CASE REPORT

A case of atypical *Bartonella henselae* infection in a patient with methimazole-induced agranulocytosisAlexander Kaysin,¹ Anthony J Viera²¹Department of Family Medicine, MAHEC Family Health Center, Asheville, North Carolina, USA²Department of Family Medicine, University of North Carolina, Chapel Hill, North Carolina, USA

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Accepted 10 August 2015

SUMMARY

Antithyroid medications such as methimazole and propylthiouracil are commonly used to treat hyperthyroid disorders. Thionamide-induced agranulocytosis is a rare but life-threatening potential side effect of these medicines. In addition to routine monitoring of blood counts, healthcare workers caring for patients on such medication need to be mindful of atypical presentations of acute agranulocytosis throughout the treatment course. The manifestations of underlying infectious aetiologies can be mistaken for more common illness and result in delayed diagnosis. We present a case of a 41-year-old woman receiving methimazole for Grave's disease, who presented to outpatient care with high fever, pharyngitis, lymphadenopathy and jaundice. After failing to respond to empiric antibiotics, a diagnosis of neutropenia was made and the patient was admitted for inpatient care with eventual recovery following a course of granulocyte colony-stimulating factor. A diagnosis of atypical *Bartonella henselae* was eventually made and treated appropriately. The patient was later discharged and underwent radioactive iodine ablation.

BACKGROUND

The prevalence of thionamide-induced agranulocytosis is believed to be 0.2–0.5%.^{1–3} Researchers have documented a possible age-dependent and dose-dependent relationship.^{4–6} This case demonstrates the importance of primary care providers and other prescribers of these drugs to maintain active drug monitoring with periodic follow-up and a high index of suspicion for iatrogenic immunodeficiency in patients on methimazole and propylthiouracil (PTU) who present with infectious symptoms of unclear aetiology. Such awareness needs to be maintained even in young and otherwise healthy patients receiving low-dose therapy who previously tolerated an agent in the same class. Published studies have given caution to prescribing methimazole at a dosage >30 mg/day in patients over 40 years of age.^{4–6} This case demonstrates a need to maintain caution at any dose even in relatively young patients. We likewise describe an unusual presentation of febrile neutropenia with an elusive source that was later determined to be caused by an atypical infection of *Bartonella henselae*.

CASE PRESENTATION

A 41-year-old woman, a university researcher, presented to her family practitioner with a 3-day history of fever, headache, severe sore throat, with absence of cough, and tender cervical lymph nodes,

symptoms that were initially attributed to streptococcal pharyngitis. A rapid strep test was found to be negative, however, the patient was empirically treated with penicillin. With symptoms worsening and persistent high fevers with night sweats, headaches and fatigue, the patient returned and had investigations performed including Monospot for Epstein-Barr Virus (EBV) and complete blood count (CBC) with differential. The Monospot was positive and CBC revealed severe neutropenia with agranulocytosis (ANC 0) along with a platelet count decline from 268 to 171 × 10⁹/L. On examination, the patient was a thin-appearing but well-nourished and well-developed woman of stated age who appeared fatigued but alert and fully oriented, and in no distress. Physical examination was significant for mild jaundice, tender cervical lymphadenopathy and a small round erythematous and scaly rash over the right scapula. No palpable organomegaly was found on initial examination.

After obtaining blood and urine cultures, the patient was admitted to our inpatient facility and started on empiric broad spectrum intravenous antibiotics given the concern for sepsis, in addition to supportive care. The patient was symptomatically hyperthyroid, requiring continuation of propranolol, although she did not appear to have thyroid storm.

A detailed history revealed that the patient was initiated on methimazole 20 mg daily for the treatment of Grave's disease 1 month prior to admission and after 11 years of disease remission following her last pregnancy, at the age of 30 years. She was previously treated with PTU for about 8 years with good tolerance and with no h/o neutropenia or pancytopenia. She had no other known risk factors for immunocompromising conditions, harmful occupational exposures, serious childhood illness, malignancies or prior known atypical infections. Her only other medication was propranolol and an occasional over-the-counter antihistamine for seasonal allergies. In addition, she had a history of two Caesarean sections. The family history was unremarkable and there were no reported recent travel events, sick contacts, insect or animal bites or exposures. However, the patient's community in Southeastern USA is in close proximity to forested land, which did raise the possibility of an occult insect bite.

INVESTIGATIONS

Investigations were instituted to uncover the aetiology of this patient's condition. Haematology panel confirmed agranulocytosis with severe

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To cite: Kaysin A, Viera AJ. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-209314

neutropenia: white cell count (WCC) 0.3 ($4.5\text{--}11.0\times 10^9/\text{L}$) comprised of neutrophils 0 ($2.0\text{--}7.5\times 10^9/\text{L}$), lymphocytes $0.3\times 10^9/\text{L}$ ($1.5\text{--}5.0\times 10^9/\text{L}$), monocytes 0 , eosinophils 0 and basophils 0 . There was a relative decline in platelet count from baseline 270 to 171 ($150\text{--}440\times 10^9/\text{L}$) and a low-normal red blood cell count (3.88 ($4.0\text{--}5.2\times 10^{12}/\text{L}$)), haemoglobin 11.4 g/dL ($12.0\text{--}16.0$ g/dL) and haematocrit 33.4% ($36.0\text{--}46.0\%$). Furthermore, mean corpuscular volume was normal at 86 fL ($80\text{--}100$ fL) and ferritin was elevated to 283 $\mu\text{g/L}$. Other inflammatory markers were also significantly elevated. Direct bilirubin was elevated at 3.3 mg/dL with otherwise unremarkable liver and kidney function tests. Thyroid function tests were consistent with known active Grave's disease. HIV was negative. Chest X-ray revealed no signs of infection or other cardiopulmonary abnormalities. Abdominal ultrasound was performed, revealing hepatomegaly with a heterogeneous echotexture and normal gallbladder. Absence of the left kidney was incidentally found.

A lupus investigation showed an antinuclear antibodies of 1:160 with negative double-stranded DNA antibodies and anti-histone antibodies, which reduced the likelihood of an autoimmune aetiology such as systemic lupus erythematosus and lupus-like syndromes. Multiple bacterial and fungal blood and urine cultures remained negative as did hepatitis serologies. Further into the patient's hospital course, a chest X-ray was reordered given respiratory symptoms, revealing small bilateral pleural effusions with adjacent atelectasis. We then proceeded to rule out a cardiogenic cause with what turned out to be a normal ECG and a transthoracic echocardiogram, which was unremarkable aside from mild left ventricular diastolic dysfunction. Given the patient's marked cervical lymphadenopathy, fevers with night sweats and fatigue, a lymph node biopsy with cultures was performed, revealing reactive changes but no evidence of malignancy (eg, lymphoma), tuberculosis, fungal or bacterial infection. As the patient's condition dramatically improved to a point of sufficient recovery and resolution of the neutropenia, she was discharged with close outpatient follow-up given the ongoing febrile episodes. Shortly thereafter, serological investigations looking into fungal, rickettsial and parasitic causes came back revealing positive *B. henselae* IgM titres at $>1:20$ (negative laboratory reference $<1:20$) and negative *B. henselae* IgG $<1:128$, which elevated the diagnosis of acute *B. henselae* infection. Further testing for *B. quintana*, *Brucella* and *Francisella tularensis* resulted in negative titres.

DIFFERENTIAL DIAGNOSIS

Initial concern was for bacterial sepsis in the setting of neutropenic fever, which was ruled out by multiple negative blood and urine cultures. Lupus and related illnesses were considered but excluded on the basis of inconclusive and mostly negative autoimmune laboratories. Viral lymphadenitis and infectious mononucleosis were considered but found to be inconclusive with negative EBV IgM. There was concern for rickettsial diseases, such as Rocky Mountain spotted fever, given their prevalence in Southeastern USA. Treatment with doxycycline was therefore provided empirically. Additional considerations were haemophagocytic lymphohistiocytosis (HLH), Kikuchi disease and lymphoma, which were not well supported by the history, investigations and course of illness. The patient's ferritin of 283 $\mu\text{g/L}$ also went against HLH, which is normally associated with a ferritin >500 $\mu\text{g/L}$.

TREATMENT

The patient was admitted to the inpatient centre and methimazole immediately discontinued. Intravenous fluids were

administered and, after collecting multiple sets of cultures, broad-spectrum antibiotics including vancomycin and cefepime were started, and later changed to meropenem for broader coverage due lack of adequate response. Doxycycline was added towards the latter part of the hospital course. Filgrastim 300 μg daily was started shortly after admission with resolution of neutropenia on day 8. Additional supportive treatments were used including propranolol for symptomatic hyperthyroidism, antipyretics and analgesics. Radioactive iodine ablation (RAIA) was scheduled on an outpatient basis and a course of prednisone 1 mg/kg was planned for prophylaxis against worsening Grave's orbitopathy following RAIA. Close outpatient follow-up was recommended.

OUTCOME AND FOLLOW-UP

After discontinuation of the methimazole, the patient was treated with granulocyte colony-stimulating factor (ie, filgrastim) with a gradual improvement of her absolute neutrophil count to normal levels. At the time of discharge, her blood counts were as follows: WBC $7.3\times 10^9/\text{L}$ ($4.5\text{--}11.0\times 10^9/\text{L}$) comprised of neutrophils $3.7\times 10^9/\text{L}$ ($2.0\text{--}7.5\times 10^9/\text{L}$) with $2+$ neutrophil left shift, lymphocytes $2.3\times 10^9/\text{L}$ ($1.5\text{--}5.0\times 10^9/\text{L}$), monocytes $0.7\times 10^9/\text{L}$ ($0.2\text{--}0.8\times 10^9/\text{L}$), eosinophils $0\times 10^9/\text{L}$ ($0.0\text{--}0.4\times 10^9/\text{L}$) and basophils $0\times 10^9/\text{L}$ ($0.0\text{--}0.1\times 10^9/\text{L}$). In spite of the broad-spectrum intravenous antibiotics, the patient continued to have high spiking fevers of 104°F , which were responsive to antipyretics. With immunological recovery and addition of doxycycline 100 mg two times per day for a 21-day course, the patient demonstrated marked clinical improvement. The effectiveness of this treatment with rapid resolution of lymphadenopathy and fevers gave further evidence for associated acute *B. henselae* infection. The patient was later scheduled for RAIA given the contraindication to any further use of antithyroid medication.

DISCUSSION

Thionamide-induced bone marrow suppression is not fully understood. Several investigations have found convincing evidence of an immune-mediated mechanism that can suppress the growth of colony-forming unit-granulocyte-macrophage colonies rather than predominantly through direct drug toxicity.^{7 8} In addition, several case studies have documented the co-occurrence of plasmacytosis and/or pancytopenia in addition to agranulocytosis via an interleukin 6-mediated mechanism, levels of which are typically elevated in autoimmune hyperthyroid diseases such as Grave's.⁸ Indeed, research has demonstrated the suppression of plasmablastic cell proliferation by anti-IL-6 antibodies, further supporting this immune-mediated mechanism.⁸

The occurrence of methimazole-induced agranulocytosis is estimated to be 1% at a daily dose of $30\text{--}60$ mg and up to 8% at doses higher than 120 mg.⁸ Our case is unusual in that it presents a rather young patient on low-dose methimazole who had previously tolerated this drug for many years and developed agranulocytosis after 1 month of reinitiating therapy following disease recurrence.

Although this patient received timely care and admission to a tertiary care facility, it may be inferred that infectious symptoms such as fever in a patient on antithyroid medication should raise early suspicion for immunosuppression along with atypical presentations of various pathogens. Careful history taking with attention to possible routes of exposure or inoculation related to ecological factors needs to be carried out. A full blood count analysis should be an early step in the work-up. In our case,

through a laborious investigation, the infectious aetiology was eventually and incidentally determined to be *B. henselae*, commonly known as cat-scratch disease (CSD), despite our patient recalling no apparent exposure to cats. The presence of a positive Monospot test was likely an incidental and unremarkable factor given the negative EBV IgM.

There is literature supporting the transmission of the Gram-negative *B. henselae* bacteria directly from cats and, sometimes, from other animals including dogs, as well as a less common indirect pathway via insect vectors such as fleas.^{9 10} In hindsight, the documented rash on the patient's shoulder, alongside the lymphadenitis and fevers, supports exposure through an insect vector. We further suspect that this patient's transient hepatopathy was the result of an opportunistic infection from atypical CSD involving a condition known as peliosis hepatis.^{9–11} Other manifestations of atypical CSD, seen in 10–14% of infected patients, may include neuroretinitis, which can present with unilateral non-suppurative conjunctivitis, encephalitis, aseptic meningitis, Bell palsy and transverse myelitis.⁹ However, severe neurological complications are typically seen in about 2% of patients.⁹ There have also been infrequent

reports of endocarditis, bacillary angiomatosis, pneumonia with pleural effusion and multifocal osteomyelitis.⁹ Extended treatment with macrolides, rifampin, fluoroquinolones, tetracyclines such as doxycycline or combination antimicrobials from 3 weeks to 4 months is recommended depending on disease severity, and age and immune system status of the patient.¹⁰ Fortunately, the development of liver failure and other life-threatening complications is rare.¹⁰

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Learning points

- Cases of methimazole-induced agranulocytosis can occur spontaneously at any point in the treatment course, especially in older patients on higher doses.
- Routine monitoring of full blood counts in patients taking antithyroid drugs may help identify more cases of agranulocytosis before complications develop.
- A high index of suspicion needs to be maintained, when encountering patients with a constellation of infectious symptoms while on antithyroid medication, for atypical presentations of common as well as more unusual infections.

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