Atrial flutter regression in HIV-associated pulmonary arterial hypertension after treatment with bosentan

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Abstract

Pulmonary arterial hypertension (PAH) is a rare condition characterized by an increase in pulmonary arterial resistance leading to right heart failure and death. Arrhythmias are a growing problem in PAH; therefore, maintenance of sinus rhythm is considered to be an important treatment aim in these patients. We described the case of a 46-year-old woman with HIV-associated pulmonary arterial hypertension who developed atrial flutter. After treatment with bosentan, it was observed a significant improvement in clinical and haemodynamic parameters. In addition, the AFL, which had previously persisted to both antiarrhythmic drug therapy and electrical stimulation, and had recurred after transthoracic electrical cardioversion, disappeared in absence of any antiarrhythmic drug. Though the precise factors responsible for supraventricular arrhythmogenesis are still largely obscure, it is likely that initiation and maintenance of AFL may depend on all the conditions that can lead to increase in right atrial pressure, size, and wall stress, such as PAH. In our case, bosentan reduced both mean pulmonary artery pressure (mPAP) value and right heart chambers pressures. Therefore, it is conceivable that with the anatomical substrate needed for the maintenance of AFL being disappeared, sinus rhythm was restored.

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Introduction

Pulmonary arterial hypertension (PAH) is a rare condition characterized by an increase in pulmonary arterial resistance leading to right heart failure and death [1]. An important treatment target, in patients with PAH, is to maintain sinus rhythm; indeed, arrhythmias are important contributors to morbidity and mortality in these patients [2]. In this case, a woman with PAH associated to HIV developed typical atrial flutter (AFL), which disappeared only with bosentan therapy, in absence of any antiarrhythmic drugs.

Case report

A 46-year-old woman was admitted in March 2009 to our hospital following one month of dyspnea on exertion and asthenia. She was known to have had HIV infection since 2006, presumably contracted after unprotected sex. Thus, she was under treatment with highly active antiretroviral therapy (HAART). The patient had a 30-pack-year history of smoking, but had no history of intravenous drug use or anorectic drug ingestion. She had not previously experienced any opportunistic infections or liver problems. Approximately one year before the admission, on January 2008, a routine transthoracic echocardiography (TTE) detected elevated systolic pulmonary artery pressure (sPAP=110 mmHg) but the woman did not undergo any further investigations of this finding due to her negligence. Later, on March 2008, a routine electrocardiogram (ECG) showed typical counterclockwise atrial flutter and right ventricular hypertrophy. AFL was persistent despite standard antiarrhythmic drug therapy and electrical stimulation; therefore, she underwent transthoracic electrical cardioversion (100 J) and sinus rhythm was restored. Antiarrhythmic prophylaxis with oral amiodarone (400 mg/day) and anticoagulant therapy with warfarin (for one month) were initiated. Nevertheless, on October 2008, a new episode of AFL occurred: it was proposed catheter ablation but the patient declined the procedure and, discouraged by the recurrence of AFL, refused any antiarrhythmic drug/procedure. Then, when she was admitted to our ward, her therapy included HAART and warfarin. Physical examination revealed a blood pressure of 130/80 mmHg, a respiratory rate of 16 breaths/min, a heart rate of 65 bpm with irregular heartbeats and an accentuated pulmonary component of second heart sound. Lung sounds were normal and she had no signs of right ventricular failure. Arterial blood gas values were the following: pH 7.45, pO2 79 mmHg, pCO2 34 mmHg, SO2 96%. Spirometric values were in the normal range. ECG and TTE confirmed the findings observed on January/March 2008. A chest radiograph demonstrated cardiac hypertrophy and central pulmonary arterial dilatation. A ventilation and perfusion lung scan was normal. High-resolution computed tomography and abdominal ultra-

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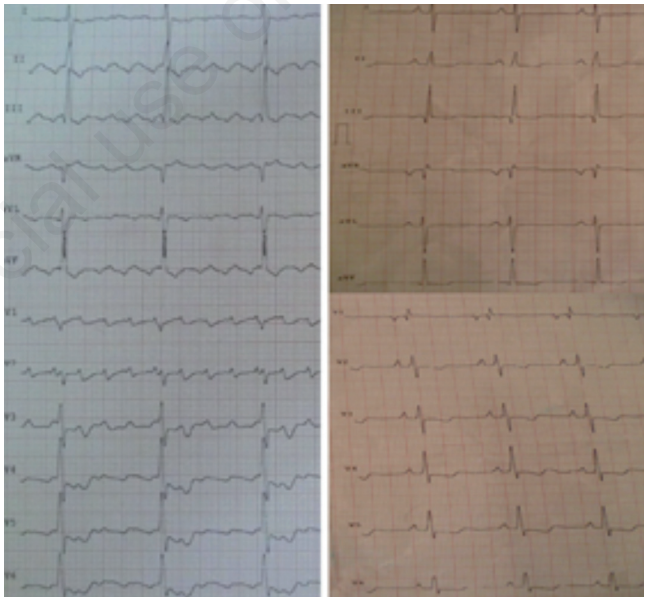
sound scan did not add any further information. The white blood cell count was 6500/mm^3 and CD4 cell count was 540/mm^3. Laboratory findings were unremarkable (except for confirmation of HIV positivity). Anti-nuclear antibodies were in the normal range. Right heart catheterization showed a mean pulmonary arterial pressure (mPAP) of 69 mmHg, a pulmonary capillary wedge pressure (PCWP) of 11 mmHg, an increase in pulmonary vascular resistance (PVR= 728 dynes/sec/cm), a cardiac index (CI) of 2.5 L/min/m^2, a right atrial pressure (RAP) of 22mmHg, and a right ventricular pressure (RVP) of 60mmHg. The patient was diagnosed with pulmonary arterial hypertension (PAH) associated with HIV infection. She was in World Health Organization functional class III (WHO-FC III). The 6-minute walk test (6MWT) distance was 310 m. The woman started treatment with bosentan, an unselective oral antagonist of endothelin-1 (ET-1) receptor, at the dose of 62.5 mg twice daily with uptitration to 125 mg twice daily after four weeks. Surprisingly, after 3 months of treatment, atrial flutter disappeared and sinus rhythm was restored (Figure 1). After 6 months of treatment, the patient's condition had clinically and haemodynamically improved (WHO-FC I, 6-MWT distance of 515 m, mPAP of 26 mmHg, PVR of 305 dynes/sec/cm, CI of 3.9 L/min/m^2). After 2 years, clinical parameters remained stable (Table 1). Moreover, it is important to highlight that, since June 2009, the patient was monitored with ECG once a month during the following 18 months and it was not observed any AFL recurrence, although she was not in treatment with antiarrhythmic drugs.

Discussion

We described the case of a 46-year-old woman with HIV-associated PAH who developed AFL. After treatment with bosentan, it was observed a significant improvement in clinical and haemodynamic parameters. In addition, the above-mentioned arrhythmia, which had previously persisted to both antiarrhythmic drug therapy and electrical stimulation, and had recurred after transthoracic electrical cardioversion, disappeared in absence of any antiarrhythmic drug. No relapses were recorded during the following 18 months. This result lead us to consider the role of bosentan in AFL regression in patients with PAH. In this regard, it is important to highlight the causative relationship between PAH and the onset of arrhythmias. A series of 231 patients with PAH or chronic thromboembolic pulmonary hypertension (CTEPH) followed over a 6-year period was studied for supraventricular tachyarrhythmias (SVTs); in this study, 31 episodes were observed in 27 patients (11.7%), and 15 were AFL [3]. It is widely accepted that, in typical AFL, the characteristic macroreentry circuit is limited to the right atrium [4]. Though the precise factors responsible for supraventricular arrhythmogenesis are still largely obscure, it is likely that initiation and maintenance of AFL may depend on all the conditions that can lead to increase in right atrial pressure, size, and wall stress [5], such as PAH. In our case, treatment with bosentan reduced both mPAP value and right heart chambers pressures. Therefore, it is conceivable that with the anatomical substrate needed for the maintenance of AFL being disappeared, sinus rhythm was restored.

It is broadly recognized the positive prognostic role of restoration of sinus rhythm in PAH patients with arrhythmic complications [2]. On the other hand, to our knowledge, this is the first case described in the literature in which treatment with an endothelin receptor antagonist (ERA) in a patient with PAH determined the regression of sustained SVT without the need of antiarrhythmic drug/procedure. In this regard, it is important to remark that ET-1 may promote the development of arrhythmias, and a number of animal studies have shown that ET-1 antagonists, including bosentan, may have antiarrhythmic properties [2]. With regard to HAART, there are lacking and conflicting data about its impact on PAH; in fact, some works suggest that it has no effects on the occurrence or severity of PAH [6], with others reporting that HAART reduces mortality associated with HIV-PAH [7].



March 2009 June 2009

Figure 1. Change in electrocardiography (ECG) after bosentan therapy.

Table 1. Hemodynamic parameters and functional status.

	March 2009	September 2009	March 2011
mPAP mmHg	69	26	NA
PVR dynes/sec/cm	728	305	NA
CI L/min/m^2	2.5	3.9	NA
PCWP mmHg	11	8	NA
RAP mmHg	22	6	NA
RVP mmHg	60	15	NA
WHO-FC	III	I	I
6-MWT m	310	515	530

mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; CI: cardiac index; PCWP: pulmonary capillary wedge pressure; RAP: right atrial pressure; RVP: right ventricular pressure; WHO-FC: World Health Organization functional class; 6-MWT: 6-minute wolk test. NA: not available.

It is important to underline that bosentan or any other ERA could never take the place of specific therapy for arrhythmic complications in patients such as ours. However, we suggest it could be a suitable alternative treatment. Indeed, cardiac arrhythmias are important contributors to morbidity and mortality in patients with PAH, and maintenance of sinus rhythm is an important treatment goal in these patients [2]; therefore, it should be highlighted that the role of ET-1 antagonists as potential antiarrhythmic agents, besides their other beneficial effects, may be of great clinical relevance. Prospective controlled trials might be helpful for a more comprehensive evaluation of our finding.

Conclusions

In HIV-PAH patients with supraventricular tachyarrhythmias complications, treatment with endothelin receptor antagonists may induce not only an haemodynamic improvement, but also arrhythmia regression. There is still uncertainty about the role of HAART on PAH. Further studies are needed to confirm our report.

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