CASE REPORT

Carbimazole-induced exudative pleural effusions

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SUMMARY

Carbimazole, an antithyroid drug, is associated with a significant number of side effects, but pleuropulmonary complications are rare. We report the case of a 42-year-old Caucasian man who developed dyspnoea secondary to bilateral exudative pleural effusions while on carbimazole therapy. Extensive investigations, including a vasculitic screen, ruled out other potential causes for this patient's clinical presentation. This patient's pleural effusions gradually resolved within a few months of stopping carbimazole therapy, suggesting a role for the latter in the aetiopathogenesis of his presentation. Clinicians should consider discontinuing treatment with carbimazole and introducing alternative antithyroid therapy in this setting, once other potential causes of a pleural effusion have been systematically ruled out.

CASE PRESENTATION

A 42-year-old man was admitted with a 3-week history of worsening shortness of breath, both at rest and especially on exertion. This was increasingly interfering with his activities of daily living. He also suffered from a dry cough over the previous month and complained of mild pleuritic chest pain on deep inspiration. He denied any other symptoms such as haematemesis, fever, night sweats, rashes, anorexia, weight loss, joint pains or morning stiffness. He was prescribed co-amoxiclav by his general practitioner, for a presumed bronchitis; however, this did not ameliorate his symptoms. He was known to suffer from Graves' disease, treated with carbimazole for the previous 2 years and 3 months. During that time, he was taking 10 mg once daily and was always compliant with his medication.

Physical examination was unremarkable, save for clinical signs consistent with bilateral pleural effusions.

BACKGROUND

Carbimazole belongs to the thionamide class of antithyroid drugs (together with methimazole and propylthiouracil). It is a prodrug, undergoing quick and almost complete metabolism into its active metabolite thiamazole (also known as methimazole). Carbimazole is widely prescribed in the treatment of hyperthyroidism, suppressing thyroid hormone synthesis through inhibition of iodide organification and iodothyronine residue coupling. It is associated with a significant number of adverse effects including bone marrow suppression (with possible associated neutropaenia, eosinophilia, leucopaenia, agranulocytosis, thrombocytopaenia and aplastic anaemia/pancytopaenia), rashes, pruritus, hypersensitivity disorders and liver impairment.¹ Pleuropulmonary complications have rarely been reported. Antineutrophil cytoplasmic antibody (ANCA)-positive vasculitis is known to complicate antithyroid drug therapy; pulmonary involvement occurs in 27% of such cases. However, propylthiouracil was the culprit drug in 88% of cases, 75% of affected patients were females, while 50% were of Japanese origin.²

Pulmonary complications occurring secondary to an ANCA-positive vasculitis in the setting of carbimazole therapy usually involve pulmonary haemorrhage.³ Pulmonary capillaritis with associated intra-alveolar haemorrhage has also been reported with methimazole.⁴ However, to our knowledge, carbimazole-induced pleural effusions have been reported in only two patients.^{5,6} We report a case of carbimazole-induced exudative bilateral pleural effusions in a middle-aged Caucasian man.

INVESTIGATIONS

The patient's arterial blood gases confirmed hypoxaemia (PO₂ 76 mm Hg) and hypocapnoea (PCO₂ 28.2 mm Hg) in the setting of respiratory alkalosis (pH 7.48). A chest X-ray (CXR) demonstrated bilateral pleural effusions (figure 1), worse on the right, involving one-third of the pleural cavity. His ECG and blood investigations, including a complete blood count, renal and liver profiles, serum albumin, corrected serum calcium, erythrocyte sedimentation rate (ESR) and serum lactate dehydrogenase levels, were all normal. C reactive protein (CRP) was minimally raised at 13 mg/L (normal range (NR) 0–10 mg/L). Urinalysis was unremarkable. Thyroid function tests (TFTs) demonstrated a normal free thyroxine (15.4 pmol/L (NR 11–18 pmol/L)) in the setting of a minimally raised thyroid stimulating hormone level (4.58 mIU/L (NR 0.3–3 mIU/L)). As a result, his carbimazole dose was reduced to 7.5 mg daily.

Echocardiography confirmed normal left and right ventricular systolic and diastolic function, size, wall motion and thickness. Moreover, no valvular pathology was found, with the exception of trace pulmonary valve and mild mitral valve regurgitation. A ventilation perfusion scan was performed, which showed no signs of pulmonary embolism. In addition, a diagnostic right pleurocentesis was carried out under ultrasound guidance. The aspirated pleural fluid was a straw coloured exudate with a pH of 8 (excluding an empyema), and its Gram stain, culture (including for mycobacteria) and sensitivity were negative. Cytology showed numerous lymphocytes, scattered

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Figure 1 Initial chest-X ray showing bilateral pleural effusions, worse on the right.

macrophages, occasional eosinophils, few neutrophils and rare mesothelial cells, but no malignant cells were seen. Similar pleural fluid results were obtained on resampling 3 weeks later.

CT of the thorax, abdomen and pelvis showed bilateral pleural effusions, larger on the right, with subsegmental atelectatic changes and minimal ascites. Viral and vasculitic screens (including ANCA) were all negative. Serum ACE and complement levels were also normal. Mycoplasma IgM antibody was not detected. Genetic screen for familial Mediterranean fever was performed; however, no mutations were identified. Tumour marker (human chorionic gonadotrophin, serum carcinoembryonic antigen, carbohydrate antigen 19-9, prostate-specific antigen and α -fetoprotein) levels were also normal.

OUTCOME AND FOLLOW-UP

About 2 months later, the patient developed significant derangement of his liver function tests (alanine aminotransferase 146 U/L (NR 5–41 U/L), serum alkaline phosphatase 159 U/L (NR 40–129 U/L), γ -glutamyl transpeptidase 96 U/L (NR 8–61 U/L) and bilirubin 5.4 μ mol/L (NR 1.72–17.1 U/L)) and a moderate rise in inflammatory markers (ESR 35 mm first hour (NR 8–12 mm first hour) and CRP 52 mg/L (NR 0–10 mg/L)). His TFTs were normal while an ultrasound of his abdomen showed no liver pathology. The patient's inflammatory markers and liver profile normalised within a few weeks of cessation of carbimazole therapy.

A repeat CXR carried out approximately 6 weeks after stopping carbimazole therapy demonstrated minimal reduction of his bilateral pleural effusions; however, these continued to improve, and eventually resolved completely—approximately 5 months later (figure 2). During this period, the patient was not on any medications. He developed T3 toxicosis off carbimazole, prompting start of propylthiouracil with the aim of achieving euthyroidism prior to surgery. Fortunately, his pleural effusions did not recur until he successfully underwent a total thyroidectomy 7 months later.

DISCUSSION

Carbimazole has been reported to cause a pulmonary renal syndrome with complicating pulmonary haemorrhage, similar to

Figure 2 Chest-X ray showing complete resolution of the patient's pleural effusions approximately 5 months after stopping carbimazole therapy.

that seen in Goodpasture's syndrome.^{3 7} The mechanism of action is poorly understood. As for propylthiouracil, it appears that, in the presence of hydrogen peroxidase, activated neutrophils release myeloperoxidase, which converts propylthiouracil into a cytotoxic agent. The latter is immunogenic to T-cells, resulting in B-cell activation, which, in turn, produces ANCA. Moreover, propylthiouracil and its metabolites may accumulate inside neutrophils, where they bind and change the configuration of myeloperoxidase. Neutrophil proteins are thus rendered as immunogenic antigens (such as elastase and nuclear antigens), promoting antibody production. Nonetheless, propylthiouracil and propylthiouracil-induced myeloperoxidase ANCA can inhibit the oxidation activity of myeloperoxidase in a dose-dependent fashion.⁸

There are as yet no data to suggest that myeloperoxidase can be altered by carbimazole,² an observation that could explain why carbimazole has been associated with an ANCA-negative vasculitis/serositis. Reports of carbimazole-induced/carbimazole-associated ANCA-negative vasculitis/serositis are few and sparse in the medical literature. One such case involved an elderly woman with a unilateral exudative pleural effusion, whose vasculitic screen was negative.⁶ Additionally, a 50-year-old woman has been reported to develop carbimazole-induced lupus complicated by bilateral exudative pleural effusions.⁵ Carbimazole has also been associated with leucocytoclastic vasculitis, interstitial nephritis⁹ and gastric eosinophilic granulomatous vasculitis.¹⁰ While the mechanism remains elusive, a local inflammatory process/vasculitic reaction is likely, particularly given that there are as yet no data to suggest that myeloperoxidase can be altered by carbimazole.²

As for the timing of such adverse events, carbimazole induced a pleural effusion after 6 months of high dose treatment (40 mg daily) in one case⁵ and after 3 months of treatment at a lower dose (20 mg daily) in another patient.⁶ Our patient presented with bilateral pleural effusions 27 months into his carbimazole therapy. Vasculitis complicating antithyroid drug therapy is more likely either soon after drug exposure, or in those on long-term (>18 months) treatment. However, a study by Gunton *et al*² reported no significant association between duration of carbimazole therapy and ANCA positivity.

As all the investigations to exclude other possible pathology were normal and the pleural effusions gradually resolved on cessation of carbimazole therapy indicate that the latter was the culprit for the patient's clinical presentation. To our knowledge, this is the third reported case of carbimazole-induced ANCA-negative exudative pleural effusion, unlike propylthiouracil-induced, which is a well-known cause of such an adverse reaction.^{11–13}

Learning points

- ▶ Clinicians should consider stopping carbimazole and offer alternative therapy for hyperthyroidism in patients presenting with unexplained pleural effusions while on carbimazole treatment.
- ▶ Carbimazole should, however, only be stopped after other potential causes for such a serositis have been ruled out.
- ▶ Further research is required to underpin the underlying mechanism of carbimazole-induced vasculitis/serositis.

Contributors All the authors were involved in the care of the patient and made significant contributions to the manuscript. SV was the consultant who identified carbimazole as the cause for the patient's pleural effusions following thorough investigations. CDCA drafted the paper, while the rest of the authors were involved with the review, editing and revision of the paper.

Competing interests None declared.

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