Ambrisentan-induced severe asymptomatic thrombocytopenia

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Introduction

A systematic review has reported that the prevalence of connective tissue disease (CTD)-associated pulmonary arterial hypertension (PAH) is estimated to be 13% (1). The latest guidelines recommend monotherapy with ambrisentan for patients in World Health Organization functional class (WHO-FC) II (2), which offers a relative lack of drug interactions and safety (3).

Case Report

A 48-year-old Caucasian woman was referred to Pauls Stradins Clinical University Hospital by her family physician in October 2018. She presented with complaints of progressive exertional dyspnea over the previous 1.5 years. A transthoracic echocardiogram in September 2018 showed a right ventricular systolic pressure of 85 mm Hg. The patient has had Raynaud's syndrome since childhood and is a former smoker of 15 pack-years. On admission, there were no relevant abnormalities found during routine physical examination. There was also no family history for cardiovascular or autoimmune diseases. Laboratory data revealed no significant changes in full blood count, an increased creatinine level of 101 µmol/L, and a plasma brain natriuretic peptide level of 150.06 pg/mL.

A complete rheumatological panel was done (Table 1). The thyroid hormone levels were in the normal range, and hepatitis B, hepatitis C, and human immunodeficiency virus infections were excluded. Right heart catheterization confirmed the diagnosis of precapillary pulmonary hypertension with mean pulmonary artery pressure of 58 mm Hg, pulmonary artery wedge pressure of 7 mm Hg, cardiac output of 3.3 l/minute, cardiac index of 2.1 l/minute/m^2, pulmonary vascular resistance of 15.5 Wood units, and negative response to adenosine in a vasoreactivity study.

To rule out other possible causes, contrast-enhanced pulmonary angiography and ultrasonography of the abdomen, thyroid gland, and parotid and submandibular salivary glands were performed with no abnormal findings. Pulmonary function tests revealed normal lung function with decreased total lung capacity (89%) and residual volume (34%). Her 6-minute-walking test distance was 456 metres with a dyspnea score on Borg's scale of –0, and WHO FC II.

Table 1. Complete rheumatological panel

	Result
ANA, CU	195.6
ENA	Positive
Anti-SSA (Ro 60 and 52 kDa)	Negative
Anti-SSB/LA	Negative
Anti-Sm/RNP	Positive
Anti-Sm	Negative
Anti-Scl 70	Negative
Anti-Jo1	Negative
Anti-dsDNS, IU/mL	55.5
p- and c-ANCA	Negative
RF, IU/mL	20

ANA - anti-nuclear antibodies; Anti-dsDNS - anti-double stranded DNA; ENA - extractable nuclear antigen antibodies; p- and c-ANCA - perinuclear and cytoplasmic antineutrophil cytoplasmic antibodies; RF - rheumatoid factor

The diagnosis of PAH-CTD was made after exclusion of pulmonary hypertension due to lung diseases, chronic thromboembolic pulmonary hypertension, and other rare conditions. PAH-specific therapy with ambrisentan (5 mg PO daily) and heart failure treatment with spironolactone (25 mg PO daily), torasemide (10 mg PO twice per week), and digoxin (0.125 mg PO daily) was started. At the time of discharge, the patient was referred to a rheumatologist.

Two months later, a routine check-up by the patient's family physician demonstrated a platelet count of 8×10^9/L without any symptoms of external bleeding, petechiae, or ecchymosis. The patient was readmitted to the hospital for further investigation and treatment. Antiphospholipid antibodies immunoglobulin M and immunoglobulin G, serum protein electrophoresis, and anti-platelet antibody assay were negative. Ultrasonography of the abdomen, thyroid gland, and parotid and submandibular salivary glands showed no pathology. Ambrisentan-induced thrombocytopenia was verified by exclusion. Pulse therapy was initiated with methylprednisolone (500 mg intravenously). Seven days after treatment, the platelet count reached 156×10^9/L. The PAH-specific treatment regime was changed to monotherapy with sildenafil (20 mg PO TID). During the 2-month follow-up period, the platelet count was 217×10^9/L, but at 5 months it was 219×10^9/L (Fig. 1).

Discussion

According to meta-analysis, thrombocytopenia as an adverse event was reported for endothelin receptor antagonists in 3 studies (4). It was not mentioned in the ARIES-E clinical trial subgroup analysis for patients with CTD-PAH (1). In Phase 3 efficacy studies of ambrisentan in patients with PAH, thrombo-

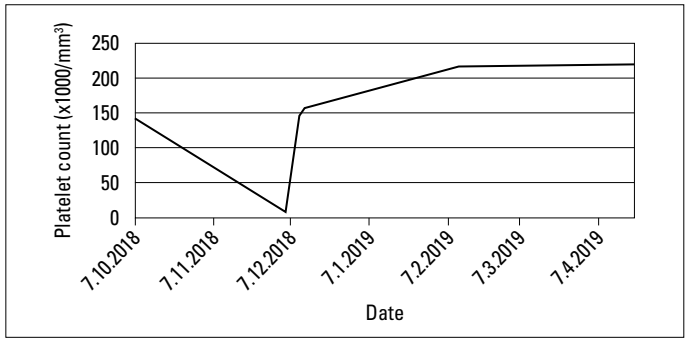

Figure 1. Response of platelet count after discontinuation of ambrisentan and therapy with methylprednisolone

cytopenia as a serious adverse event was reported for only 1 patient (5). The switch of PAH therapy group was made because bosentan has been reported as a less tolerable drug with a more significant risk for side effects (6). For patients with PAH WHO-FC II, monotherapy is the first choice (2).

The exposure to a new treatment regime is a common cause for drug-induced thrombocytopenia (7-10). However, other possible causes of thrombocytopenia, such as immune thrombocytopenic purpura with antiplatelet antibodies, lymphoproliferative malignant diseases and infections, were excluded. For financial reasons, drug-dependent platelet antibody was not performed in a specialized scientific laboratory. In addition, bone marrow biopsy was not done due to the rapid normalization of the platelet count after methylprednisolone pulse therapy.

Conclusion

Thrombocytopenia is a frequent finding in patients with systemic lupus erythematosus. However, a sudden decrease in platelet count after the start of treatment with ambrisentan and the absence of previously documented episodes of thrombocytopenia is highly suggestive of an adverse drug reaction. This is a rare adverse event resulting from medication which has not previously been reported in the literature.

Ethical Approval: Authors state that permission to publish the case report was granted by Local Ethics Committee - Clinical Research Ethics Committee of Pauls Stradins Clinical University Hospital. Nr. 151209-6L. December 15, 2009.

Informed consent: Authors state that there is evidence of patient consent to publish the case report.

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