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 immunomeditated 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.

1Department of Medicine Michele Ferrannini
2Department of Internal Medicine Gisella Vischini
“Tor Vergata” University, Rome Nicola Di Daniele
Italy
E-mail: m.ferrannini@inwind.it


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.

Department of Medicine, Shiga University of Medical Science Otsu, Shiga 5202192, Japan
E-mail: toshiro@belle.shiga-med.ac.jp
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 ultralarge 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 uninhibited platelet aggregation, two important antithrombotic
effects of NO. Gladwin et al. demonstrated this concept in paroxysmal nocturnal haemoglobinuria and in sickle cell disease [3]. A similar mechanism and intense haemolysis may also explain some of the non-cardiac symptoms of TTP including abdominal pain, fever and transient neurological symptoms and renal impairment [4].

An early increase in VWF has been reported to be a risk factor for adverse outcomes in the acute coronary syndrome. The deficiency of ADAMTS-13 in TTP should also theoretically cause platelet aggregation by the ultralarge VWF multimers and contribute to the increased incidence of cardiac events. Matsukawa et al. showed a plasma ADAMTS13 value and the VWF/ADAMTS13 ratio as being useful for monitoring in-hospital outcome events in patients with acute myocardial infarction (MI) and also for the prediction of 1-year adverse cardiovascular events after the infarct [5]. Though they demonstrated that plasma ADAMTS13 antigen levels decreased significantly during the first 3 days of hospitalization, the levels were noted to increase gradually afterwards. This finding could be explained as binding of the ADAMTS13 to the VWF in the lesion responsible for coronary thrombus formation and forming a tight enzyme–substrate complex resulting in the reduction of measured ADAMTS13. Plasma samples obtained more than 6 months after an MI, reveal a positive rather than negative association of ADAMTS13 levels with risk of MI in men and concluded that a detrimental effect of low levels of ADAMTS13 is unlikely [6]. So, the question remains whether ADAMTS-13 deficiency in TTP is responsible for the cardiac dysfunction.

It is interesting to observe that NO, either endogenous or exogenous, represents one of the most important defences against myocardial ischaemia-reperfusion injury. The fundamental molecular explanation for NO-mediated cardiac protection is the interaction with components of the electron transport chain and/or the mitochondrial permeability transition pore to limit post-ischaemic myocardial damage. Nitrates, especially long-acting formulations, are also an important part of the treatment of an acute cardiac ischaemic episode. The replenishment of NO with the resulting inhibition of platelet aggregation and vasodilatation would help in preventing coronary ischaemia.

The effectiveness of plasma exchange in patients with TTP has been attributed to the removal of ADAMTS13 autoantibodies and replacement of normal protease activity. However, plasma exchange also seems to be effective for patients who do not have a severe deficiency of ADAMTS13 activity, raising doubts on other factors like NO playing a role in the clinical manifestations. It may be hypothesized that this procedure cleans haemolytic products from the plasma and restores the NO necessary for the platelet antiaggregatory function and the maintenance of vasodilatation. Does this mean a role may exist for nitric oxide suppliers like long-acting nitrate compounds? It would, however, be unethical to replace a very effective treatment like plasma exchange (in spite of its though with its multiple risks) with a tablet formulation but it would be still worthwhile to consider administrating nitrates or novel compounds with similar action to the treatment armamentarium of TTP. This strategy may help reduce the cardiac dysfunction with TTP.

Conflict of interest statement. None declared.

Department of Haematology
University of Liverpool
Liverpool, UK
E-mail: jeckothachil@yahoo.co.uk

5. Matsukawa M, Kaikita K, Soejima K et al. Serial changes in von Willebrand factor-cleaving protease (ADAMTS13) and prognosis after acute myocardial infarction. Am J Cardiol 2007; 100: 758–63
doi: 10.1093/ndt/gfn173

Advance Access publication 14 April 2008

Reply

Sir,

Dr Thachil correctly highlights the important association of thrombotic thrombocytopenic purpura (TTP) and acute myocardial infarction (AMI) which is consistent with our and others’ findings [1,2]. The clinical relevance of this severe TTP complication is further emphasized by recent case series and case reports that describe 12 additional cases of AMI associated with TTP [3]. Furthermore, the author presents two interesting pathophysiological hypotheses which may link TTP with AMI. First, increased levels of ultralarge multimers of the von Willebrand factor (vWF) as present in TTP by decreased or inhibited ADAMTS13, the vWF cleaving enzyme, were associated with adverse outcome in AMI. Secondly, free haemoglobin released by haemolysis during TTP captures nitric oxide (NO). Decreased levels of NO in turn could reduce inhibition of platelet aggregation and coronary vasoconstriction, which are potential factors to induce or aggravate AMI.

However, we would like to comment on several aspects of this letter that put some of the statements provided into perspective. Although AMI has predominately been described in TTP, it is also associated with other types of thrombotic microangiopathy (TMA). These TMA types which account for the majority of all cases, frequently differ from TTP in respect to their pathophysiology, lack of association with decreased or inhibited ADAMTS13 and response to plasma exchange [4]. Despite the effects of NO on coronary vasomotor tone and platelet activation, both effects are moderate, and other major control pathways require consideration in this context. While endothelin and α-adrenoceptors