CASE REPORT

A hunt for the source of sepsis

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SUMMARY

A 42-year-old woman presented with a 2-day history of drowsiness, confusion, worsening headache, high fevers, urticarial rash, bilateral leg pains and urinary retention. Preceding this was a 1-month history of headache unresponsive to various analgesics for which her general practitioner started carbamazepine. Suspected central nervous system infection was investigated and treated with cefotaxime. A full septic screen, lumbar puncture and MRI of the spine were all inconclusive. After 3 days, the patient deteriorated and repeated blood tests—initially unremarkable—revealed neutropaenia and acutely deranged liver function. Connective tissue disorder was considered due to a negative septic screen and lack of response to antibiotics, but autoimmune screens failed to reveal a culprit. At this point, carbamazepine was suspected and stopped, after which the patient and her blood results recovered dramatically. This adds to previous reports of known reactions to carbamazepine and reinforces recommendations that patients should be made aware of potential complications of this drug.

BACKGROUND

Carbamazepine is an antiepileptic medication which is also licensed for use in trigeminal neuralgia. This case describes a rare but life-threatening reaction to this commonly used drug. In this case, symptoms masqueraded as infection which led to diagnostic difficulty. This example may increase awareness of this drug reaction and encourage readers to expand their differential diagnosis when dealing with a patient with fever. The case also reiterates the importance of taking a thorough history and questioning whether each part of it could explain a patient's symptoms.

CASE PRESENTATION

A 42-year-old previously healthy woman presented to the medical assessment unit with a 2-day history of feeling generally unwell, hot and sweaty with recorded temperatures of over 38°C, loss of appetite and lower back pain radiating into both legs associated with a feeling of heaviness. She also had an urticarial rash on her legs, and reported that she was unable to urinate that day or open her bowels for 5 days. Prior to this, she had been suffering from headaches for a month, and her general practitioner had tried various therapies, eventually starting carbamazepine.

The patient was found to be in painless urinary retention on admission and was catheterised. On examination, observations were within normal limits aside from a temperature of 38.5°C. On inspection, the patient was drowsy but easily

roused to voice. When awake, she was visibly distressed by her head and leg pains. The patient's chest was clear, heart sounds were normal and the abdomen was soft. An urticarial rash was visible on both legs. Cranial nerves and a full neurological examination including per rectum were normal. Although the patient reported aches and stiffness on movements including in her neck and back, specific meningitic signs were negative. There was no obvious focus of infection or cause for her symptoms found on examination.

Initial management included a full septic screen and initiation of ceftriaxone for suspected central nervous system (CNS) infection. An MRI of the spine was arranged given the bilateral leg symptoms and urinary retention, which showed only a mild disc prolapse with no evidence of cauda equina or spinal cord impingement. This allowed the acute medical team to proceed with a lumbar puncture to look for evidence of CNS infection, which yielded a white cell count (WCC) of 1/mm³, a red cell count 14/mm³ and no visible organisms. The patient was put on laxatives, piriton to control the rash and analgesia.

The results of the initial septic screen were unremarkable (clear chest X-ray and catheter urine was negative). Initial blood tests showed a C reactive protein of 70 mg/L WCC of $4.1 \times 10^9/L$ and neutrophils of $3.2 \times 10^9/L$.

On the third day of admission, an on-call medical senior house officer was asked to review the patient because she felt generally unwell and had a temperature of 39.9°C. A viral respiratory PCR screen was sent along with an HIV test. The possibility of a connective tissue disease was proposed because of the persistence of temperature in spite of antibiotics and the negative results from the septic screen. An immunology/vasculitic screen was sent. Results from all of the above were later found to be negative.

On day 4, high temperatures persisted and blood tests showed that the WCC had dropped to $2.4 \times 10^9/L$. Neutrophils were $1.5 \times 10^9/L$ and appropriate neutropenic precautions were put into place including moving the patient to a side room on the medical ward, and starting barrier nursing. It was also noted that liver function tests (LFTs) were grossly deranged. γ -Glutamyl transpeptidase (GGT), which had been 126 iu/L at admission, had risen to 1239 iu/L (figure 1). A non-invasive liver screen (NILS) was sent and an ultrasound liver was requested, showing mild fatty changes but no focal abnormality.

The following day, the patient reported severe headaches and that the pains were worsening and spreading throughout her body. She also described

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Figure 1 A table to show the pattern over time of liver function tests for our patient (ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; GGT, γ -glutamyl transpeptidase).

	Previous	Day 1	Day 4	Day 6 (drug stopped)	Day 8 (peak)	Day 9	Day 40
Bilirubin	5	15	46	86	146	132	24
GGT	54	126	1239	3200	4057	3977	580
ALP	72	81	97	342	371	338	131
ALT	26	91	159	521	699	583	211
AST	24	27	112	256	505	434	124

the pains as 'deep' and seeming to focus around her joints. The consultant leading the ward round detected tenderness around all the joints of her lower limbs and therefore queried whether this could represent polyarthritis. A rheumatology referral was sent, including a proposed differential diagnosis of systemic lupus erythematosus (SLE) and systemic polyarthritis of as yet undetermined aetiology. The ceftriaxone, which had been started on admission to cover a CNS infection, was stopped after 5 days due to lack of evidence of infection or improvement in the patient's condition.

A member of the rheumatology team reviewed the patient. The history was reviewed as well as the available laboratory results (some elements of the vasculitic screen and NILS were still awaited). These included a negative antinuclear antibody, a cytoplasmic antineutrophil cytoplasmic antibody (ANCA), a perinuclear ANCA and a double-stranded DNA. The extractable nuclear antigens screen was non-specific. The hepatitis screen and Epstein-Barr virus were also negative. The LFTs continued to deteriorate with a GGT of 3200 iu/L and the full blood count showed a worsening neutropaenia of $0.9 \times 10^9/L$. Transaminases were also raised with an alanine transaminase (ALT) and aspartate aminotransferase (AST) of 521 iu/L and 256 iu/L, respectively. Bilirubin was 149 micromol/L (figure 1).

On examination, the patient was found to have enlarged cervical lymph nodes, and this together with the neutropaenia raised suspicion around carbamazepine as the causative agent. Carbamazepine can also cause hepatitis, vanishing biliary duct syndrome, multiorgan hypersensitivity, drug-induced lupus, rashes and fevers, neutropaenia and lymph node enlargement.

TREATMENT

The rheumatology recommendation was therefore to stop carbamazepine and recheck antihistone in case of drug-induced lupus. Testing atypical respiratory serology (mycoplasma and legionella) was also recommended. The patient was later seen by a gastroenterologist who agreed that the rapid deterioration in liver function was consistent with drug reaction, and therefore supported the suggestion to stop carbamazepine.

Carbamazepine was stopped and the patient reported improved symptoms within 2 days. On the third day after stopping carbamazepine, the derangement in LFTs began to resolve.

OUTCOME AND FOLLOW-UP

The patient was discharged 2 weeks later, with outpatient gastroenterology follow-up to monitor LFTs as they slowly normalise. None of her symptoms have relapsed.

DISCUSSION

Carbamazepine is an antiepileptic, licensed for use in cases of focal and secondary generalised tonic-clonic seizures, primary generalised tonic-clonic seizures, trigeminal neuralgia and prophylaxis of bipolar disorder unresponsive to lithium.¹ It is metabolised by oxidation in the liver to carbamazepine-10, 11-epoxide before it is excreted in the urine.² Patients should be informed regarding signs of adverse effects when starting treatment. They should also be advised to seek medical attention if they develop a fever, rash, mouth ulcers, bruising or abnormal bleeding.¹

Side effects of carbamazepine include dry mouth, nausea, vomiting, oedema, ataxia oedema, dizziness, drowsiness, fatigue, headache, arthralgia, muscle pain, hyponatraemia, blood disorders (eosinophilia, leucopenia, thrombocytopenia, haemolytic anaemia and aplastic anaemia), urticaria, abdominal pain, hepatitis, vanishing biliary duct syndrome, lymph node enlargement, SLE and antiepileptic hypersensitivity syndrome.¹

Learning points

- ▶ The case reiterates the importance of not only taking a thorough history, but actively treating each part of the history with suspicion. The drug history was accurately taken in this case, but it was simply recorded without anyone questioning whether it could be responsible.
- ▶ The side effects of carbamazepine on this scale are rare, but the drug effect should be considered in any patient with a constellation of symptoms that is difficult to explain, and a thorough review of the drug card with a British National Formulary (BNF) in hand may prove worthwhile.
- ▶ Carbamazepine is a potentially dangerous drug with a long list of severe possible side effects. It should not be started without suitably counselling patients on the symptoms that represent adverse drug reaction.
- ▶ Infection is not the only cause of a high temperature. Although it is clearly important to perform a septic screen, one must keep an open mind for other causes of high temperature. The differential diagnosis includes various infections (bacterial, viral, fungal and protozoal), neoplasia (in particular haematological but also hypernephroma and hepatoma), connective tissue disorders, drug reactions as in this case, and others such as pulmonary embolism, myocardial infarction and familial Mediterranean fever.⁶
- ▶ Patients with severe hypersensitivity to carbamazepine should avoid taking other aromatic anticonvulsants.

Carbamazepine is a known cause of acute drug-induced liver injury. The British National Formulary (BNF) states that carbamazepine 'should be withdrawn immediately' in cases of newly deranged LFTs or acute liver disease.¹ In 1999, there were over 250 published cases of carbamazepine-induced hepatic injury.³

Anticonvulsant hypersensitivity syndrome can occur within 2 months of starting treatment with aromatic anticonvulsants such as phenytoin, phenobarbital and carbamazepine. Its features include fever, rash and internal organ involvement (usually the liver). Although rare, it can be fatal.⁴

Hepatotoxicity caused by carbamazepine is usually rapidly reversible when the medication is stopped. Prednisolone has been used to aid recovery from liver damage in such cases, but there is a lack of studies regarding its effectiveness. A more recent study by Lee *et al*⁵ showed that the use of systemic steroids did not significantly improve recovery from liver injury in 136 cases of drug-induced systemic hypersensitivity.

Contributors ST saw and diagnosed the patient. He wrote his findings in the written report and gained consent from the patient. LG aided in the writing of the

report and performed a review of the literature. HS and AA provided advice and critically reviewed the report. All authors read and approved the manuscript.

Competing interests None.

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