



Case report

Varicella zoster meningoencephalitis following treatment for dermatomal zoster in an alloBMT patient

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Summary:

Herpes zoster infections are frequently observed after allogeneic bone marrow transplantation (alloBMT). In the majority of cases, the infection is restricted to specific dermatomes and responds to oral acyclovir, without visceral dissemination. We report the case of a 40-year-old male who developed dermatomal herpetic infection 8 months post alloBMT. The herpetic rash responded well to treatment with high-dose oral acyclovir. However, within a week of cessation of therapy, the patient re-presented with dermatomal zoster and meningoencephalitis. Although the cutaneous lesions resolved with intravenous acyclovir, clinical features of meningoencephalitis persisted, along with evidence of varicella zoster virus (VZV) DNA in cerebrospinal fluid (CSF). A satisfactory response to treatment was observed only after the addition of intravenous foscarnet to acyclovir. Based on our experience with this patient, we suggest that in a subset of alloBMT recipients, late dermatomal herpes zoster infections may respond only partially to treatment with standard oral acyclovir. The use of oral acyclovir preparations with higher bioavailability (valacyclovir) or intravenous acyclovir early on may prevent the considerable morbidity associated with disseminated zoster infection. *Bone Marrow Transplantation* (2000) 26, 795–796.

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visceral infections involving the liver, lungs, pancreas and stomach.⁴ Here, we report a patient who developed dermatomal zoster following alloBMT for chronic myeloid leukaemia (CML). Despite a good clinical response to high-dose oral acyclovir, he proceeded to develop VZV meningoencephalitis within a week of ceasing therapy. He was treated with a combination of intravenous acyclovir and foscarnet, and made a gradual but complete recovery.

Case report

A 39-year-old Asian man presented with a 3-month history of epigastric discomfort and tiredness. He had hepatosplenomegaly and a white cell count of $190 \times 10^9/l$. A variant Philadelphia chromosome involving the long arms of chromosomes 9, 22 and the short arms of chromosome 19 was identified by cytogenetic analysis of marrow cells and molecular studies detected the *bcr-abl* gene re-arrangement, confirming a diagnosis of CML in chronic phase. Following leukopheresis, the patient was commenced on hydroxyurea, and α -interferon was added subsequently.

The patient's three siblings were not histocompatible. However, since he was born of a consanguineous marriage, his patients were tissue-typed and his 60-year-old mother was found to be HLA compatible. Both donor and recipient showed evidence of previous infection with cytomegalovirus (CMV).

As the patient failed to achieve a haematological or cytogenetic remission despite being on α -interferon (12 mU/day) together with hydroxyurea, an alloBMT was performed 8 months after the initial diagnosis. Pretransplant conditioning consisted of fractionated total body irradiation 1440 cGy and cyclophosphamide (120 mg/kg). Graft-versus-host disease (GVHD) prophylaxis consisted of Campath (10 mg/day from day -5 to day +4), cyclosporin A and short-course methotrexate. Subcutaneous LMW heparin (3500 U/day) was used as prophylaxis against veno-occlusive disease (day -6 to day +15). G-CSF (263 μ g) was commenced on day +7 until engraftment. Standard prophylactic doses of ciprofloxacin, acyclovir and fluconazole were used to prevent bacterial, viral and fungal infections, respectively.

The immediate post-transplant period was uncomplicated and neutrophil engraftment ($>0.5 \times 10^9/l$) was achieved on day +18. On day +32, CMV polymerase chain reaction

Restoration of immune function is delayed after alloBMT.¹ Mechanisms that maintain latency of viruses such as varicella zoster virus (VZV) in previously infected individuals are therefore impaired in recipients of alloBMT.² Consequently, re-activated infections with VZV are common in the post-alloBMT setting and may result in either dermatomal or disseminated zoster infections.^{2,3} Dermatomal herpes zoster infections are often treated with oral acyclovir, while intravenous acyclovir is used to treat disseminated

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(PCR) analysis was positive in the blood and he was treated with intravenous ganciclovir for 4 weeks followed by oral ganciclovir. On day +54, he developed haemorrhagic cystitis secondary to polyomavirus (BK) infection. The urinary symptoms improved with conservative management, and he was discharged on day +73. By day 100, CMV PCR was negative and therefore ganciclovir was stopped. However, at day +140, PCR analysis indicated re-activation of CMV and therefore intravenous ganciclovir was re-commenced and given for a further 4 weeks.

At day +218, he developed a dermatomal zoster infection affecting the right thoracic segment. The lesions resolved after 2 weeks of high-dose oral acyclovir. However, 5 days after completing treatment, he presented with recurrence of the herpetic rash, along with headache, fever, vomiting and signs of meningeal irritation. No focal neurological deficits were apparent on clinical examination. A CT scan indicated atrophy within the posterior fossa, and MRI scan was consistent with focal infiltrative meningitis. CSF protein level was elevated (7.3 g/l). Numerous polymorphonuclear leucocytes and a few immature granulocytes were present in the CSF along with a few eosinophils, suggesting an acute infective process. Bacteria including acid-fast bacilli were not detected in CSF either on microscopy or culture. CMV PCR on the CSF was negative. However, the presence of VZV DNA within the CSF was identified by PCR in two different laboratories. Treatment with high-dose acyclovir (10 mg/kg three times a day) was initiated. Regular intravenous methotrimoprim, along with a continuous infusion of cyclizine was used to control nausea and vomiting. Despite rapid resolution of the herpetic rash after a few days of intravenous acyclovir therapy, the signs of meningism were slow to resolve and therefore, intravenous foscarnet was added 2 weeks after starting intravenous acyclovir. The combined use of acyclovir and foscarnet resulted in gradual, but steady improvement in symptoms. After a week of combination therapy, the CSF protein level had declined and VZV was no longer detectable in the CSF. Liver, kidney and pancreatic function remained normal throughout, and varicella gastritis was excluded by upper gastrointestinal endoscopy. White cell counts were maintained within normal limits by the use of G-CSF on alternate days. Twenty-eight days after his admission with varicella meningoencephalitis, the patient was discharged.

Discussion

Immune mechanisms that prevent re-activation of latent viruses are impaired following myeloablative therapy. Infections with herpes viruses are therefore common in recipients of alloBMT and contribute to morbidity and mortality in these patients. Most herpetic infections are uncomplicated and are treated with high-dose oral acyclovir. Intravenous treatment with acyclovir is recommended in

disseminated disease or in cases of suboptimal response to oral treatment.

Previous studies on the use of acyclovir in patients with dermatomal zoster have indicated that the oral and intravenous routes of administration are equally effective in preventing dissemination of disease,⁴ even in recipients of alloBMT.⁵ It is therefore not entirely clear why our patient developed meningoencephalitis within a week of completing a 14-day course of treatment with oral acyclovir. It is possible that in an immunocompetent individual, acyclovir may reduce the viral load to a level that is maintained in a latent state by immune mechanisms. However, in some immunosuppressed patients, it is possible that high plasma levels of acyclovir are needed to control virus replication. More predictable plasma levels of acyclovir are achieved by using a drug with a high bioavailability, ie valacyclovir or by intravenous infusion.⁶ In the post-alloBMT setting, the lack of adequate antigen-specific adaptive immune responses may have resulted in a rapid increase in viral load on stopping oral acyclovir, accounting for the relapse seen in our patient. We do not think that the relapse seen in our patient was due to resistant virus because of the rapid healing of the skin lesions after he received intravenous acyclovir.

A recent report on the treatment of Herpes simplex keratitis in a heavily immunosuppressed live transplant recipient has also indicated the efficacy of intravenous over oral acyclovir.⁷ We therefore suggest that alloBMT patients with dermatomal zoster infections be treated with valacyclovir or intravenous acyclovir, rather than oral acyclovir, even when the infection occurs relatively late after the transplant.

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