CASE REPORT

Methimazole-induced antineutrophil cytoplasmic antibody–associated diffuse alveolar haemorrhage in a Chinese woman with Graves' disease

Emmy YF Lau 劉婉芬
SY So 蘇淳養
Eric Chan 陳育達
Janette Kwok 郭少燕
John Ma 馬道之
Annie WC Kung 龔慧慈

We report on a case of diffuse alveolar haemorrhage in a Chinese woman due to methimazole-induced antineutrophil cytoplasmic antibodies. A literature search for anti-thyroid drugs associated with antineutrophil cytoplasmic antibody–induced diffuse alveolar haemorrhages is reviewed. Diffuse alveolar haemorrhage is a rare complication of thiourea agents and the treatment often requires corticosteroids or other immunosuppressants, together with withdrawal of the causative agent.

Introduction

Hyperthyroidism due to Graves' disease is a common disease affecting women of reproductive age. Anti-thyroid medication is often the preferred treatment of choice, especially in Europe and Asia. Positivity for autoantibodies against the cytoplasmic determinants of neutrophilic granulocytes (antineutrophil cytoplasmic antibody [ANCA]) has become increasingly recognised in patients treated with thiourea anti-thyroid medications, but cases of clinical vasculitis with major complications are rare.

This case report describes a Chinese female who experienced severe pulmonary haemorrhage and haematuria after 5 years of methimazole (MMI) therapy, and reviews the findings from a literature search for ANCA-induced diffuse alveolar haemorrhage (DAH).

Case report

A 44-year-old Chinese woman with a history of thyrotoxicosis treated with MMI presented with a 6-day history of haemoptysis, dyspnoea, and fleeting joint pain to the Hong Kong Sanatorium and Hospital in March 2004. She had no cough, fever, nor skin rash. She was diagnosed with thyrotoxicosis in 1998, and initially treated with propylthiouracil (PTU) for 1 year. After a few months of remission, her thyrotoxicosis relapsed so she was then put on MMI continuously. Prior to admission she was taking 15 mg MMI daily.

On admission, the patient was clinically euthyroid but had bilateral mild exophthalmos. She had a small diffuse goitre, but there was no associated thrill or bruit. There was no finger clubbing or lymph node enlargement, and her temperature was 37°C. Her blood pressure was 120/80 mm Hg and her pulse rate was 94 beats/min. Her chest was clear but her oxygen saturation was only 91% on room air. A chest X-ray (CXR) showed diffuse mottling of both lung fields in the upper and middle zones. Urinalysis revealed microscopic haematuria (92 red blood cell count per μL) without proteinuria. There were no cellular casts in her urine. Blood tests revealed normal free thyroxine (T_4) and free triiodothyronine levels, and suppressed thyroid-stimulating hormone of lower than 0.03 mIU/L. Her haemoglobin level was 76 g/L and the erythrocyte sedimentation rate was increased at 131 mm/h. Her renal and liver function tests were normal.

Her anti-thyroglobulin antibody level was 370 IU/mL (reference level, <34 IU/mL) and her anti-thyroid peroxidase antibody level was higher than 1000 IU/mL (<12 IU/mL). Immunoglobulin (Ig) G, IgA, and IgM levels were normal. She was negative for antinuclear antibodies and anti-glomerular basement membrane antibodies, but her ANCA was positive at a titre of 1:2560 (reference level, <1:20) on indirect immunofluorescence. An enzyme-linked immunosorbent assay for anti-myeloperoxidase (MPO) antibody (perinuclear ANCA) showed a markedly elevated level of 188 RU/mL (reference level, <5 RU/mL). Her anti-proteinase 3 (PR3) antibody (cytoplasmic ANCA) level was 2 RU/mL (reference level, <20 RU/mL). Her human leukocyte antigen (HLA) genotype was A*1101, A*30, B*13, B*15(62), DRB1*15, DRB1*07.

In view of her abnormal CXR and impaired renal function, magnetic resonance imaging (MRI) of her chest was performed, which revealed diffuse infiltrative lesions

Key words
Antibodies, antineutrophil cytoplasmic; Antithyroid agents; Hemorrhage; Methimazole; Thiouracil

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University of Hong Kong, Queen Mary Hospital, Pokfulam Road, Hong Kong:
Department of Medicine
EYF Lau, FHKCP, FHKAM (Medicine)
SY So, FRCP (Lond), FHKAM (Medicine)
J Ma, MB, BS, FRCP
AWC Kung, FRCP, FHKAM (Medicine)
Department of Pathology
E Chan, MRCPath, FHKAM (Pathology)
J Kwok, MB, BS, FRCPA

Correspondence to: Prof AWC Kung
E-mail: awckung@hkucc.hku.hk

一名患有格雷夫斯病的華籍女病人因服用他巴唑引致抗中性粒細胞胞質抗體有關的彌漫性肺泡出血

本文報告一名華籍女病人因服用他巴唑（methimazole）引致抗中性粒細胞胞質抗體有關的彌漫性肺泡出血案例，並回顧與此病有關的抗甲狀腺藥物的文獻。彌漫性肺泡出血是使用硫脲劑的一種併發症，一般須用皮質類固醇或其他免疫抑制劑，並配合停止服用致病物來醫治。

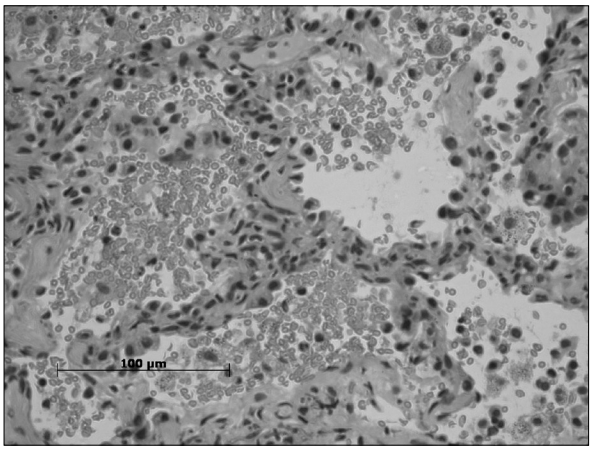

FIG. Haematoxylin-and-eosin-stained lung tissue obtained during bronchoscopy (x 400)
It showed fresh haemorrhage, fibrin aggregates within airspaces and moderate amounts of haemosiderin-laden macrophages

in both lung fields. A bronchoalveolar lavage and lung biopsy showed organising inflammation and haemorrhage mixed with inflammatory cells including haemosiderin-laden macrophages (Fig). These findings were consistent with alveolar haemorrhage syndrome. Cultures for bacteria, mycobacteria tuberculosis and fungi were all negative. The patient was diagnosed with MMI-induced MPO-ANCA positive vasculitis with diffuse lung haemorrhage and possible glomerulonephritis.

The MMI was discontinued and the patient was treated with 30 mg prednisolone per day. Her haemoptysis subsided but the fleeting joint pain continued for a further month. She was given radioactive iodine treatment and was rendered hypothyroid, requiring thyroxine replacement. Her haematuria ceased after 3 months of steroid treatment; the corticosteroid dosage was gradually lowered and eventually stopped after 4 months of treatment. She was subsequently referred to Queen Mary Hospital for management of her hypothyroidism. At 36 months after her presentation with haemoptysis, her anti-MPO level was 20 RU/mL and anti-PR3 level was 11 RU/mL. Her CXR and chest MRI were normal and she was symptom-free.

Discussion

Since Dolman et al[1] first reported it in 1993, a number of reports of patients developing ANCA positive vasculitis in association with anti-thyroid drug therapy have appeared in the literature. Despite the widespread use of anti-thyroid drugs, serious cases of anti-thyroid-drug-induced-ANCA–associated vasculitis are rare. Studies have shown that 15 to 37% of patients treated with PTU developed ANCA, in contrast to 0 to 3% of patients treated with carbimazole (CMZ) or MMI.[2] Nevertheless, most patients with a positive serum ANCA do not have clinical evidence of vasculitis, and major clinical complications are rare. An English-language literature search found only 30 cases of PTU-, MMI- or CMZ-induced ANCA–positive vasculitis involving one or more organ systems. Of these cases, 11 manifested as DAH (Table[3-13]). All were female and two of them were pregnant on presentation. More than half were of Asian ethnic origin. Propylthiouracil was implicated in nine out of 11 cases. Our index case represents the 12th case of DAH associated with the use of anti-thyroid drugs. The onset of the vasculitis varied considerably, from 2 months to 10 years after initiation of the anti-thyroid drugs, and there was an association with the starting or cumulative dose of the thiourea agent. In addition to DAH, renal involvement (glomerulonephritis) was seen in seven cases, arthritis in one, and both skin and nerve involvement in another. The MPO-ANCA was positive in all, whereas only one patient was positive for anti-PR3. In all cases, cessation of the initiating drug, and in most cases the addition of steroid therapy resulted in improvement in the clinical condition. Ohtsuka et al[12] reported a 44-year-old woman who was successfully treated with drug withdrawal alone and no steroid maintenance therapy. There was only one death. This patient died of DAH despite concomitant therapy with steroids and cyclophosphamide.

It was observed that subjects with antibodies against MPO are more likely to develop clinical vasculitis than those carrying antibodies against PR3, and that the prevalence of MPO-ANCA in patients with vasculitis was significantly higher than that in patients without vasculitis.[14,15] An association between the duration of PTU treatment and the proportion of patients positive for MPO-ANCA was also noted.[16] When she presented with pulmonary haemorrhage, our patient had an extremely high MPO-ANCA titre but was negative for anti-PR3, although in the literature, PTU-induced ANCA has been reported as recognising multiple antigens including MPO, PR3, human leukocyte elastase, lactoferrin, bactericidal/permeability-increasing protein, cathepsin G, and azurocidin.

At present, the mechanism for the immunological characteristics of anti-thyroid drug–induced ANCA is unclear. Jiang et al[17] proposed that

TABLE. A summary of reported cases of diffuse alveolar haemorrhage associated with MPO-ANCA induced by anti-thyroid drugs*

Reference	Drug	Ethnicity	Sex/age (years)	Duration of treatment	Other manifestations	Anti-MPO	Anti-PR3	Management†	Outcome
Present case	PTU/MMI	Chinese	F/44	PTU for 1 year, MMI for 4 years prior to presentation	Haematuria	+		S	Improved
Kang et el[3]	PTU	Korean	F/25 pregnant	NA	Glomerulonephritis	+		S	Improved
Calañas-Continente et el[4]	CMZ	Spanish	F/52	10 Years	Necrotising GN	+		SC	Improved
Pirot et al[5]	PTU	NA	F/12	9 Years	-	+		S	Improved
Nakamori et al[6]	PTU	Japanese	F/54	4 Years	Haematuria	+		S	Improved
Yamauchi et al[7]	PTU	Japanese	F/59	5 Years	-	+	+	-	Improved
Katayama et al[8]	PTU	Japanese	F/66	8 Years	Haematuria	+		S	Improved
Seligman et al[9]	PTU	Caucasian	F/33	2 Years	-	+		SC	Died
Tsai et al[10]	MMI	Chinese	F/18	PTU x 2 years, MMI x 1 week prior to presentation	Skin and nerve	+		SP	Improved
Dhillon et al[11]	PTU	NA	F/23 pregnant	PTU + MMI x 7 years, PTU x 2 weeks prior to presentation	Crescentic GN	+		SP	Improved
Ohtsuka et al[12]	PTU	Japanese	F/44	2 Years	Haematuria	+		-	Improved
Romas et al[13]	PTU	NA	F/39	17 Months	Arthritis	+		-	Improved

* ANCA denotes antineutrophil cytoplasmic antibody, CMZ carbimazole, GN glomerulonephritis, MMI methimazole, MPO myeloperoxidase, NA not available, PR3 proteinase 3, and PTU propylthiouracil

† S denotes steroid, C cyclophosphamide, and P plasmapheresis

activated neutrophils, in the presence of hydrogen peroxidase, release MPO from their granules and convert PTU into cytotoxic products. Propylthiouracil has been shown to accumulate in neutrophils, and in the presence of MPO, PTU could be converted to PTU sulfonate, which is immunogenic for T lymphocytes.[18] The activated T cells will in turn stimulate B cells to produce ANCA. Whether this mechanism also applies to MMI is unclear.

It should be noted that patients with pulmonary haemorrhage and glomerulonephritis as a complication of anti-thyroid drug–induced vasculitis are mostly of Oriental ethnicity. It is not certain whether anti-thyroid drug–induced vasculitis has a genetic basis, as hydralazine- and penicillamine-induced vasculitis are also strongly linked to HLA antigens. Of course, this could also be related to different prescribing patterns, with Asian physicians preferring to use long-term anti-thyroid medication in patients with relapsing Graves' disease versus the radioactive iodine therapy and thyroidectomy favoured by US and European doctors.

As in most reported cases, the ANCA was only measured when our patient presented with evidence of systemic vasculitis. Although there is a limitation in inferring causation in the development of MPO-ANCA and DAH to MMI, as the titre of MPO-ANCA decreased after withdrawal of MMI, we concur with other authors that ANCA may have been present prior to the initiation of anti-thyroid drug treatment.

To determine the incidence of ANCA in Chinese patients with autoimmune thyroid disease, we screened for ANCA, anti-MPO and anti-PR3 antibodies in 50 consecutive untreated new patients, all of them ethnically Chinese, who presented to the Thyroid Clinic at Queen Mary Hospital, a referral centre serving a population of 1 million, as well as 50 patients who had been on thiourea agents for more than 2 years. Over 95% of the treated patients were prescribed CMZ. None of the patients tested had any of these antibodies. This patient is also the first we have seen in our hospital with an anti-thyroid drug–induced MPO-ANCA DAH. Given that Graves' disease has a prevalence of 2% in the adult population (unpublished data) and that anti-thyroid drug–induced ANCA positivity has an extremely low prevalence, we would not advocate regular screening for ANCA and its antigen specificities in patients on anti-thyroid drugs. In populations with a high prevalence of anti-thyroid drug–induced ANCA positivity, such as children, or among those being given PTU, screening may be warranted to inform treatment adjustment decisions.

In conclusion, this case report highlights a rare but potentially lethal complication resulting from MMI treatment for Graves' disease. Early recognition of this unusual but important complication, with cessation of the culprit drug and treatment with steroids, led to a full recovery.

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