Increase in severity of graft versus host disease by cytomegalovirus

A L McCarthy, J S Malik Peiris, C E Taylor, M A Green, L Sviland, A D J Pearson, A J Malcolm

Abstract
An allogeneic transplant recipient developed severe graft versus host disease (GvHD) 48 days after transplantation that was concomitant with a cytomegalovirus (CMV) viraemia, from which she subsequently died. CMV infection was detected in blood by the polymerase chain reaction and later in tissue by immunohistochemical techniques. CMV should be considered in patients in whom GvHD does not respond to appropriate treatment, and this case suggests that herpes viruses may increase the severity of GvHD by synergistically enhancing the graft versus host reaction.

Graft versus host disease (GvHD) is a major complication of bone marrow transplantation (BMT) and continues to be the main factor that currently limits allogeneic BMT. An increasing number of studies over the past decade have reported an association between herpes viruses and GvHD and, in particular, the frequent clinical association of cytomegalovirus (CMV) with GvHD. Attempts to link herpes virus infection and GvHD in a causal relationship have so far mainly been based on serological studies. No previous study, as far as we know, has examined the target organs in GvHD for viral infection.

The organs affected in GvHD are primarily the skin, gut, and liver. We have been pro-

spectively studying skin and rectal biopsy material from bone marrow transplant recipients in Newcastle upon Tyne to investigate the association between herpes viruses and GvHD using the polymerase chain reaction, and in situ hybridisation, to detect viral DNA, in addition to standard histological and immunohistochemical techniques.

It has been postulated that exposure to viral antigens due to reactivation, reinfection, or de novo infection with herpes viruses can initiate or exacerbate GvHD. A mechanism for this may be that in GvHD viral antigen or virally induced changes in the expression of histocompatibility antigens on host cells may serve as a target for donor immune surveillance. We report a case that is consistent with this hypothesis.

**Case report**

A 44 year old woman with chronic myeloid leukaemia in chronic phase who was seronegative for CMV before transplantation received an allogeneic bone marrow transplant from her HLA identical brother, who was seronegative for CMV. Skin and rectal biopsy specimens were normal before the transplantation. She was conditioned for the transplantation by total body irradiation and 60 mg/kg cyclophosphamide daily for two successive days and she was transplanted with filtered irradiated blood product support.

The initial period after the transplantation was uneventful. She developed mild GvHD (grade 1)* 21 days after BMT which responded to high dose methylprednisolone. However, 48 days after BMT she developed an extensive skin rash and diarrhoea and her condition began to deteriorate. Biopsy specimens of both skin and rectum taken at this stage showed evidence of more severe GvHD (grade 2). She was treated with high dose methylprednisolone but did not respond to this. Concomitant with this deterioration, peripheral blood taken on day 48 after BMT was positive for CMV by the DEAFF test (seven day culture). Ganciclovir was started on day 55 at a dose of 300 mg twice daily. However, the patient's platelet count fell after two days of treatment, raising the possibility of ganciclovir toxicity. Ganciclovir was discontinued 64 days after BMT. The following day, 65 days after BMT, intravenous anti-CMV immunoglobulin was started at a dose of 18 g once a day for three days until 67 days after transplantation. By 61 days and 70 days post BMT, peripheral blood had become negative for CMV by the DEAFF test (table).

Her clinical condition worsened and liver function tests continued to become increasingly abnormal, with a steady rise in conjugated bilirubin (55 μmol/l at 63 days, 344 at 71, 1014 at 78). Her alkaline phosphatase activity also rose but her alanine amino transferase activity was only marginally raised. There was little to suggest disease in other organ systems, the chest radiograph being persistently normal and clinical examination of the chest indicating no abnormalities. Her liver failure was thought to be due to GvHD; CMV hepatitis was not considered the most likely diagnosis in view of the sharp rise in conjugated bilirubin and only a marginal increase in alanine transferase.

She deteriorated further and died of liver failure 78 days after transplantation. At necropsy, the cause of death was found to be disseminated CMV infection, with immunohistochemical evidence of CMV in the lungs, liver, small intestine, rectum, kidney and spleen.

As part of the research protocol, peripheral blood leucocytes taken on days 48, 61, and 70 after transplantation were analysed for CMV by the polymerase chain reaction (PCR) using primers to the CMV IE gene* and found to be positive for CMV. Peripheral blood leucocytes taken before transplantation were negative for CMV by the PCR.

The rectal biopsy specimen taken on day 50 was also retrospectively analysed as part of the research protocol and was found to be positive for CMV antigen by immunohistochemical techniques using the Dakopatts monoclonal antibody CCH2 (table).

This case report raises several interesting
The cyanide poisoning necropsy: an appraisal of risk factors

A R W Forrest, J H Galloway, D N Slater

Abstract
Blood cyanide concentrations were measured in samples obtained from a pathologist before and after carrying out a necropsy on the body of a victim of cyanide poisoning. There was no significant increase in his blood cyanide concentration after carrying out the procedure. It is suggested that an important factor in determining the risk to those carrying out necropsies of the bodies of victims of cyanide poisoning is the amount of cyanide remaining in the stomach. There are several ways in which the theoretical risk inherent in carrying out such necropsies could be reduced, such as the use of a full face respirator, or the removal, intact, of the upper gastrointestinal tract to a fume cupboard for examination.

It has been suggested that those involved in the post mortem examination of the bodies of those dying of overdoses of cyanide may be at risk of exposure to toxic concentrations of cyanide. We recently had the opportunity to assess this risk in practice. A 40 year old industrial chemist was found dead at home. At the scene were copious amounts of vomit and a note stating that he had taken cyanide with the intention of ending his life. A post mortem examination was carried out within 24 hours of the discovery of the body by an experienced pathologist (DN) in a post mortem suite equipped with down draught ventilation. This ventilation system produces at least 12 changes of air per hour. Both the pathologist and the anatomical pathology technician in attendance wore anti-splash facemasks and "double" surgical masks. The time taken to carry out the necropsy was 35 minutes, the amount of dissection carried out being the minimum necessary to establish the cause of death. Of necessity this included opening the upper gastrointestinal tract for the recovery of gastric...
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