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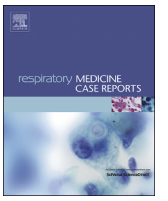

Case Report

Sartan-induced interstitial lung disease

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ABSTRACT

Background: Lung toxicity of angiotensin receptor blockers (sartans) have very seldom been reported in the literature despite their wide use. We here report a case of interstitial lung disease elicited by sartans, with two episodes induced by two different sartans at 10 years of interval.
Case presentation: In 2012, eprosartan was the very likely cause of a drug induced interstitial lung disease in a 60 year old man. Indeed, his symptoms, consisting in a MMRC2 dyspnea and recurrent hemoptysis, completely disappeared after the removal of this drug. When the circumstances rendered it necessary to start another angiotensin receptor blocker (namely valsartan) ten years later we did not expect the same reaction to occur given among other things a very poor literature on the topic. After a few months with this medication, he however developed similar symptoms and a Chest CT imaging that was comparable to what he had in 2012.This time also the clinical picture resolved completely when the sartan was stopped.
Conclusion: We report this first case of a drug induced interstitial lung disease induced by two different angiotensin receptor blockers (sartans) with a new drug challenge ten years after the first one.

1. Introduction

The very high interhuman variability in drug resorption and metabolism makes it very complicated to exclude the possible occurrence of adverse events with any drug. It is also sometimes difficult to prove that a link really exists between the medication and the observed manifestations. This is perhaps even truer if the drug is widely used but has never or very rarely induced such reactions. We present a case of lung toxicity induced by widely used Angiotensin receptor blockers (also named Sartans) with, we believe, the sufficient proof of similar manifestations occurring at 10 years interval and elicited by two different Sartans.

2. Case presentation

A 60 years-old patient was first seen at the outpatient clinic in 2012. He was treated with low dose aspirin, rosuvastatin for hypercholesterolemia, bisoprolol and eprosartan for arterial hypertension. His medical history was besides unremarkable and he was a non-smoker. He presented with a one-year history of daily limited hemoptysis with productive cough and MMRC2 dyspnea. He had already undergone a chest-CT in another center and a diagnosis of fibrosing interstitial lung disease (ILD) had been made. A treatment with oral methylprednisolone had been prescribed for a few months without any symptomatic improvement. Physical examination found an oxygen saturation of 93 % and bilateral lung crepitations. We performed a new chest CT and found bilateral septal thickening, condensations, ground glass opacifications and traction bronchiectasis with a basal predominance (Fig. 1A). A broncho-alveolar

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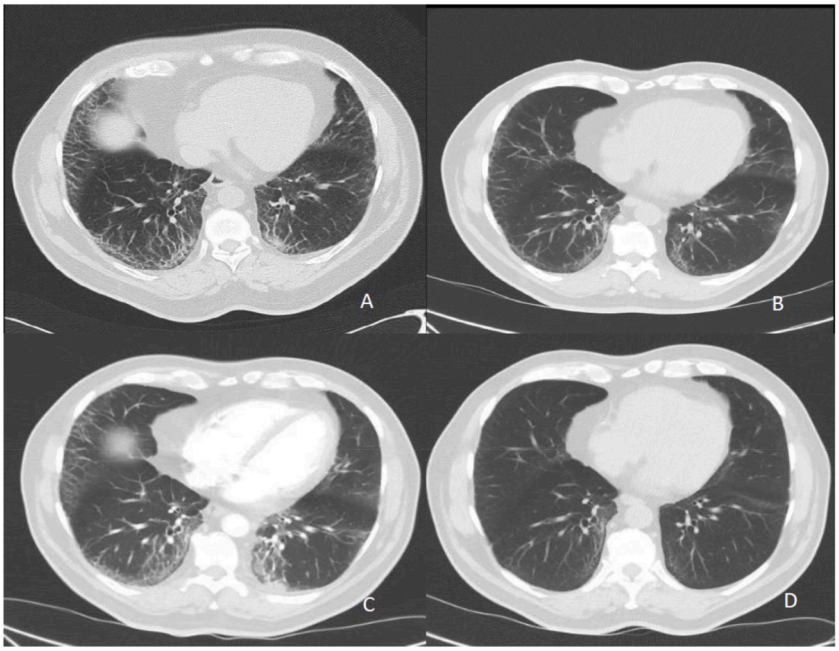

Fig. 1. Chest CT evolution
Fig. 1. A 2012, *Patient presenting with haemoptysis, eprosartan and low dose corticosteroids as active treatments* Fig. 1. B 2021, *heart failure due to ischemic cardiomyopathy, no haemoptysis* Fig. 1. C 2021, *valsartan treatment, two weeks after the recurrence of haemoptysis* Fig. 1 D. 2022, 6 months *after the removal of valsartan.*

lavage (BAL) was performed that found 202 elements/μl of which 1 % neutrophiles, 2 % monocytes, 17 % macrophages and 78 % lymphocytes. CD4/CD8 ratio was 1. There were no biological or clinical signs of any auto-immune disease or vasculitis. The patient had no known exposition, in particular to birds or molds. The possibility of a drug-induced interstitial lung disease (ILD) was considered. At that time, there were no description of lung toxicity for aspirine, bisoprolol and rosuvastatine but a literature research found a report about an eprosartan-induced ILD [1] and this medication was thus stopped. The patient soon presented a major improvement of his symptoms with a complete disappearance of the hemoptysis, cough and dyspnea. There was no new chest CT performed at that point.

He sought no further medical assistance for the next 10 years when he returned to our outpatient clinic with complains of chest pain and dyspnea. He had in the meantime developed diabetes and was treated with low dose aspirin, metformin and bisoprolol. Given the symptoms, he was swiftly addressed to the cardiology department where a diagnosis of heart failure with reduced ejection fraction (HFrEF) due to an ischemic cardiomyopathy was made. The patient underwent an angioplasty and stenting of the left anterior descending artery. Rosuvastatin, ezetimibe, clopidogrel and spironolactone were added to his other medications. A new chest CT was performed at that point which showed limited reticulations probably related to the ILD diagnosed in 2012 (Fig. 1B). Due to the heart failure, the cardiologist asked us for the permission to start valsartan in order to be able to introduce later the association sacubitril/valsartan (Entresto®) which we agreed given the absence of any described class effect for lung toxicity due to angiotensin receptor blockers. The cardiac situation subsequently stabilized and the left ventricular function normalized. Eight months after initiating these new medications, the patient presented with MMRC 2 dyspnea and daily hemoptysis. There were no clinical or echocardiographic sign of cardiac dysfunction and a new chest CT was performed. This revealed the reappearance of abnormalities that were very similar to those found in 2012 with bilateral basal ground glass opacification and septal thickening (Fig. 1C). Patient refused to perform a new BAL. The blood test revealed no signs of infection. The research for auto-antibodies was not performed. Given the patient's medical history, valsartan/sacubitril was interrupted, the other medications remained unchanged. Two weeks after this treatment had been stopped, the hemoptysis disappeared as the dyspnea. The Chest CT performed 6 months later with otherwise unchanged medications and environment showed a spectacular improvement (Fig. 1D).

3. Discussion and conclusion

This case is one of the few reports of an interstitial lung disease related to sartans. We only found one previous publication involving eprosartan [1] and one involving valsartan [2]. Eprosartan and valsartan share some common features: they both act by blocking angiotensin receptor 1 (AT_1R), do not require metabolic activation (they are no prodrugs) and have a mainly biliary elimination [3]. They have however dissimilarities notably in biodisponibility, chemical structure and thereby in their mode of interaction with the AT_1R [4]. There have been evidences of antifibrotic activity for valsartan in bleomycin murine models, probably via the increase of prostaglandin E2 synthesis [5,6]. It is then unclear why both eprosartan and valsartan elucidated similar but quite unusual reactions in our patient. Hemoptysis is indeed not the most typical manifestation drug-induced of lung toxicity and its occurrence might suggest a vascular damage.

Our case presents with the original feature of a second drug trial almost ten years after the first and with a different drug of the same family and producing the same effects. As these medications are widely used, the clinicians should be aware of the risk developing lung toxicity and of a potential class effect.

Informed consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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Not of application.

Author contribution

Caroline Dahlqvist wrote the original draft.
Luc Delaunois and Fabian Demeure reviewed the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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