Transfusion associated graft versus host disease in an immunocompetent patient

N'T J O'Connor, P Mackintosh

Abstract
Transfusion associated graft versus host disease is a rare disorder usually confined to patients who are immunosuppressed. A case is described in a 77 year old woman who was presumed immunocompetent. She was transfused with one unit of blood from an individual who was homozygous for the same HLA haplotype as her. The diagnosis of transfusion associated graft versus host disease should be suspected in a patient who develops aplastic anaemia within 30 days of a transfusion of blood products.

It is suggested that blood donations from first degree relatives should not be permitted, unless the donation is irradiated to prevent lymphocyte proliferation.

Case report
A 77 year old woman with a history of rheumatoid arthritis was admitted for elective right knee replacement. This was carried out with no problem and she received 2 units of blood during surgery. Thirteen days later she complained of malaise, had a diffuse rash, and a wound infection caused by Staphylococcus aureus: treatment was started with oral flucloxacillin and fusidic acid. She failed to improve over the next 10 days having a persistent rash and low grade fever. On the twenty third postoperative day she had moderate anaemia (haemoglobin 95 g/l) but otherwise normal haematology, and a further 3 unit blood transfusion was administered. Two days later she had profuse diarrhoea and a widespread maculopapular erythoderma, rash, and was noted to be jaundiced, confused, and feverish. Investigations showed pancytopenia (white cell count 0.4 × 10⁹/l, no neutrophils, and a platelet count of 55 × 10⁹/l), grossly deranged liver function tests (bilirubin, alkaline phosphatase, and transaminase values were all increased to around four times as high as normal). A hepatitis C antibody test was negative and bone marrow aspirate and trephine biopsy specimen established the diagnosis of aplastic anaemia. Full supportive care with blood products and intravenous broad spectrum antibiotics was given but the aplasia worsened. She developed renal failure and died 10 days after aplastic anaemia had been diagnosed.

Further investigations aimed at elucidating the aetiology of this woman’s aplastic anaemia depended on the clinical suspicion of transfusion associated graft versus host disease (TA-GvHD). A skin biopsy specimen was taken and showed mild acanthosis, eosinophilic keratinocytes, and a trivial inflammatory cell infiltrate, consistent with GvHD. HLA typing was undertaken on circulating lymphocytes from the patient (five days after aplasia was diagnosed), her daughter, husband, and the five people whose blood she received (table). HLA typing on the patient’s lymphocytes showed 100% lymphocytotoxicity with HLA-A1 and B8 antisera but much more variable reactions with sera directed against the antigens of the haplotype A3-B5, which had been established by tissue typing the patient’s husband and daughter. A range of A3 antisera gave, on average, 60% cytotoxicity while the B5 antisera varied from 0–70% reactions. As no other relatives were available for study the patient’s second haplotype, A1-B8, could not be confirmed as her own, but there was no evidence of any other class I HLA antigen expression. Unfortunately the patient died before class II typing could be carried out. These data are compatible with a dual population of lymphocytes being present in the patient, derived from the blood donor. One blood donor was homozygous for the haplotype A1-B8, which correlates with the strong reactions seen in the circulating lymphocytes taken from the patient; these antigens were not present in any of the other blood donors. Blood from this donor was six days old at the time of transfusion—some 25 days before aplastic anaemia was diagnosed.

Discussion
Possible aetiological mechanisms for the severe and fatal aplastic anaemia included idiosyncratic drug reaction, transmitted viral infection, or TA-GvHD. The clinical picture was strongly suggestive of TA-GvHD in that she also had diarrhoea, severe hepatitis, and gross erythroderma. The features in this woman

| HLA haplotype results on peripheral blood lymphocytes |
|-----------------|---|---|---|
| Patient         | A1 | B8 | A3* | B5* |
| Husband         | A2 | B44| A1  | B8  |
| Daughter        | A2 | B44| A3  | B5  |
| Blood donor     | A1 | B8 |     |     |

*Lymphocyte reactions for A3 and B5 were weaker than expected: A3 60% and B5 variable (0–70%)
were not typical of acute GvHD following marrow transplantation because the rash was not maximal over the palms and soles and the liver enzyme abnormalities did not indicate a cholestatic picture. However, a skin biopsy specimen was suggestive of GvHD and lymphocyte HLA typing confirmed the diagnosis of TA-GvHD. No treatment has been found to alter the natural history of this disorder, although high dose steroids and cyclosporin have been tried. The disease is almost universally fatal, due to bone marrow failure.

TA-GvHD has been reported between four and 30 days following transfusion and requires the transfer of only 10 lymphocytes/kg, so it may occur after transfusion of a single unit of blood, and is commoner with fresher blood, because this contains a higher proportion of viable lymphocytes. The syndrome depends on the transfer of viable T lymphocytes, which are histoincompatible with the host, and on the recipient’s immune system not rejecting these lymphocytes. Therefore, TA-GvHD usually affects patients who have severely impaired cellular immune function—especially those with congenital immunodeficiency, marrow transplant recipients, and sometimes in patients receiving intensive cytotoxic drugs for lymphoma or leukaemia. Our patient became aplastic 25 days after receiving the implicated unit of blood, and this relatively late onset may reflect the fact that she was not immunocompromised and that the unit of blood was six days old at the time of transfusion, rather than being very fresh.

Until recently TA-GvHD had only been recognised in severely immunocompromised patients, but the syndrome is a very rare complication of transfusion in immunocompetent persons, especially Japanese patients undergoing cardiac surgery (risk 1 in 650), and in those who receive blood from a close relative. The risk seems to be particularly high if a person heterozygous for one HLA haplotype is transfused with blood which is homozygous for the same HLA haplotype; this was the case in our patient. The host fails to recognise the graft as foreign because of the shared haplotype, and after engraftment donor lymphocytes reject the host by recognising the non-shared haplotype and this gives rise to aplastic anaemia and the constellation of features described above. The high incidence of TA-GvHD in Japanese patients undergoing cardiac surgery was attributable to two facts: (i) there are relatively few HLA haplotypes in the population, so it is comparatively common for HLA haplotypes to be shared by blood donors and recipients of blood; and (ii) very fresh blood (one to two days old) was being used for cardiac surgery. Although TA-GvHD has been described following blood transfusion from an unrelated donor, and not associated with cardiac surgery, we believe this is the first such case in an immunocompetent person that has been confirmed by HLA studies.

TA-GvHD is underdiagnosed because the patient is usually moribund and the findings may be wrongly attributed to underlying disease, intercurrent infection, or a severe drug reaction. Furthermore, the clinical features are poorly recognised, and may not all be present in one case. However, the diagnosis should be suspected in a patient who develops aplastic anaemia within 30 days of transfusion of blood products. TA-GvHD is a very rare complication of transfusion and although its true incidence is not known, the risk of this fatal complication is a strong argument against permitting directed blood donations from first degree relatives, unless the donation is irradiated to prevent lymphocyte proliferation.

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