Nephrotic Syndrome in a Patient with Relapsed of Chronic Myeloid Leukemia after Peripheral Blood Stem Cell Transplantation

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SUMMARY

Nephrotic syndrome (NS) is a well documented complication after allogeneic peripheral blood stem cell transplantation. It is usually due to autoimmune glomerulonephritis and thought to be a clinical manifestation of graft versus host disease. NS has also been reported to be associated with other hematological malignancies. We report a case of nephrotic syndrome in a patient who relapsed after allogeneic peripheral blood stem cell transplantation (PBSCT) for chronic myeloid leukemia (CML). The renal biopsy was suggestive of minimal change disease. There was no other evidence of graft versus host disease. He was treated with high dose prednisolone, with no response and finally succumbed to the underlying disease.

KEY WORDS:
Nephrotic syndrome, GVHD, PBSCT, Chronic myeloid leukemia

INTRODUCTION

Nephrotic syndrome is characterized by a number of renal and extra-renal features. The most prominent features are heavy proteinuria, hypoalbuminemia, edema and hyperlipidemia. Eighty percent of adult NS are due to primary glomerulonephritis. Other uncommon causes of NS include hematological malignancies. NS is also recognized as a possible complication of interferon-α therapy in CML patients. It is not commonly seen in patients with CML without interferon therapy and there have only been four cases reported through our literature review.

NS has also been reported in patients who had undergone allogeneic haematopoeitic stem cell transplant and this was thought to be related to the presence of GVHD and a possible immune mechanism has been postulated.

We describe a patient who developed NS after relapse of his CML after allogeneic PBSCT. The underlying cause of his NS was not determined.

CASE REPORT

CTW, a 32 year-old man was referred to us for allogeneic PBSCT. He presented with hepatosplenomegaly in March 2003. A bone marrow examination confirmed a diagnosis of CML with 30% of blast cell. Cytogenetic study revealed presence of Philadelphia chromosome and additional multiple translocations at chromosome 1q and 21q.

He received allogeneic PBSCT from his HLA-identical brother in September 2003 after conditioning therapy of high dose busulphan and cyclophosphamide. The transplantation was uneventful and marrow at day 21 showed trilineage engraftment with no evidence of disease. At day 84 post PBSCT, a routine bone marrow examination revealed a normal marrow with normal cytogenetic. He had cyclosporine and short term methotrexate as GVHD prophylaxis therapy. There was no evidence of GVHD during the first six months post transplantation.

Unfortunately, his CML relapsed six months after PBSCT. The bone marrow aspirate showed 40% of myeloid blast cells and Philadelphia chromosome was detected. Cyclosporine was stopped and he was advised to commence chemotherapy with donor lymphocyte infusion but this was refused. Therefore, imatinib mesylate 600mg daily was started. His renal and liver functions were normal.

Six weeks later, patient complained of facial puffiness and abdominal distension. On physical examination, he had generalized edema with presence of ascites. There was no evidence of chronic GVHD. Albumin level dropped from 32g/dl to 14g/dl. Total cholesterol level was 8.3mmol/l and 24-hour urine protein was 12.07g. These findings were consistent with nephrotic syndrome. Imatinib was stopped in view of its possible role of causing generalized edema. Subsequent renal biopsy showed no significant glomerular morphological abnormality under microscopic examination. A minimal change disease was assumed to be the cause of the nephrotic syndrome although immunoflouroscence and electronmicroscopic study of the tissue was not done.

A connective tissue screening showed a high titre of anti-nuclear factor (ANF) (1:320) with normal dsDNA and complement levels. There was also a persistent raised alkaline phophastase level. A liver biopsy was performed to exclude possible GVHD. However, the biopsy revealed features of extramedullary hemopoiesis with no evidences of GVHD. HBsAg, anti-HCV antibody and cytomegalovirus serology were negative.

He was treated empirically as minimal change glomerulopathy with high dose prednisolone. However, there was no response after six weeks of treatment. High dose of imatinib was resumed when his oedema was controlled with diuretics. His condition deteriorated and he passed away few months later.

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DISCUSSION

There are several case reports of NS occurring after PBSCT. Most of the cases were membranous nephropathy and other pathologies are due to diffused proliferative glomerulonephritis and minimal change disease. All of the cases have concurrent evidence of GVHD, either acute or chronic. It is suggested that GVHD in these cases triggered an autoimmune response, thereby causing immune-complex deposition in the glomeruli.

In our patient, NS is unlikely to be related to GVHD since there was no sign of GVHD. However, it is interesting to note that a high titer of anti-nuclear antibodies (ANF) was detected in this patient. In murine experimental chronic GVHD, ANF which generates immune-complex is found to deposit or form in the kidney. This is further supported by the fact that most of the cases reported in various journals responded partially or completely to immunosuppressant including steroids. Although the significance of ANF in human GVHD cases remains unknown, most authors agreed that NS post PBSCT might be an autoimmune glomerulonephritis other than that induced by GVHD. Therefore, the high titer of ANF here might be a sign of autoimmune process that may be due to other unknown factors instead of GVHD.

CML is also known to cause NS. There was a case of CML patient presented with NS reported by Yoshizaki N *et al* in 1989. The histology of the renal biopsy was membranous proliferative glomerulonephritis. Other case reports had also been published which established an association between NS and CML. The histology of the renal biopsies was either minimal change disease[1] or membranous glomerulonephritis[2].

Rarely, NS is observed in patients with CML after treatment of interferon-α[3]. The pathophysiology for it is unknown. Jadoul et al reported 12 cases of nephropathy after treatment with interferon-· for CML which showed thrombotic microangiopathy.

In this case, this patient had no interferon therapy before or after his transplantation and NS occurred soon after he relapsed and after commencing imatinib mesylate. There has been no known association of imatinib mesylate with NS. Imatinib mesylate is a tyrosine kinase inhibitor which targets at the molecular level. One of the adverse effects is generalized edema which can occur in 90% of patient. Majority of patients who are on this drug complained of weight gain and occasionally oedema. There have been some cases of pleural effusion and cardiac failure associated with this drug but thus far there has been no report of NS.

We felt that the most likely cause of our patient's NS is due to CML although it occurred only after PBSCT but not at the early stage of the disease. It is important to note that it occurred rapidly after the GVHD prophylaxis therapy was stopped. The possible explanation could be that the NS was initially suppressed by the cytotoxic and immunosuppressive therapies during and after the PBSCT. It is likely that the NS in this patient was an autoimmune event, which was unmasked by the withdrawal of the immunosuppresant. However, the exact mechanism of it still remains uncertain. The high titer of the ANF further supports the likelihood of the autoimmune origin of his NS. Perhaps the cause of the non-responsiveness of the proteinuria to steroids was due to the persistence of CML. Unfortunately, the patient refused to receive further therapy and subsequently succumbed to his underlying disease.

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