TRANSPLANT INTERNATIONAL

LETTER TO THE EDITORS

Immune thrombocytopenic purpura and Kaposi's sarcoma in a liver transplant recipient

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Dear Sirs,

Liver transplantation is the treatment of choice for end stage liver disease. Immunosuppression required after liver transplantation (LT) may increase the risk of infections, malignancies and haematological diseases [1]. Kaposi's sarcoma (KS) is a multifocal vascular cancer most commonly observed in association with human immunodeficiency virus (HIV) infection. Human herpes virus 8 (HHV8) infection is necessary to develop KS. KS is a cancer commonly seen in liver transplant recipients [2]. Recently a prevalence of KS of 0.84% [2] has been reported.

Immune thrombocytopenic purpura (ITP) is a rare complication after LT [3]. Lymphoid tissue and passenger lymphocytes from a donor organ may be one of the possible causes of ITP after LT [4]. Moreover, many drugs (immunosuppression) or virus (HIV, EBV, CMV, Parvovirus B19, HCV) after LT can cause non-autoimmune thrombocytopenia. We have recently encountered a patient who had severe, life-threatening primary ITP and KS after LT. The donor was a 60-year-old man who had died of a cerebral haemorrhage. He had no history of severe illness. His platelet count was 253.000/μl just before his death.

The recipient was a 61-year-old man with alcoholic liver cirrhosis and hepatocellular carcinoma. He was transplanted in May 2010. He received tacrolimus-based immunosuppressive therapy. The platelet count at the time of LT and 2 months later were 66 000 cells/μl and 62 000 cells/μl respectively. In October 2010 purple nodules appeared in the leg and a biopsy showed KS. KS was effectively treated reducing immunosuppression (achieving a basal serum concentration of tacrolimus ≈4 μg/l and adding low dose everolimus). In January 2011, the platelet count had fallen to 35 000 cells/μl. Remission of KS was observed. Everolimus and trimethoprim-sulfamethoxazole were discontinued without clinical improvement in the subsequent 15 days. The patient was admitted to our Liver Unit in February 2011 for purpura and severe thrombocytopenia (7000 cells/μl). On admission, the physical examination showed moderate splenomegaly and cutaneous purpura. Platelet blood transfusion was needed to prevent major haemorrhages. Serologies were negative for HIV, parvovirus B19 and HCV. The polymerase chain reaction was negative for CMV, EBV, HHV-8, HHV-6. The Helicobacter Pylori stool antigen test was negative. Antinuclear antibodies, antiphospholipid antibodies and the lupus anticoagulant were negative. Anti-platelet antibodies count (anti glycoprotein IIb-IIIa) was positive and the bone marrow biopsy revealed megakaryocytes present in increased numbers excluding a myelosuppression. On the basis of these data, we made a diagnosis of ITP and started therapy with methylprednisolone 2 mg/kg per day for 7 days and intravenous immunoglobulin (IVIg) 1 g/kg per day for 2 days. The purpura and platelet count improved rapidly (Fig. 1). Corticosteroid therapy was progressively tapered and shifted to prednisone (Fig. 1). There was no recurrence or progression of KS. In October 2011 the patient was in good clinical condition, the platelet count was 88 000 cells/μl. Currently he is taking prednisone (15 mg) and tacrolimus (basal serum concentration ≈6 μg/l).

The diagnosis of KS and of ITP in our patient appears well supported by clinical data and biopsy report. An association between KS and ITP can occur in the context of an immunodeficiency, mainly in HIV [5]. ITP has been also reported in patients with KS who also have malignant disorders of the reticuloendothelial system, such as Hodgkin's disease, lymphosarcoma or Castleman's disease [6,7]. The association between ITP and KS has previously been reported in only one renal transplant recipient [8]. KS and ITP, taken individually, have already been described as possible complications after LT. To the best of our knowledge this is the first description of an association between ITP and KS in a liver transplant recipient.

We hypothesize four possible reasons for this association in our patient:

1 Immune thrombocytopenic purpura might have been unrelated to KS by pure chance

2 Kaposi's sarcoma might have induced the ITP by vessel wall abnormalities and the abnormal sequestration of platelets in peripheral tissues [9]

3 The modification of the immunosuppressive regimen which was made after the diagnosis of KS may have

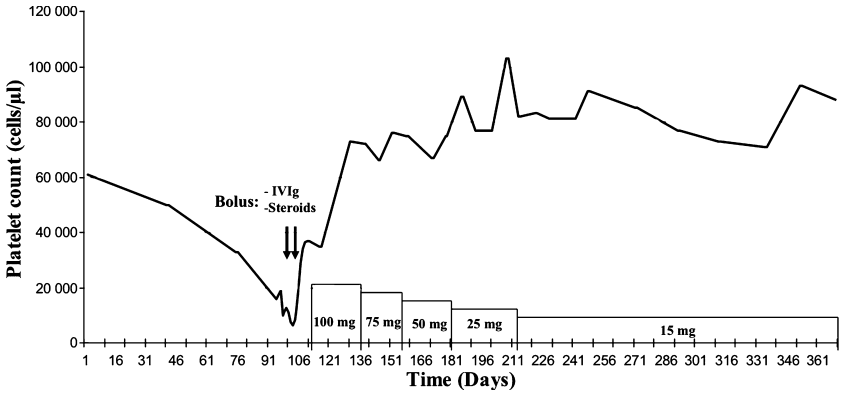

Figure 1 Platelet count from October 2010 to July 2011. On day 103 we started therapy with IVIg (1 g/kg per day) for 2 days and methylprednisolone (2 mg/kg per day) for 7 days (bolus). Under the square is reported the dose of prednisone administered.

altered the immune homeostasis, thereby causing a defect in central tolerance and allowing the selection of autoreactive clones [10]

4 A viral infection (active or latent) may have triggered the ITP

All four assumptions are questionable. The first hypothesis cannot be excluded entirely. However, whereas the incidence of KS after LT is equal to 0.7% [6] and the estimated one for ITP after LT is around 0.05 [6,9], the calculated probability of an association between these two pathological conditions is <0.00035%. The second hypothesis, although attractive, is questionable based on the observation of clinical remission of KS at the time of the development of ITP. As regards the third hypothesis, de novo autoimmune disease such as hepatitis can occur after LT despite immunosuppressive therapy with CNI, mycophenolate mofetil, sirolimus and everolimus. Usually the change of the immunosuppressive regimen appears to be successful in the treatment of this complication. Finally, as regards the fourth hypothesis we had no clinical and microbiological evidence of an active viral infection at the time of development of ITP.

Immune thrombocytopenic purpura represents a life-threatening disease with a poor prognosis if not treated promptly [3]. Its management in a liver transplant recipient who is also affected by KS is a difficult challenge for two main reasons: (i) the introduction of steroids can lead to a recurrence of KS [11] and (ii) despite previous experience with a high dose IVIg in the management of severe thrombocytopenia after liver transplant, there are still some concerns about the fact that the use of immunoglobulin can cause acute hepatocellular rejection. Given the severity of thrombocytopenia in our patient, we used jointly steroids and immunoglobulin. Combining steroids with high dose IVIg was not what in American football is known as the ''Hail Mary pass'', but the result of pharmacodynamic considerations. In fact, we thought that the combination would ensure a synergistic effect by blocking, on the one hand, the synthesis of anti-platelet autoantibodies and by inducing a competitive blockade of FC receptor on macrophages with subsequent reduced platelet clearance on the other. This treatment resulted in a prompt increase in the number of platelets, allowing us to taper quickly the dose of steroids. We did not observe either a recurrence of KS or any evidence of graft damage during the 8-month follow-up.

In conclusion, these observations provide the first clinical evidence of an association between KS and IPT after liver transplantation and provide new insights into the combined used of steroids and high dose IVIg in the treatment of this complex clinical condition.

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Conflicts of interest

The authors of this manuscript have no conflicts of interest to disclose.

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