


doi: 10.1093/ndt/gfn202

Advance Access publication 10 April 2008

Reply

Sir,

We thank Dr Philip W. Connelly for his interest in our paper, and for raising valuable comments on our methodology of measuring paraoxonase activity in HDL-containing supernatant from serum after the precipitation of apolipoprotein B-containing lipoproteins using the dextran-sulfate method. Paraoxonase 1 is an important HDL-associated antioxidative enzyme and there are data showing that paraoxonase 1 is active in the HDL-containing supernatant after dextran-sulfate precipitation. Navab et al. have reported that adding purified human paraoxonase 1 to HDL-containing supernatant after dextran-sulfate precipitation of plasma from patients with coronary heart disease can restore the antioxidative function of HDL [1].

Paraoxonase has multiple activities including organophosphatase, phosphotriesterase, arylesterase and thiolactonase [2]. The EnzChek® Paraoxonase Assay from Invitrogen™ used in our study is a homogeneous fluorometric assay for the organophosphatase activity of paraoxonase. The substrate is a fluorogenic organophosphate analogue as indicated in the protocol provided by the manufacturer. As pointed out by Dr Connelly, the EnzChek® Paraoxonase Assay has also been used by Rector et al. for the measurement of paraoxonase-1 activity in serum and in HDL [3], and the results are corroborated by the measurement of enzyme mass but not by serum arylesterase activity. We welcome Dr Connelly’s suggestion that arylesterase activity should also be measured. We have shown that the organophosphatase activity in HDL was significantly reduced in diabetic subjects with microalbuminuria or proteinuria. Since we compared diabetic subjects with healthy controls in our study, and serum, plasma and HDL samples from diabetic subjects and healthy controls were all handled in the same manner, any methodological problem would apply to both groups and therefore unlikely to bias our results.

Conflict of interest statement. None declared.

Sir,

Recently we read with interest the paper of Terrier et al [1] and the letter of Sugimoto et al [2] regarding the occurrence of membranous nephropathy (MN) after haematopoietic stem cell transplantation (HSCT). Terrier used Rituximab, a monoclonal CD20 antibody, in 1 out of 5 patients without important benefit; Sugimoto used corticosteroid therapy with success. Looking at the data, a large body of evidence suggests a role of activated B lymphocytes in the pathogenesis of idiopathic MN; therefore, it is considered an immunemediated glomerulonephritis [3]. In MN post-HSCT renal damage could be due to conditioning therapy, nephrototoxic therapies to prevent GVHD and their natural withdrawal in the follow-up with a decrease in immuno-suppression [4]. Hence, direct nephrotoxic effects as well as direct or indirect humoral activation could be invoked as pathogenetic mechanisms [1].

We report a case of nephrotic syndrome (NS), without cGVHD manifestation, due to MN post-HSCT treated with Rituximab. A 68-year-old white woman with follicular Non-Hodgkin’s Lymphoma (NHL, stage III) underwent an allogenic HSCT from an HLA-identical donor. A conditioning regimen consisting of steroids and cyclosporine (CsA) was stopped early due to worsening of renal function and hypertensive crisis with remission of treatment-related complications. Twenty-three months after transplantation and 10 months after the interruption of all immunosuppressive therapies, she presented with NS, with protein excretion of 35.2 g/24 h, serum albumin level 2.8 g/dl, moderate renal function impairment [creatinine 0.88 mg/dl, measured creatinine clearance –(CrCl) 28 ml/min, calculated CrCl 49.9 ml/min]. She had never presented any evidence of cGVHD nor NHL recurrence. A renal biopsy found subepithelial deposits in electron microscopy, and IgG and C3 in granular deposits by immunofluorescence indicating early stage MN. At first, she was treated only with corticosteroid

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Advance Access publication 2 April 2008

Rituximab in membranous nephropathy after haematopoietic stem cell transplantation

Sir,

1. Navab M, Hama SY, Hough GP et al. A cell-free assay for detecting HDL that is dysfunctional in preventing the formation of or inactivating oxidized phospholipids. J Lipid Res 2001; 42: 1308–1317


doi: 10.1093/ndt/gfn205

Advance Access publication 10 April 2008

Conflict of interest statement. None declared.
therapy (methylprednisolone 1 g/day for 3 days; then prednisone decreased until 0.5 mg/kg/day), proteinuria relapsed after the first month. Patient was not eligible for combining corticosteroids and CsA therapies due to previous nephrotoxicity, and other myelosuppressive therapies were avoided. Then therapy was changed to Rituximab, 375 mg/m² weekly for four doses. The results were a sustained complete remission of proteinuria (7 months at the last follow-up), serum albumin and renal function normalization and the absence of adverse effects. In our case the onset of MN seems to be temporarily associated with the suspension of immunosuppressive therapy but patients did not manifest any evidence of cGVHD. As well as other few reports described, MN after HSCT without GVHD is thought to be a renal manifestation of GVHD. Thus we cannot exclude both a de novo MN occurred after HSCT and a secondary form in which MN may be the unknown form of renal cGVHD. Our case merits presentation because of the encouraging results we had with Rituximab. There are few reports describing rituximab use in MN post-HSCT with discordant results. According to immunomediated MN theory, also in the secondary form, an agent that specifically interferes with B cells would ideally represent the first step towards selective therapy.

Conflict of interest statement. None declared.

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Editorial Note: Dr Terrier et al declined the invitation to reply to this letter.

doi: 10.1093/ndt/gfn110

Advance Access publication 2 April 2008

Reply

Sir,
We thank Dr Ferrannini et al. for their interest in our letter. Our and their cases did not show any history or manifestations of chronic graft-versus-host disease (GVHD); thus, there is a possibility that de novo membranous nephropathy (MN) might have occurred in these cases. However, these MN developed after the cessation of immunosuppressive therapy; therefore, we cannot completely exclude that MN was a renal manifestation of GVHD. Further, the study of Dr Ferrannini et al. indicated that activated B lymphocytes might have played an important role in the development of MN after allogeneic haematopoietic-stem-cell transplantation (HSCT) because Rituximab, a monoclonal CD 20 antibody, had dramatically improved nephrotic range proteinuria. Further accumulation of clinical studies including case reports is necessary to confirm the pathogenesis of MN post-allogeneic HSCT.

Conflict of interest statement. None declared.

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doi: 10.1093/ndt/gfn170

Advance Access publication 10 April 2008

The role for adjunctive treatment to plasma exchange in thrombotic thrombocytopenic purpura

Sir,
Cardiac involvement in thrombotic thrombocytopenic purpura (TTP) is being increasingly recognized as one of the leading causes of mortality in this condition [1,2]. Physicians have previously rarely reported any symptoms related to the heart during acute episodes of TTP despite cardiac involvement being a persistent feature in autopsy studies, both pre- and post-plasma exchange era. This may be due to several reasons including emphasis on Moschowitz’s pentad, the common symptoms of dyspnoea and tiredness thought to be due to anaemia rather than heart failure and the relatively younger population affected by TTP who usually do not have cardiac risk factors [2].

Recently, there has been increasing interest in the understanding of the pathophysiology of TTP where the lack of ultra-large von Willebrand factor (VWF) multimer cleaving enzyme (ADAMTS-13) due to congenital deficiency or inhibition by antibodies has been demonstrated to be the causative factor for acute TTP. However, it is difficult to explain all the different clinical features of TTP only as consequences of ADAMTS13 deficiency or inhibition. The fragmentation of erythrocytes from the haemolysis releases free haemoglobin into the plasma, which overwhelms the protective haemoglobin scavenging mechanisms (like haptoglobin). The cell-free haemoglobin is free to bind to nitric oxide (NO), the endothelial-derived relaxation factor, at intensity much higher compared to non-haemolytic states. This would result in intense vasoconstriction and inhibited platelet aggregation, two important antithrombotic