

## Case report

# Development of rheumatoid arthritis following autologous peripheral blood stem cell transplantation

R Imamura, H Inoue, K Kato, S Kobayashi, H Tsukamoto, K Nagafuji, K Shimoda, H Nakashima, T Otsuka, H Gondo and M Harada

Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan

### Summary:

**A 51-year-old man with non-Hodgkin's lymphoma (NHL) was treated with high-dose chemotherapy followed by autologous peripheral blood stem cell transplantation (PBSCT). Although he had HLA-DRB1 0405 and a positive rheumatoid factor, he was unlikely to develop rheumatoid arthritis (RA) according to diagnostic criteria. However, the patient developed RA 40 days after transplantation. Our experience suggests that the systemic autoimmune disease, RA, may occur in patients with predisposing factors after autologous PBSCT.**

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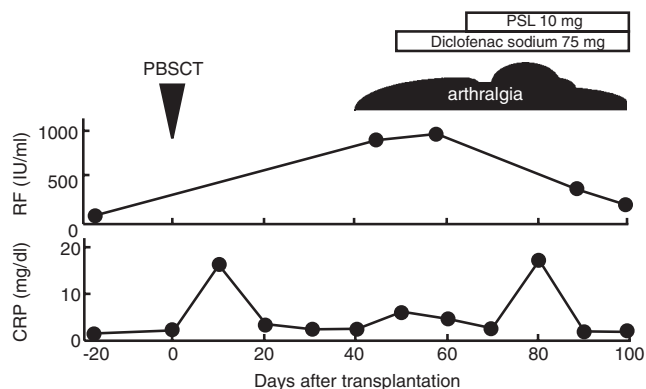
A 51-year-old Japanese man was referred to our institution on 11 September 2000 with a tumor in the thyroid gland. The tumor was histologically characterized as NHL, diffuse, large cell, B cell type, clinical stage IVA. Laboratory tests demonstrated that levels of lactate dehydrogenase, alkaline phosphatase, and soluble IL-2 receptor were all increased at 775 U/l, 417 U/l and 1460 U/ml, respectively. His HLA type was A2, A24, B39, B59, DRB1 1501, DRB1 0405, and rheumatoid factor was positive (51 IU/ml).

After three cycles of CHOP (cyclophosphamide 750 mg/m<sup>2</sup>, doxorubicin 50 mg/m<sup>2</sup>, vincristine 1.4 mg/m<sup>2</sup> and prednisolone 60 mg/m<sup>2</sup>, 5 days), etoposide 500 mg/m<sup>2</sup> was administered intravenously (i.v.) for 3 days and then followed by G-CSF at 100 µg/m<sup>2</sup> day i.v. for mobilization of peripheral blood stem cells (PBSC): 13.0 × 10<sup>6</sup> CD34-positive cells/kg were collected during hematologic recovery and cryopreserved without purging. After three more cycles of CHOP, he received high-dose chemotherapy followed by autologous PBSCT in February 2001. Pretransplant chemotherapy consisted of ranimustine 200 mg/m<sup>2</sup> i.v. for 2 days, carboplatin 300 mg/m<sup>2</sup> i.v. for 4 days, etoposide 500 mg/m<sup>2</sup> i.v. for 3 days, and cyclophosphamide 50 mg/kg i.v. for 2 days. Frozen-thawed PBSC (6.5 × 10<sup>6</sup> CD34-positive cells/kg) were infused on the day of transplantation. G-CSF 200 µg/m<sup>2</sup>/day was administered i.v. from day 1 to day 9.

Regimen-related toxicities including grade 3 neutropenia and grade 2 oral mucositis were well tolerated. Granulocytes exceeded 500 µl on day 9 post transplant. Thereafter, his clinical course was uneventful until day 40. At that time, he complained of the sudden onset of polyarthralgia. Shoulders, elbows, hands and knees exhibited symmetrical bilateral polyarthritides associated with intense inflammatory signs. Metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints also showed arthritis. Pronounced pitting edema was observed in the hands and feet.

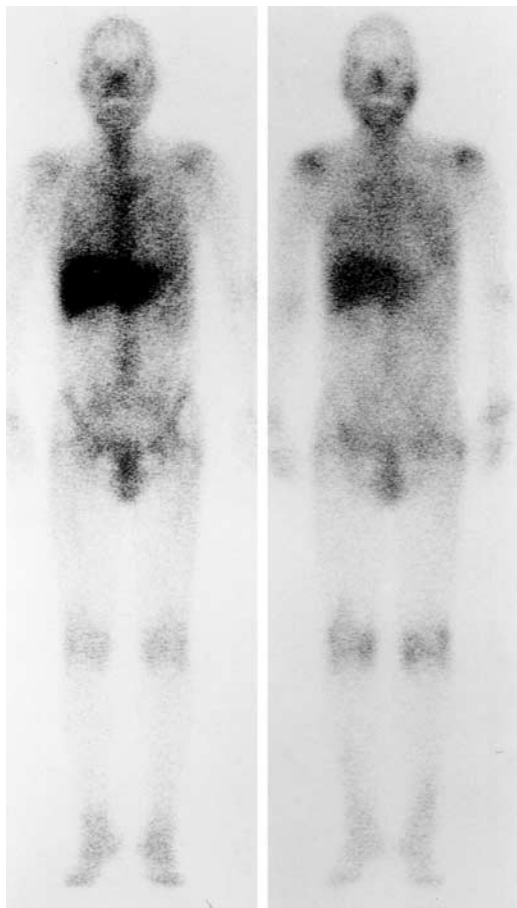
Laboratory tests on day 45 were as follows: hemoglobin concentration, 6.2 g/dl; white blood cell count, 5.7 × 10<sup>9</sup>/µl (55% neutrophils); platelet count, 50 × 10<sup>9</sup>/µl; ESR, 85 mm/h; CRP, 6.1 mg/dl. He was serologically negative for parvovirus, enterovirus, hepatitis B virus, hepatitis C virus and streptococcus. The serum level of rheumatoid factor was increased to 898 IU/ml (Figure 1). Neither antinuclear

Recent advances have significantly reduced transplant-related morbidity and mortality after autologous stem cell transplantation.<sup>1</sup> Transplant-related mortality has been reported to be 5 to 10% in autologous stem cell transplantation for non-Hodgkin's lymphoma (NHL).<sup>1</sup> However, various types of autoantibodies have been described in patients receiving autologous stem cell transplantation.<sup>2,3</sup> Autoantibodies in autograft patients are generally limited and transient, and clinical manifestations are generally mild and specific.<sup>4</sup> Autoimmune thyroiditis, immune-mediated thrombocytopenia, and autoimmune hemolytic anemia have been reported after autologous stem cell transplantation.<sup>2,3</sup> We describe a 51-year-old man who developed rheumatoid arthritis (RA) following high-dose chemotherapy and autologous peripheral blood stem cell transplantation (PBSCT) for non-Hodgkin's lymphoma (NHL). Development of RA is discussed with regard to predisposing factors for autoimmune disease and immunologic reconstitution after autologous PBSCT.



**Figure 1** Clinical course: PSL, prednisolone; RF, rheumatoid factor; CRP, C-reactive protein; PBSCT, peripheral blood stem cell transplantation.

antibody nor anti-DNA antibody was detected, and complement levels were within the normal range. Scintigraphy on day 59 showed high gallium uptake at the shoulders, elbows, hands and knees (Figure 2), although there was no erosion radiologically. His clinical findings fulfilled five criteria for RA, including morning stiffness lasting more than 4 h, arthritis of 11 joint areas, arthritis of the hand, MCP and PIP joints, symmetrical arthritis of the shoulder,



**Figure 2** Gallium scintigraphy: left, before transplantation (day -11); right, after transplantation (day 59).

elbow, hand and knee, and positive serum rheumatoid factor;<sup>5</sup> these symptoms and signs persisted for 6 weeks. For control of the disease, oral diclofenac sodium 75 mg/day and prednisolone 10 mg/day were instituted on day 49 and day 63, respectively. These were effective and led to gradual improvement in disease symptoms.

## Discussion

Generation of various autoantibodies has been reported in allogeneic and autologous stem cell transplant recipients.<sup>2,3</sup> Autoimmune thrombocytopenia following autologous hematopoietic cell transplantation, for example, has been described in patients with acute myelogenous leukemia, lymphoblastic lymphoma, or breast cancer,<sup>6</sup> but the exact mechanism is not known. Several possibilities have been proposed, which include transient immune system imbalance post transplant, impaired suppressor T cell function, immune dysregulation due to thymic damage caused by chemoradiotherapy, and altered expression of self-antigens occurring as a result of physical damage to stem cells during marrow handling, or viral infections. The frequency of this phenomenon does not differ between the two types of transplants, but autoantibodies in autograft recipients are generally transient, and few autoantibodies are generated.<sup>4</sup> Clinical manifestations are also limited to a few organs.<sup>4</sup> However, our patient with NHL developed systemic RA following high-dose chemotherapy and autologous PBSCT. He had HLA-DRB1 0405 and showed positivity for rheumatoid factor, both of which are considered to be predisposing factors for RA.

A correlation has been demonstrated between predisposition to RA and a certain HLA haplotype.<sup>7</sup> DRB1 0405, observed in our patient, is the predominant allele among shared epitopes in Japanese RA.<sup>7</sup> The frequency of DRB1 0405 is reported to be significantly higher in RA patients than in normal controls (45.3% vs 28.0%), and DRB1 0405 is associated with an increased risk for developing RA.<sup>7</sup> Genetic predisposition to RA may be an important factor for the occurrence of systemic autoimmune disease after stem cell transplantation.

Organ-specific disease, such as insulin-dependent diabetes mellitus, autoimmune thyroiditis, autoimmune thrombocytopenia, and psoriasis have been reported to be transferred to allograft recipients.<sup>8</sup> However, systemic autoimmune disease such as RA or systemic lupus erythematosus is rarely transferred, possibly due to the complexity of the cellular immune disorder of RA, with multicellular dysfunction of lymphocytes, monocytes and antigen-presenting cells. Furthermore, a case report<sup>9</sup> demonstrating that allogeneic bone marrow transplantation from a donor with severe active RA did not result in adoptive transfer to the recipient suggests that additional genetic predisposing factors may be required for the development of RA, as observed in our case. Koch *et al*<sup>10</sup> described three patients who presented with rheumatic symptoms following autologous stem cell transplantation. All three patients were shown to be HLA-B27-positive, suggesting that the transient immunosuppression following autologous stem cell transplantation, and bacteremias and/or infections in the

immediate post-transplant period may trigger the initiation of rheumatic disease in susceptible patients.

Other possible explanations for the development of RA following autologous PBSCT include inhibition of thymus-dependent clonal deletion of autoreactive T lymphocytes, dysregulation of regulatory T cells which inactivate self-reacting T cell clones outside the thymus, and modification of self-antigens by viral infection or drug. Patients have developed arthritis following vaccination.<sup>11</sup> Moreover, G-CSF administration for drug-induced agranulocytosis may exacerbate RA disease activity, corresponding to an increase in neutrophil counts.<sup>12</sup> Neutrophils directly damage synovial tissues by production of O<sub>2</sub><sup>-</sup>, NO, and other chemical mediators. The increased number and function of neutrophils by G-CSF may be related to the development of RA in our patient, although G-CSF is routinely given to autograft transplant recipients. One further explanation for why the RA was not manifested until after transplant may be that the patient was immunosuppressed by this lymphoma.

Autologous stem cell transplantation has recently been investigated for patients with autoimmune disease, based on the low incidence of transplant-related mortality and on the hypothesis that there is a 'resetting' of the immune system which enables better disease control. However, remission durability of autoimmune disease after PBSCT is still unclear and early relapse has been observed. Such a 'resetting' may have resulted in RA in our patient. The development of RA after high-dose chemotherapy and autologous PBSCT in this case suggests that patients with factors predisposing to systemic autoimmune disease are at risk following autologous stem cell transplantation.

### Acknowledgements

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