CASE REPORT

Transient cefuroxime/metronidazole treatment induced factor V antibodies

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SUMMARY

A 29-year-old patient presented with an appendicular infiltrate, initially treated with intravenous antibiotics, but later requiring percutaneous drainage. Both prothrombin time (PT) and activated partial thromboplastin time (aPTT) were prolonged on 3 days of antibiotic treatment and unresponsive to vitamin K or prothrombin complex concentrate. Laboratory investigation ultimately showed reduced factor V activity and factor V antibodies. In contrast to previously described cases of factor V antibodies, PT and aPTT were only mildly prolonged and residual factor V activity was still >20%. Draining of the abscess did not induce significant bleeding. Afterwards, no haemostatic medication was required. The patient was discharged from the hospital without complications. One week after cessation of the antibiotic treatment, PT and aPTT were within normal range again, with a factor V activity level of 36%. In conclusion, we present a patient with transient factor V antibodies, induced by antibiotics, without clinical bleeding tendency.

BACKGROUND

Acquired factor V inhibitors are rare autoantibodies that may be induced by antibiotic treatment.¹ In general, the inhibitor level does not correlate with the level of factor V deficiency.² However, even a low level of factor V inhibitor (2–5 Bethesda units) can result in an almost complete loss of factor V activity and severe bleeding risk.³ In this case report, we present a patient with factor V inhibitor at a very low titre (~1 BU), induced by antibiotic treatment, resulting in modest reduction of factor V activity (25% activity left). The patient had no clinical bleeding tendency. Furthermore, 1 week after cessation of the antibiotic treatment, the inhibitor was cleared from the circulation without treatment.

CASE PRESENTATION

A 29-year-old man with no significant medical history presented at the emergency room with abdominal pain. His medical history did not reveal bleeding problems for himself or for any family member. He presented with abdominal pain in the right lower quadrant for the past 4 days. Based on clinical examination, laboratory tests and ultrasonography, an appendicular infiltrate was diagnosed. The patient was treated with intravenous antibiotics (cefuroxime/metronidazole), according to national guidelines. After 3 days, the patient developed a fever up to 39°C. His abdomen was tense and an abscess was suspected. Ultrasonography confirmed

the diagnosis and percutaneous drainage was indicated. Laboratory testing showed a prolonged prothrombin time (PT) and a prolonged activated partial thromboplastin time (aPTT; [table 1](#)). To correct a possible underlying deficiency, 10 mg vitamin K was supplemented orally. However, PT and aPTT remained unchanged. The patient was then given prothrombin complex concentrate, which also did not result in a normalisation of the clotting tests. After 3 days the prothrombin time – international normalised ratio was 1.8 and the abscess was drained percutaneously. No bleeding complications occurred. After 11 days, the intravenous antibiotics were switched to amoxicillin/clavulanic acid orally and the patient recovered well. He was discharged 1 day later. One week after discharge, PT and aPTT had normalised ([table 1](#)).

INVESTIGATIONS

Since both PT and aPTT were prolonged and vitamin K deficiency was excluded, differential diagnosis included an atypical lupus anticoagulant (LAC), the presence of a factor inhibitor or a factor deficiency in the common pathway, or a combination of these factors. Therefore, mixing studies and factor-specific activity assays (factors II, V, VII and X) were performed.

Diluted Russell's viper venom time (dRVVT) screening suggested the possible presence of a LAC (screen/confirm ratio=1.52; reference <1.45) although weak and not confirmed by silica clotting time (screen/confirm ratio 0.83; reference <1.24). In addition, the inadequate fractional shortening of the aPTT after addition of phospholipids (91 s without, 62 s with additional phospholipids) indicated a non-LAC inhibitor, rather than a LAC. This was further confirmed by an incomplete normalisation of PT in mixing studies. Interestingly, even though vitamin K and prothrombin complex concentrate was administered only 2 days before, factor V and VII activity levels were reduced, whereas factor II and X activity levels were normal.

Combined, the failure of both PT and aPTT to correct pointed towards the presence of an inhibitor in the common pathway. The presence of a factor V inhibitor was confirmed by Bethesda assay in which a low titre inhibitor was found (1 BU).

OUTCOME AND FOLLOW-UP

The patient fully recovered from the appendicular infiltrate and was seen 1 week later. PT (14) and aPTT (33.1) were found to be in the normal range,

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Table 1 Laboratory results at different timepoints after hospital admission

	Reference range	Day 4 15:26	Day 5 08:00	Day 7 08:00	Day 7 16:52	Day 10 08:00	Day 17 16:44
PT patient	10–14 s	25.8	24.4	20.1	20.4	19.5	13.9
PT 1+1				14.2			
PT normal				11.5			
aPTT	25.0–35.0 s	38.3	36.3	37.3	37.0	39.8	33.1
Fibrinogen	2.0–4.0 g/L		5.9		7.1		3.2
FII activity	80–120%				96		
FV activity	70–130%				23		36
FVII activity	65–150%				49		85
FX activity	80–120%				107		

aPTT, activated partial thromboplastin time; F, factor; PT, prothrombin time.

LAC tests as well as factor V inhibitor was negative and factor V was 36%.

DISCUSSION

Antibiotic-induced factor V inhibitors are exceedingly rare and in most cases associated with either aminoglycosides or β -lactamase antibiotics.¹ In our patient, factor V antibodies developed during cefuroxime/metronidazole treatment. Only a handful of cases with possible cephalosporin-induced factor V antibodies have been described previously.¹ This could be due to the low incidence and transient nature of these antibodies. Last, the complex diagnostic tract involved in the identification of the antibody leaves ample room for misinterpretation. If factor activity is not measured, the cause of the prolonged PT and aPTT could be mistaken for a LAC in combination with a factor deficiency.

Here, the dRVVT suggested the presence of a LAC and factor V and VII activity was reduced. However, rather than two separate, transient, haemostatic abnormalities being present at the same time it is more likely that the factor V antibody presented LAC-like features. This is well known for factor VIII inhibitors.⁴ Much less is known for factor V inhibitors, although inhibitors of this type have been described before.^{5 6}

Although inhibitor titres do not correlate well with bleeding risk, residual factor V activity levels do.² Therefore, it is important to treat patients with low residual factor V levels who have an increased bleeding risk. However, although the strategy is commonly based on two steps (bleeding control followed by antibody eradication), there is no treatment consensus in the context of factor V antibodies.⁷ Common strategies include fresh frozen plasma (15% effective), platelets (69% effective), prothrombin complex concentrate (80% effective) and recombinant activated factor VII (33% effective).

In our case, PT and aPTT normalised without treatment. This is similar to a previously described patient who had a comparable antibody titre and residual factor V level.⁸ Together, these data suggest that cefuroxime/metronidazole treatment can induce low levels of factor V inhibitors. Here, this was associated with prolonged PT and aPTT but did not result in bleeding tendency and resolved without treatment.

Learning points

- ▶ Cefuroxime/metronidazole treatment can induce factor V antibodies, resulting in prolonged PT and aPTT.
- ▶ Low titre factor V antibodies may clear without treatment.
- ▶ Low titre factor V antibodies are not associated with increased bleeding tendency.
- ▶ Factor V antibodies may result in false-positive LAC tests.

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Competing interests None.

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