CASE REPORT

Carbimazole-induced lupus

Ihteshamul Haq,¹ Michael D Sosin,² Simon Wharton,¹ Anindya Gupta³

¹Department of Respiratory Medicine, Nottingham University Hospitals NHS Trust, Queen's Medical Centre, Nottingham, UK

²Department of Cardiology, Nottingham University Hospitals NHS Trust, Queen's Medical Centre, Nottingham, UK

³Department of Rheumatology, Nottingham University Hospitals NHS Trust, Queen's Medical Centre, Nottingham, UK

Correspondence to

Dr Ihteshamul Haq,
i.haq@nhs.net

SUMMARY

We describe the case of a 50-year-old lady admitted with a 3-week history of dyspnoea and left-sided pleuritic pain associated with pleural effusion. This common clinical picture nevertheless gave rise to a significant diagnostic challenge. The medical history included a diagnosis of thyrotoxicosis made 6 months previously that was being treated with carbimazole by her general practitioner. Key-investigation results were as follows: (1) pleural fluid was sterile and exudative, with no malignant cells, (2) erythrocyte sedimentation rate, C reactive protein and D-dimer were raised, (3) antinuclear antibody, anti-dsDNA and antihistone antibodies were newly positive, (4) imaging revealed a large left ventricular mass consistent with thrombus in the absence of evidence of a myocardial infarction. Based on the above investigations we hypothesised that carbimazole had induced systemic lupus erythematosus, manifesting as serositis resulting in an exudative pleural effusion and a proinflammatory/prothrombotic state. Carbimazole was stopped. The patient's pleural effusion completely resolved and she remains asymptomatic.

BACKGROUND

Drug-induced systemic lupus erythematosus (SLE) in patients with no pre-existing autoimmune disease is well documented in the literature.^{1–3} The most common drugs implicated are procainamide, hydralazine, isoniazid, quinidine and minocycline. The pathogenesis of drug-induced lupus is not well understood, however genetic predisposition may play an important role. A possible mechanism through which genetics might exert an effect is through acetylator status. Examples of drugs metabolised by acetylation include procainamide and hydralazine. Patients who are slow acetylators because of a genetically mediated decrease in the hepatic synthesis of N-acetyltransferase are more likely to develop drug-induced lupus.^{4–6} Other genetic risk factors include HLA-DR4, HLA-DR0301 and the complement C4 null allele.⁷ The exact mechanisms involved in drug-induced lupus remain uncertain. However various theories have been proposed to explain the underlying pathophysiology⁸ these include: abnormalities in oxidative drug metabolism, drugs acting as haptans or agonists for drug-specific T cells, cytotoxic drug metabolites, drugs non-specifically activating lymphocytes, drug metabolites disrupting central immune tolerance and abnormalities in thymus function.

Drug-induced SLE can arise months or years after the initiation of therapy with the putative drug and the patient may present with symptoms such as arthralgia, myalgia, malar rash and serositis.

In particular, isolated serositis in the presence of characteristic autoantibodies, without any other features of SLE, is strongly suggestive of drug induced lupus.^{7–8} Most patients are antinuclear antibody (ANA) positive, dsDNA negative and anti-histone antibody positive. Symptoms usually resolve within days or weeks of withdrawing the precipitating drug.

There are an estimated 15–30 000 cases of drug-induced SLE per year with males and females equally affected and older people and Caucasians being more susceptible.⁹ It is important to quickly recognise autoimmune phenomena caused by a drug so that it can be stopped and appropriate treatment with, for example steroids, started.

Hyperthyroidism is common, affecting 2–5% of all females at some point in their lives.¹⁰ The vast majority of these cases involve autoimmune or thyroid disease.¹⁰ Antithyroid drugs such as carbimazole and propylthiouracil (PTU) are in wide use. These medications are generally well tolerated but can be associated with a variety of adverse effects such as rash, pruritis and rarely with bone marrow suppression, neutropenia and agranulocytosis. However drug-induced SLE is not a well-recognised consequence of antithyroid drugs although PTU-induced myeloperoxidase (MPO) positive vasculitis is well documented.^{11–14}

We describe the case of a 50-year-old Caucasian lady who developed a serositis with newly positive ANA associated with pleuritic pain and pleural effusion 6 months after starting carbimazole for autoimmune thyrotoxicosis. An interesting complication in this case was the formation of a large left ventricular (LV) thrombus in the absence of any cardiac ischaemia, presumably due to a general proinflammatory/prothrombotic state brought about by the adverse drug reaction. Both these events were potentially life threatening.

Hyperthyroidism is a very prevalent healthcare problem and the use of carbimazole for its treatment is widespread. We believe that this report is important because it describes a potentially serious but underappreciated side effect of carbimazole treatment. Consideration of carbimazole-induced serositis as a differential diagnosis in similar presentations should lead to earlier diagnosis and improved patient outcomes.

CASE PRESENTATION**Initial presentation**

A 50-year-old Caucasian lady was admitted under respiratory medicine for the complaints of a 3-week to 4-week history of slowly progressive shortness of breath, worsening on exertion with a dry cough and left-sided pleuritic chest pain. She

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had not been febrile but did describe feeling lethargic with a poor appetite and 3–4 kg weight loss over 6 months. There was no history of night sweats. The patient had been on a recent short-haul flight but there had been no leg swelling.

Six months previously the patient had been diagnosed with hyperthyroidism by her general practitioner and was being maintained on 40 mg carbimazole daily. The only other history of note was periodic episodes of mild-to-moderate depression for which she took 20 mg fluoxetine daily. She was not allergic to any drugs. There was no family history of note, the patient worked in an office, lived alone, smoked 10 cigarettes/day, did not consume alcohol and was normally fit, independent and self-caring.

Clinical examination showed that the patient was stable with oxygen saturations on air of 98%, was slightly tachypnoeic with a respiratory rate of 25 but had no fever and otherwise haemodynamically stable. Cardiac and abdominal examinations were unremarkable, however chest examination revealed reduced air entry at the left base.

Initial investigations demonstrated normal renal and liver functions and normal adjusted serum calcium. Troponin I was within the normal range. The patient was slightly anaemic with a haemoglobin level of 10.7 and a mean cell volume of 91. The C reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were raised at 40 and 112, respectively, D-dimers were raised at 958 and urine dipstick showed blood ++ and protein +. Subsequent urine cultures showed no growth. The ECG showed normal sinus rhythm with no evidence of ischaemic change or right heart strain. A chest x-ray (CXR) showed a moderate left-sided pleural effusion (see figure 1).

Based on this clinical picture our initial differential diagnosis was (1) infection/inflammation, (2) malignancy or (3) pulmonary embolism (PE); and on this basis further tests were carried out as described below.

A diagnostic tap of the left pleural effusion revealed a non-turbid, straw-coloured fluid with a protein concentration of 43 g/l, pH 7.4, lactate dehydrogenase 578 and glucose 6.9. The fluid was negative for acid-fast bacilli, no organisms were seen with Gram stain; there were a few white cells and culture, including for tuberculosis (TB), failed to grow any organisms. Hence the pleural fluid was exudative but sterile. Cytology showed an abundance of acute and chronic inflammatory cells (neutrophils, polymorphs and macrophages) and reactive mesothelial cells but importantly no malignant cells.

Figure 1 Chest x-ray on initial presentation showing moderate-sized left pleural effusion.

Given her breathlessness, pleural effusion, pleuritic chest pain and raised D-dimer, we wanted to investigate for PE and malignancy. The patient therefore underwent a CT pulmonary angiogram and a CT scan of chest, abdomen and pelvis. These investigations showed no evidence of a PE or malignancy; however, there were imaging features of a large thrombus within the left ventricle (LV)—this would normally be associated with a current or prior myocardial infarction. As stated above there was no clinical or ECG evidence of cardiac chest pain and her cardiac enzymes were negative.

A transthoracic echocardiogram was performed in order to characterise the LV lesion and to assess ventricular function. The echocardiogram confirmed a large mass consistent with thrombus occupying the mid-apical LV cavity with associated hypokinesia of the surrounding myocardial segments, but no wall thinning or aneurysm formation to suggest a prior infarct.

To summarise thus far: a 50-year-old lady with a 6-month history of hyperthyroidism—treated with carbimazole—presented with shortness of breath and pleuritic pain, an exudative left pleural effusion, with raised inflammatory parameters and a large thrombus in the LV. It was difficult to relate the pleural effusion with the LV thrombus. However with regard to the differential diagnoses above we had ruled out PE, and the malignancy was very unlikely given the normal staging CT scan. We therefore concluded that an inflammatory or autoimmune process may be the underlying pathology and so we undertook further investigations to assess these possibilities. In the meantime the patient was started on 1 mg/kg enoxaparin and loaded with warfarin.

The results of an autoimmune screen are summarised in table 1. These investigations showed that the patient had a low level titre for MPO-anti-neutrophil cytoplasmic antibodies (ANCA) and she was positive for double-stranded DNA (dsDNA) but ANA negative. From these data alone and in the absence of any systemic features of vasculitis it was difficult to conclude the patient had any significant vasculitic disease. We believe the MPO positivity was an epiphenomenon as a result of increased production of autoantibodies. The patient was also screened for antiphospholipid antibodies, that is, anticardiolipin, lupus anticoagulant and antibodies to β -2-microglobulin—all were negative. Given the proteinuria on initial admission, renal ultrasound and urine protein–creatinine ratio were requested and were reported as normal.

To further investigate the LV lesion, a cardiac MRI study was requested. This demonstrated a dilated left atrium, a LV soft tissue mass that appeared to be partly thrombotic and partly fibrotic, hypokinesia of the mid-apical segments of the LV resulting in overall mild-to-moderate LV systolic dysfunction, a normal right heart, mild mitral regurgitation but importantly no evidence of a LV infarct. An LV thrombus is unusual in the absence of an infarct and the MRI were felt to be suggestive of endomyocardial fibrosis. This is an idiopathic disorder of the tropics, where eosinophilic infiltration causes acute myocarditis followed by thrombus formation overlying the lesion and eventual fibrosis. The cause is unknown but the condition involves malnutrition as well as inflammation and possibly infection. Our patient had none of these features in her history, nor did she have an eosinophilia.

Prior to discharge and in line with British Thoracic Society (BTS) guidelines we performed a thoracoscopy to obtain pleural biopsies. The visceral and parietal pleura appeared normal. Pleural biopsies were taken for histology and immunohistochemistry and we drained 1 litre of pleural fluid. The biopsies showed fibrofatty tissue with a lymphocytic infiltrate and

Table 1 Summary of key investigation results

Parameter	First admission	6-week clinic	Readmission
Erythrocyte sedimentation rate (1–20)	112	59	–
C reactive protein (0–10)	40	–	20
D-dimer (0–180)	958	403	–
Urine protein: creatine ratio (<15)	6	–	–
Anti-neutrophil cytoplasmic antibodies-myeloperoxidase (0–5)	15	17	–
Anti-neutrophil cytoplasmic antibodies-proteinase 3 (0–5)	<5	<5	–
dsDNA antibodies (0–15)	26	23	–
Crithidia test	Positive	Positive	–
Antinuclear antibody	Negative	Weakly positive	Negative
Antihistone antibody	–	–	Positive
Cardiolipin IgG (0–10)	<7.5	–	–
Cardiolipin IgM (0–7)	<5	–	–
Rheumatoid factor	<8.6	–	Negative
Anti-Ro, La, Sm RNP, Jo-1, SCL-70	Negative	–	–
Anti-HIV antigen/antibody	Negative	–	–
Complement C3 (0.75–1.65)	–	–	1.36
Complement C4 (0.14–0.54)	–	–	0.27
Immunoglobulin IgG (5.3–16.5)	–	–	15.2
Immunoglobulin IgA (0.8–4.0)	–	–	3.8
Immunoglobulin IgM (0.5–1.9)	–	–	2.6
Serum paraproteins	–	–	Non-detected
β-2-Glycoprotein IgG (0–5)	–	–	1.7
β-2-Glycoprotein IgM (0–5)	–	–	3.6
Thyroid peroxidase antibodies (0–60)	–	–	137.1
Thyroid receptor antibodies (0–0.9)	–	–	7.1
Thyroid stimulating hormone (0.3–5.5)	1.9	6.4	0.7
Thyroxine (10–19)	–	8.0	14

The numbers in brackets refer to normal values.

reactive mesothelial hyperplasia. There was no evidence of vasculitis or malignancy.

The patient was less breathless after thoracoscopy and was discharged on warfarin with a plan to follow her up in clinic after 6 weeks for a repeat cardiac MRI.

Clinic follow-up at 6 weeks

The repeat cardiac MRI showed that the apical mass had largely resolved and we therefore presumed that it had been a thrombus. Overall LV systolic function was now back to normal but the MRI scan showed that a moderate, loculated, left-sided pleural effusion was still present. More importantly the patient was increasingly breathless again and experiencing many of the same symptoms that prompted her initial admission. Despite this, the ESR and D-dimer values showed some improvement. Further blood tests demonstrated that dsDNA antibodies were present as confirmed by the Crithidia test and interestingly the patient was now weakly positive for ANA, having been previously ANA negative (see table 1).

The inflammatory markers and autoimmune tests were positive in a very similar pattern to her initial presentation and her repeat CXR showed reaccumulation of the left-sided pleural effusion, which was consistent with the patient's worsening symptoms. We therefore felt that this must be an autoimmune

connective tissue disorder and arranged a rheumatological opinion and follow-up.

Re-admission to hospital

While waiting for her rheumatological appointment, the patient deteriorated, with her dyspnoea and pleuritic chest pain prompting an acute hospital admission. This time she was admitted to the rheumatology department. A CXR showed a significantly worse left pleural effusion, in comparison with previous radiographs and in addition, there was a new right-sided effusion (see figure 2). Blood tests showed that full blood count, urea and electrolytes and liver function and thyroid function tests were all normal but C reactive protein was slightly raised at 20. Thyroid peroxidase antibodies were significantly raised and ANA was found to be negative as was the rheumatoid factor. However, antihistone antibodies were positive (see table 1).

This latter finding along with reactive mesothelial hyperplasia on histology, pleural effusions and changing ANA titres led us to conclude that the most likely diagnosis was carbimazole-induced lupus. Isolated serositis is a recognised phenotype of this condition. Carbimazole was stopped and the patient was started on 30 mg prednisolone daily.

A repeat CXR performed 10 days later showed almost complete resolution of the pleural effusions (see figure 3) and the patient was asymptomatic and back to her normal self.

Figure 2 Chest x-ray on second admission to hospital showing large left and small right pleural effusions.

DIFFERENTIAL DIAGNOSIS

A summary of the diagnostic pathway that we followed during this presentation is illustrated in figure 4. At each stage the differential diagnoses are shown as well as the investigation strategy used to explore each possibility. We also illustrate the management and follow-up decisions that were made. Figure 4 illustrates the route we followed that allowed us to elucidate the final diagnosis.

OUTCOME AND FOLLOW-UP

The patient was reviewed in outpatient rheumatological clinic 3 weeks after being discharged from her second hospital admission. Carbimazole had been stopped and the patient had been started on a tapering dose of prednisolone (with bone and stomach protection). The patient was completely asymptomatic and this was reflected in her CXR that showed complete resolution of the right pleural effusion and a very small amount of residual fluid on the left (see figure 3). She was ANA negative. The rheumatological plan was to continue to wean steroids over 4–6 weeks and then review again. If all is well then she will be discharged.

The data in table 1 suggests that the patient has a diagnosis of autoimmune thyrotoxicosis—almost certainly Graves disease

Figure 3 Chest x-ray 3 weeks after stopping carbimazole and starting prednisolone; there is almost complete resolution of the pleural effusions.

and therefore it is important that she has a definitive plan to control future episodes of hyperthyroidism. Given that she has a diagnosis of carbimazole-induced serositis it would be unwise to use other antithyroid medication such as propylthiouracil because it is also associated with drug-induced autoimmune phenomena, as discussed above. The patient will therefore be seen in Endocrine clinic to discuss future management of her thyroid disease and to consider other options such as radioiodine treatment.

In terms of cardiac involvement serial imaging showed that she had an LV thrombus in the absence of a current or prior myocardial infarct. After being on warfarin for 6 weeks the thrombus resolved. It seems likely that the carbimazole caused an inflammatory reaction and hypercoagulable state, which allowed a thrombus to develop in the apical portion of the LV. The clot resolved with warfarin therapy and LV function returned to normal. We plan to continue warfarin for 6 months.

In the last few weeks, just prior to submission of this report, we reviewed the patient and noted that she has had a minor flare of her symptoms, with evidence of a very small amount of pleural fluid on the left side of her lung and a rise in ESR. The symptoms were easily controlled by NSAIDs. A review of the literature shows that the effects of drug-induced lupus can last for up to 7 months.^{1–5} The immunological profile, however, remains normal following discontinuation of carbimazole, (previously ANA and Crithidia positive). We therefore feel there is little doubt that this is a case of drug-induced serositis.

DISCUSSION

Although some drugs can induce the formation of autoantibodies, most such subjects do not develop signs or symptoms of autoimmune disease. However, occasionally a patient will develop the phenotype of drug-induced lupus.

Carbimazole-induced autoimmune disease (lupus or vasculitis) is rare and there are only 10 case-reports in the literature.^{15–18} Of these, only one case report described a carbimazole-induced exudative pleural effusion.¹⁶ In that report a 77-year-old patient who presented with breathlessness was found to have atrial fibrillation, pulmonary embolus, congestive cardiac failure and new onset hyperthyroidism secondary to multinodular goitre. The patient was started on carbimazole but presented 3 months later with a large left-sided exudative pleural effusion. She was fully investigated for potential causes such as occult malignancy or infection. On stopping carbimazole the patient made a good recovery. The patient was ANCA negative and her antihistone antibodies were not measured. A BTS report identifies 11 drugs known to induce pleural effusions¹⁹ including amiodarone, nitrofurantoin, phenytoin and methotrexate but carbimazole is not in that list.

The mechanism of carbimazole-induced serositis and indeed the mechanisms underlying the drug-induced lupus in general remain unclear. Some well-established models and theories have been briefly outlined above in the Introduction section. The list of drugs that have been shown to cause drug-induced lupus is long and varied, however the pattern of antibodies produced is nearly always identical. This suggests that there may be a common pathway for lupus-induction.

The cardiac MRI was initially reported as being suggestive of endomyocardial fibrosis (EMF), thought to be associated with hypereosinophilic syndromes, while this patient did not have eosinophilia at any stage, EMF would not be ruled out on this account, as most patients with EMF do not have eosinophilia at diagnosis. In fact we could only find one study that reports more than a 50% prevalence of eosinophilia in EMF²⁰ and at

Figure 4 Schematic representation of the differential diagnoses (blue circles), investigations and the pathway followed to reach the final diagnosis.

least three other reports that show a low prevalence.^{21–23} It has been suggested that eosinophilia is only seen in people who present within the first 6 months of the disease process. As most people present themselves later the majority would not be expected to have eosinophilia. EMF is primarily a restrictive cardiomyopathy and the patient discussed here had none of the phenotypic features consistent with restrictive cardiomyopathy. Furthermore, the demographics of this patient would be very unusual for this condition, that is, a white European middle-aged female who has never been to the tropics. EMF is a disease of young people with a bimodal age distribution—with peaks at 10 and 30 years. Perhaps the most compelling argument against EMF is that the ventricular thrombus resolved on withdrawal of the causative drug. EMF would be very unlikely to do this as it is a progressive illness, fatal if untreated.

Given the positive p-ANCA and MPO at presentation, allergic granulomatosis of Churg-Strauss (CSS) was also considered. However, this condition would be extremely unlikely in view of the fact that the patient has never had eosinophilia or asthma. Eosinophilia is almost universal at presentation and a history of

asthma, usually dating back 8–10 years, is reported in more than 95% of cases of CSS.^{24–25} Both eosinophilia and asthma are included in the widely used classification criteria for CSS proposed by the ACR and by Lanham.^{26–27}

One important take-home message from this report is that antihistone antibodies are positive in over 95% of cases of drug-induced lupus. It is also true that antihistone antibodies are normally present in 40–50% of patients with idiopathic SLE. These antibodies are formed against a histone dimer (H2A-H2B) and DNA.²⁸ It is therefore very useful to look for this antibody when drug-induced vasculitis is a clinical possibility. The BTS guidelines on the management of a unilateral pleural effusion have a clear set of investigative steps that are designed to reach a diagnosis in a logical and methodical way.¹⁹ We followed this algorithm closely and reached the end point without achieving a diagnosis. The correct diagnosis was only reached as the condition evolved. The guidelines at this point focus on repeated cytology and pleural biopsy looking for malignancy, TB and fungal infection as possible causes of undiagnosed pleural effusions. Chronic pulmonary emboli could

also be a cause of the pleural effusion however this would not give rise to any specific pleural fluid markers. Based on our experience it is reasonable to also consider drugs as being the potential causes of the pleural effusion and perhaps future guidelines may reflect this. For example, having worked through the algorithm and having ruled out causes such as malignancy, PE, TB and fungal infections, withdrawal of pre-existing drug(s) may be an appropriate next step.

Learning points

- ▶ Carbimazole is not a drug normally associated with serositis. However this is now the second case report that describes this phenomenon. Given the widespread use of carbimazole, this complication needs to be considered in subjects with recent pleural pain or effusion.
- ▶ Antihistone antibodies have a sensitivity of 95% in cases of drug-induced vasculitis.
- ▶ If the cause of an exudative pleural effusion is not completely and immediately obvious after usual investigations then withdrawal of drug therapies should be considered.

Competing interests None.

Patient consent Obtained.

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