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ARTICLE

Incapacitating Lower Limb Pain Syndrome in Cord Blood Stem Cell Transplant Recipients with Calcineurin Inhibitor

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Calcineurin-inhibitor induced pain syndrome (CIPS) is a newly described entity with a characteristic feature of sudden onset of severe lower limb pain, and high levels of cyclosporine or tacrolimus may be involved in the pathogenesis. This syndrome is rarely seen in recipients of hematopoietic stem cell transplantation (HSCT) compared with other organ transplant recipients, however, heightened awareness of this complication after HSCT may be needed for hematologists, as misdiagnosis can result in catastrophic consequences. We report herein two cases of lower limb pain syndrome, with some clinical features resembling CIPS, occurring during the early phase of cord blood stem cell transplantation for hematological malignancy. (Pathology Oncology Research Vol 10, No 4, 204–206)

Keywords: calcineurin inhibitor, lower limb pain, pruritus, cord blood stem cell transplantation

Introduction

HSCT recipients are at high risk for several neurological complications. These complications arise from the primary disease for which the patient is undergoing HSCT, from infection that may develop during HSCT, or as a consequence of the conditioning and immunosuppressive treatments. Regarding drug-related neurotoxicities, up to 20% of transplant recipients who receive calcineurin inhibitors (CIs) such as cyclosporine (CSP) and tacrolimus (FK) develop neurological adverse events, including tremors, dysesthesia, seizures, altered mental status, cortical blindness, encephalopathy, or even coma.[1-4] Recently, an alternative form of CI-associated neurological complication, designated as CI-induced pain syndrome (CIPS), has been recognized in the setting of organ transplantation.[5] This rare syndrome was first described by Lucas et al in 1991 among renal transplant recipients with CSP immunosuppression.[6] Publications thereafter revealed the unique clinical profiles of this syndrome, featuring acute onset of severe pain localized in bilateral lower limbs, high blood levels of CSP at onset, lack of response to common painkillers, patchy osteoporosis of bone, bone marrow edema in magnetic resonance imaging (MRI), increased uptake in the bone scintigraphy, and otherwise a relatively favorable outcome.[7-10] In 1999 and 2002, FK was reported as causing a similar pain syndrome.[11,12] However, no cases of CIPS occurring in patients undergoing HSCT have yet been reported. We here outline our experiences of two cases with severe lower limb pain syndrome, possibly consistent with a diagnosis of CIPS, that developed in the early post-HSCT period.

Case report

Case 1

An 18-year-old female with acute myelogenous leukemia received unrelated umbilical cord blood stem cell transplantation (CBSCT), which was performed as early as 5 months after initial related peripheral blood stem cell transplantation due to relapse. The protocol for CBSCT was fludarabine 30 mg/m^2 x 5 days, melphalan 40 mg/m^2 x 2 days, and 400 cGy of total body irradiation (TBI). CSP was administered continuously to prevent graft-versus-host disease (GVHD), and the dose was

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adjusted to maintain levels at 150-250 ng/ml. The early post-transplant course was complicated by heart failure, neutropenic fever and hearing disturbance. On day 18, the patient developed systemic pruritus with no apparent skin rash, which was thought to be related to jaundice (maximum total bilirubin, 9.3 mg/dl) at that time. On day 21, the patient complained of intermittent pain in the lower limbs. Severe pain initially emerged for about 1 second every hour, but the interval shortened to every 1 min to several minutes. The type of pain was sharp, stinging, and electric shock-like, and migrated within a short period. The pain occurred even at rest, but was not induced by motion, or by pressing down or touching the lower limb. Neurological examination showed no obvious deficit, including sensory disturbance and muscle weakness. No deterioration of mental status was noted. Laboratory data demonstrated increased level of alkaline phosphatase (1218 IU/l). Other findings, including magnesium (1.7 mg/dl) and creatine kinase, were within normal limits. CSP level was 223.7 ng/ml (under continuous intravenous injection) at onset of pain. At that point, infection or hemorrhage in the region of S1~2 or nervous cutaneous femoris posterior was considered a possible cause, but no further clarification, including MRI could be performed because of the poor general condition. Although the clinical picture seen in this case might be consistent with CIPS, CSP was continued due to our unawareness of this complication at that time. Pain was not relieved by any conventional pain control programs; continuous intravenous injection of buprenorphin or administration of ketamine and lidocaine were no longer effective. The patient was therefore put under deep sedation, which eventually ameliorated the attack. However, the patients ultimately died due to acute respiratory failure at 9 days after onset of CIPS.

Case 2

A 32-year-old male with relapsed acute lymphoblastic leukemia underwent UCBSCT. The patient was conditioned with cytarabine 8 g/m^2 and cyclophosphamide 120 mg/m^2, followed by TBI, 1200 cGy. CSP was started on day -1, with no other medication used for GVHD prophylaxis. The dose of CSP was adjusted to maintain trough levels at 250-350 ng/ml. On day 6, the patient was neutropenic and febrile (38.3ºC) with skin rash and moderate fluid retention (>5% gain of body weight), and was placed on broad spectrum antibiotics and 1 mg/kg of prednisolone (PSL). Although symptoms stabilized after these therapies, the patient developed melena on day 8. Subsequent colonoscopy revealed acute GVHD of the gut, which was confirmed by pathology. PSL was increased to 2 mg/kg, and immunosuppressive treatment was changed from CSP to FK. However, on day 12 the patient experienced irritating pruritus, which grew intense and eventually became spasmodic. Moreover, periodic fits of severe pain in the lower limbs arose secondary to intolerable pruritus. The pain was electric shock-like, running swiftly through the entirety of both limbs, but was not exaggerated by touch or passive and active motions. Neurological examination showed no deficit except for slight laterality in the deep tendon reflex. No sensory disturbance or muscle weakness was noted. Mental status was quite normal at onset of pain. No changes in skin temperature or color were noted in the affected areas. Laboratory findings at that time revealed slightly increased levels of serum lactate dehydrogenase (493 IU/l) and creatine phosphokinase (357 U/l). Alkaline phosphatase (179 IU/l) and magnesium (1.9 mg/dl) were within normal limits. Plasma FK concentration at the onset of these episodes was 8.8 ng/ml, and CSP level before switching to FK was 311.5 ng/ml. Laboratory parameters of parathyroid function were normal. MRI of the spinal cord showed no evidence of a mass or focal myelopathy, but MRI of the proximal lower limbs demonstrated soft tissue and muscle edema. The patient went into a state of delirium after learning that the fierce pain was not controlled by any kind of measures including continuous administration of morphine, ketamine or carbamazepine. The patient was therefore sedated, but successive attacks were still evident and forcing the whole body to shake every 15 min. Although initial diagnostic assessments could not completely exclude any other possibilities such as infection, hemorrhage or infarction, the characteristic pain suggesting CIPS and the previous failed experience of Case 1 prompted us to discontinue FK. The patient also underwent calcium channel blocker therapy for hypertension, with some expectation of the possible beneficial effect on CIPS.[8] After initiation of these therapeutic approaches, the patient did not complain of lower limb pain, some discomfort in the groin was reported.

Discussion

CIPS is a newly established disease entity, characterized by severe pain in the lower limbs, frequently with symmetrical involvement, accompanied by radiographic evidence of patchy osteoporosis of bone, bone marrow edema on MRI and increased uptake on bone scan.[5] This rare syndrome was first described in organ transplant recipients.[6] The pathogenesis remains unclear, but vascular disturbance of bone perfusion and permeability associated with high levels of CSP or FK has been postulated.[5,11] Although we could not perform a thorough radiological examination, typical clinical symptoms such as debilitating bilateral lower limb pain with preceding intolerable pruritus suggested the diagnosis of CIPS. Some of these features might also be seen in patients with reflex sympathetic dystrophy syndrome (RSDS).[13,14] However, our cases did lack several crucial symptoms of RSDS; i.e., no increased tempera-

ture in painful areas, no changes in skin color, and no hypersensitivity to touch were observed in either cases. Another possible underlying cause for lower limb pain could be avascular bone necrosis, but the distinct clinical signs and symptoms occur much later following transplantation and usually affect weight-bearing bones such as the femoral head. This would not explain the characteristic pain profiles seen in our cases. Thus, the clinical features seen in our two cases seems to best fit CIPS. Compared to previous reported cases of CIPS, the pain profiles seen in our two cases differed in the following aspects: First, pain was somehow much more aggressive in our cases. Our two patients experienced unpredictable and intermittent pain like a sudden jolt of energy, tossed about in excruciating pain and eventually became deeply debilitated. The pain itself was not exacerbated with activity or relieved by rest, whereas based on previous reports, patients with CIPS after organ transplant seemed to complain of less severe pain, and activities of daily life were not completely disturbed as patients were able to use wheelchairs and crutches, or even walk.[5,12] Second, onset of pain in our patients was earlier than previously noted; while patients in a setting of organ transplantation usually develop CIPS several months after transplantation,[7-10] our two patients developed symptoms in the immediate post-transplant period. Third, plasma concentrations of CI at onset of clinical symptoms were not as high as suggested in previous reports,[5,11] even though the close relationships between the early onset of symptoms and CI administration, and clinical improvement of symptoms after discontinuation of the drug suggested a possible association between CI and lower limb pain syndrome. Considering these apparent discrepancies in our cases, it is tempting to speculate that CIPS in HSCT might be of a different etiology to previously reported cases in organ transplantation.

Another striking aspect of our experience with CIPS after HSCT is that both cases received unrelated cord blood cells as a stem cell source after conventional conditioning regimen. No possible cases of CIPS were observed in 189 cases of allogeneic bone marrow transplantation (BMT) and 65 cases of allogeneic peripheral blood stem cell transplantation (PBSCT) we have been involved in over the last 5 years, while 2 of the 34 cases of CBSCT during the same period displayed potential CIPS. Whether CBSCT recipients more frequently develop immunosuppression-induced bone loss, and its degree and persistence are more profound than in BMT or PBSCT recipients, is currently unclear. Although the precise role of human T cells in the regulation of osteoclast generation remains unresolved, recent reports have demonstrated that resting T cells negatively regulate osteoclast generation via production of GM-CSF and interferon-γ by $CD4^+$ T cells, and that CSP stimulates osteoclast generation through the inhibition of the production of these cytokines.[15] Taken together with these findings, the profile of naïve T cells with a low ability to produce several cytokines, especially interferon-γ, observed in CBSCT recipients may explain the higher incidence of bone pain syndromes including CIPS.

In summary, our experience with a small number of patients warrants a larger study with a series of patients to evaluate whether this syndrome represents a distinct entity. Physicians should be alert to this potential complication in the setting of HSCT, especially after CBSCT.

References

1. *Kunzendorf U, Brockmoller J, Jochimsen F, et al:* Cyclosporin metabolites and central-nervous-system toxicity. Lancet 1: 1223-1223, 1988
2. *Walker RW, Brochstein JA:* Neurologic complications of immunosuppressive agents. Neurol Clin 6: 261-278, 1988
3. *Reece DE, Frei-Lahr DA, Shepherd JD, et al:* Neurologic complications in allogeneic bone marrow transplant patients receiving cyclosporin. Bone Marrow Transplant 8: 393-401, 1991
4. *Bechstein WO:* Neurotoxicity of calcineurin inhibitors: impact and clinical management. Transpl Int 13: 313-326, 2000
5. *Grotz WH, Breitenfeldt MK, Braune SW, et al:* Calcineurin-inhibitor induced pain syndrome (CIPS): a severe disabling complication after organ transplantation. Transpl Int 14: 16-23, 2001
6. *Lucas VP, Ponge TD, Plougastel-Lucas ML, et al:* Musculoskeletal pain in renal-transplant recipients. N Engl J Med 325: 1449-1450, 1991
7. *Sanches EN, Criado AB, Guajardo AS, et al:* Leg bone pain syndrome due to cyclosporine in a renal transplant patient. Clin Exp Rheum 12: 653-656, 1994
8. *Gauthier VJ, Barbosa LM:* Bone pain in transplant recipients responsive to calcium channel blockers. Ann Intern Med 121: 863-865, 1994
9. *Stevens JM, Hilson AJW, Sweny P:* Post-renal transplant distal limb bone pain. Transplantation 60: 305-307, 1995
10. *Goffin E, Vande Berg B, Pirson Y, et al:* Epiphyseal impaction as a cause of severe osteoarticular pain of lower limbs after renal transplantation. Kidney Int 44: 98-106, 1993
11. *Villaverde V, Cantalejo M, Balsa A, et al:* Leg bone pain syndrome in a kidney transplant patient treated with tacrolimus (FK506). Ann Rheum Dis 58: 653-654, 1999
12. *Malat GE, Dupuis RE, Kassman B, et al:* Tacrolimus-induced pain syndrome in a pediatric orthotopic liver transplant patient. Pediatr Transplant 6: 435-438, 2002
13. *Blombery PA:* A review of reflex sympathetic dystrophy. Aust Fam Physician 24: 1651-1655, 1995
14. *Munoz-Gomez J, Collado A, Gratacos J, et al:* Reflex sympathetic dystrophy syndrome of the lower limbs in renal transplant patients treated with cyclosporin A. Arthritis Rheum 34: 625-630, 1991
15. *Shinoda K, Sugiyama E, Taki H, et al:* Resting T cells negatively regulate osteoclast generation from peripheral blood monocytes. Bone 33: 711-720, 2003