ANONYMOUS

Witness Name: GRO-B
Statement No.: WITN0407001
Exhibits: WITN0407002-WITN0407004

INFECTED BLOOD INQUIRY

WITN0407003

CASE REPORT

Eur J Haematol 1987:39;185–189

Key words: bone marrow transplantation – HIV infection

HIV infection due to a platelet transfusion after allogeneic bone marrow transplantation

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A 36-yr-old man with chronic granulocytic leukaemia received a bone marrow transplant from his histocompatible sister in December 1982. His post-transplant course was complicated by Grade III graft-versus-host disease and multiple infectious episodes until his death from pneumonia on d +190. He was later found to be seropositive for anti-HIV at the time of his death. Retrospective analysis of stored sera showed a transient period of seropositivity from d +11 to d +20 thought to reflect passive transfer of antibody from a blood product transfused prior to d +11 when he was also exposed to infectious virus. He remained seronegative until d +78 when anti-HIV was again found. Seropositivity persisted until his death and was attributed to endogenous antibody response. Although it is unclear whether his clinical course was due to AIDS, exposure of an immunosuppressed patient to HIV may be associated with more rapid development of clinical disease.

Accepted for publication March 19, 1987

The risk of acquiring infection with the Human Immunodeficiency Virus (HIV) from transfused blood products has led to the introduction of routine screening of volunteer blood donors for serum antibodies to HIV (anti-HIV) and the subsequent exclusion of seropositive donors. However, recipients of blood products donated prior to the introduction of screening may yet develop HIV-related illnesses. If the chance of receiving an infectious blood product is directly related to the number of units transfused, the patients who require prolonged blood product support, such as recipients of allogeneic bone marrow transplants (BMT), will be at greatest risk.

In 1985, 3 patients who had developed the acquired immunodeficiency syndrome (AIDS) between 2 and 5 yr after BMT were reported from France (1). In each case the marrow donor was identified as the source of the infection. Following this report we investigated a group of patients considered to have been at risk of exposure to HIV for serological evidence of anti-HIV. The group consisted of 28 patients, 25 transplanted since January 1984 and 3 transplanted earlier, who had developed late infectious com-

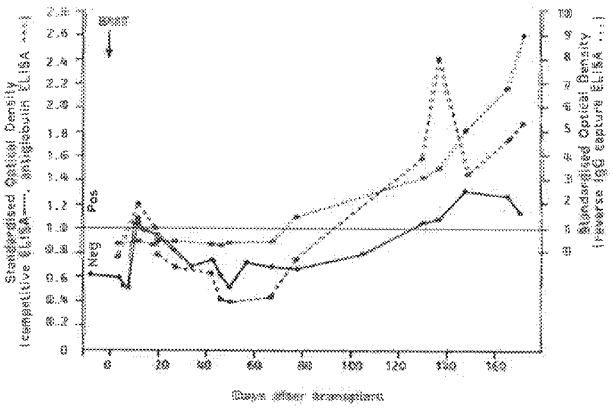

Figure 1. Anti-HIV levels pre- and post-transplant by competitive, antiglobulin and reverse IgG capture ELISAs. Standardised optical density values > 1.0 indicate seropositivity.

plications. We report details of the 1 patient found to be seropositive for anti-HIV and the events preceding his death 6 months after BMT.

Case history

A 30-yr-old married man with no known risk factors for AIDS presented in November 1980 complaining of fatigue and abdominal pain. Examination revealed splenomegaly. The full blood count and bone marrow aspirate were consistent with a diagnosis of Philadelphia chromosome-positive chronic granulocytic leukaemia (CGL). He was treated with busulphan and, in October 1982, underwent splenectomy. In December 1982 he was treated by allogeneic BMT with cells from his HLA-identical sister. Chemoradiotherapy consisted of daunorubicin 60 mg/m², cyclophosphamide 60 mg/kg on two occasions, and fractionated total body irradiation totalling 10 Gy. Cyclosporine was given to prevent graft-versus-host disease (GVHD). His immediate post-transplant course was uneventful and he was discharged on d +28.

2 d later he was readmitted with an illness of sudden onset comprising fever, sore throat, conjunctivitis, truncal rash and abnormal liver function tests. Grade III GVHD was suspected and a skin biopsy was consistent with this diagnosis. He responded well to intravenous methyl prednisolone and was discharged 3 wk later. For several weeks he remained unwell with fever, malaise, anorexia, bone stools, skin rash, lymphadenopathy, hepatomegaly and thrombocytopenia, despite good control of his GVHD. On d +102 he was readmitted with oral candidiasis and herpes simplex and disseminated herpes zoster. He responded well to treatment with acyclovir. On d +130 he was admitted with coryza, earache, cough and fever, and had a skin rash consistent with measles. These resolved spontaneously within a week. Shortly afterwards, however, he developed a new fever, associated with dyspnoea and a productive cough, and chest x-ray showed left lower lobe collapse. *Staphylococcus aureus* was cultured from the sputum and initially there was a good response to vancomycin. His symptoms did not entirely resolve and bronchial washings from bronchoscopy performed on d +156 were positive for *Aspergillus fumigatus*, *Candida albicans*, *Branhamella catarrhalis* and cytomegalovirus. He was treated with amphotericin B, augmentin, vancomycin and assisted ventilation, but his condition deteriorated and he died 5 wk later, on d +190. Post mortem examination was not performed.

Antibodies to HIV

Samples of sera from this patient had been frozen at −20°C at various times throughout the transplant period and were available for analysis. Sera were variously assayed for anti-HIV by three different methods: a commercial competitive assay (Wellcozyme, Wellcome Foundation Ltd), a commercial antiglobulin assay (Dupont Anti HTLV III ELISA, Dupont Ltd) and by a reverse capture ELISA assay. In the latter test, serum at a dilution of 1:100 is incubated over an anti-human IgG solid phase which is then incubated first with HIV antigen and then with horse-radish peroxidase-conjugated monoclonal anti-gag P18.

Both patient and donor were seronegative at the time of transplant and the recipient remained seronegative 8 d later. However anti-HIV was detected by antiglobulin and competitive assays in serum stored from d +11, and was also present in subsequent specimens at declining levels up to and including d +20. Thereafter, the sera were consistently negative, until d +78 when reactivity was demonstrated in the reverse capture assay only. In serum taken on d +120 antibody was again detected by all three assays and persisted until his death on d +190 (Figure 1).

The initial period of seropositivity from d +11 to d +20 was thought to reflect passive transfer of antibody, probably together with virus, from a blood product from an infected donor transfused prior to d +11, since the antibody level declined thereafter, becoming undetectable until the patient himself began to produce antibody 16 wk later.

By d +120 the patient had received platelets and red blood cells from a total of 108 different donors. The Regional Blood Transfusion Centre at Edgware was consulted and investigations were undertaken to identify the source of the virus and the passively acquired antibody.

Identification of anti-HIV positive blood donor

A list of all blood and platelet donations given to the patient was supplied to the Transfusion Centre and investigations were limited to males whose donations had been transfused to the recipient in the 3 d immediately preceding the positive anti-HIV result on d +11. Donors who had given blood since the introduction of routine anti-HIV screening in 1985 were also excluded. This left only 2 males, aged 30 and 60 yr, whose platelet donations had been transfused at the specified time. The younger man had ceased donation after December 1982 as he belonged to a 'high risk' group. Anti-HIV positivity had been confirmed some months prior to this enquiry and although he had been counselled at this time, he had not been advised to inform the transfusion centre director.

In view of the low prevalence of anti-HIV in blood donors in the U.K. and the fact that 1 high-risk donor was identified who was known to be seropositive, it was presumed that this donor was responsible for the transfusion-transmitted HIV infection. It is, however, impossible to be certain that he was infected at the time of the implicated donation.

Discussion

The accepted definition of AIDS formally precludes its diagnosis in a patient who is already immunosuppressed and hence the role of HIV in causing disease in a patient after BMT must always be equivocal. In general, infection is common in the heavily immunosuppressed BMT recipient, and is more frequent in the presence of GVHD (2).

In retrospect this patient was unique in our transplant experience by virtue of the number and variety of his infective episodes, although these were not considered suspicious at the time of his death. HIV infection may have been responsible for at least some of the problems encountered in his post-transplant course. Two factors support a causal role for HIV in this patient. Firstly, the development of an acute *mononucleosis*-like illness shortly after initial exposure to HIV is well-documented and our patient had an otherwise unexplained episode of ill-health consistent with such an infection (3–7). A clinical syndrome comprising some or all of the features of fever, night sweats, malaise, headache, sore throat, myalgia, arthralgia, nausea, vomiting, diarrhoea, truncal erythematous rash and lymphadenopathy begins 6 to 38 d after initial infection and persists for approximately 14 d. Thrombocytopenia and lymphopenia are common in the early stages and may be followed by a proliferative lymphocyte response coincident with the development of lymphadenopathy (4). Seroconversion may occur during the acute episode or be delayed for up to 2 months from onset (4, 6, 7). Our patient developed a sudden illness consisting of fever, malaise, sore throat, anorexia, loose stool and lymphadenopathy

which was clinically indistinguishable from acute GVHD. This initially responded to high-dose methylprednisolone but complete recovery was never achieved. He became lymphopenic with a nadir of 0.09 × 10⁹/l 33 d after exposure to HIV. After initial engraftment and good platelet recovery, his platelet count dropped to 20 × 10⁹/l 22 d after infection. Both platelet and lymphocyte numbers subsequently returned to normal. Seroconversion occurred 50 d after the onset of this clinical illness. In retrospect, the entire episode may have been due to acute HIV infection and was therefore mistakenly attributed to GVHD.

Secondly, the terminal multiple infections of this patient may also have been HIV-related. The incubation period for HIV has been estimated at 15–57 months (median 28 months) and HIV might therefore be considered unlikely to cause clinical problems within 6 months of exposure (8). However, infants with congenital HIV infection can die within 12 months of birth, a fact which is normally attributed to their immature immune system (9). If this is the cause of a more rapid evolution of the disease then the same logic might apply to a patient whose immune system has been rendered artificially immature after BMT.

In this case we were able to document a transient reactivity for anti-HIV early after BMT. The rapid loss of antibody reactivity indicated that this was likely to have been passively acquired and implicated blood products used between d +8 and +11. Similar findings have been seen in post-transfusion hepatitis B (10). Seropositivity was detectable by competitive and antiglobulin assays only at this time. In contrast, the patient's active anti-HIV response was, surprisingly, detected by the reverse capture assay first. The lag in development of positive results by competitive and antiglobulin assays may have reflected the immune paresis of the patient following BMT.

Transmission of HIV after BMT should be preventable if appropriate steps are taken. We recommend screening not only of blood product donors but also of the bone marrow donor and recipient and any other person who may be asked to donate granulocytes or HLA-matched platelets by 'in-house' cell separation. If a potential donor is found to be seropositive this must be a strong contraindication to use as a donor for marrow or any other blood product.

Our patient received platelets from a man who subsequently discovered that he was in a 'high-risk' group and voluntarily withdrew from regular blood donation. Although this individual was counselled 2 yr later he was not asked or warned about blood donation. It is clearly essential that any patient found to be anti-HIV positive should be asked if he has ever donated blood. If the answer is yes, permission should be sought to inform the relevant Blood Transfusion Centre and permit the necessary steps to be taken to try to prevent secondary spread of infection from infected recipients.

Acknowledgements

Dr. Apperley was supported from a grant from the S. Warburg Voluntary Trust. Dr. Rombos was supported by the European Science Exchange Programme. We are grateful to Dr. Julian Duncan (Wellcome Foundation, Beckenham, Kent) for the gift of the HRPO labelled anti-gag conjugate and to Dr. R. S. Tedder for his advice throughout.

References

1. Gluckman E, Socie B, Gluckman JC, et al. Two cases of acquired immune deficiency syndrome (AIDS) after allogeneic bone marrow transplant (BMT) - transmission of LAV by healthy marrow donors (A). Exp Haematol 1984;13:528.
2. Winston DJ, Gale RP, Meyer DV, et al. Infectious complications of human bone marrow transplantation. Medicine 1979;58:1–31.
3. Editorial. Needlestick transmission of HTLV-III from a patient infected in Africa. Lancet 1984;2:1376–7.
4. Cooper DA, Gold J, MacLean P, et al. Acute AIDS retrovirus infection. Lancet 1985;1:537–40.
5. Tucker J, Ludlam CA, Craig A, et al. HTLV-III infection associated with glandular-fever-like illness in a haemophiliac. Lancet 1985;1:586.
6. Carne CA, Tedder RS, Smith A, et al. Acute encephalopathy coincident with seroconversion for anti-HTLV-III. Lancet 1985;2:1206–8.

7. Ruskin MHA, Ridley CM, Smith MD, Kelsey MC, Parker N. The acute exanthem associated with seroconversion to human T-cell lymphotropic virus III in a homosexual man. J Infect 1986;12:161–3.
8. Curran JW, Lawrence DN, Jaffe H, et al. Acquired immune deficiency syndrome (AIDS) associated with transfusion. N Engl J Med 1984;310:69–75.
9. Scott GB, Sischi MA, Klimas N, et al. Mothers of infants with acquired immune deficiency syndrome (AIDS). Evidence for both symptomatic and asymptomatic carriers. JAMA 1985;253:363–6.
10. Naginton J, Wreghitt TG, Tedder RS, Dane DS. Hepatitis B carrier state produced by a blood transfusion. J Clin Path 1980;33:851–2.

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