Case Report

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A case of hepatopulmonary syndrome solved by mycophenolate mofetil (an inhibitor of angiogenesis and nitric oxide production)

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The autoimmune lymphoproliferative syndrome (ALPS) is a rare, multisystemic disease, caused by an inherited defect in the Fas apoptotic pathway, characterized by a chronic non-malignant lymphoid accumulation and autoimmune manifestations. Lung, kidney, liver, and gut infiltration is described in severe, multisystemic cases; so far there has been no description of hepatopulmonary syndrome (HPS), for which orthotopic liver transplantation (OLT) is currently the only known effective treatment.

A teenage boy, diagnosed with ALPS at 4 years of age (lymph nodes enlargement, splenomegaly, immune cytopenias), was stable until 13 years of age, when he developed insidious hypoxemia (PaO_2 = 46.7 mmHg).

He was diagnosed with HPS on the basis of hypoxemia, non-cirrhotic liver disease with portal hypertension, and pulmonary vascular dilatation (intrapulmonary shunt = 45%). He was treated with oxygen (maximum 6 L/min), prednisolone and sirolimus. There was significant regression of all manifestations of ALPS, except for the pulmonary symptoms, therefore, after evaluation in referral centers in England, OLT was proposed. Since he was to undergo major surgery, sirolimus, which has wound-healing problems, was switched to mycophenolate mofetil (MMF). Following this change, we observed a huge improvement in pulmonary symptoms and reduction of oxygen needs. The intrapulmonary shunt decreased from 45% to 0% in less than a year, and it has not changed since (18 months after complete normalization), on continued treatment with MMF. Indication for OLT was suspended. In the last year, lymphoid proliferation increased again, with huge splenomegaly, but no recurrence of HPS. The addition of sirolimus to MMF produced again a rapid resolution of lymphoid proliferation.

The dramatic and unexpected regression of HPS may have been due to inhibition of angiogenesis and nitric oxide (NO) production by MMF (both important pathways/mediators in HPS pathogenesis). Therefore, we propose to perform clinical trials with MMF, and/or other angiogenesis and NO inhibitors, on a long-term treatment basis, to confirm their potential as a valid alternative to medical treatment of HPS.

Introduction

ALPS is a rare genetic disorder of disrupted lymphocyte homeostasis caused by defective Fas-mediated apoptosis [1,2]. Manifestations usually appear in the first 5 years of life. Patients can develop a myriad of clinical manifestations, including non-malignant lymphoproliferative manifestations, life-long autoimmune disease, and increased propensity to malignancy. Although lung lymphoid infiltration has been described, HPS has never been reported in association with ALPS [1,2].

HPS is a serious vascular complication that occurs in patients with liver disease and/or portal hypertension, and causes an abnormal age-corrected alveolar–arterial oxygen gradient [5,6]. The diagnosis of HPS in a child with liver disease is established by demonstration of hypoxemia (PaO_2 <80 mmHg) or elevated alveolar–arterial oxygen gradient on arterial blood gas analysis (>15 mmHg), and the presence of intrapulmonary shunting using contrast-enhanced echocardiography or technetium-99 m-labeled macroaggregated albumin (99mTc-MAA) perfusion scan. The diffusing capacity may be reduced because the

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Abbreviations: ALPS, autoimmune lymphoproliferative syndrome; HPS, hepatopulmonary syndrome; OLT, orthotopic liver transplantation; PaO_2, partial pressure of oxygen in arterial blood; MMF, mycophenolate mofetil; NO, nitric oxide; Hb, hemoglobin; WBC, white blood cells; tBil, total bilirubin; cBil, conjugated bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamiltransferase; APTT, activated partial thromboplastin time; ANA's, antinuclear antibodies; CT, computerized tomography; ^{99m}Tc-MAA, technetium-99m-labeled macroaggregated albumin; CO, carbon monoxide; eNOS, endotelial nitric oxide synthase; ET-1, endothelin-1; iNOS, inducible nitric oxide synthase; HMOX1, heme oxygenase 1; IFN-γ, interferon-gamma; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor.

alveolar–capillary interface is too wide to allow for complete equilibration of carbon monoxide with hemoglobin [3].

ALPS therapy is primarily directed toward autoimmune manifestations, particularly autoimmune cytopenias. Patients usually respond to courses of immunosuppression, steroids being the first line treatment. MMF, sirolimus and tacrolimus are effective in chronic recalcitrant autoimmune cytopenias and major lymphoid proliferation, and may spare the use of steroids [2,4].

Currently, OLT is the only established effective therapy for HPS, with priority criteria over other patients enrolled in the list, since these patients have higher morbidity and mortality [5,6].

We report the clinical course of a teenage boy with ALPS and chronic liver disease with portal hypertension that evolved to HPS. He was treated with steroids and sirolimus with improvement in all but pulmonary symptoms, and subsequently, with MMF treatment, there was a complete resolution of the HPS.

Case report

A thirteen-year-old boy, first and unique child of a healthy Portuguese non-consanguineous couple, was diagnosed at the age of 4 years with ALPS on the basis of two major criteria (chronic lymph nodes enlargement and progressive splenomegaly, and lymphocytosis with 33% of double-negative (i.e., CD4−/CD8−) T cells), and two minor criteria (autoimmune cytopenias (thrombocytopenia, haemolytic anemia, neutropenia) and hypergammaglobulinemia). The diagnosis was later confirmed by genetic analysis that identified a mutation in the Fas ligand (*CD95L*) gene (single bp deletion in exon 2) [2].

At 9 years of age, he had severe nose and gingival bleeding. He was pale and had generalized lymphadenopathy and hepatosplenomegaly. Laboratory evaluation showed anemia (Coombs test positive) and thrombocytopenia. He received red blood cell transfusions, intravenous immunoglobulin, and prednisolone. Subsequently, his condition remained stable, and he was treated with prednisolone 5 mg every other day.

At the age of 13 years, he had dyspnea on exertion with progression to shortness of breath and tachypnea at rest. He was thin and small for his age (weight – 29.3 kg, p <5; height – 140.5 cm, p <5). He had signs of central cyanosis (lips, ears), mildly jaundiced sclera, facial spider nevi, palmar erythema and marked digital clubbing (Fig. 1A–C). Peripheral oxygen saturation was 87% (he needed oxygen, 4 L/min via nasal cannula, to maintain oxygen saturation around 93–95%). He had cervical lymphadenopathy (1 cm). Pulmonary and cardiac auscultation was unremarkable. He had a slight abdominal collateral venous circulation. The liver edge was palpable 4 cm below the right margin rib, and the spleen 12 cm below the margin rib. Laboratory evaluation was as follows: Hb 10.6 g/dL (Coombs test positive), WBC 7.16×10^9/L (lymphocyte 46%), platelets 8.5×10^9/L, tBil 1.88 mg/dL, cBil 0.97 mg/dL, AST 160 UI/L (N <34), ALT 110 UI/L (N <44), GGT 80 UI/L (N <66), albumin 35.2 g/dL, APPT 31.2″(N: 29.4″), IgG-2920 mg/dL, IgA-1480 mg/dL, ANA's 1/360, anti-smooth muscle 1/40, double negative (CD4−/CD8−) T cell in peripheral blood 18.1%.

The abdominal ultrasound with Doppler study showed a nodular coarse liver with no focal lesions. The hepatic vessels had normal flow velocities and waveforms. There was a giant splenomegaly (20 cm) with small varices and no ascites. The liver histology showed severe sinusoisal fibrosis (with sinusoidal blood dilatation, numerous lymphocytes, and distortion of trabeculae), mild/moderate pericentrovenular fibrosis, and features of nodular regenerative hyperplasia (Fig. 2A–C). The upper endoscopy showed one grade II varix in the lower esophagus, mild hypertensive gastropathy, and non-specific duodenitis signs.

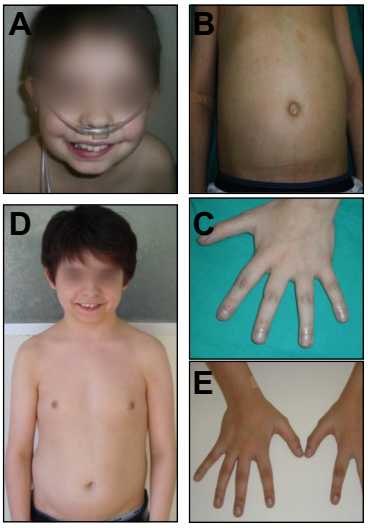

Fig. 1. Clinical features of the patient at 13 years of age (A–C) and 9 months after starting MMF treatment (D and E). (A) Signs of central cyanosis, (B) abdominal distension (giant splenomegaly) and slight collateral venous circulation, (C) digital clubbing, (D) general improved condition and catch-up growth, no signs of central cyanosis and no abdominal distension, and (E) no digital clubbing. (This figure appears in color on the web.)

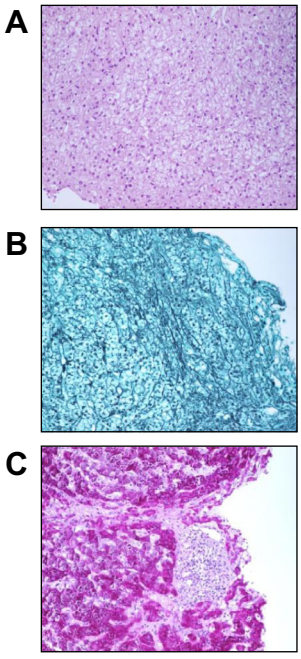

Fig. 2. Liver histology. (A) Discrete lymphocytic infiltrate without necroinflammatory activity interface and no fibrous expansion nor formation of fibrous septa; (B and C) severe sinusoidal fibrosis and mild/moderate fibrosis pericentrovenular, with areas of congestion/sinusoidal blood dilatation and numerous lymphocytes. (This figure appears in color on the web.)