

Autoimmune hepatitis induced by bosentan in a patient with pulmonary arterial hypertension (RCD code: II-1A.1; VIII)

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Abstract

Endothelin receptor antagonist (ERA) therapy-induced increase in liver transaminases in patients with pulmonary arterial hypertension (PAH) is an adverse effect of bosentan which is not fully understood. A 62-year-old female with a 1.5-year history of progressively worsening dyspnoea was diagnosed with idiopathic PAH (IPAH). After 2 months of PAH treatment with bosentan, levels of liver transaminases were elevated and autoimmune hepatitis was diagnosed. This clinical case demonstrates the challenge of diagnosing autoimmune hepatitis induced by ERA therapy in clinical practice. A thorough understanding of the pathogenesis and clinical presentation of autoimmune hepatitis, as well as the possibility to perform specific investigations with multiple serological markers are crucial for establishing the correct diagnosis. JRC D 2019; 4 (4): 101–105

Key words: rare disease, endothelin receptor antagonist, echocardiography, computed tomography, transaminase

Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease of the pulmonary vasculature that has a very poor prognosis leading to right heart failure and death. In 1996, the first PAH-specific pharmacologic agent (infused epoprostenol) was introduced. Since that time, phosphodiesterase-5 inhibitors, endothelin receptor antagonists (ERA), prostaglandins, soluble guanylate cyclase stimulators, and selective IP prostacyclin receptor agonists have been developed for PAH treatment [1–3].

The role of increased endothelin activation in PAH pathogenesis leading to vasoconstriction and mitogenicity is well established [4]. In 2001, the FDA approved the dual endothelin receptor antagonist, bosentan. This was been demonstrated to be effective in the treatment of different forms of PAH (idiopathic, associated with congenital heart defects, and Eisenmenger syndrome) in 5 studies (pilot, BREATHE-1, BREATHE-2, BREATHE-5, and EARLY) and led to improved exercise capacity, World Health Organization (WHO) functional class, haemodynamics, echocardiographic parameters, and increased time to clinical worsening [5]. Since then, the selec-

tive ET_A antagonist, ambrisentan, and the dual ERA, macitentan, have been approved [6, 7].

According to 7 published randomised controlled trials of bosentan as monotherapy for PAH in adults, their open-label extension studies, and the TRAX-PMS post-marketing study, tolerability of bosentan is most commonly limited by hepatotoxicity. Less frequent adverse effects are haematologic, neurologic, cardiovascular, respiratory, and gastrointestinal in nature. The FDA requires liver function tests to be done every month and haematocrit monitoring every 3 months. Increased liver transaminases are defined as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values which are 3 times the upper limit of normal (ULN). Incidence of increased liver transaminases in the bosentan treatment groups varied between 0 and 14% [8–11]. In the BREATHE-5 trial, 1 patient (3%) in the bosentan-treated group developed elevation of liver enzymes greater than 59 times ULN and was withdrawn from treatment. The EARLY and STRIDE-2 trials demonstrated 11% and 5% greater incidence in the bosentan treatment group and the placebo group, respectively [11], while in the ASSET-1 trial there were no cases of elevated liver enzymes in both groups [9]. In 30 months

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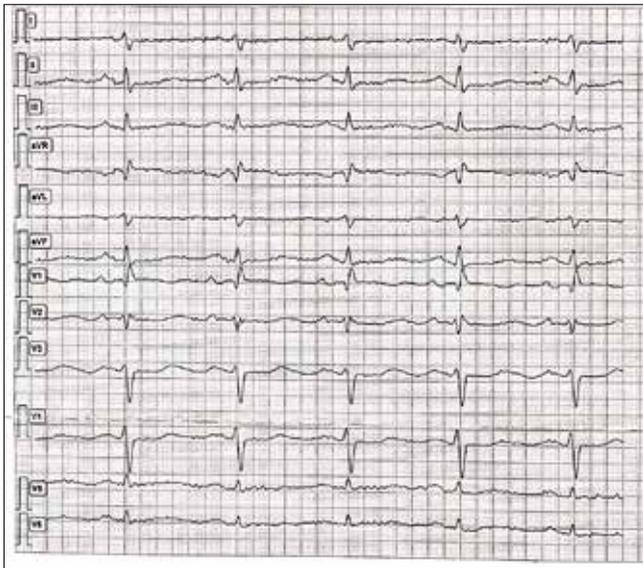


Figure 1. Electrocardiography

of post-marketing surveillance from the TRAX-PMS database, of the 4 623 bosentan-naïve patients in Europe, 7.6% developed elevated aminotransferases, corresponding to an annual rate of 10.1%. The severity of liver enzyme elevation was most commonly between 3 and 59 times ULN, and there were no cases of permanent or fatal liver injury associated with bosentan use [12].

Hepatotoxicity is an adverse effect of bosentan which is not well understood. Bosentan is metabolised by cytochrome P450 isoenzymes 2C9 and 3A4 in the liver and is excreted into the bile [13]. The mechanism of hepatotoxicity is associated with its influence on hepatobiliary transporters and accumulation of cytotoxic bile acids. In vitro studies using sandwich-cultured hepatocytes showed that bosentan inhibits both the basolateral sodium-taurocholate cotransporting polypeptide (NTCP) and the organic aniontransporting polypeptides (OATPs), which are responsible for hepatic uptake of bile acids, as well as the bile salt export pump (BSEP) and the multidrug resistance-associated protein 2 (MRP2), which excrete bile acids into the bile canaliculi [14]. Interestingly, BSEP inhibition alone is related to the development of cholestatic liver disease, as seen in hereditary BSEP deficiency. Another mechanism of bosentan-induced hepatotoxicity is inhibition of the ET-B receptors on hepatocytes and induction of portal sinusoid constriction [15]. In a case-control study comparing polymorphisms in the genes encoding OATP, CYP2C9, and BSEP (CYP2C9, SLCO1B1, SLCO1B3, and ABCB11) in PAH patients with or without bosentan-related hepatotoxicity, no significant associations were found [16].

We present the case of a female patient diagnosed with IPAH with no evidence of liver disease, who developed autoimmune hepatitis (AIH) after 2 months of treatment with bosentan.

Case report

A 62-year-old female presented with a 1.5-year history of progressively worsening dyspnoea, non-productive cough, fatigue, and

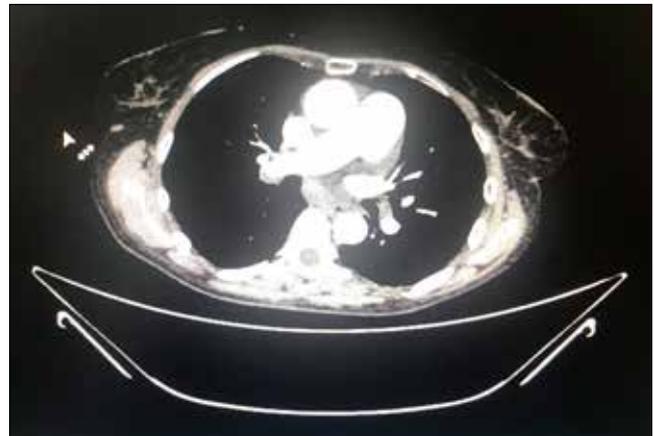


Figure 2. Computed tomography of the patient showing pulmonary arteries dilatation

weakness. Her symptoms were initially associated only with moderate exertion but progressed to dyspnoea on minimum exertion.

The patient had no previous significant history of cardiopulmonary disease. Her previous surgical, family, and social history were otherwise non-contributory.

On presentation, the patient's vital signs were normal and physical examination findings were remarkable for pale skin, an increased pulmonic second heart sound on cardiac auscultation, increased work of breathing, and mild bilateral oedema. Neither jugular venous distention nor orthopnoea was noted. Her blood pressure was 120/80 mmHg, heart rate was 80 bpm, and peripheral capillary oxygen saturation was 93%. Respiratory examination was unremarkable with normal vesicular breath sounds, no rhonchi or wheezing, and there was no crepitation over lung bases. Abdominal, musculoskeletal, and other systemic examinations revealed no abnormalities. In the 6-minute walk test, the patient walked 252 metres with desaturation to 87%.

Laboratory tests: red blood cells $5.0 \times 10^{12}/L$, Hb 139 g/L and haematocrit 42.0, leukocytes $6.3 \times 10^9/L$, thrombocytes $230 \times 10^9/L$, creatinine 70.2, glomerular filtration rate 78 ml/min/1.73 m², ALT 21.6 IU, AST 33.7 IU, total bilirubin 18.3 $\mu\text{mol}/L$, low density lipoprotein 2.83 mmol/L.

Laboratory testing including thyroid function, HIV, HBsAg, AntiHCV, and anti-nuclear antibodies (ANA) was unremarkable. N-terminal-prohormone brain natriuretic peptide was 2 678 pg/ml.

Electrocardiography revealed sinus rhythm with heart rate of 87 beats per minute and presence of incomplete right bundle branch block (QRS 100 msec).

Chest radiography revealed enlarged central pulmonary arteries and tapering of peripheral arterial branches.

A transthoracic echocardiogram suggestive of pulmonary hypertension revealed dilated right ventricular (RV) end-diastolic diameter (30 mm), reduced tricuspid annular plane systolic excursion (TAPSE) (10 mm), severe tricuspid insufficiency, estimated systolic pulmonary artery pressure of 122 mm Hg, pulmonary artery diameter 31 mm, increased septal flattening with D-shaped left ventricle (LV), left ventricular ejection fraction of 69%, abnormal diastolic function, haemodynamically irrelevant pericardial effusion (100 ml), and inferior vena cava 1.74 cm with collapsibility of 28%.



Figure 3. Abdomen ultrasound with enlarged parapancreatic lymph nodes

Pulmonary function testing showed a mild ventilation abnormality with restrictive pattern (forced expiratory volume in 1 second – 73.7% and forced vital capacity 68.3%).

Abdominal ultrasound showed left liver lobe size of 5.7 cm and right liver lobe size of 11.1 cm. Parenchyma was heterogeneous. The common bile duct measured 0.4 cm in diameter. There was no dilatation of the intra- or extrahepatic bile ducts. Portal vein was 0.9 cm in diameter. Thickened wall of the gallbladder was observed with a thickness of 0.4 cm and was hyperechoic. Gallstones of 0.5 and 0.9 cm in diameter were noted. Internal structure of the pancreas was coarse and heterogenous.

High resolution computed tomography (CT) angiography showed main pulmonary artery (36 mm) and right (28 mm) and left (27 mm) pulmonary artery dilatation in contrast to pruning of the peripheral blood vessels, enlarged right ventricle, RV/LV 1.2, and a pericardial effusion of 12 mm. Structure of the lungs and airways were normal with no signs of interstitial lung disease or emphysema.

As the patient did not present with symptoms, signs, or history of chronic lung disease, and no pathognomonic findings were revealed by additional assessments, the diagnosis of lung disease as a probable cause for pulmonary hypertension (PH) was rejected.

Haemodynamic evaluation by right heart catheterization (RHC) indicated a mean pulmonary arterial pressure (mPAP) of 53 mmHg with a pulmonary capillary wedge pressure of 11 mmHg; cardiac output was 3.12 L/min, cardiac index was 1.90 L/min/m², and pulmonary vascular resistance was 13.4 Wood Units (1076.9 dyn·s/cm⁵). Vasodilator testing was negative. The patient was assessed as class III according to the WHO Classification of Functional Status of Patients with Pulmonary Hypertension.

Despite an intermediate pre-test probability of left heart disease phenotype as the cause of PH, due to the patient's age and presence of dyslipidaemia, the patient underwent coronary angiography as a part of the diagnostic workup. This revealed 80% stenosis of the left anterior descending artery, 80% stenosis of the left circumflex artery, and 70% stenosis of the posterior descending artery. Because of this, revascularisation with stenting was performed.

Treatment with rosuvastatin 20 mg, aspirin 75 mg, ticagrelor 90 mg bid, valsartan 80 mg, amlodipine 5 mg, and torsemide 10 mg was initiated. Follow-up examination at 3 months post-treatment initiation confirmed worsening of dyspnoea. Thus, treatment for



Figure 4. Elastography demonstrating F2-F2 Metavir in 5–6 liver segments

precapillary PAH of intermediate risk using sildenafil and bosentan 62.5 mg twice daily was initiated. After 1 month of liver function monitoring, the dose of bosentan was increased to 125 mg twice daily. After 2 months of PAH treatment, liver transaminases began to increase: AST to 144 IU/L and ALT to 110 IU/L. On abdominal ultrasound there were no new findings in comparison with the previous investigation, no signs of active cholecystitis, hepatic cirrhosis, portal hypertension, or congestion of the liver. Taken together, we suspected that these abnormalities were related to drug-induced hepatotoxicity and decided to discontinue bosentan administration. However, the patient returned with complaints of nausea, postprandial fullness, presented with jaundice, and 2 episodes of fever 38–39°C. Transaminase levels further increased (AST 459 IU/L, ALT 230 IU/L, total bilirubin 81.3 μmol/L, conjugated bilirubin 513 μmol/L, unconjugated bilirubin, gamma-glutamyl transferase 157 IU/L). Examination of blood serology for hepatitis A, B, C, and E infection and human herpes virus was negative. Cell blood count revealed red blood cells 3.3×10^9 /L, Hb 86 g/L, leukocytes 5.8×10^9 /L, thrombocytes 330×10^9 /L, ESR 13 mm/hour, Fe 5.23 μmol/L. Consultation with a haematologist led to the diagnosis of iron deficiency anaemia and treatment with maltofer 300 mg was initiated. Liver enzymes began to decrease 2 months later but remained above ULN (ALT 53 IU/L, AST 94 IU/L, total bilirubin 31.6 μmol/L). Because of this, further investigations were performed 4 months later. Gastroduodenal endoscopy showed local atrophic hyperplastic gastropathy but no signs of esophageal or gastric varices. Abdominal ultrasound revealed signs of chronic liver disease without portal or hepatic vein thrombosis, enlargement of liver or pancreatic lymph nodes. This was then confirmed by abdominal CT (liver lymph nodes were 25 and 15 mm, mild increase of paratracheal, bifurcation, and retroperitoneal lymph nodes was found).

Elastography revealed F2-F2 Metavir in 5–6 liver segments. According to ACG Clinical Guidelines for Abnormal Liver Chemistries management 2017 [17], the evaluation of hepatocellular injury

includes testing for AIH. In our patient, AMA-M2 was 10.82 U/ml, IgA 4.32 g/l, and tests for ANA IgG were positive. After consultation with a gastroenterologist, the diagnosis of AIH was established. The patient had a pre-treatment AIH score of 15 according to the system proposed by the International Autoimmune Hepatitis Group (18). Unfortunately, liver biopsy was not performed. Treatment with ademetonine was initiated and transaminase levels normalised after 2 months. Moreover, the patient continued to receive treatment for latent anaemia.

Discussion

AIH is an unresolving inflammation of the liver of unknown cause in which T cell-mediated immune attack upon liver antigens leads to a progressive fibrotic process [5, 6]. Presentation at onset varies from nonspecific symptoms such as fatigue, jaundice, nausea, abdominal pain, and arthralgias to acute liver insufficiency. Its diagnosis is often challenging and is based on clinical presentation, elevation of ALT, AST, and gammaglobulins – in particular serum IgG levels, autoantibodies, and histology [17–19].

In the clinical case described in this article, the elevation of aminotransferase levels during therapy with bosentan occurred and we suspected drug-induced hepatotoxicity. However, due to worsening of the elevated aminotransferases and onset of fatigue, jaundice, nausea, abdominal pain, and anaemia even after discontinuation of bosentan, we proceeded with further investigations to exclude viral hepatitis and oncologic aetiologies. Diagnosis of AIH based on the Revised International Autoimmune Hepatitis Group Modified Scoring System with a pre-treatment score of 15 was established.

Hepatotoxicity of bosentan is well known in the literature, however, only a few cases of bosentan-induced AIH have been described. One of them was observed among 33 pediatric PAH patients treated with bosentan for 27 months in the FUTURE-2 study [19]. They observed an increase in liver enzymes, which remained elevated despite dose reduction, as well as the presence of F-actin antibody and anti-smooth muscle antibody (ASMA). The drug was discontinued and the patient showed further improvement, so treatment with bosentan was resumed. A few days later, transaminases again increased, which led to the permanent discontinuation of bosentan treatment.

In a case presented by Naito et al., a 48-year-old woman had signs of precapillary PAH on RHC and tests were positive for anti-nuclear and anti-centromere antibodies, but the patient had neither symptoms nor signs of connective tissue disease or portal hypertension, therefore, she was diagnosed with IPAH [20]. After 2 years of treatment with sildenafil and bosentan, the patient developed elevation of transaminase levels (AST 204 IU/L; ALT 421 IU/L) without signs of hepatic cirrhosis, portal hypertension, or decompensated heart failure. Bosentan was discontinued and liver enzymes normalised. After subsequent administration of ambrisentan, AST and ALT again increased, along with severe thrombocytopenia and presence of a high level of soluble interleukin-2 receptor. Despite discontinuation of ambrisentan and sildenafil, levels of transaminases did not improve and the platelet count continued to decrease, suggesting the presence of acquired thrombocytopenia mediated by an immune response due to ERA treatment. Liver biopsy primarily

indicated the presence of drug-induced hepatotoxicity, particularly considering the adverse effects of ERAs, however, AIH was not completely ruled out as a differential diagnosis. One month after the initiation of prednisolone, the platelet count and transaminase levels returned to normal ranges. Monotherapy with tadalafil was introduced and a third episode of liver dysfunction developed. All drugs were discontinued at this time, but the patient's liver function did not improve. Taken together, there was no association between liver dysfunction and treatment with PAH-specific drugs, which suggested the diagnosis of AIH.

This case is interesting due to the presence of PAH with features of an autoimmune disorder which did not meet the diagnostic criteria for connective tissue disease at the time of presentation. Our case also demonstrates the challenge of AIH diagnosis even after performing a liver biopsy, which could not clearly differentiate between an autoimmune mechanism of inflammation and drug-induced inflammation. Klein et al. [21] reported the case of a 47-year-old woman with a diagnosis of AIH at presentation, and subsequently, developed systemic scleroderma 5 years later. Seven years later, she presented with exercise-induced dyspnoea and haemodynamic features of PAH. At the time of sitaxentan treatment initiation, AIH was in remission. Elevation of transaminases in association with an increased IgG level were found 14 months after therapy with sitaxentan. Considering the increase in IgG globulins and reappearance of anti-actin antibodies, the investigators favoured the concept that sitaxentan led to an exacerbation of AIH.

Conclusions

This clinical case demonstrates the challenge of diagnosing AIH induced by ERA therapy in clinical practice. Careful patient examination including laboratory and liver morphology investigations allow an early diagnosis of AIH and exclusion of an oncologic aetiology. Liver biopsy is important, however, in our case, a diagnosis was established without histopathology examination. A thorough understanding of the pathogenesis and clinical presentation of autoimmune hepatitis, as well as the possibility to perform specific investigations with multiple serological markers are crucial for establishing the correct diagnosis.

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