

Rituximab treatment for pulmonary arterial hypertension in adult-onset Still's disease

Sirs,
Pulmonary arterial hypertension (PAH) complicating adult onset Still's disease (AOSD) has been rarely reported, in most cases with poor outcomes. We present here a patient with AOSD and PAH treated successfully with rituximab.

A 43-year-old woman was diagnosed with AOSD based on a one-year duration polyarthritis, intermittent high fever, evanescent maculopapular rash, hepatomegaly, leukocytosis, elevated erythrocyte sedimentation rate (ESR) and serum ferritin; rheumatoid factor and antinuclear antibodies were negative; the patient met Yamaguchi's criteria for AOSD (1).

The patient was previously treated with prednisone 10 mg per day, sulfasalazine and non-steroidal anti-inflammatory drugs, but arthritis persisted. The patient was referred to our center one year after the diagnosis because of progressive dyspnea. Physical examination revealed blood pressure 122/88 mmHg, pulse 100 per minute, respiratory rate 26 per minute; fever and arthritis were not detected. Laboratory findings included ESR 92 mm/hr and leukocyte count of 11,800 per mm³. Chest x-ray, pulmonary CT-scan and pulmonary function tests were normal. Two transthoracic Doppler echocardiograms performed 14 days apart showed normal ejection fraction

(60%), and an estimated pulmonary artery systolic pressure (ePAP) of 63 mmHg and 65 mmHg, respectively, suggesting severe pulmonary arterial hypertension. The diagnosis of PAH was based on Yoshida criteria for PAH in rheumatic diseases (3), and the association with AOSD was assumed since no other causes were found.

The patient was treated with sildenafil, and bolus of methylprednisolone with cyclophosphamide every month for 3 months, with no significant improvement. Because of the persistency of elevated ESR and ePAP despite treatment, she was started on rituximab 2 gr (one gram 14 days apart). Serial measurements of ESR and ePAP estimated by echocardiogram were performed during treatment with rituximab and thereafter. Dyspnea disappeared, ESR decreased to 8 mm/hr and PAH decreased to 30 mmHg (Fig. 1). Rituximab (1 gr) was prescribed in 3 other occasions 11 months apart. At last follow-up 30 months after starting rituximab, patient continue asymptomatic.

AOSD is a systemic inflammatory disorder characterised by seronegative inflammatory polyarthritis with systemic involvement. The most commonly reported pulmonary manifestations include pleuritis, pleural effusion, pneumonitis and diffuse infiltrates on chest x-ray. The association of PAH and AOSD is uncommon; seven cases has been reported since 1990 (4-9). The available data showed 5 female patients, the range of age from 18 to 41 years, and the disease duration to the PAH diagnosis ranged from 6 months to 9 years. Four of these patients died (4-6), two patient outcomes were not

reported (7, 8) and one patient did well on anakinra (9). PAH has been reported also in other rheumatic diseases, with a 3-fold increased mortality when compared with idiopathic forms of PAH (2).

The measurement of ePAP by Doppler echocardiogram is the most useful screening tool for patients with symptoms consistent with PAH (2, 3). Indeed, right heart catheterisation is not mandatory in systemic rheumatic diseases, as per recent criteria (3). The diagnosis of PAH by echocardiogram is based on an ePAP ≥ 36 mmHg (3).

Rituximab has been used in three other cases of AOSD but without PAH. In our case, rituximab was used because of failure to other treatments, and after the reported dramatic clinical response in a patient with systemic lupus erythematosus associated PAH (10). Alterations in cytokine production may have an important role in the pathogenesis of AOSD, with a predominance of Th1 cytokine-producing cells in both peripheral blood cells and affected tissues. It is possible then that B cell depletion after rituximab treatment might down regulate the release of T cell mediate pro-inflammatory cytokine release in AOSD. It seems now that PAH complicating adult-onset Still's disease may have a better prognosis.

J. PADILLA-IBARRA, *Medical Student*¹
A. SANCHEZ-ORTIZ, *MD*²
C. SANDOVAL-CASTRO, *Medical Student*¹
C. RAMOS-REMUS, *MD, MSc*²

¹Universidad de Guadalajara, Guadalajara, México; ²Unidad de Investigacion en Enfermedades Cronico-Degenerativas, Guadalajara, México.

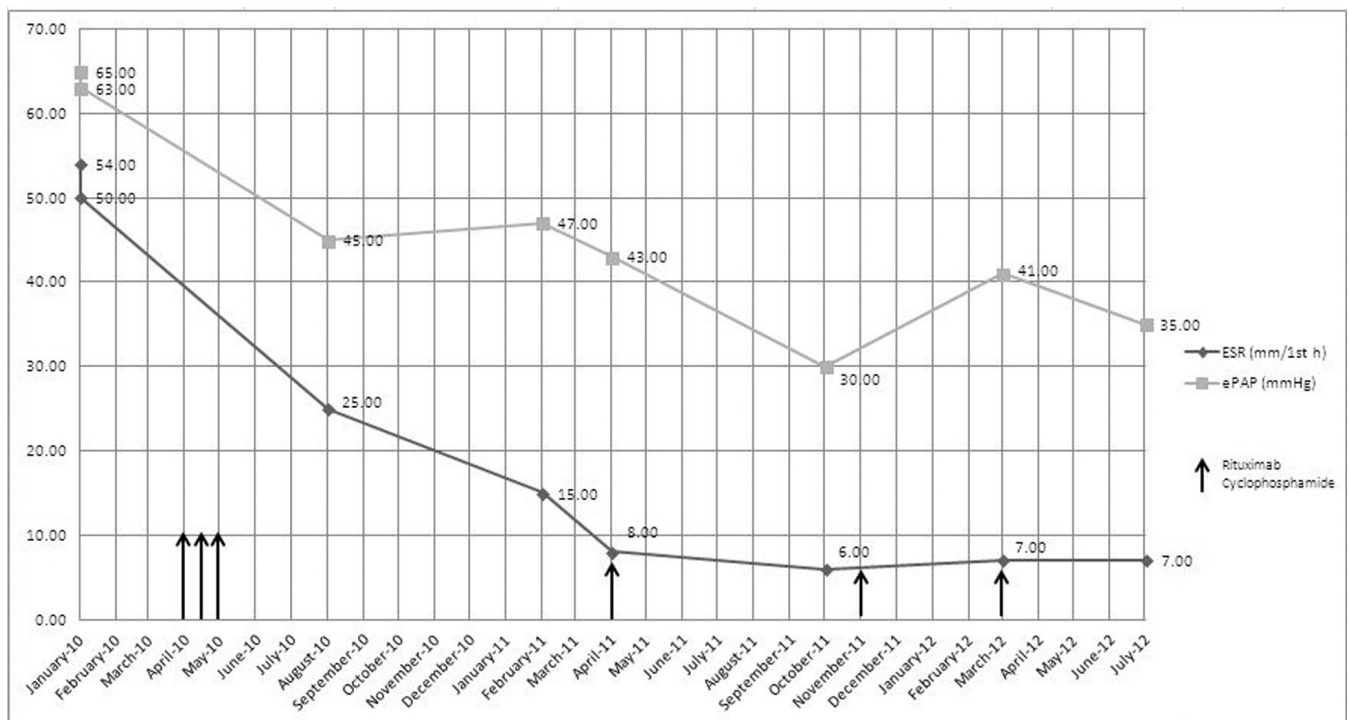


Fig. 1. Decreased levels of ESR and estimated pulmonary artery systolic pressure (ePAP) after treatment with rituximab and cyclophosphamide.

Letters to the Editors

Address correspondence and reprint requests to:
Cesar Ramos-Remus, MD,
MSc, Colomos 2292, Providencia,
Guadalajara 44620, Mexico.
E-mail: rramos@cencar.udg.mx
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