Short reports

Acquired factor XI inhibitor in chronic lymphocytic leukaemia

M J Goodrick, A G Prentice, J A Copplestone, D H Pamphilon, R J Boon

Abstract

A 71 year old man with chronic lymphocytic leukaemia (CLL) experienced excessive bleeding following transurethral resection of the prostate. Investigations showed a prolonged kaolin cephalin clotting time (KCCT) with low concentrations of factor XI. The prolonged KCCT was largely corrected by mixing with normal plasma but this correction was lost on incubation, confirming the presence of an inhibitor. He was treated with pulsed methylprednisolone and chlorambucil which resulted in the resolution of the bleeding problem and the loss of detectable circulating inhibitor.

Inhibitors directed against specific coagulation factors may be suspected because of unexpectedly severe bleeding in a patient with a previously stable or predictable coagulation state. These inhibitors can develop in congenital factor deficiency or in various clinical conditions such as systemic lupus erythematosus (SLE). Acquired inhibitors to contact factors of coagulation are rare.¹ We describe an acquired factor XI inhibitor in association with chronic lymphocytic leukaemia (CLL).

Case report

A 71 year old man presented with acute urinary retention and a long history of prostatism. He had had CLL for the previous 10 years and had received intermittent chlorambucil and prednisolone. More recently he had achieved a partial response to combination chemotherapy with cyclophosphamide, vincristine, and prednisolone. He declined further treatment after five courses.

When the urinary retention was investigated he was found to have benign prostatic hypertrophy and a urethral stricture. He underwent transurethral resection of the prostate and incision of stricture with a platelet infusion to correct thrombocytopenia (preoperative platelet count $101 \times 10^9/l$). Postoperatively he developed excessive and persistent haematuria despite platelet support. The platelet count was consistently above $100 \times 10^9/l$ and the direct antiglobulin test was negative throughout.

Laboratory investigations

Clotting studies showed a significantly prolonged KCCT which was largely corrected by the addition of normal plasma. The correction was lost after incubating the mixture at 37°C for 30 minutes (table). Further correction tests were then performed using methods described by Exner *et al*² in which test plasma was mixed with normal plasma in varying concentrations and a KCT was performed on each mixture immediately and after two hours' incubation at 37°C. This confirmed a type 2 pattern, suggestive of an inhibitor with a factor deficiency.

Specific factor assays showed a reduced factor XI concentration (18%). All of the other relevant intrinsic pathway factors were normal, although prekallikrein and high molecular weight kininogen were not measured.

An inhibitor assay was performed which, taking into account the concentration of factor XI present in the test plasma, showed an inhibitor concentration of 0.8 Bethesda Units.

The FXI inhibitor concentration was unaffected by using a mixture of test plasma incubated with anti-human IgG (National Blood Transfusion Service, Bristol). Conversely, inhibitor activity was abolished by the addition of 2-mercaptoethanol, suggesting that the inhibitor was an IgM antibody. There was no detectable paraprotein. Serological investigations for autoantibodies were negative.

The patient was given 1g of pulsed methylprednisolone intravenously on alternate days to a total of 3 g, and 8 mg of chlorambucil by mouth daily for 10 days. Bleeding stopped clinically within five days. Chemotherapy was given monthly and 10 months later he remained free of bleeding problems. Testing after treatment showed loss of inhibitor activity and an increase in the factor XI concentration (39%).

Discussion

Although rare, factor XI inhibitors have been previously described in people who are congenitally deficient,³ usually, but not always, following plasma infusion.⁴ Factor XI inhibitors have also been described in patients with connective tissue disease, particularly SLE, Waldenström's macroglobulinaemia, bronchial carcinoma and acute myeloid leukaemia.⁵

Department of
Haematology,
Derriford Hospital,
Plymouth

A G Prentice
J A Copplestone
R J Boon

National Blood
Transfusion Centre,
Bristol

M J Goodrick
D H Pamphilon

Correspondence to:
Dr M J Goodrick, South
West Regional Transfusion
Centre, Southmead Road,
Bristol BS10 5ND

Accepted for publication
5 September 1991

Results of coagulation studies

	Pretreatment	Immediately after treatment	One month after treatment
Bleeding time (mins)	4.5		9
Prothrombin time (secs)	14	13	12
Control time (secs)	12	12	12
Kaolin-cephalin clotting time (KCCT) (secs)	72	40	42
Control time (secs)	40	41	47
KCCT corrections (secs)			
1 in 2 STAT	49		
30 mins	54		
Control STAT	40		
30 mins	44		
1 in 5 STAT	53		
30 mins	79		
Control STAT	41		
30 mins	44		
FVIII:c (%)	80		160
FIX:c (%)	90		110
FXI:c (%)	18	27	39
FXII:c (%)	65		44
FXI inhibitor (Bethesda Units)	0.8	0.4	<0.1

In patients with haemophilia who developed antibodies to factor VIII there is usually no detectable circulating factor VIII. In our patient there was a detectable concentration of factor XI in the plasma despite the presence of free antibody. It may be that the patient was producing sufficient factor XI to compensate for the destruction by the low inhibitor concentration, although the factor XI did not return to normal after the inhibitor became undetectable. Alternatively, it may be that the inhibitor required a cofactor which was depleted before the removal of all factor XI, although in this case an Exner test inhibitor pattern of type 3 would be expected.

In previous reports in which the acquired inhibitor has been further characterised it has been found to be of the IgG type.^{3,6} In our case incubation with anti-human IgG did not affect the factor XI inhibitor concentration, confirming that it was not an IgG type. Conversely, inhibitor activity was abolished by the addition

of 2-mercaptoethanol (2ME), which disrupts pentameric IgM, so the observed effect strongly suggests an IgM antibody. Unfortunately no further investigations such as incubation with anti-human IgM could be performed to confirm this.

- 1 Giddings JC. Hereditary coagulation disorders. In: *Laboratory techniques. Blood coagulation and haemostasis*. Edinburgh: Churchill Livingstone, 1980.
- 2 Exner T, Rickard KA, Kronenberg H. A sensitive test demonstrating lupus anticoagulant and its behavioural patterns. *Br J Haematol* 1978;40:143–51.
- 3 Musclove CE, Amato D, Oforu F, Armstrong AL, Abbott D. Transfusion-induced specific anti-factor XI inhibitor in a patient with previously unrecognised FXI deficiency. *Am J Clin Pathol* 1988;89:418–22.
- 4 Schnall SF, Duffy TP, Clyne LP. Acquired FXI inhibitors in congenitally deficient patients. *Am J Hematol* 1987;26:323–8.
- 5 Reece EA, Clyne LP, Romero R, Hobbins JC. Spontaneous FXI inhibitors. *Arch Int Med* 1984;72:1748–54.
- 6 De La Cadena RA, Baglia FA, Johnson CA, *et al*. Naturally occurring human antibodies against two distinct functional domains in the heavy chain of FXI/FXIa. *Blood* 1988;72:1748–54.

Solitary ganglioneuroma of the rectum: Report of two cases

T W Beer

Abstract

Two cases of solitary rectal ganglioneuromas are reported, one in a patient with several previously resected colorectal adenomas, the other in a patient with no known predisposing pathology. No prior reports of cases of solitary rectal ganglioneuroma have been published as far as is known, and the origin of similar lesions which have been reported at other sites in the gastrointestinal tract is a subject for speculation.

Ganglioneuromas are rare tumours and seldom encountered in the gastrointestinal tract. The first documented case was reported in 1928,¹ with subsequent reports predominantly concerning lesions of the stomach or duodenum, with a few reports of tumours in the large bowel.

Most ganglioneuromas arise in the posterior mediastinum, retroperitoneum, or adrenal in childhood or early adult life. Maturation of childhood neuroblastomas to ganglioneuromas has also been documented.²

Department of
Histopathology, Royal
Hospital,
Wolverhampton
T W Beer

Correspondence to:
Dr T W Beer,
Pathology Laboratory,
Lakin Road,
Warwick CV34 5BJ.

Accepted for publication
5 September 1991