J Anesth (2008) 22:61–63
DOI 10.1007/s00540-007-0574-2

Journal of
Anesthesia

Calcineurin-inhibitor-induced pain syndrome after bone marrow transplantation

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Abstract
Calcineurin-inhibitor-induced pain syndrome (CIPS), a rare complication seen in patients with organ transplants, is associated with the use of calcineurin inhibitors (CIs) such as cyclosporine (CSP) and tacrolimus (FK). Patients with this syndrome usually present with severe leg pain. This case report demonstrates the successful pain control of this pain syndrome in a 42-year-old female patient who had been given CIs (FK and CSP) as an immunosuppressive agent after a bone marrow transplant. Twenty-one days after the transplantation, she complained of severe pain in her bilateral lower extremities; this lasted several weeks, and was resistant to ordinary analgesics such as intramuscular pentazocine, intravenous morphine, and even oral nifedipine, which is generally accepted as an effective analgesic agent for the pain in this syndrome. Due to the presence of allodynia, our patient's pain had neuropathic pain-like characteristics, unlike the pain in previously reported patients with other organ transplants. Her pain was successfully relieved by the administration of oral amytriptyline, clonazepam, oxycodone, and intravenous lidocaine, all of which ordinarily have an analgesic effect on neuropathic pain. CIPS in patients with hematopoietic stem cell transplants treated with FK may have a mechanism by which neuropathic pain may develop that is different from that in patients with other organ transplants.

Key words Calcineurin inhibitor · Leg pain · Bone marrow transplantation

Introduction

In organ-transplant patients, the use of immunosuppressive agents is a prerequisite for the long-term viability of the transplanted organs, including hematopoietic stem cells (HSC) such as those from bone marrow, cord blood stem cells, and peripheral blood stem cells. Of the immunosuppressive drug used, calcineurin inhibitors (CIs) such as cyclosporine (CSP) and tacrolimus (FK) are well known to have neurotoxic effects, including tremor, headache, confusion, seizures, and even coma [1]. In addition to these neurological complications, CIs have been reported to cause severe pain in the legs, which was first described in 1991 by Lucas et al. [2]. Since then, this pain syndrome, termed calcineurin-inhibitor induced pain syndrome (CIPS), has been reported in several patients with transplantation of solid organs [3–6], but this syndrome has been noted in only two HSC transplant patients, who were recipients of cord blood stem cell transplantation and treated with CSP [7]. On the other hand, FK-related CIPS was first described in 1999 by Villaverde et al. [8]. However, no cases of CIPS occurring in patients who have had bone marrow transplantation and been treated with FK have as yet been reported.

Here we describe a case of severe bilateral leg pain that developed 3 weeks after bone marrow transplantation, consistent with a diagnosis of CIPS.

Case report

A 42-year-old woman with a relapse of acute lymphocytic leukemia received a second allogeneic bone marrow transplant, 7 years after the initial transplant. Intravenous administration of FK at the dosage of $26\,\mu g \cdot kg^{-1} \cdot day^{-1}$ was initiated 1 day prior to the procedure and was continued to prevent graft-versus-host disease (GVHD). The FK dosage was adjusted to maintain serum levels at the desired therapeutic window of between 4 and $8\,ng \cdot ml^{-1}$, but because the initial blood concentration of FK was $12.5\,ng \cdot ml^{-1}$, the dosage was reduced to $6.5\,\mu g \cdot kg^{-1} \cdot day^{-1}$ and the FK level finally reached $8\,ng \cdot ml^{-1}$.

On day 12, however, because GVHD of the skin occurred, the dose of FK was increased. Also, 60 mg oral

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Received: January 7, 2007 / Accepted: September 3, 2007

methylprednisolone was simultaneously administered at the onset of GVHD. Although the GVHD was well controlled, 21 days after the bone marrow transplantation the patient complained of stabbing-like pain in her bilateral thighs. Because she was suspected to have CIPS, FK administration was discontinued. The pain worsened, and another intermittent, electric shock-like pain developed in the same regions. She experienced the pain even at rest, and it was obviously worsened by passive and active physical motion.

On day 24, instead of FK, CSP was intravenously administered, and maintained at the desired levels. The pain persisted even after the immunosuppressive drug was changed. Not only intramuscular pentazocine but also intravenous morphine, 20 mg·day^{-1} oral nifedipine, and an intravenous drip infusion (div) of ketamine failed to relieve her pain. Because intravenous lidocaine showed a definite analgesic effect, 50 mg lidocaine, by div, was given three times per day.

However, because the pain was so severe as to interfere with the patient's daily activities, she was referred to our pain clinic. On day 26, when the patient visited us for the first time, she could not walk by herself because of severe leg pain accompanied by itching. She complained of sleep disturbance due to the pain and appeared to be depressed and anxious. Although neurological examination of her lower extremities could not be carried out because of the severe allodynia, neurological examination of other regions demonstrated no abnormalities. Laboratory data showed no obvious abnormalites. Radiological examinations, including X-ray of her pelvis and femurs, computed tomography (CT) scan of her abdomen and pelvis, magnetic resonance imaging (MRI) of her head and total spine, and a bone scintigram, indicated no obvious abnormalities which might explain her pain.

To control her pain, oral amitriptyline (10 mg·day^{-1}) was commenced, in addition to clonazepam (0.5 mg·day^{-1}), and the dose of amitriptyline was gradually increased until a final dosage of 50 mg·day^{-1} was achieved. Instead of morphine, a fentanyl patch (2.5 mg·3 days^{-1}) was applied. Eight days after she had first visited us, her sleep disturbance was definitely alleviated by the use of the above medication. The dosage of intravenous lidocaine was increased to 60 mg·h^{-1} and the pain intensity decreased to approximately 30% of the maximum. On day 51, although the allodynia in her legs had disappeared, the gait disturbance persisted because of muscle weakness. Whether or not this was of neurogenic origin was unclear. The motor function of her legs gradually recovered through rehabilitation. The intravenous lidocaine was changed to oral mexiletine, at a maximum dosage of 450 mg·day^{-1}. On day 68, the narcotic drug was again changed, from a fentanyl patch to oxycodone (20 mg·day^{-1}), which seemed to have an analgesic effect on the neuropathic pain. Because she did not complain of a worsening of the pain, the oral clonazepam was discontinued, on day 78, and the dosage of amitriptyline was gradually reduced to 10 mg·day^{-1}, on day 92.

The patient was eventually completely free of pain and itching, and because her leukemia was well controlled, she was discharged from the hospital, without any problems, on day 122. Her final medication for analgesia was 10 mg·day^{-1} of oxycodone, 300 mg·day^{-1} of mexiletine, and 10 mg·day^{-1} of amitriptyline, all given orally.

Discussion

CIPS characterized by severe lower limb pain is a recently established pain syndrome associated with the use of CIs in organ-transplant patients, including those with HSC transplants. The diagnosis of this syndrome is associated with typical findings such as patch osteoporosis of bone on radiograms, edema of bone marrow on MRI, and increased uptake on bone scintigrams [9].

Although none of the radiological examinations done for our patient showed obvious findings such as those described above, the clinical features, such as intractable pain in the bilateral legs, strongly suggested that the patient suffered from CIPS.

Clinical symptoms and findings similar to those in our patient can also be seen in patients with reflex sympathetic dystrophy (RSD) or complex regional pain syndrome (CRPS). However, the Gibbons' RSD score for our patient was one point because of the presence of allodynia only, ruling out a diagnosis of RSD. Other possible underlying pathology could be that the pain had originated from a disease of the spine, such as lumbar spinal canal stenosis or disc hernia. However, no findings consistent with such diseases were noted on MRI. Other candidates for the cause of her pain could include polyneuropathy, osteoporosis, avascular bone necrosis, and orthopedic leg deformity, but these diseases would not have explained the characteristic profiles of the pain observed in our patient.

Two cases very similar to that in our patient were described by Kida et al. [7]. The similarities are as follows: (1) the pain was somewhat more aggressive compared to that previously reported, (2) the onset of pain was rather earlier than previously noted, (3) the blood concentration of CI at the onset of the lower-limb pain was not as high as the level suggested in the patients with previously reported cases [8,9], and (4) the leg pain was accompanied by itching in the same region. These similarities seem to correspond to the differences seen between the previously reported cases and ours.

On the other hand, the discrepancies between the two above reported cases and the features in our patient

were as follows: (1) allodynia was present in our patient, but it was not described in the other reports, (2) the CI administered in those patients was CSP, but FK was used for the initial treatment in our patient.

The etiology of this rare pain syndrome has yet to be clarified, but it has been postulated to arise from vascular impairment of bone marrow and from a permeability disorder associated with high levels of CIs [8,9]. The mechanism by which the pain in our patient developed in no regions other than the lower extremites, although CIs were administered systemically, is unclear. The leg bones seem to be preferentially affected because of the high venous pressure resulting from the upright position [9].

The neurotoxic effects of CIs, such as selective toxicity to glial cells [10] and the induction of apoptosis in oligodendrocytes [11], have been investigated; however, the neuropathic mechanism causing the allodynia that occurred in the legs of our patient is currently unclear. The above-mentioned high venous pressure in the lower limbs may have affected not only the bones but also the peripheral nervous system. According to Sander et al. [12], CIs have been reported to modulate the activity of both *N*-methyl-D-aspartate (NMDA) and γ-aminobutyric acid (GABA) receptors. These mechanisms may have participated in the neuropathic pain-like characteristics of the pain in our patient, or, alternatively, an unknown neural impairment induced by FK may have been involved.

Furthermore, in our patient, the itching seen in the area affected by the pain may also have arisen from damage to the peripheral nervous system caused by the CIs. Considering the apparent differences between the features in our patient and the others reported, it is tempting to speculate that the pain of CIPS in HSC transplant patients treated with FK might have a pathogenesis and mechanism—which may cause neuropathic pain—that differ from those previously reported for patients with solid organ transplants treated with FK.

The use of calcium channel blockers is recommended for the therapy of CIPS [9], because of the ability of these agents to antagonize CSP- or FK-related vasoconstriction [9]; however, oral nifedipine had no analgesic effect in our patient. Pain relief was obtained for our patient by the administration of intravenous lidocaine combined with oral amitriptyline and clonazepam, all of which are well known to have an analgesic effect on neuropathic pain.

In conclusion, CIPS should be considered in cases in which an organ transplant patient complains of severe leg pain. CIPS in patients with HSC transplants, such as our patient, possibly has a mechanism, by which neuropathic pain develops, that differs from that in patients who have had other organ transplants. Establishing diagnostic and therapeutic criteria for CIPS will require further study of the precise etiology of the the mechanisms of the pain and the clinical features of this rare pain syndrome.

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