



Case report

Late-onset unilateral renal dysfunction combined with non-insulin-dependent diabetes mellitus and bronchial asthma following allogeneic bone marrow transplantation for acute lymphoblastic leukemia in a child

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Summary:

We report a child with T cell acute lymphoblastic leukemia who developed late-onset multiple complications after allogeneic bone marrow transplantation from an HLA-matched sibling. The preparative regimen consisted of total body irradiation (TBI, 12 Gy), splenic irradiation (6 Gy) and cytosine arabinoside (3 g/m² × 10). Splenic irradiation was added because of persistent splenomegaly in spite of intensive chemotherapy. He developed bronchial asthma 1½ years post transplant. He presented with microhematuria and proteinuria 4½ years post-transplant, which were due to unilateral left renal dysfunction. He developed type II, non-insulin-dependent diabetes mellitus 8 years post-transplant. A biopsy from the left kidney was not compatible with diabetic nephropathy. All these complications appear to be independently related to BMT, particularly TBI and/or splenic irradiation.

Keywords: BMT nephropathy; diabetes mellitus; bronchial asthma

versial.^{5,6} It is generally considered that insulin-dependent diabetes mellitus (IDDM) is related to immunological mechanisms, and there is a report of adoptive transfer of IDDM.^{7,8} However, it is supposed that non-insulin-dependent diabetes mellitus (NIDDM) has nothing to do with immunological mechanism in humans although immunological mechanisms have been reported to be implicated in an animal model.⁹ This is the first report of a patient who developed unilateral renal dysfunction and NIDDM after allogeneic BMT for which total body irradiation (TBI) and/or splenic irradiation were used in the preparative regimen.

Case report

A 7-year-old boy was diagnosed with acute lymphoblastic leukemia in September 1987. Blasts were phenotypically T cell antigen positive with chromosomal hypodiploidy. He had hyperleukocytosis (WBC 730 × 10⁹/l) and massive hepatosplenomegaly at the time of diagnosis. He was treated with vincristine, l-asparaginase, doxorubicin and prednisolone with response. Second-line chemotherapy with methotrexate (MTX) and l-asparaginase were given. He achieved a complete hematological response after 5 weeks, although splenomegaly persisted. He was referred for BMT following maintenance chemotherapy for 2 months. Before grafting, he was prepared with high-dose cytosine arabinoside 3 g/m² twice daily i.v. for 5 consecutive days (total 10 doses), total body irradiation (TBI) of 12 Gy in four fractions and splenic irradiation of 6 Gy in four fractions. Splenic irradiation avoided irradiation to adjacent organs. He received a marrow allograft from an HLA-matched younger sister. GVHD prophylaxis was with cyclosporine and intravenous MTX according to the Seattle protocol. He had a fever caused by respiratory syncytial virus infection on days 5 to 22. On day 19, renal toxicity from cyclosporine resolved after 2 days discontinuation. The peripheral blood leukocyte count exceeded 1.0 × 10⁹/l on day 22 and the platelet count exceeded 50 × 10⁹/l on

Late-onset complications after bone marrow transplantation often become life-threatening or decrease quality of life in patients. Significant complications include second malignancy, growth retardation, thyroid dysfunction, gonadal dysfunction and cataract formation. Recently nephropathy and diabetes mellitus (DM) have been noted.¹⁻⁴ We describe a patient with the successive complications of asthma, nephropathy and DM after BMT which are gradually reducing quality of life. In this case nephropathy was a unilateral renal dysfunction related to splenic top-up irradiation. Whether additional splenic irradiation has a beneficial effect for hematological malignancy is contro-

day 36. His bone marrow showed complete chimerism with 46 XX female type on day 75. He was discharged on day 78.

In 1989, he was referred to Mie University Hospital for further follow-up. One and a half years after BMT he presented with symptoms of bronchial asthma which was confirmed by a positive acetylcholine inhalation test (threshold level: 5000 $\mu\text{g}/\text{ml}$; normal level: over 10000 $\mu\text{g}/\text{ml}$) and positive exercise test. His total IgE increased to 1458 IU/ml from 312 IU/ml prior to transplantation. This respiratory problem was not related to bronchiolitis obliterans as there was no progression and broncho-dilators were effective. Skin tests revealed similar results between donor and recipient (donor: alternaria +, aspergillus -, penicillium ++, candida ++, cotton ++, cryptomeria -; recipient: alternaria +, aspergillus -, penicillium +, candida -, cotton +, cryptomeria -). Although he had no allergic history, the donor had atopic skin and allergic conjunctivitis. The bronchial asthma was well controlled after almost 1 year taking broncho-dilators and anti-allergic drugs. In May 1992 he presented with microscopic hematuria (3+) and proteinuria (41 mg/dl). A left atrophic kidney and a right compensatory hypertrophic kidney were revealed on computed tomography (Figure 1a) while CT examination before BMT had shown no abnormal findings. Although the BUN (16 mg/dl) and creatinine (0.6 mg/dl) were within normal limits and hypertension was not present, a renogram showed a severely hypofunctional pattern from the left kidney and a delayed pattern from the right kidney (Figure 1b). From 1994, his weight gain became notable (+12 kg/year). Obesity (body mass index = 26.7; normal level: 19.7–25.3), hyperlipidemia (total cholesterol: 189 mg/dl; triglyceride: 392 mg/dl) and high

uric acid (14.4 mg/dl) were present. In January 1996, glycosuria (139 mg/dl) developed and non-insulin-dependent diabetes mellitus (NIDDM) was diagnosed after a 75 g oral glucose tolerance test (data of pre, 30, 60, 120, 180 min were 138, 290, 347, 288, 143 mg/dl for blood sugar and 11, 45, 100, 180, 33 $\mu\text{U}/\text{ml}$ for insulin). Anti-glutamic acid decarboxylase antibody was negative. There was no DM in his family within the third degree of kinship. The DM was controlled by diet but the nephropathy gradually worsened. In July 1997 a left renal biopsy was performed with the intent of establishing a relationship between the nephropathy and the DM. Histological findings (Figure 1c and d) showed focal sclerotic changes of the glomeruli which were not compatible with typical diabetic nephropathy. After BMT he remained in complete remission and showed no symptoms or laboratory data of chronic GVHD. Karnofsky's score was 90% 9 years post-transplant.

Discussion

Late onset complications after BMT often affect quality of life. We describe a case which showed successive complications after BMT over a long follow-up period.

Late onset renal dysfunction (BMT nephropathy) occurs in up to 20% of long-term BMT survivors.^{1,3} BMT nephropathy is the modern counterpart of classical radiation nephritis. It is generally concluded that TBI is the major cause of this syndrome. Acute radiation nephritis is first clinically apparent 6–12 months following exposure of both kidneys to moderate doses of radiation whereas chronic radiation nephritis appears 18 months or more following the treatment.² In this case the nephropathy is of the latter type

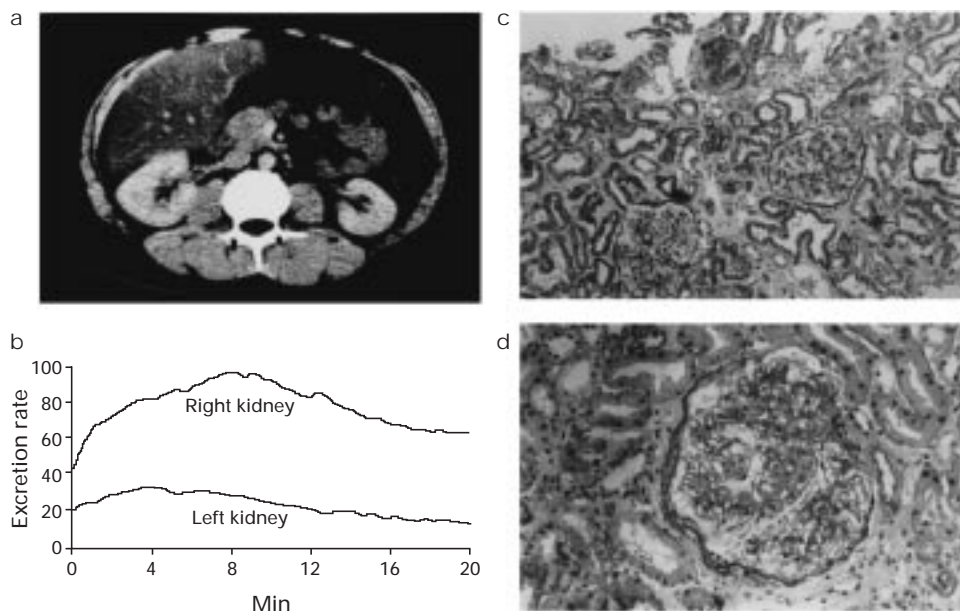


Figure 1 Findings of left renal dysfunction. (a) Abdominal CT scan with contrast enhancement showing left atrophic kidney and right compensatory hypertrophic kidney. (b) Renogram showing severe hypofunctional pattern on the left kidney and delayed excretion on the compensated right kidney. Histology of left renal biopsy taken after the time of overt diabetes mellitus, showing (c) some glomeruli degenerated with relatively conserved interstitial and vascular area (PAS, $\times 100$). Approximately 10% of glomeruli had extensive mesangiolytic changes associated with expansion of basement membrane (PAS, $\times 400$) (d) and the other 10% of glomeruli contained hyalinization and segmental sclerotic change. These findings were not compatible with typical diabetic nephropathy, but with chronic radiation nephritis.

because the symptom of nephropathy appeared over 4 years after BMT. Recent results indicate that chronic radiation-induced tissue injury involves a complex and dynamic interaction between parenchymal and vascular cells within a particular organ. Injury to the glomeruli seems to be of particular importance in chronic nephropathy. It involves the glomerular capillary endothelial cell, but at later times the response is predominantly a mesangial cell response, expressed as mesangial hypertrophy and increased mesangial matrix leading to capillary obliteration and glomerulosclerosis.² In this case the main site responsible is the glomerulus. Recent experimental data demonstrate significant protection of radiation-induced nephropathy by post-treatment administration of modulating agents such as angiotensin-converting enzyme (ACE) inhibitors,¹⁰⁻¹² antiplatelet agents¹³ or anti-inflammatory agents.¹⁴

Why the renal dysfunction and atrophy occurred only in the left kidney in this case is open to question. It is generally accepted that the threshold dose for eliminating useful renal function is 15 Gy irradiation delivered even with conventional fractionation.² This patient received 12 Gy of TBI in addition to 6 Gy of splenic irradiation. It seems that the additional 6 Gy of splenic irradiation negatively influenced the left kidney. Dieterle *et al*¹⁵ described additional splenic irradiation rendering a left kidney irreversibly damaged after the toxic effects of cyclosporine. An earlier retrospective analysis showed no difference in survival depending upon whether patients with CML had received prior splenic irradiation or not.⁶ Recently, however it has been considered to offer an advantage, particularly in terms of relapse prevention, without influence on transplant-related mortality among some subgroups.⁵

IDDM are recognized as organ specific autoimmune diseases occurring in genetically predisposed subjects after exposure to one or more environmental factors. Vialettes *et al*⁷ and Lampeter *et al*⁸ described transfer of IDDM by allogeneic bone marrow transplantation. However, it is generally considered that NIDDM is an etiological multi-factorial disease and not related to immunological mechanism. Recently, however, Than *et al*⁹ reported that NIDDM was possibly caused by an immunological mechanism based on the findings NIDDM recovered after allogeneic bone marrow transplantation using an animal model for NIDDM (KK-Ay mouse). To date, there are no reports of patients developing NIDDM after allogeneic BMT. Schouten *et al*⁴ described NIDDM in patients treated with high-dose therapy and autologous BMT. This is the first case of developed NIDDM, rather than IDDM following allogeneic transplantation. At the present time the 14-year-old donor has no symptoms of DM. The donor should be carefully followed for NIDDM secondary to immunological mechanisms, and transfer of NIDDM by BMT to the recipient.

It is known that irradiation can damage endocrine cell function.¹⁶ This patient received TBI and splenic irradiation. Beta cell damage could, therefore, to some extent be explained by the effects of irradiation. The renal histology demonstrated glomerular mesangiolysis and sclerosed glomeruli, but the interstitial and vascular areas were relatively well conserved. Thus the findings were not compatible with typical diabetic nephropathy.

The patient presented with bronchial asthma. His and his

donor's skin tests showed similar patterns. Before BMT he had no allergic history, but his donor had atopic skin and allergic conjunctivitis. It seems that the bronchial asthma and allergic predisposition were transferred by BMT. Agosti *et al*¹⁷ reported that IgE-mediated reactivity is frequently transferred during bone marrow transplantation.

Finally, these successive complications after BMT appeared independently but all of them seemed related to BMT, particularly TBI and/or splenic irradiation. Splenic irradiation prior to transplantation for CML is likely to be of benefit in preventing relapse without conferring any side-effects,⁵ but in this case the additional splenic irradiation possibly produced side-effects late after BMT. Further follow-up is necessary.

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