

*Editorial***Transfusion associated graft versus host disease and its prevention**

Transfusion associated graft versus host disease (TA-GVHD) is a rare but lethal complication of transfusion,<sup>1</sup> generally associated with immunosuppressed patients. As described in the case report in this issue,<sup>2</sup> however, the condition can occur in fully immunocompetent individuals, with the onset of symptoms usually 1–2 weeks after transfusion. Patients experience the classic features of GVHD: skin rash, diarrhoea, fever, and hepatic liver damage with or without jaundice. What makes TA-GVHD so devastating is the involvement of the bone marrow, with severe hypoplasia leading to profound pancytopenia. The disease then follows a downhill course with death, usually caused by infection, in more than 90% of cases. Once established, the condition is not amenable to treatment. Fortunately, it appears to be entirely preventable if cellular blood components (red cells and platelets) are  $\gamma$  irradiated before transfusion. This is currently performed only for patients deemed at particular risk of TA-GVHD; however, recognition and reporting of cases in other patient groups is extremely important. Only in this way can new risk factors be recognised, and irradiated components provided.

**Pathology and diagnosis**

After blood transfusion into an immunocompetent recipient, donor leucocytes can be demonstrated in peripheral blood, but normally disappear after a few days.<sup>3</sup> The underlying pathology of TA-GVHD involves failure of elimination of these allogenic cells, enabling engraftment and expansion of CD4+ and cytotoxic CD8+ donor derived T cell clones.<sup>4</sup> These recognise HLA class II determinants in the recipient,<sup>5</sup> resulting in massive release of inflammatory cytokines such as tumour necrosis factor and interleukin 1.<sup>6</sup> There is then recruitment and activation of additional T cells, and upregulation of HLA class II expression, resulting in a “cytokine storm” and widespread tissue damage.

The most important step towards the diagnosis of TA-GVHD is to think of it! Rashes, diarrhoea, deranged liver function, and bone marrow dyscrasias are common in sick patients, and are usually attributed to drug treatment. TA-GVHD must be considered in any patient with this constellation of symptoms, whether immunosuppressed or not, if there has been a recent transfusion. Diagnostic biopsy of skin or bone marrow is usually possible, but liver biopsy is generally precluded because of thrombocytopenia. The histological appearances in the skin may be helpful, but are not pathognomonic.<sup>7</sup> The bone marrow is hypoplastic in established cases. If the patient is not yet severely leucopenic, consideration should be given to HLA genotyping from peripheral blood to see whether a donor HLA haplotype can be identified. Close discussion with the tissue typing laboratory and the supplying blood centre is essential. Polymorphic non-HLA determinants have also been shown to be useful in identifying donor derived DNA using the patient's skin, hair or even nail clippings.<sup>8</sup>

**Risk factors for TA-GVHD**

The three well recognised risk factors for TA-GVHD are: the volume and age of the blood transfused as this determines the number of viable T cells in the transfused component; HLA haplotype sharing between donor and recipient; and depressed immune function. There is therefore a spectrum of risk of TA-GVHD after any transfusion, although one or more of these risk factors has been identified in most reported cases.

Transfusion of very fresh blood has no widely proved benefit, but may enhance the risk of TA-GVHD as T cell viability decreases sharply during blood storage. In the case reported here<sup>2</sup> the blood given was less than 72 hours old. The critical number of T cells required may be very low; a case has been described after transfusion of red cells that had been passed through a “3-log” leucocyte depleting filter.<sup>9</sup>

HLA haplotype sharing is best recognised in transfusions between family members, but can occur by chance in any population of unrelated individuals. The most dangerous situation is if the donor is homozygous for an HLA haplotype shared with the recipient as this will be associated with least immune recognition and elimination of transfused cells. In certain populations, which have remained relatively isolated throughout history such as the Japanese, there are very few HLA haplotypes in the population, and the risk of TA-GVHD occurring by chance is as high as 1 in 600.<sup>10</sup> The risk of this in the UK population is not known precisely, but has been calculated as 1 in 17 700–39 000 for the USA.<sup>11</sup>

Immunodeficiency/suppression in the recipient, particularly major defects of T cell number or function, is best illustrated by early reports of TA-GVHD in children with severe combined immunodeficiency,<sup>12</sup> and is evident in other conditions with specific defects in cell mediated immunity, such as adenosine deaminase deficiency and Hodgkin's disease. Curiously perhaps, TA-GVHD is not associated with AIDS. The reason for this is not precisely known, but it may be that donor T cells also become infected with the human immunodeficiency virus and cannot proliferate.

**TA-GVHD in cardiology: who should receive irradiated blood components?**

$\gamma$  Irradiation of cellular blood components to 25 Gy (red cells and platelets) is now well established as a means of preventing TA-GVHD. At present, this is carried out only for defined patient groups.<sup>13</sup> These are principally patients with major immune deficiency or suppression, such as recipients of bone marrow transplants or fetal transfusion, patients with Hodgkin's disease, and those receiving purine antagonists as part of chemotherapy protocols. Thus, patients at risk for TA-GVHD will only rarely be under the care of a cardiologist or cardiac surgeon. However, the following should be borne in mind.

Rarely, patients will wish to receive blood from relatives, or parents will wish to donate for their children. In general, this source of blood is no safer than the voluntary, multiply tested donor, and so the practice is not encouraged. If performed, the blood must be irradiated as there is a high chance of a shared HLA haplotype between donor and recipient.

In infants with di George's syndrome, cardiac defects may require surgery and transfusion before the associated immunodeficiency is fully diagnosed or even recognised.<sup>13</sup> Absence of a thymic shadow or absolute lymphopenia may provide a clue to the presence of immunodeficiency. If in doubt, irradiated blood should be given as a precaution.

In Japan, the association between TA-GVHD and cardiac surgery has been recognised for some time.<sup>14</sup> This is now attributed to a combination of HLA haplotype sharing and the use of relatively fresh blood. Because such cases are rare outside Japan, irradiated blood is not currently recommended for cardiac surgery patients. The risks and benefits of very fresh blood need to be considered in this context.

Patients undergoing transplantation of solid organs do not appear to be at particular risk of TA-GVHD, despite immunosuppression. However, one pitfall for the unwary is the rare occurrence of GVHD arising from lymphoid tissue in the transplanted organ itself. I have personally seen a case associated with liver transplantation; in theory, lung or heart/lung transplant could occasionally give rise to similar problems. Reaching the correct diagnosis in such circumstances presents a considerable challenge for the tissue typing laboratory.

It is not clear how often cases of TA-GVHD are missed. New at risk groups may emerge as a result of novel chemotherapy or immunotherapy for malignancy and autoimmunity, which affect T cell number or function. A voluntary, anonymous reporting system (serious hazards of transfusion (SHOT)) has now been set up in the UK to receive and collate reports of major transfusion complications, including TA-GVHD.<sup>15</sup> A haematological opinion should be sought early in suspected cases, and confirmed cases reported to SHOT. In this way, new risk factors for TA-GVHD can be recognised early, and irradiated blood components provided in future. In its first year, SHOT

received reports of only four cases of TA-GVHD, with no single common link.<sup>16</sup> Several years' reporting may be required before a new risk factor is recognised, so complete reporting of every case is strongly encouraged.

I am grateful to Mrs Carol Holmes for help with preparation of this manuscript.

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