LETTER TO THE EDITOR

Successful treatment of Evans syndrome post liver transplant with splenectomy and switch from tacrolimus to cyclosporine

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Evans syndrome (ES) is a rare disorder characterized by the association of autoimmune thrombocytopenia (ITP) and autoimmune haemolytic anaemia (AIHA) [1]. It's a chronic disease with frequent exacerbations and remissions. The first line therapy usually consists of corticosteroids and i.v. immunoglobulin (IVIG). Second line therapy is discussed, and several immunosuppressive agents such as rituximab, cyclosporine, mycophenolate mofetil [2] have been used. The splenectomy can also be considered as a therapeutic option. We report a case of severe Evans syndrome after a liver transplant.

Case report

An 8-year-old boy is referred for a refractory Evans Syndrome. This child is the third son of Turkish parents who are family-related. He had two brothers: the first one died at 13 months after a liver transplant for biliary tract atresia and the second one was stillborn with osteogenesis imperfecta.

This boy was diagnosed as having an idiopathic sclerosing cholangitis in early childhood and at the age of five, he received a liver transplant. The immunosuppressive post transplant therapy used was mycophenolate mofetil and tacrolimus.

A first episode of haematological abnormalities occurred twenty months later and was diagnosed as a Parvovirus B19 infection (aregenerative anaemia with haemoglobin: 52 g/l, reticulocyte count <20 G/l and platelet count: 110 G/l). Specific anti-parvovirus B19 antibodies were positive for IgM but negative for IgG. He was treated with IVIG (1 g/kg/day) and mycophenolate mofetil was withdrawn.

Two months after this episode, the diagnosis of ES was suspected because of thrombocytopenia and persistent anaemia (haemoglobin: 101 g/l, platelets: 36 G/l, reticulocytes: 78 G/l). The bone marrow aspiration revealed a hypercellular marrow with normal myeloid and erythroid elements and increased megakaryocytes. The direct Coombs test (DAT) was positive for IgG. Then, the patient developed a haemorrhagic syndrome and repeated red blood cell and platelet transfusions were needed without persistant efficiency. The initial treatment of the disease consisted of IVIG (1 g/kg/day) and corticosteroids (one bolus 1 g/1.73 m^2 and 2 mg/kg/day thereafter). A significant clinical improvement was noticed but severe thrombocytopenia and anaemia (DAT still positive) persisted.

Three months after the initial diagnosis of ES, the patient received anti CD20 monoclonal antibody (rituximab: 375 mg/m^2/week×4) and IVIG (1 g/kg/day) because of an acute haemorrhagic diarrhoea. There was poor clinical response.

Sixteen months later, a lymphoproliferative syndrome occurred with the persistence of severe ES. Clinical presentation included a cervical lymphadenopathy (7×5 cm), a voluminous splenomegaly and jaundice. Biological exams showed haemolysis with anaemia (haemoglobin: 52 g/l), hyperbilirubinaemia (192 μ/mol/l), and a DAT positive for IgG. A severe thrombopenia was associated (platelets <10 G/l) with the detection of platelet antibodies. There was no bone marrow infiltration and the bone marrow karyotype was normal. There was no evidence of autoimmune lymphoproliferative syndrome (Fas-dependent).

The histological study of the cervical adenopathy revealed a B-cell monoclonal lymphoproliferative syndrome. The lymphoproliferative syndrome was not induced by EBV infection (polymerase chain reaction analysis did not reveal the presence of EB viral DNA in the adenopathy and was weakly positive in blood) [3].

Because of the ineffectiveness of IVIG therapy, and also because of the transfusion-dependent nature of the cytopenias with life threatening haemorrhagic syndrome, multiple alternative treatments were successively administered: corticosteroids (2 mg/kg/day), rituximab (375 mg/m^2/week×4), pulse of methylprednisolone, cyclophosphamide (500 mg/m^2×1) and fludarabine (25 mg/m^2/day for 5 days). They were all ineffective.

A rescue splenectomy was then performed. Five days post splenectomy, the red blood cell (RBC) transfusions

were stopped. However a severe thrombopenia (Platelets <20 G/l) persisted with less haemorrhagic signs.

Under the assumption that tacrolimus was responsible for the occurrence of ES, it was replaced by cyclosporine. The blood cell counts (RBC and platelets) improved without further intervention. Currently, the child is in complete clinical and biological remission 40 months after the tacrolimus withdrawal.

Discussion

The management of ES remains a challenge. This disease is characterized by alternating periods of remission and exacerbation. The response to treatment varies even within the same individual across time [2,4].

The first-line therapy [2] is usually corticosteroids and/or IVIG, with a good initial response. However, relapse is frequent and the options for second-line therapy include multiple immunosuppressive drugs, such as cyclosporine [5], vincristine, danazol and more recently rituximab [6,7].

''Rescue'' splenectomy is generally performed when haemolysis becomes uncontrollable with drug treatment. It often leads to improvement, and complete normalization of the blood-cell count. But this improvement is unfortunately transient and relapse occurs in most cases 1–2 months after the surgery. Prasad *et al.* [4] report on 42 patients and note that the splenectomy response varies from 1 week to 5 years with a median of 1 month only.

The role of immunosuppressive drugs in the occurrence of ES should be considered and discussed [8]. Acute haemolytic anaemia has been reported in patients treated with tacrolimus, some of them also having post-transplant lymphoproliferative disorder (PTLD) [9]. In these cases, the haemolysis was shown to be either a drug-induced hypersensitivity to complement-mediated haemolysis or secondary to allo-antibodies derived from passenger lymphocytes contained within the graft. DiGiuseppe *et al.* [9] have reported a case of PTLD in a child treated with tacrolimus for liver rejection. This child was diagnosed to have fulminant AIHA. In the study of Emre *et al.* [10] 388 liver transplant recipients received tacrolimus as primary immunosuppression. Seventy had to switch to cyclosporine. For one patient, the reason for switching was the occurrence of AIHA. Therefore, if the side effects of tacrolimus persist despite dose reduction, switching to cyclosporine is recommended and often leads to the resolution of these adverse effects [11]. The above arguments justify the therapeutic changes in our patient.

Some reports have also shown that Human Parvovirus B19 could be responsible for an autoimmune haemolytic anaemia [12–14], autoimmune thrombocytopenia and neutropenia. The molecular basis of the autoimmunity occurrence and pathogenesis is unclear. In our patient, the role of Human Parvovirus B19 in the occurrence of autoimmune haemolytic anaemia and thrombocytopenia, as well as the tacrolimus toxicity, can be hypothesized.

A common genetic aetiology like an apoptosis disease, which could explain the sclerosing cholangitis and autoimmunity such as ES can also be mentioned in our case but without documentation (Fas-induced apoptosis was normal). This aetiology is likely since the parents are consanguineous and that two of their children have already died, one of them after a liver transplant.

In conclusion, tacrolimus withdrawal should be considered in patients with haemolytic anaemia occurring during immunosuppressive treatment post transplantation.

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