Spontaneous regression of the inhibitor against the coagulation factor XIII A subunit in acquired factor XIII deficiency

Fumihiro Ishida¹; Kentaro Okubo¹; Toshiro Ito¹; Nobuo Okumura²; Masayoshi Souri³; Akitada Ichinose³

¹Hematology Division, Second Department of Internal Medicine, Shinshu University School of Medicine, Matsumoto, Japan; ²Biomedical Laboratory Sciences, School of Health Sciences, Shinshu University, Matsumoto, Japan; ³Department of Molecular Patho-Biochemistry and Patho-Biology, Yamagara University School of Medicine, Yamagara, Japan

Dear Sirs,

Acquired coagulation factor XIII (FXIII) deficiency is a rare bleeding disorder, in which severe haemorrhagic symptoms develop, often with significant mortality (1, 2). It usually develops in elderly populations.

Two types of acquired FXIII deficiency are recognised. The first type is caused by specific inhibitors against FXIII and the second type involves less severe clinical symptoms associated with various conditions, often without any bleeding diathesis, from unidentified mechanisms. An IgG subtype of inhibitor against FXIII A subunit (FXIII-A) is a major contributor to the former type.

Because of its rarity, management of acquired FXIII deficiency has not been clearly standardised; however, FXIII supplementations and immunosuppressive therapies have been utilised.

Here, we report a case of acquired FXIII deficiency with FXIII-specific inhibitor treated with FXIII concentrates, which subsequently resulted in spontaneous disappearance of the inhibitor with satisfactory clinical outcome.

A 76-year-old Japanese male was referred to our hospital in 2004 because of extensive haematomas. His history contained no potentially contributive factors, except for lung cancer, which was curatively resected at 60 years old without any haemorrhagic complications, and diabetes mellitus treated with metformin hydrochloride and insulin.

A month earlier, a haematoma developed at his buttock after a bruise with spontaneous regression. Four days before, he noticed a spontaneous haematoma on his right forearm with pain during sleep, which extended gradually to the whole of his right upper limb and also his anterior chest. On admission, he was anaemic and extensive subcutaneous haematoma was recognised.

His haemoglobin level was 5.5 g/dl and coagulation panel showed no abnormalities except for solubility of the clot in urea. His plasma FXIII antigen level was 12% (normal: >70%) and FXIII activity also decreased to 18% of that of controls. Cross-mixing test for FXIII activity implied an inhibitor for FXIII but the results were inconclusive (Fig. 1A). FXIII-A was recognised to a limited extent in his plasma but a significant amount of FXIII B subunit (FXIII-B) was found (3). Later, anti-FXIII-A antibody was recognised (Fig. 1B), which was identified as IgM and IgG type (Souri and Ichinose, manuscript in preparation). Administration of FXIII concentrate at 14 U/kg gave a significant increase in FXIII activity that peaked at 120 minutes with 48% activity and the estimated half-life of the administered FXIII was 16 hours (h). Although acquired FXIII deficiency was strongly suspected, the existence of the inhibitor against FXIII was not clearly shown in initial examinations and administration of FXIII concentrate caused an increase in FXIII activity, which implied a low titre of the inhibitor. Considered together with the possible deteriorative effects of immunosuppressive therapy for the elderly, administration of FXIII concentrate twice a week was initiated while withholding immunosuppressive drugs including corticosteroids. With constant...
supplementations of FXIII, the haematomas were gradually ameliorated to a generally stable condition, although newer lesions occasionally appeared. Metformin hydrochloride was also discontinued because of its latent inhibitory effect against FXIII (4). The patient was discharged one month later and FXIII concentrate was supplemented intermittently at an ambulatory setting. The patient’s bleeding symptoms waxed and waned and remained at a manageable level for months; thereafter, bleeding diathesis gradually improved with normalisation of plasma XIII activity. Four years later, the FXIII antigen was at 113% with no detectable anti-FXIII antibody (Fig. 1B).

Gene sequencing analyses of the exons and the boundary areas of FXIII-A and FXIII-B were also performed to identify potential causes of alterations of FXIII structure in this patient. No abnormality was detected (data not shown).

Immunosuppressive therapy for acquired FXIII deficiency, which includes corticosteroid, cyclophosphamide, and rituximab, has succeeded in some cases. Infectious complication is a concern, which leads to significant mortality in the patients with acquired coagulation inhibitors under immunosuppressive therapy, especially in elderly populations (5). Considering that the inhibitor was at a low titre level and that the patient’s bleeding symptom was limited to subcutaneous, evaluation of a challenge test with FXIII concentrate, concomitant diabetes, and potential risk for infectious complications, together with his age and non-real-time identification of the inhibitor, we only administered FXIII concentrate in our patient, which was sufficient to achieve haemostasis.

There is controversy over the indication of the concerned blood components for the patients with acquired inhibitors (6), and FXIII concentrate has been recommended for acquired FXIII deficiency, presumably because of the lack of valuable bypassing agents. Although the half-life was shortened to 16 h, a sustained increase in plasma FXIII activity was obtained after administration of FXIII concentrate in our patient, which was sufficient to achieve haemostasis.

The natural history of the inhibitor against FXIII is unclear. There are several reports with spontaneous remission, although the therapies of each case were not always described in detail (2). In acquired haemophilia A, in which immunosuppressive therapy is the mainstay of its management, one-third experienced spontaneous remission without immunosuppressive therapies (7) and 10–20% of the patients who underwent therapeutic attempts to eliminate the inhibitors did not achieve complete remission (5).

Optimal managements for acquired FXIII deficiency need to be defined in terms of the bleeding risks, individual comorbidities, and therapeutic efficacies.

Acknowledgements

This study was supported in part by a research grant from the Japanese Ministry of Health, Welfare, and Labor.

References