keller J, Terse A, *et al.* Transforming growth factor- β 1 regulates Cdk5 activity in primary sensory neurons. *J Biol Chem* 2012;287:16917–29.
- 14 Xu Q, Zhang XM, Duan KZ, *et al.* Peripheral TGF- β 1 signaling is a critical event in bone cancer-induced hyperalgesia in rodents. *J Neurosci* 2013;33:19099–111.
- 15 Kinoshita A, Saito T, Tomita H, *et al.* Domain-specific mutations in TGF β 1 result in Camurati-Engelmann disease. *Nat Genet* 2000;26:19–20.
- 16 Saito T, Kinoshita A, Yoshiura Ki, *et al.* Domain-specific mutations of a transforming growth factor (TGF)-beta 1 latency-associated peptide cause Camurati-Engelmann disease because of the formation of a constitutively active form of TGF-beta 1. *J Biol Chem* 2001;276:11469–72.
- 17 Chao CC, Hu S, Sheng WS, *et al.* Tumor necrosis factor-alpha mediates the release of bioactive transforming growth factor-beta in murine microglial cell cultures. *Clin Immunol Immunopathol* 1995;77:358–65.
- 18 Samad F, Uysal KT, Wiesbrock SM, *et al.* Tumor necrosis factor alpha is a key component in the obesity-linked elevation of plasminogen activator inhibitor 1. *Proc Natl Acad Sci U S A* 1999;96:6902–7.
- 19 Phan SH, Gharaee-Kermani M, McGarry B, *et al.* Regulation of rat pulmonary artery endothelial cell transforming growth factor-beta production by IL-1 beta and tumor necrosis factor-alpha. *J Immunol* 1992;149:103–6.
- 20 Sullivan DE, Ferris M, Nguyen H, *et al.* TNF-alpha induces TGF-beta1 expression in lung fibroblasts at the transcriptional level via AP-1 activation. *J Cell Mol Med* 2009;13:1866–76.

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