Eur Respir J 1997; 10: 2159–2162
DOI: 10.1183/09031936.97.10092159
Printed in UK - all rights reserved

European Respiratory Journal
ISSN 0903 - 1936

CASE STUDY

Migratory pulmonary infiltrates in a patient treated with sotalol

M. Faller*, E. Quoix*, E. Popin*, A. Gangi**, B. Gasser+, C. Mathelin‡, G. Pauli*

Migratory pulmonary infiltrates in a patient treated with sotalol. M. Faller, E. Quoix, E. Popin, A. Gangi, B. Gasser, C. Mathelin, G. Pauli. ©ERS Journals Ltd 1997.
ABSTRACT: Beta-blockers may induce several types of adverse respiratory reaction such as asthma, interstitial lung disease with or without pleural effusion, systemic lupus erythematosus or hypersensitivity pneumonitis. More recently, bronchiolitis obliterans with organizing pneumonia (BOOP) has been described. We report here on pulmonary migratory infiltrates with combined histopathological features of both BOOP and eosinophilic pneumonia in a woman treated with sotalol long-term. The patient improved only partially with steroids. Tapering off corticosteroid dosage resulted in relapse, and complete recovery was only obtained after sotalol was stopped.
Eur Respir J 1997; 10: 2159–2162.

*Service de Pneumologie, **Service de Radiologie, +Institut d'Anatomie Pathologique and ‡Service de Gynécologie-Obstétrique, Hôpitaux Universitaires de Strasbourg, 67091 Strasbourg Cedex, France.

Correspondence: G. Pauli, Service de Pneumologie, Hôpitaux Universitaires de Strasbourg, B.P. 426, F-67091 Strasbourg Cedex, France

Keywords: Adverse effects, beta-blocker, bronchiolitis obliterans with organizing pneumonia, drug-induced eosinophilic pneumonia, pulmonary migratory infiltrates, sotalol

Received: October 24 1996
Accepted after revision May 31 1997

The diagnosis of drug-induced pulmonary disease is hampered by several difficulties. More than one pattern of respiratory complications may be related to a single drug. Often, many drugs that are potentially toxic to the lung are taken concomitantly by the patient. Pulmonary manifestations related to the underlying disease may also be a complicating factor.

Beta-blockers have been implicated in asthma attacks [1], hypersensitivity pneumonitis [2], systemic lupus erythematosus [3, 4] and diffuse interstitial pneumonitis with or without pleural effusion [5]. More recently, a pattern of bronchiolitis obliterans with organizing pneumonia (BOOP) was reported with the use of the β-blocker acebutolol [6]. We report here on the development of migratory pulmonary infiltrates in a patient treated with sotalol. Sotalol is a cardioselective β-blocker marketed in France since 1974, that is prescribed for cardiac arrhythmias because of its cardioselective activity and its moderately negative inotropic activity. The infiltrates cleared up only after sotalol was stopped

Case report

A 61 yr old woman was admitted to our hospital in September 1993. She was a farmer and had a 6 month history of nonproductive cough and increasing dyspnoea. There was no weight loss; moderate fever (38.2°C) developed subsequently. She was a nonsmoker. Her medical history was characterized by bilateral breast carcinoma, which was treated by bilateral tumourectomy in July 1989. Postoperative radiotherapy was given between August and October 1989, using 64 Gy delivered in 34 fractions over the left and right breast with tangential fields, and 40 Gy in 22 fractions to each internal mammary lymph node chain with frontal fields. The patient then received tamoxifen (Nolvadex®; Zeneca, Cergy, France) 40 mg·day^{-1} between 1989 and 1991, and 30 mg·day^{-1} thereafter. She had moderate systemic hypertension, and suffered from bouts of supraventricular arrhythmia and a moderate Raynaud's phenomenon. She was treated for several years with acetylsalicylate (Aspegic®; Synthelabo, Meudon-la-Forêt, France) 100 mg·day^{-1} and sota-lol (Sotalex®; Bristol-Myers-Squibb, Paris, France) 160 mg *b.i.d.* for the last 9 months. She also received urapidyl (Eupressyl®; Byrk, Lemée-sur-Seine, France), 60 mg *b.i.d.* since April 1993. This replaced an association of enalapril and hydrochlorothiazide (Corenitec®; Merck-Sharp-Dohme-Chibret, Paris, France), which had been given until January 1993. A chest radiograph in April 1993 was normal, but in June 1993, an alveolar opacity of the lingula and a slight infiltrate in the culmen were noted, for which antibiotics were given without any improvement.

On admission, the clinical and pleuropulmonary examination were normal, except for the cutaneous sequelae of breast surgery and radiation therapy. The chest radiograph (fig. 1a) showed retraction of the lingula and alveolar opacities in the right middle lobe. Erythrocyte sedimentation rate was 45 mm·h^{-1}. The white blood cell count, including eosinophils, was normal. Serum electrophoresis displayed a normal pattern. There were no precipitins against farmer antigens or *Aspergillus* spp. Immunological investigation showed no circulating immune complexes and normal levels of C3, C4, and CH50. Antinuclear antibodies and rheumatoid factor were absent. The nailfold capillaroscopy was normal. The computed tomography (CT) scan (fig. 2) confirmed partial lingular atelectasis with an infiltrate in the right middle

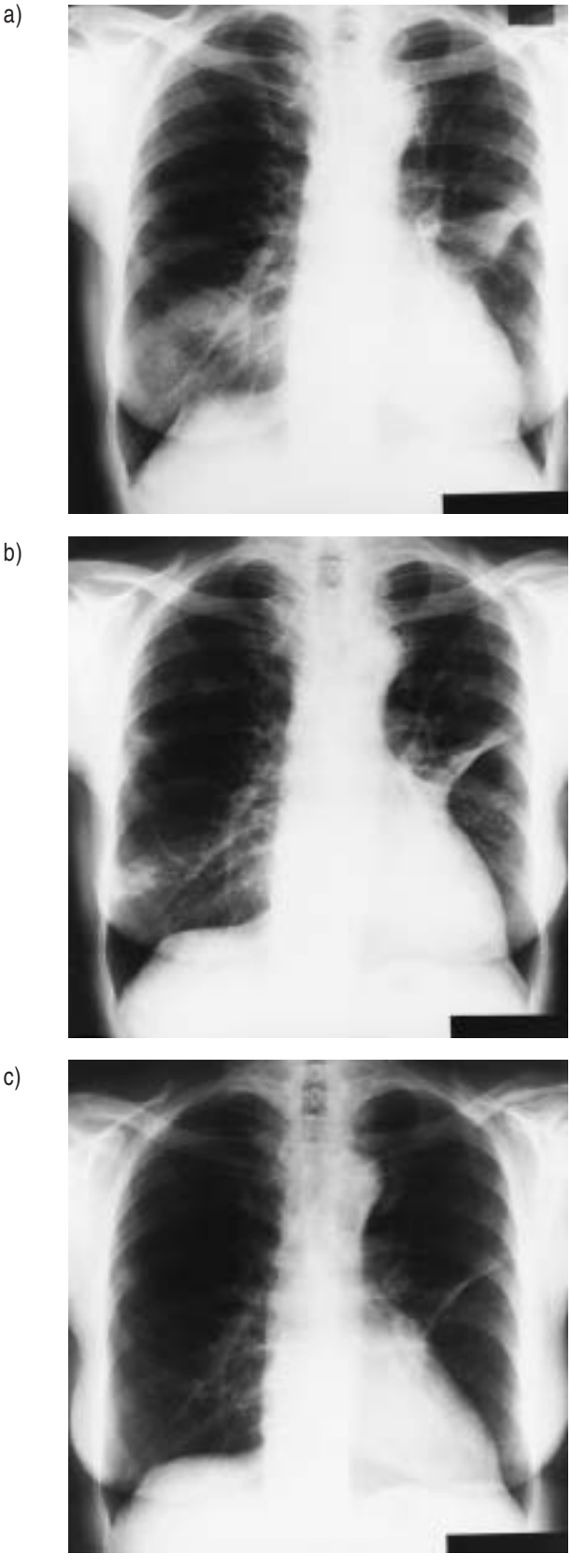

Fig. 1. – Posteroanterior chest radiographs: a) September 1993, showing a retractile lingular opacity and an alveolar shadow in the right middle lobe; b) April 1994, showing a nodular infiltrate in the culmen and right axilla c) October 1994; after sotalol was stopped, only slight residual atelectasis was seen in the lingula.

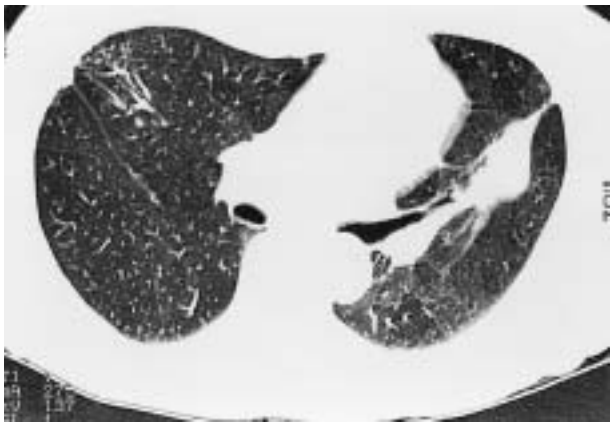

Fig. 2. – Computed tomography scan showing a dense opacity in the lingular area, along with a nodular infiltrate and streaks over the right middle lobe area.

lobe. An oesophageal diverticulum of the middle third was also seen, and was confirmed by a baryum oesophageal series.

Pulmonary function tests, measured by plethysmography, showed a restrictive defect with total lung capacity of 78% predicted, forced vital capacity (FVC) of 94% pred, and a normal forced expiratory volume in one second (FEV_1)/FVC ratio of 79%. Arterial oxygen tension (breathing room air) was 10.4 kPa (78 mmHg) and P_{a,CO_2} was 5.9 kPa (44 mmHg). Fibreoptic bronchoscopy showed that the lingular orifice was narrowed by mucosal inflammation. Bronchial biopsies in this area showed subacute nonspecific inflammation. A CT scan-guided lung biopsy was performed in the right middle lobe, and showed the combination of organizing pneumonia with obstruction of small airways by buds of connective tissue, along with features of pulmonary eosinophilic infiltration (fig. 3).

Oral prednisolone 1 $mg \cdot kg^{-1}$ *i.e.* 60 $mg \cdot day^{-1}$ was started on October 15, 1993 for 1 month, and then progressively tapered. Partial clinical and radiological improvement occurred. Fever was no longer present, but a dry

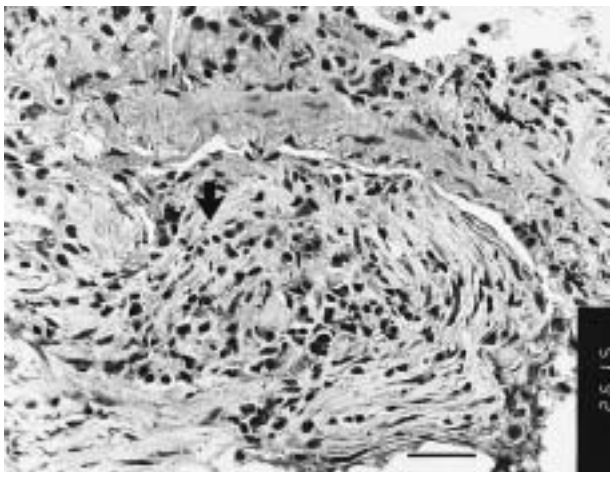

Fig. 3. – Lung biopsy specimen obtained *via* computed tomography-guided transthoracic needle biopsy. A bud of connective tissue consistent with bronchiolitis obliterans with organizing pneumonia is seen. At some places, a prominent eosinophilic infiltrate was present. The location of eosinophils is indicated by the arrows. (Haematoxylin and eosin stain; internal scale bar = 100 μm).

cough persisted. There was some decrease in the right middle lobe opacities. Because of raised blood pressure, nicardipine (Loxen® 50 LP; Sandoz) was given. In January 1994, when the dose of prednisolone was tapered to 10 mg, infiltrates recurred in the left upper region. The dosage of prednisolone was again increased to 40 mg·day^{-1} for 2 weeks, without improvement. In April 1994, when receiving 12.5 mg·day^{-1} of prednisolone, the patient developed new infiltrates (fig. 1b). In June 1994, while prednisolone was given at 7.5 mg·day^{-1}, there were persistent dry cough and infiltrates in both upper lobes. Sotalol was discontinued and replaced by propafenone (Rythmol®; Knoll) 150 mg *b.i.d.*. All other drugs including prednisolone 7.5 mg·day^{-1} were kept unchanged. The cough disappeared completely within the next month, and the chest radiograph cleared during the next 2 months, except for a slight band of atelectasis in the lingula (fig. 1c). Steroids were progressively tapered and finally stopped in October 1994. When last evaluated in November 1996, the clinical and radiological status was normal, except for the slight lingular atelectasis noted above.

Discussion

The patient presented with nonproductive cough and dyspnoea. A moderate fever was lacking at the beginning but appeared later. She had migratory opacities on the chest radiograph, which improved only partially on steroids. She also had slight hypoxaemia and a moderate restrictive pulmonary function defect. This clinical and radiological pattern was consistent with a diagnosis of BOOP or of chronic eosinophilic pneumonia (CEP) [7, 8]. Although there was no peripheral eosinophilia, the lung biopsy showed infiltrating eosinophils in addition to changes suggestive of BOOP (fig. 3). Such an overlap between BOOP and CEP has already been described in varied contexts [8–11]. In fact, about 25% of CEP cases show some histological evidence of bronchiolitis obliterans or BOOP, and similarly, about 25% of patients with BOOP eventually demonstrate increased percentage of eosinophils in the BAL [8]. It has even been suggested that untreated CEP may be the initiating stage of some cases of BOOP [7].

Regarding the patient, other conditions had to be discussed as possible causes for BOOP and/or eosinophilic pneumonia. Firstly, the patient was taking multiple drugs. Until now, no cases of BOOP have been reported with the use of tamoxifen or acetylsalicylate, although both of these drugs may be responsible for pulmonary infiltrates with eosinophilia [12, 13]. These drugs had been administered to the patient for several years without any adverse effects to the lung, and they were continued during and well after the resolution of pulmonary infiltrates. BOOP has not been described with drugs such as hydrochlorothiazide or enalapril [12]. Hydrochlorothiazide may cause pulmonary oedema or nonspecific subacute interstitial lung disease [12]. Enalapril may be associated with cough and/or acute upper airway obstruction [12]. These two drugs were stopped in April 1993 at the time of onset of the dry cough, and this did not prevent the development of BOOP. Finally, urapidyl has not been involved in the development of BOOP or eosinophilic pneumonia [12], and in any event that drug was introduced after the onset of the cough.

Secondly, even though such digestive disease as ulcerative colitis may associate with BOOP or with CEP [14, 15], to the best of our knowledge, no case of BOOP has been described in association with an oesophageal diverticulum.

The history of breast radiation raises more questions. Indeed, some cases of BOOP have been described following radiation therapy for breast carcinoma [16–18], although this complication is far less common than classic radiation pneumonitis or fibrosis. In the patient, the interval between the end of radiation therapy on the one hand, and the development of BOOP on the other, was 4 yrs. Although free intervals of up to 18 yrs have occasionally been reported [19], we believe that lengthy intervals such as these cast doubt on the reality of an association between radiation therapy and BOOP. The extent to which prior radiation therapy acted as a "priming" factor in our case, as suggested by others [16], remains unknown. Again, we want to stress that remission of clinical symptoms (particularly dry cough), and of radiographic opacities could only be obtained when sotalol was stopped.

In summary, we believe that our patient developed a drug-induced migratory lung reaction with a bronchiolitis obliterans with organizing pneumonia/chronic eosinophilic pneumonia histopathological pattern, and that this was secondary to the intake of sotalol. Whether β-blockers other than acebutolol [6] or sotalol (present case) may induce bronchiolitis obliterans with organizing pneumonia, with or without accompanying features of eosinophilic lung disease, remains to be determined.

References

1. Criag TJ. Drugs to be used with caution in patients with asthma. Review. *Am Fam Physician* 1996; 54: 947–953.
2. Lombard JN, Bonotte B, Maynadie M, *et al*. Celiprolol pneumonitis. *Eur Respir J* 1993; 6: 588–591.
3. Wilson JD. Antinuclear antibodies and cardiovascular drugs. *Drugs* 1980; 19: 292–305.
4. Record NB. Acebutolol-induced pleuropulmonary lupus syndrome. *Ann Intern Med* 1981; 95: 326–327.
5. Musk AW, Pollard JA. Pindolol and pulmonary fibrosis. *Br Med J* 1979; ii: 581–582.
6. Camus Ph, Lombard J-N, Perrichon M, *et al*. Bronchiolitis obliterans organising pneumonia in patients taking acebutolol or amiodarone. *Thorax* 1989; 44: 711–715.
7. Allen JN, Davis WB. Eosinophilic lung diseases. *Am J Respir Crit Care Med* 1994; 150: 1423–1438.
8. Jedelinic PJ, Sicilian L, Gaensler EA. Chronic eosinophilic pneumonia: a report of 19 cases and a review of the literature. *Medicine* 1988; 67: 154–162.
9. Bartter T, Irwin RS, Nash G, Balikian JP, Hollingworth HH. Idiopathic bronchiolitis obliterans organizing pneumonia with peripheral infiltrates on chest radiogram. *Arch Intern Med* 1989; 149: 273–279.
10. Cooney TP. Interrelationship of chronic eosinophilic pneumonia, bronchiolitis obliterans and rheumatoid disease: a hypothesis. *J Clin Pathol* 1981; 34: 129–137.
11. Yousem SA, Lifson JD, Colby TV. Chemotherapy-induced eosinophilic pneumonia: relation to bleomycin. *Chest* 1985; 88: 103–106.

12. Foucher P, Biour M, Blayac JP, *et al.* Drugs that may injure the respiratory system. *Eur Respir J* 1997; 10: 265–279.
13. Allen JN, Davis WB, Pacht ER. Diagnostic significance of increased bronchoalveolar lavage fluid eosinophils. *Am Rev Respir Dis* 1990; 142: 642–647.
14. Camus Ph, Piard F, Ashcroft T, Gal AA, Colby TV. The lung in inflammatory bowel disease. *Medicine* 1993; 72: 151–183.
15. Swinburn CR, Jackson GJ, Codben I, Ashcroft T, Morritt GN. Bronchiolitis obliterans organizing pneumonia in a patient with ulcerative colitis. *Thorax* 1988; 43: 735–736.
16. Bayle JY, Nesme P, Bejui-Thivolet F, Loire R, Guerin J-C, Cordier JF. Migratory organizing pneumonitis "primed" by radiation therapy. *Eur Respir J* 1995; 8: 322–326.
17. Crestani B, Kambouchner M, Soler P, *et al*. Migratory bronchiolitis obliterans organising pneumonia after unilateral radiation therapy for breast carcinoma. *Eur Respir J* 1995; 8: 318–321.
18. King TE. BOOP: an important cause of migratory pulmonary infiltrates. *Eur Respir J* 1995; 8: 193–195.
19. Tobias ME, Plit M. Bronchiolitis obliterans organizing pneumonia migratory infiltrates: a late complication of radiation therapy. *Am J Roentgenol* 1993; 160: 205–206.