Improved PAH in a Patient with Large Granular Lymphocyte Leukemia under Methotrexate

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Abstract

We report the case of a 39 year old woman who developed pulmonary hypertension (PH) associated to T-cell large granular lymphocyte leukemia (LGL leukemia). Initial therapy with sildenafil did not improve the patient’s symptoms sufficiently. Methotrexate (MTX) therapy was started 20 mg s.c./week. The patient’s symptoms rapidly improved, exercise capacity increased and pulmonary hemodynamics ameliorated. A year later, MTX was reduced and then stopped due to side effects (nausea). Shortly after, the patient’s clinical condition and PH hemodynamics measured by echocardiography worsened. Re-introduction of MTX led to re-improvement with regain of full daily activity in functional class I. Our case is the second case showing a clear improvement of LGL leukemia associated PH.

Keywords: Pulmonary Arterial Hypertension; Methotrexate; Large Granular Lymphocyte Leukemia

Introduction

A 39-yr-old woman with a medullary T-cell-lymphocytosis (LGL: large granular lymphocyte leukemia) known for 18 years presented with fatigue and slowly progressive exertional dyspnea over the last 4 years. The patient does not recall that she had enlarged lymph nodes. The patient underwent splenectomy at the age of 13 due to an Evan’s syndrome. The patient is HIV negative and has no autoimmune disorder. After diagnosis, the patient was initially treated with Cladribin and CVP (cyclophosphamid, vincristine, prednisone), which led to complete remission until a relapse 9 years later, which was successfully treated with MTX and prednisone.

At our hospital, the first hematological control was in 2012 and macrocytic hyperchromic anemia with thrombocytopenia was found (hemoglobin 111 g/l, thrombocytes 46G/l, leucocytes 4.97 G/l: from which neutrophiles 2.39 G/l and lymphocytes 3.29 G/l (56.5% lymphocytes)). The bone marrow was hypercellular with 80% infiltration of atypical T-lymphocytes, compatible with a LGL-leukemia. She was in dyspnea WHO functional class III at her first visit in our PH outpatient clinic with a 6 minute walk distance (6MWD) of 495 m. Her cardiovascular history was unremarkable. Due to relapsing histoplasmosis the patient was under suppressive itraconazole therapy since 2004 and well controlled ever since.

Thoracic computed tomography was without signs for reactivated histoplasmosis but showed a markedly dilated pulmonary artery (38 mm). The diffusion capacity for carbon monoxide was highly reduced (39% predicted) and echocardiography revealed a D-shaped septum/right ventricle with a tricuspid pressure gradient of 50mmHg. Right heart catheterization confirmed precapillary pulmonary hypertension with a mean pulmonary artery pressure (mPAP)
of 51 mmHg, a pulmonary vascular resistance (PVR) of 5.46 WU and arterial respectively mixed venous oxygen saturation (SaO₂ resp. SmvO₂) of 89 resp. 67%, and pulmonary hypertension (PH) associated to LGL was diagnosed.

Therapy with sildenafil in reduced dose due to interactions with itraconazole was started (10 mg tid) and slowly increased to 25 mg tid. However, PDE-5-inhibitor therapy did not improve her fatigue and dyspnea, and exercise capacity assessed by the 6MWD remained unchanged (~508 m, with desaturation to 89%, Borg scale 4). Endothelin receptor antagonist therapy was not added due to its interactions with itraconazole. Parenteral prostanoid therapy was refused by the patient who was fully active working despite severe limitation.

Literature review revealed a similar patient with LGL-leukemia related PH who responded to immunosuppressive therapy with MTX as second therapy [1]. After interdisciplinary discussion it was decided that with stable histoplasmosis (negative chest CT and urinary PCR) but unstable PH a trial with MTX was started (20 mg s.c./week).

Six weeks after starting MTX a major improvement could be noticed: the patient felt less dyspneic and fatigue (WHO class II), the tricuspid pressure gradient improved to 30 mmHg and the 6MWD improved to 601 m. In the following months, the MTX dose was slowly reduced and finally stopped due to nausea on application days. Consequently, the patient’s dyspnea worsened again to functional class NYHA III and she felt dizzy under exercise. The 6MWD slightly deteriorated (585 m) with a Borg scale of 8 and oxygen desaturation to 87%. The tricuspid pressure gradient increased to 40 mmHg. MTX was reintroduced with 15 mg s.c./week.

Three months later, the clinical state improved (NYHA II), the 6MWD increased to 600 m and pulmonary hemodynamics was markedly improved (mPAP 32 mmHg, PVR 208 dynes, SaO₂ 96%, SmvO₂ 72%).

**Discussion**

PH is a disease with multiples etiologies defined by mPAP ≥25 mmHg at rest [2]. According to the international classification, PH associated to hematological disorders belongs to class V [3].

Our patient undoubtedly profited from MTX therapy as objective and subjective clinical improvement was observed. The therapy with PDE5 inhibitor was maintained at stable low dose. The correlation between clinical improvement after the initiation MTX and the worsening condition in parallel to dose reduction strongly argues for the effectiveness of MTX in PH associated with LGL and points towards an immunological pathogenesis of PH in this condition.

Until now, few cases were published about the association between PH and T-cell LGL leukemia [4-6]. The etiopathological link between PH and LGL is mainly attributed to two distinct pathways. First, it has been demonstrated that LGL infiltrating cells expressed Fas ligand, which activate pro-apoptotic pathways in pulmonary endothelial cells with consecutive Fas-expression [4]. Fas is a known pathogenetic contributor in PH [4]. Second, leukemic cells are directly cytotoxic for pulmonary endothelial cells by activating intracellular signaling pathways (Ras and phosphatidylinositol-3-kinase) via natural killer receptors expressed on their surface and thus may lead to PH [7].

More generally, the association between PH, loss of self-tolerance and autoimmunity is known for years [8-10]. One of the main hypothesis is that it comes to an early loss of self-tolerance in case of defect in the CD4 T-cell compartment as a deficiency of CD4, decreased CD4/CD8 ratio or diminished percentage of CD4+CD25+ described as T regulatory population [8]. Once this immune dysregulation occurred, auto-reactive B and T cells are activated [8]. The autoimmune injury is mediated through a production of auto-antibodies targeting endothelial cells in order to induce vascular apoptosis [8].

Inflammation is a persistent key element in the pathogenesis of PH. Recently, the constant presence of perivascular and interstitial inflammatory infiltrates (predominantly lymphocytes) in lung tissue from patients with pulmonary arterial hypertension was demonstrated [11]. There was a significant correlation between the degree of inflammation and intima and media remodeling so as a trend toward correlating with mPAP [11]. A correlation between survival and level of circulating cytokines has also been suggested [12].

**Conclusion**

This case underlines the necessity to administrate an immunosuppressive therapy in order to reduce the inflammatory response and to improve a PH associated to LGL leukemia.

**References**


4. Lamy T, Bauer FA, Liu JH, Li YX, Pillemer E et al. Clinicopathological features of aggressive large granular lymphocyte leu-


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