Reminder of important clinical lesson

An unexpected case of coumarin poisoning with coumatetralyl

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A healthy man in his 40s presented with a 1-month history of haemoptysis and was unexpectedly found to have an elevated international normalised ratio (INR). He denied any known exposures to anticoagulants. Testing for the possible aetiologies of a high INR revealed coumarin poisoning with coumatetralyl as the cause. The approach to an elevated INR and management and diagnosis of suspected coumarin poisoning is reviewed.

BACKGROUND

We describe how a systematic work-up based on a patient's coagulation profile led us to suspect coumarin poisoning despite our patient having no known exposure to this drug class. The case illustrates the importance of considering poisoning when laboratory results indicate such a possibility. We also discuss the management for, and testing of, suspected coumarin poisoning.

CASE PRESENTATION

A man in his 40s presented to the emergency room with a 1-month history of nocturnal haemoptysis and possible melena, and a 2-day history of severe, diffuse abdominal pain. He denied any other respiratory, abdominal or bleeding symptoms. His medical history included type 2 diabetes and a previous appendectomy and cholecystectomy. He had no personal or family history of bleeding diatheses. His medications were insulin and metformin. He did not drink alcohol or smoke. He denied any other drug use or chemical exposures at work.

On examination, he was afebrile and his vital signs were stable on ambient air. Head and neck examination was within normal limits. Heart and lungs were clear to auscultation. His abdomen was diffusely tender to light palpation, but otherwise was soft and had normal bowel sounds with no organomegaly. There was no ecchymoses, petechiae or evidence of joint bleeding. His neurologic examination was within normal limits.

INVESTIGATIONS

The patient's haemoglobin was 129 g/l and platelet count was 356 000/mm³. International normalised ratio (INR) was 3.0 and partial thromboplastin time (PTT) 34 s (normal 23–31 s). Liver transaminases, albumin and bilirubin were normal. A chest x-ray was normal, and a CT scan of the abdomen did not reveal any haemorrhage or other explanation for his abdominal pain. Further tests described below were sent, and he was discharged with a prescription for oral vitamin K and follow-up was arranged. He was unable to fulfil the prescription and returned 2 days later with an INR of >9.5 and a PTT of 83 s.

Upon his return, further results were available. Factor 7 activity was low and lupus anticoagulant antibody was not present. A disseminated intravascular coagulation panel, including fibrinogen and d-dimer, was also normal. A general serum and urine toxicology screen that specifically requested coumarin testing was positive for coumatetralyl (a first generation coumarin similar to warfarin), cocaine metabolites and levamisol (a chemical used in refining cocaine).

DIFFERENTIAL DIAGNOSIS

Initially, this patient largely had an isolated elevation in his INR. The differential diagnosis of a high INR is relatively narrow¹ and includes liver dysfunction; vitamin K deficiency, particularly from antibiotics that reduce the growth of vitamin K-producing gut bacteria; inherited and acquired factor 7 deficiency; and the lupus anticoagulant. Finally, coumarins, the family of vitamin K antagonists, will primarily elevate the INR, but also affect PTT to some degree, particularly at high doses. The patient's second set of coagulation tests demonstrating a markedly high INR and PTT also raises the possibility of disseminated intravascular coagulation.

TREATMENT

The patient was empirically treated with 10 mg of intravenous vitamin K.

OUTCOME AND FOLLOW-UP

The next morning the patient's INR had decreased to 1.4, his PTT to 32, and his abdominal pain had almost fully resolved. We attributed his coagulopathy to coumarin poisoning. The mechanism of his abdominal pain was not clear.

DISCUSSION

Aetiologies of haemoptysis are broadly divided into bleeding lesions and diffuse bleeding due to defective coagulation. After identifying defective coagulation in our patient, we focused our investigations on explaining the initially disproportionate elevation of INR compared to PTT.

This finding led us to highly suspect coumarin poisoning, despite the patient's denial of taking this drug class. Presence of severe abdominal pain without evidence of any intra-abdominal bleeding in our patient would be an uncommon presentation of coumarin toxicity. We hypothesise that the patient may have consumed another unidentified substance to account for the abdominal pain.

Coumarins, which were originally – and continue to be – used as rodenticides, are a common group of anticoagulants. The medical prototype physicians are most familiar with is, of course, warfarin. Coumarins act by inhibiting post-translational carboxylation of several coagulation factors, including factors 2, 7, 9, 10, as well as proteins C and S.² Since they are exogenous compounds they should not be detectable in patients who have no known exposure, and as such their presence indicates poisoning.

There are many reported cases of warfarin and superwarfarin poisoning³ and unintentional transcutaneous poisoning can also occur.² However, coumarin poisoning with no admitted exposure is quite unusual, although it has been described in Munchausen's syndrome.⁴ Even more unusually in this case, coumatetralyl has a short half life,⁵ and its prolonged effect in this patient suggests persistent consumption. When coumarin poisoning is suspected, it is important to request toxicology for a general coumarin screen, as testing solely for warfarin can miss other drugs in the class.⁴

As this was a case of suspected poisoning, we had also sent off a general toxicology screen and found cocaine and levamisole, which our patient denied knowingly taking. Our literature search failed to uncover any reports of coumarins being used to manufacture or contaminate cocaine. Interestingly, levamisole may potentiate the activity of warfarin, although it is debatable whether such an interaction truly exists⁶ and levamisole's effect on coumatetralyl is unknown. With respect to other potential drug interactions, there is some weak evidence that biguanides like metformin could enhance the elimination of coumarins⁷ although, even if true, such an interaction was clearly insufficient to prevent dangerous anticoagulation for this patient.

Anticoagulation due to coumarin toxicity is readily reversible with vitamin K. In fact, a trial of vitamin K serves as a diagnostic and therapeutic step, as successful normalisation of INR narrows the differential diagnosis to vitamin K deficiency and coumarins. Administration of vitamin K is recommended early if these diagnoses are likely, and it does not compromise the detection of coumarins. If the patient is unstable as a result of significant haemorrhage, immediate reversal with fresh-frozen plasma or prothrombin complex concentrate is warranted.⁸ Importantly, if the coumarin identified reveals itself to be a superwarfarin, then a prolonged course of vitamin K and close follow-up is necessary.²

Once coumarin poisoning has been confirmed, the physician must try to identify the mechanism of exposure. Clinicians are left primarily with the history, and while collateral history may be helpful, interviewing others requires the competent patient's consent and can still be highly subjective. The patient had no documented

psychiatric history, had an unremarkable mental status examination and gave no obvious reason to suspect self-poisoning. However, a formal psychiatric evaluation to explore the possibility of a factitious disorder would have been mandated if he continuously re-presented with coumarin poisoning or other unusual conditions.⁴ As we could not confidently confirm the mechanism of exposure and did not feel there was imminent public danger, we did not believe there was a medicolegal duty to report the case to authorities. Our regulatory college does not list possible adult poisoning as a circumstance requiring mandatory reporting.⁹ We would naturally suggest that if there are doubts, individual clinicians consult their institution's legal office (as we did) to confirm local legislative requirements.

On follow-up several months later, the patient was doing well. He believed he knew how he had been exposed to coumatetralyl and had taken measures to remove himself from the situation. For personal reasons, he declined our offer to help legally report the case on his behalf.

Learning points

- ▶ The pattern of coagulopathy is an important clue to its aetiology.
- ▶ Successful empiric correction of an isolated high INR with vitamin K narrows the possible causes to vitamin K deficiency and coumarin exposure.
- ▶ Warfarin is not the only coumarin patients can be exposed to.
- ▶ Requesting a toxicology screen specifically for coumarins can secure the diagnosis of poisoning.

Competing interests None.

Patient consent Obtained.

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