Neoplasms-induced bleeding in inherited, heterozygous FXIII-A deficiency

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Summary
Inherited mild factor XIII deficiency belongs to one of the most underdiagnosed bleeding disorders so far. This is, because most patients do not develop bleeding complications in daily life. Patient, methods: A man (age: 64 years) without a history of bleeding presented with painful swelling of neck, weight loss, anemia and episodic bleeding from the right tonsil necessitating tonsillectomy. Histologic and immunohistochemical examination revealed cytokeratin-positive epitheloid angiosarcoma. Blood coagulation status showed significantly elevated D-dimer and decreased FXIII levels (FXIII-activity 35%, FXIIIA-Ag 16–26%). Plasma mixing studies excluded neutralizing antibodies against FXIII. Results: A novel heterozygous F13A1 gene nonsense mutation (p.Glu103Ter, c.307G>T) was found confirming heterozygous FXIII-A deficiency. The same mutation was detected in two asymptomatic relatives. For further clinical management the patient had to undergo several revisions due to delayed, Hb relevant bleeding after cervical lymph nodes extirpation and resection of tonsil. Two chemotherapy cycles with paclitaxel and palliative radiotherapy of the neck area were performed, but the patient died unfortunately two months after diagnosis. Conclusions: It is a unique case showing the combination of a highly aggressive angiosarcoma and presence of inherited FXIII deficiency. It is also a rare example demonstrating the benefit of FXIII genotyping besides the expected acquired FXIII deficiency possibly due to neoplasms induced increased consumption by elevated crosslinking of fibrin fibers.

Schlüsselwörter
FXIII, erworbener FXIII-Mangel, angeborener FXIII-Mangel, F13A1, F13B

Zusammenfassung

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Malignom-assoziierte Blutung bei einem Patienten mit hereditärem, heterozygoten Faktor-XIII-Mangel

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Factor XIII (FXIII) is a coagulation factor acting at the end of the coagulation cascade to stabilize preformed fibrin clots. Enzymatically, it is a protransglutaminase. In the plasma, the zymogenic FXIII circulates in the form of a heterotetramer (FXIII-\(A_2B_2\)) composed of two catalytic A subunits bound to two carrier B subunits. Intracellularly, FXIII is found as a homodimer composed of two A subunits (\(A_2\)) (1, 2).

FXIII deficiency is rare in humans and in most cases associated with acquired deficiency. It may occur in several disorders, like

- hematologic malignancies,
- disseminated intravascular coagulation,
- major surgery,
- liver diseases,
- Henoch-Schönlein purpura,
- chronic inflammatory bowel disease.

FXIII activity can be reduced in these disorders by 50% or more. Decreased FXIII levels in these disease states are not due to anti-FXIII inhibitors (3–5).

Inherited, severe (FXIII activity < 1%), FXIII deficiency is an autosomal recessive disease affecting in Germany approximately one out of 1–2 million inhabitants. It is associated with

- a life-long bleeding tendency,
- pregnancy loss and
- impaired wound healing (3, unpublished data).

On the other hand the heterozygous (only one affected allele) FXIII deficiency is expected to be more common affecting approximately one out of 1000 inhabitants with a reduction of FXIII activity by 50% in most cases (4). Nevertheless, larger part of patients with heterozygous deficiency are usually exempt of spontaneous bleeding and bleeding after minor trauma.

The majority of the patients with inherited, severe FXIII deficiency have mutations in \(F13A1\) gene encoding FXIII-A Subunit (FXIII-A) and only very few in \(F13B\) gene encoding FXIII-B subunit (FXIII-B) (6). Although, FXIII-B subunit deficiency in heterozygous status seems to be more present at least in German population (7).

Here, we report a patient who was accidentally diagnosed to have mild inherited FXIII deficiency after having developed bleeding in the tissues of the neck associated with a rare neoplasm.

Patient, material, methods

Coagulation assays were performed using standard procedures. Patient underwent a complete coagulation check involving global coagulation tests (aPTT, prothrombin time, thrombin time, reptilase time, thrombelastography), D-dimers, measurement of coagulation factors (fibrinogen, FII, FV, FVII, FVIII, FIX, FX, FXI, FXII, FXIII, von Willebrand factor, \(\alpha\)-2-antiplasmin) and platelet function tests using PFA100 and standard thrombocyte aggregation. FXIII activity was determined using Berichrom FXIII chromogenic assay (Siemens Healthcare Diagnostics, Germany) on a BCS XP coagulation analyser. FXIII-A antigen concentration was measured by automated latex enhanced immunoassay (Instrumentation Laboratory, Bedford, USA).

The genomic DNA was extracted from peripheral blood after informed consent for genetic analysis. The exons and the flanking regions of \(F13A1\) and \(F13B\) genes were amplified by polymerase chain reaction (PCR) using primers as described previously (7, 8). The DNA amplicons were analyzed by direct sequencing on an Applied Biosystems Analyzer (Applied Biosystems, Germany). Informed patient consent was obtained in accordance with the Declaration of Helsinki.

Case report

A man (age: 64 years) of Causasian origin without a history of bleeding presented in January, 2012 with abdominal pain and weight loss to local physicians. A diverticulosis of colon sigmoideum and descendens was diagnosed after colonoscopy. No malignancy had been identified. Two weeks later he was admitted to the local hospital because of secondary anemia showing no bleeding source. In addition, he underwent an ultrasound procedure and thyroid scintigraphy (technetium-99m) because of previously known swelling of the neck area and palpable thyroid gland. The ultrasound showed multinodular goitre (struma multinodosa) with a significantly increased left lobe (8.8 x 5.1 x 5.8 cm, 124 ml in volume) containing a big cold knot and moderately (7.8 x 2.6 x 2.3 cm, 22.3 ml in volume) increased right lobe also containing smaller knots. The increased thyroid resulted in trachea and oesophagus dislocation.

An operative therapy was discussed, but not performed. The weight loss was explained due to insufficient control of diabetes mellitus (type 2), and insulin therapy was proposed instead of oral antidiabetic drugs.

In May, 2012 he developed a strong pain on the left neck area irradiating to the front side of the chest and temporal region. Several days prior to this event he was involved in strenuous physical activity. He took drugs for pain management but did not take medical advice.

Four weeks later a coagulation analysis including FXIII-A antigen measurement in the peripheral outpatient clinic was performed, because of the suspected soft tissue hematoma and chronic pain of the left area of the neck. Factor XIII-A antigen levels were significantly reduced (16–18% of normal) and d-dimers were 20-fold of normal. While the remaining coagulation parameters (fibrinogen, FII, FV, FVII, FVIII, FIX, FX, FXI, FXII, von Willebrand factor, \(\alpha\)-2-antiplasmin) and platelet function tests were within the normal range. His hemoglobin concentration was 11.7 g/dl (normal range: 14–18 g/dl) and C reactive protein (CRP) was increased (5.08 mg/dl, normal: <0.8 mg/dl).

The patient was admitted to our Haemophilia Center for further diagnosis and management of the bleeding complication. We performed FXIII activity and FXIII-A antigen measurement and confirmed FXIII deficiency (FXIII: 35% of normal, FXIII-A: 26%). Plasma mixing studies excluded neu-
tralizing antibodies against FXIII. Ultrasound of the neck area confirmed sternocleidomastoid muscle hematoma.

After administration of 2500 IU (30 IU/kg body weight) FXIII concentrate (Fibrogammin®) the FXIII activity rose to 83% one hour after substitution and decreased to 53% 24-hours later. Despite of weekly substitution with 2500 IU of FXIII concentrate the patient experienced bleeding of the right tonsil necessitating resection of the right tonsil.

Histologic evaluation revealed the presence of an epithelioid tumor. Immunohistochemistry showed a strong expression of CD31, co-expression of cytokeratin and absence of CD34 staining establishing the diagnosis of cytokeratin-positive epithelioid angiosarcoma. A computed tomography (CT) of neck and chest area showed a 5.6 x 6.6 x 7.7 cm lesion in the left thyroid gland dislocating trachea, cervical bulky lymph nodes (6.7 x 3.3 cm, axial diameter) on the right side and enlarged jugular lymph nodes on both sites. In addition there were signs of residual hematoma of the right sternocleidomastoid muscle.

Haemostatic management (regular substitution with FXIII concentrate keeping trough levels >50% of normal) and antifibrinolytic treatment (1 g three times daily) improved the bleeding symptoms significantly. However, the patient still had to undergo several revisions due to delayed, haemoglobin relevant bleeding after cervical lymph nodes extirpation (Fig. 1). He also experienced delayed bleeding after tonsil resection necessitating tonsillectomy. Two chemotherapy cycles with paclitaxel and palliative radiotherapy of the neck area were performed, but the patient died unfortunately two months after diagnosis.

**F13A1** gene analysis

A novel heterozygous F13A1 gene nonsense mutation (p.Glu103Ter, c.307G>T) was found confirming inherited mild FXIII deficiency. This type of mutation results in expression of truncated FXIII-A molecule consisting of 102 out of 731 amino acids. It is very likely that this mutated protein is unstable and does not appear in the peripheral blood flow. No mutations have been found in F13B gene.

We analyzed also four relatives of the propositus including two sons showing normal FXIII activity and wild type F13A1 genotype. Contrastingly the sister of the patient and her son showed decreased FXIII levels (FXIII activity: 43–57%, FXIII-A antigen: 43–53%), a heterozygous status of nonsense mutation in F13A1 gene (Fig. 2) was diagnosed.

**Discussion**

Sarcomas arising in the soft tissue of the oral cavity are very rare representing 0.14% of head and neck malignancies among 11 250 patients described in the review of
Gorsky and Epstein (9). The prognosis of this type of neoplasm remains poor. To our knowledge it is the first case showing angiosarcoma and co-incidence of inherited FXIII deficiency. It may be speculated that FXIII was found to be reduced basically for two major reasons:

- increased consumption of FXIII-A in crosslinking of different substrates including fibrin fibers in the clots and
- due to impaired FXIII-A synthesis in the presence of a heterozygous defect in the F13A1 gene.

Despite of regular FXIII concentrate substitution and antifibrinolytic therapy this patient experienced multiple bleeding complications after resection of the right tonsil and lymph nodes extirpation. This might be in part explained by the nature of the neoplasm involving vessels and possible fibrinolytic activity of the neoplasm. In addition, it may be speculated that because of the neoplasm nature the dosage of FXIII concentrate and antifibrinolics had to be even higher. Independent from these specifications substitution of FXIII concentrate had a significant clinical effect in reducing blood loss which at least is an indirect evidence that the mild deficiency of FXIII contributes to the bleeding symptoms.

As discussed previously (4) mild FXIII deficiency might not be rare in the general population. Our previous publications based on limited patient numbers have demonstrated heterogeneous FXIII deficiency to be associated with bleeding tendency under haemostatic stress situations like surgery, trauma, pregnancy, menorrhagia etc. (8, 10).

In the family on focus, no serious bleeding has been recognized in his 56-year-old sister although she experienced Caesarean section, thyroid surgery and dental extraction. Her menstrual bleeding until menopause (at the age of 47) was without increased blood loss. On the other hand she complained to have small (<2 cm in size) subcutaneous haematomas after trauma, episodic epistaxis and prolonged bleeding after injuries without medical care and specific treatment. Her 22-year-old son also being heterozygous for FXIII deficiency did not yet experience haemostatic stress situations like surgery or traumas.

**Conclusion**

We report a very rare case of cytokeratin-positive epithelioid angiosarcoma combined with a heterozygous FXIII deficiency. FXIII genes analysis was an important diagnostic step in order to explain FXIII deficiency besides elevated d-dimers.

The diagnosis of neoplasm was recognized with some delay because of goitre.

**Conflict of interest**

The authors declare that they have no conflict of interest.

**References**