CASE REPORT

Carbimazole-induced eosinophilic pleural effusion

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Accepted 23 April 2018

SUMMARY

We report the case of a 41-year-old woman who presented with a unilateral exudative effusion with prominent eosinophils on pleural cytology. Carbimazole had been started 4 weeks prior to presentation. No immediate cause was identified on imaging or laboratory testing. The effusion persisted at 2-month follow-up. Further investigation at this time, including autoimmune serology was negative. At 2-month follow-up, the effusion was loculated on ultrasound imaging and had a low fluid pH on diagnostic aspiration, in keeping with an empyema. The patient received treatment for pleural empyema, including antibiotics, intercostal drain insertion and video-assisted thoracoscopic pleural biopsy. Carbimazole was stopped, and following treatment for the empyema, the effusion did not reaccumulate. This case illustrates the diagnostic difficulties that pleural effusions may present. It demonstrates that drug reactions should be considered in the differential diagnosis following thorough investigation for other potential causes and also describes the complications that may occur.

BACKGROUND

This is an unusual case of an eosinophilic exudative pleural effusion in a woman who had recently restarted carbimazole therapy for primary hyperthyroidism. The pleural effusion was complicated by the development of an empyema.

CASE PRESENTATION

A 41-year-old woman presented with a history of worsening dyspnoea over several weeks. She also reported recent weight loss of approximately one stone. This was on a background of primary hyperthyroidism secondary to Graves' disease that had been diagnosed 2 years previously. Her hyperthyroidism was treated with carbimazole therapy for 1 year, at which stage, the patient stopped taking carbimazole. Four weeks prior to presenting to the Emergency Department (ED), the patient recommenced carbimazole therapy on the advice of her general practitioner.

As well as carbimazole, other current medications at the time of presentation included propranolol and selenium. The patient was a current smoker with a 20 pack-year history. On examination, in ED, the patient was noted to have reduced breath sounds on the left side.

INVESTIGATIONS

On initial presentation to ED, chest radiograph confirmed the presence of a unilateral left pleural

effusion. The patient was admitted to hospital for further investigation and management. On admission, she had mildly elevated inflammatory markers with C-reactive protein 14 mg/L, white cell count $13.6 \times 10^9/L$ and peripheral eosinophilia of $0.82 \times 10^9/L$. The peripheral eosinophilia reached a peak of $1.62 \times 10^9/L$ 2 days later. Routine biochemistry including renal function, liver function and bone profile was unremarkable. A diagnostic pleural aspiration was performed. Fluid protein was elevated at 46 g/L; lactate dehydrogenase was 490 U/L and glucose 4.8 mmol/L, in keeping with an exudative effusion. Microbiology including Gram stain, culture and tuberculosis culture were negative.

A CT thorax was performed and showed the left-sided unilateral effusion with no other identifiable pathology. Following the pleural aspiration, the patient was discharged for outpatient urgent follow-up. She reattended the outpatient department 7 days later and the effusion persisted on imaging. An elective outpatient therapeutic pleural aspiration was performed. Biochemical analysis of the pleural fluid was again consistent with an exudative effusion and all microbiological testing was negative. The fluid was noted to be blood stained. Cytology showed mostly acute inflammatory cells with prominent eosinophils. No malignant cells were seen. Further urgent outpatient investigation and follow-up of the unexplained unilateral exudative effusion was arranged. Unfortunately, at this stage the patient failed to attend further follow-up appointments.

DIFFERENTIAL DIAGNOSIS

The investigations at this stage confirmed a unilateral exudative pleural effusion with prominent eosinophils on cytology and a peripheral eosinophilia. The British Thoracic Society Pleural Disease Guideline 2010 recommends diagnostic pleural aspiration followed by CT thorax to investigate unilateral exudative effusions, with further investigations thereafter if the cause is not identified.¹ The differential diagnosis for exudative effusions includes infection, particularly parapneumonic or TB related, malignancy and other less common causes such as pulmonary embolism, rheumatoid arthritis and other autoimmune pleuritis and drugs.

Eosinophilic pleural effusions, usually defined as eosinophils >10%, have an estimated relative incidence of 5%–16% of all pleural effusions.² One review of 2205 pleural effusions from a single tertiary referral centre over a 12-year period found that 7.2% of the effusions were eosinophilic.² The most common cause of eosinophilic effusions in this

To cite: Ferguson C, Bradley C, Kidney J. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2018-224701

study was malignancy, followed by pleural infections and chest trauma. Drug reactions are also recognised as a cause of pleural effusions and, in particular, are recognised as a cause of eosinophilic pleural effusions.³

Much of our knowledge of drug-related effusions is based on case reports. A thorough and detailed diagnostic approach should be undertaken in all patients with unexplained effusions, with consideration of a drug-induced effusion also. As patients often respond clinically to withdrawal of the offending agent, it is important that this potential cause of an effusion is not overlooked.⁴

TREATMENT

As above, the patient failed to attend review for 7 weeks after the second pleural aspiration. On her re-presentation, chest radiograph confirmed the persisting left-sided effusion. A bedside limited thoracic ultrasound was performed. This showed loculations within the effusion. A diagnostic pleural aspiration was performed and showed a low fluid pH of 7.07, low glucose of 0.3 mmol/L with total fluid protein of 61 g/L. It was suspected an empyema had developed in the left pleural cavity and the patient was admitted for further management.

A large bore chest drain was inserted. Microbiology cultures of pleural fluid were positive for *Streptococcus oralis*. Pleural fluid cytology again showed acute inflammatory and mesothelial cells with a prominent population of eosinophils.

Further investigations for an underlying cause of the unilateral effusion were negative. These included an autoimmune screen (antinuclear antibody (ANA), antineutrophil cytoplasmic antibody (ANCA), antiglomerular basement membrane antibody, rheumatoid factor and anticyclic citrullinated peptide), HIV screen and inhaled allergen screen (total IgE, radioallergen sorbent test, Aspergillus serology). Serum antihistone antibody was not checked.

Thyroid function tests (TFTs) were also intermittently monitored. TFTs were normal when the carbimazole therapy was restarted 3 months previously, suggesting spontaneous remission of Graves' disease. Repeat TFTs on carbimazole demonstrated hypothyroidism (thyroid stimulating hormone 112.9 mU/L, free T4 <5 pmol/L) with TFTs returning to normal again on withdrawal of the medication.

Repeat CT imaging confirmed the loculated pleural effusion suspicious of an empyema. Intravenous antibiotics were commenced. The carbimazole therapy was stopped at this time given the history of an unexplained unilateral effusion with prominent eosinophils on cytology. Corticosteroid treatment for suspected drug-related effusion was considered, but given the suspected superimposed pleural infection, it was decided that this would not be the most appropriate course of action.

Unfortunately, the effusion failed to resolve with a single intercostal drain and the patient was transferred to the thoracic surgery department. She underwent a video-assisted thoracoscopic pleural biopsy and insertion of a second intercostal drain. The histopathology from the pleural biopsies showed thickened pleura and reactive changes in keeping with an empyema, with no evidence of malignancy.

OUTCOME AND FOLLOW-UP

The patient completed a prolonged course of antibiotics and was discharged from thoracic surgery with an indwelling intercostal drain and ambulatory Portex bag. Decortication was considered but a conservative approach was adopted. At subsequent clinic review, the drain was successfully removed and the left lung re-expanded.

The patient has also been regularly followed up by the endocrine team. She is clinically and biochemically euthyroid and remains on no antithyroid medication. She has been referred for consideration for thyroidectomy. Carbimazole was stopped 5 months ago and the indwelling intercostal catheter was removed 4 months ago. The effusion has not reaccumulated and the peripheral eosinophilia has resolved.

DISCUSSION

Propylthiouracil (PTU), carbimazole and methimazole are thionamides used in the medical management of thyrotoxicosis. Methimazole is the active metabolite of carbimazole. Systemic adverse effects including rash, fever, arthralgia and agranulocytosis have been described.⁵ The mechanism is not well understood but is considered immunological in origin.⁶ There have been cases of vasculitis secondary to thionamides reported, with most caused by PTU. More rarely carbimazole and methimazole have been implicated.⁷ Drug-induced lupus has also been described.⁷⁻¹⁰ One review of the literature published in 1987 noted 53 cases of adverse immunological effects related to thionamides over a 35-year period.⁶

We have found eight reported cases of pleural effusion related to thionamides.^{7 8 11-17} Other pleuropulmonary complications that have been reported include alveolar haemorrhage, interstitial pneumonia and pulmonary cavities.^{7 15}

On review of the literature, we have found four cases of pleural effusions with PTU as the likely cause. In two of the cases, an eosinophilic exudate was demonstrated.^{11 12} One patient had been on PTU for 11 years when the effusion developed, while the other had only been on the drug for 4 weeks. In both cases, autoimmune screen including ANCA and ANA was negative. In one case, the effusion resolved 3 months after drug withdrawal, while in the other case corticosteroids were initiated due to persistent pleural effusion 6 weeks after drug withdrawal. The pleural effusion resolved 10 days following initiation of corticosteroids.

The other two cases report pleural effusion in the setting of drug-induced lupus or vasculitis. One of the cases reported a left-sided pleural effusion in association with positive ANA and ANCA and with associated clinical features including polyarthralgia and erythema nodosum.¹³ This was felt to be in keeping with an overlap between drug-induced lupus and ANCA-positive vasculitis. No pleural fluid sample was obtained. The patient was treated with methylprednisolone and the pleural effusion had resolved at follow-up 2 months later. In the second case, the patient presented with bilateral pulmonary infiltrates and pleural effusions, rash and respiratory failure.¹⁴ Vasculitis was suspected and ANCA serology was positive. Pleural fluid sampling demonstrated a transudate effusion, and a punch biopsy of one of the skin lesions showed evidence of vasculitis without granuloma. Intravenous corticosteroids were commenced with subsequent dramatic improvement in the pulmonary infiltrates.

Carbimazole has previously been reported in the literature as the likely cause of pleural effusion in three cases.^{8 15 17} None of these were eosinophilic exudative effusions. One patient had positive ANA, anti-dsDNA and antihistone antibodies and was therefore classified as a drug-induced lupus. The other two patients had negative autoantibodies and pleural aspiration showed an exudate with non-specific inflammatory cells. A pleural biopsy was carried out in one case which showed inflammatory changes only. In the three cases, the temporal relationship between the commencement of carbimazole and the diagnosis of a pleural effusion differed, with effusions variously diagnosed at 3, 6 and

27 months after commencement of carbimazole. The patient with carbimazole-induced lupus was treated with drug cessation, and corticosteroids were initiated. The pleural effusion had almost completely resolved 10 days later. The other two patients experienced resolution of their effusions at 5 and 3 months after drug cessation without commencement of corticosteroids.

There is one case report in the literature describing a pleural effusion as a result of methimazole.⁷ In this case, pleural aspiration did demonstrate an eosinophilic exudate; however, unlike our case, there was no peripheral eosinophilia. Autoimmune testing was negative. This patient had commenced methimazole only 6 days prior to developing a pleural effusion. The drug was withdrawn and corticosteroids initiated. Three months later, the pleural effusion had completely resolved.

We believe this is the first case reporting an eosinophilic exudative pleural effusion secondary to carbimazole. The temporal relationship between commencing carbimazole and developing a pleural effusion, along with the emergence of a peripheral eosinophilia after starting the drug are in keeping with this diagnosis. The patient was lost to follow-up for 7 weeks and at review had evidence of empyema with radiological evidence of loculations, low fluid pH and glucose and culture positive for *S. oralis*. We believe the empyema developed as a complication of the eosinophilic effusion rather than as the initial primary cause. At the initial, first presentation, the patient's inflammatory markers were not significantly raised and there were no clinical signs or symptoms of infection. In addition, two separate pleural aspirations within the first 10 days of diagnosis of the effusion showed normal pH, glucose and microbiological culture, illustrating no evidence of active pleural infection. We believe this supports our theory that pleural infection developed as a complication of the effusion.

This case also demonstrates some of the difficulties that can be encountered with outpatient management of patients. As this woman was clinically stable, elective outpatient follow-up and

management were planned following her initial acute hospital admission. Unfortunately, she did not attend the planned reviews, resulting in a delay in further investigation, diagnosis and treatment. This potentially resulted in delay stopping carbimazole, with subsequent development of complications including pleural infection, which required invasive and prolonged treatment.

Contributors CF and CB contributed equally to this report. CF was predominantly responsible for discussing differential diagnosis and discussion. CB was predominantly responsible for summarising the case and differential diagnosis. Both helped to finalise the draft of each other parts. JK contributed to editing and revising the final draft.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Learning points

- Consider drug reactions as a differential in unexplained pleural effusions, especially eosinophilic pleural effusions.
- Withdrawal of offending pharmacological agents often results in resolution of pleural effusions.
- Pleural infections and empyema can develop in chronic effusions and complicate investigation and management of the effusion.
- Delays in investigation and management may occur if follow-up is missed.

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