



## Case report

## Timolol-induced interstitial lung disease

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## A B S T R A C T

## Keywords:

Interstitial lung disease  
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Drug-induced

Timolol maleate is a non-selective beta-adrenergic receptor blocking agent with demonstrated efficacy in the treatment of open-angle glaucoma. A 76 year old female who presented with productive cough, progressive dyspnea and hypoxia after starting timolol maleate ophthalmic drops following glaucoma surgery. The patient was diagnosed with interstitial lung disease secondary to timolol treatment and after cessation of the offending agent along with corticosteroid treatment, symptoms improved drastically. Elimination of other possible causes of disease along with evolution of radiological and functional signs left us with a diagnosis of timolol-induced interstitial lung disease. To our knowledge, this is the second reported case of timolol-induced interstitial lung disease.

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## Introduction

Several types of drugs can cause drug-induced interstitial lung disease (DILD). Currently more than 300 medications are known to cause DILD and this number will undoubtedly continue to increase as the newer therapeutic agents hit the market. DILD is generally described in terms of its clinical/histopathological features and thus can be difficult to diagnose as diagnosis is often possible by exclusion alone [1]. Timolol maleate is a non-selective beta-adrenergic receptor blocking agent used in treatment of open-angle glaucoma and is a relatively well-tolerated drug. Little is known about the adverse pulmonary effects associated with Timolol maleate. It is important that health care providers be familiar with possible adverse effects of medications they prescribe as prompt recognition of the disease along with cessation of the offending agent will minimize the risk morbidity and potential mortality. We report a case of timolol-induced interstitial lung disease along with a review of the literature.

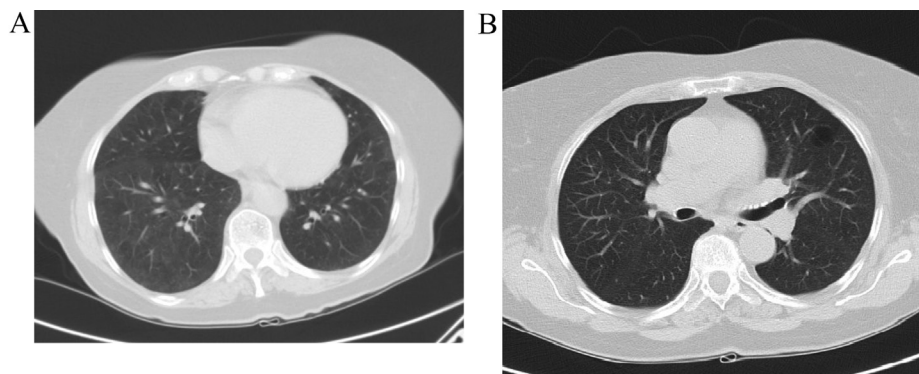
## Case report

A 76 year old Caucasian female of French ethnicity with past medical history of hypertension and glaucoma presented with a three month history of productive cough and progressive dyspnea.

Patient was seen by her primary care physician when symptoms first started and was diagnosed with bronchitis and treated with a course of antibiotics. With no resolution of symptoms, patient was treated with another course of antibiotics along with medrol dose pack. Still with progressive symptoms patient underwent allergy testing which was negative. Patient decided to seek treatment in the emergency room. She denied a history of fevers, chills, weight loss, chest pain, palpitations, chronic cough, hemoptysis, abdominal pain, nausea, vomiting, diarrhea, asthma, rash, arthritis, recreational drug abuse, exposure to pigeons or other birds, and exposure to silicon, berilym, or asbestos. Patient denied family history of pulmonary or cardiac problems. Other ambulatory medicines included losartan and protonix. Upon examination, blood pressure was 128/68 mm Hg, heart rate was 72 beats per minute (bpm) and regular, a respiratory rate of 20 breaths per minute, and temperature of 98.8°. Pulmonary examination revealed bibasilar rales with evidence of hypoxia with oxygen saturation of 84% on room air. Cardiovascular, abdominal, and neurological examinations were unremarkable. Complete blood counts and chemistry panels were within normal limits. Blood cultures were negative x 5 days. Sputum cultures were negative for acid-fast bacilli, fungal, or pneumococcal growth. Chest CT revealed a slight mosaic attenuation pattern of the lungs suggestive of air trapping (Fig. 1A). A high resolution CT (HRCT) chest was recommended. HRCT chest imaging revealed groundglass opacities and mosaic pattern suggestive of bronchial air-trapping (Fig. 2). Bronchoscopy with bronchoalveolar lavage was hypercellular with 89% neutrophils, 8% lymphocytes, 2% monocytes, and 1% macrophages. Transbronchial biopsy showed evidence of focal giant cell reaction

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**Fig. 1.** A. Chest CT revealing mosaic pattern of the lungs with air trapping. B. Chest CT post-treatment reveals resolution of air trapping along with homogenous lung density.

and negative for malignancy. CD4:CD8 ratio 2.8:1. Pulmonary function test revealed FEV1 75% and decreased DLCO suggestive of restrictive disease. The diagnosis of interstitial lung disease secondary to the use of timolol maleate was suspected and the medication was stopped. The patient was started on methylprednisolone treatment at a dose of 60 mg every 6 h with gradual tapering to 5 mg oral daily over a 3 month period. Upon followup, the patients symptoms had resolved. Repeat CT of the chest revealed no evidence of parenchymal infiltrates with complete resolution of any signs of air trapping (Fig. 1B). The patients with oxygen saturation was noted to be 96% on room air.

## Discussion

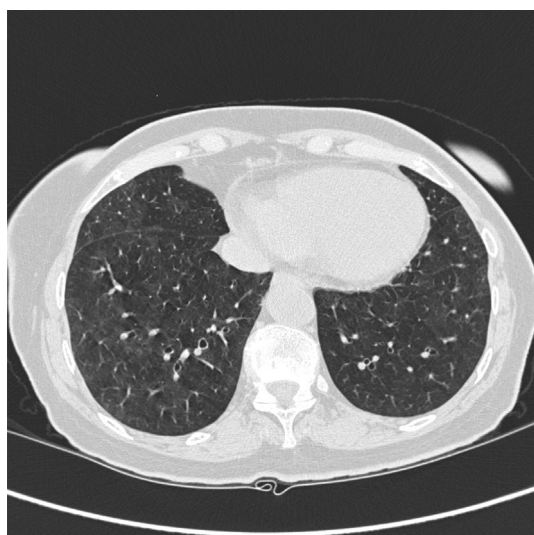
Adverse drug reactions are the seventh most common cause of death [2]. Drug induced pulmonary disease is an underdiagnosed issue. The global incidence of interstitial lung disease is not clearly known, but 2.5–3% of cases are drug induced [3,4]. Disparities in incidence regarding drug-induced interstitial lung disease in different ethnic groups have been reported. Recent studies have shown timolol maleate is metabolized by CYP2D6, a member of the cytochrome P450 family. In patients who are CYP2D6 poor metabolizers, systemic timolol concentrations may be high enough

to cause respiratory and cardiovascular adverse effects (5–10% Caucasians, 1–2% Asians) [5]. Timolol maleate is a non-selective beta-adrenergic receptor blocking agent used in treatment of open-angle glaucoma. Unlike the oral route which undergoes extensive first pass hepatic metabolism, the topical route drains into the lacrimal ducts where systemic absorption occurs via facial and ophthalmic veins which results in higher concentrations reaching systemic circulation [6]. Drugs in the same therapeutic class can induce similar pulmonary toxicity patterns [7]. Ophthalmic administration of beta-adrenergic receptor blockers cause similar effects to those reported with oral beta-adrenergic receptor blockers with the most frequent being bronchospasm. Also reported are bradycardia, pleural and pericardial effusion, bronchiolitis obliterans organizing pneumonia, and interstitial lung disease.

Although based on recent guidelines, clinical history and HRCT imaging of the chest is deemed sufficient enough for diagnosis of interstitial lung disease [8] bronchoalveolar lavage is generally indicated to exclude an infection and to support a drug etiology [9] A lymphocytic predominance is most frequently seen in analysis although neutrophilic, mixed lymphocytic and neutrophilic and or eosinophilic pattern has been reported less frequently [10] There has not been a risk-benefit analysis regarding lung biopsy vs conservative management in regards to drug-induced lung disease however in regards to drug induced interstitial pneumonitis, lung biopsy is rarely needed to confirm the diagnosis as it is not pathognomonic for drug toxicity and most cases tend to respond to withdrawal of the offending agent with or without corticosteroid therapy [11]. Transbronchial lung biopsy has been shown to have a diagnostic rate of 76% in drug induced lung disease cases [12] Pulmonary function testing demonstrates restrictive lung disease pattern with decreased total lung capacity, residual volume, forced vital capacity, and diffusion capacity, with the latter suggestive of an alveolar–capillary interface disturbance [13]. Although drug provocation testing may be the most convincing test to confirm drug induced interstitial lung disease, rechallenged patients run the risk of severe or fatal interstitial lung disease following re-exposure and is generally considered unethical [1].

The pathophysiology of timolol induced interstitial lung disease is still unknown. The physiological mechanisms underlying iatrogenic lung disease include direct cellular toxicity, cellular edema, alveo–capillary membrane leakage, activation of the inflammatory cascade and immunological phenomenon [14].

Treatment needs to be individualized based on response to therapy and presence or absence of side-effects, with the endpoint being to prevent deposition of fibrotic tissue via suppression of the inflammatory response. There is a paucity of data regarding



**Fig. 2.** HRCT chest revealing presence of areas of heterogeneous with increase in lung density and multiple areas of air trapping.

treatment agents, dosing, or duration of therapy in interstitial lung disease, thus firm recommendations cannot be made. Steroids are indicated in patients with extensive opacities on imaging, patients with significant hypoxemia, or in patients in whom drug withdrawal fails to translate into a definite improvement [9] Based on published case studies, recommendations of high dose methylprednisolone (1 g daily for 3 days) for patients with respiratory failure and lower doses of methylprednisolone (1 mg/kg every 6 h) for less severe cases have been reported with successful results [15,16].

The diagnosis of drug induced interstitial lung disease depends on a temporal association between exposure to causative agent and development of respiratory signs and symptoms [1]. We believe timolol maleate is responsible for the development of interstitial lung disease in our patient due to the following reasons:

First and foremost, other causes of lung damage were excluded including infectious, collagen vascular diseases, occupational exposures, other medication exposures, and malignancy. Lipoid pneumonia has been associated with angiotensin converting enzyme inhibitor drugs but has not been demonstrated with use of angiotensin receptor blocking agents [17]. Furthermore, there is no lipid excipients in timolol eyedrops, there was no lipid density in scanner, and no fat inclusions seen in bronchoalveolar lavage macrophages. The Naranjo adverse drug reaction probability scale with a final score of six, indicated a probable relation between timolol and development of lung disease [18]. The removal of ophthalmic treatment brought about resolution of symptoms and radiographic findings (with the addition of corticosteroid treatment).

## Conclusions

To our knowledge, this is the second literature report of interstitial lung disease related to timolol maleate treatment. This report is similar to the prior literature report in regards to presentation and workup leading to the diagnosis of timolol maleate induce lung disease but differs in treatment. We decided to use steroids as a treatment option in addition to stopping the offending agent. This decision was based on more recent anecdotal case reports which have shown a beneficial effect of steroids in ameliorating symptoms and resolution of interstitial lung disease. In the clinical setting, the persistence of dyspnea after timolol usage should urge the physician to order a CT scan of the chest. Interstitial lung disease should be considered in the differential diagnosis and the suspected offending agent should be withheld. Drug induced

interstitial lung disease carries a good prognosis and the development of lung fibrosis following early recognition and treatment of this condition is rare.

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## References

- [1] Matsuno. Drug-induced interstitial lung disease mechanisms and best diagnostic approaches. *Respir Res* 2012;13:9.
- [2] Wester K, Johnson A, Sigset O, et al. Incidence of fatal adverse reactions: a population based study. *Br J Clin Pharmacol* 2008;65:573–9.
- [3] Thommer M, Costabel U, Rizzato G, et al. Comparison of registries of interstitial lung diseases in three European countries. *Eur Respir J* 2001;18:114s–8s.
- [4] Coultas D, Zumwalt R, Black W, et al. The epidemiology of interstitial lung diseases. *Am J Respir Crit Care Med* 1994;150:967–72.
- [5] Volotinen M, Hakkola J, Pelkonen O, et al. Metabolism of ophthalmic timolol: new aspects of an old drug. *Basic & Clin Pharmacol Toxicol* 2011;108:297–303.
- [6] Juzych MS, Zimmerman TJ. b-Blockers. Philadelphia, PA: Lippincott-Raven; 1997.
- [7] Denman J, Gilbar P, Abdi E. Hypersensitivity reaction to doctoxel after previous hypersensitivity reaction to paclitaxel. *J Oncol* 2002;20:2760–1.
- [8] Hodnett PA, Naidich DP. Fibrosing interstitial lung disease. A practical high-resolution computed tomography-based approach to diagnosis and management and a review of the literature. *Am J Respir Crit Care Med* 2013;188(2):141–9.
- [9] Camus P, Famton A, Bonniaud P, Camus C, Foucher P. Interstitial lung disease induced by drugs and radiation. *Respiration* 2004;71:301–26.
- [10] Costabel U, Uzaslan E, Guzman J. Bronchoalveolar lavage in drug-induced lung disease. *Clin Chest Med* 2004;25:25–36.
- [11] Malhotra A, Muse VV, Mark EJ. Case reports of Massachusetts General Hospital. Weekly clinicopathological exercises. Case 22-2003. An 82 year-old man with dyspnea and pulmonary abnormalities. *N Engl J Med* 2003;348:1574–85.
- [12] Romagnoli M, Bigliuzzi C, Casoni G, et al. The role of transbronchial lung biopsy for diagnosis of diffuse drug induced lung disease: a case series of 44 patients. *Sarcoidosis Vasc Diffuse Lung Dis* 2008;25:36–45.
- [13] Chetta A, Marangio E, Olivieri D. Pulmonary function testing in interstitial lung diseases. *Respiration* 2004;71:209–13.
- [14] Fraser-Parg. Synopsis of disease of the chest: 2nd ed. p. 687.
- [15] Flaherty KR, Toews GB, Travis WD, Colby TV, Kazerooni EA, Gross BH, et al. Clinical significance of histological classification of idiopathic interstitial pneumonia. *Eur Respir J* 2002;19:275–83.
- [16] Nagai S, Kitaichi M, Itoh H, Nishimura K, Izumi T, Colby TV. Idiopathic nonspecific interstitial pneumonia/fibrosis: comparison with idiopathic pulmonary fibrosis and BOOP. *Eur Respir J* 1998;12:1010–9.
- [17] Prakash US, Rosenow III EC. Pulmonary complications from ophthalmic preparations. *Mayo Clin Proc* 1990;65:521–9.
- [18] Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30:239–45.