A case of acquired factor XIII deficiency secondary to plasmablastic lymphoma

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ABSTRACT

Acquired factor XIII (FXIII) deficiency is an extremely rare and potentially fatal bleeding disorder. Immune-mediated FXIII deficiency is due to the development of anti-FXIII autoantibodies which may develop with concomitant conditions that cause immune dysregulation such as malignancies or autoimmune disorders. Clinical presentation includes delayed post-operative bleeding or spontaneous soft tissue hematomas and/or cerebral bleeding. Since screening coagulation laboratory tests (prothrombin time, activated partial thromboplastin time, and fibrinogen) are typically normal, acquired FXIII deficiency is likely to be overlooked and underdiagnosed. The management of immune-mediated FXIII deficiency is based on hemostatic therapy, autoantibody removal and eradication of the underlying etiology; however, no treatment guidelines are still available. Here we report a case of acquired FXIII deficiency associated with plasmablastic lymphoma, in order to raise awareness of this rare bleeding disorder and consent prompt life-saving management.

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INTRODUCTION

Acquired factor XIII (FXIII) deficiency is an extremely rare and potentially fatal bleeding disorder due to either FXIII hyper-consumption, hypo-synthesis or inhibitor related to an immune-mediated process. The condition can be idiopathic or associated with several pathologic states such as malignancies or autoimmune disorders. Immune-mediated FXIII deficiency is typically symptomatic and clinical presentation includes delayed post-operative bleeding or spontaneous soft tissue hematomas and/or cerebral hemorrhages. Acquired FXIII deficiency is likely to be overlooked as traditional coagulation tests [prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time and fibrinogen] are in range. Treatment is based on FXIII replacement, anti-fibrinolytic administration and/or inhibitor eradication.[1-3]

Here we report a case of acquired FXIII deficiency associated to plasmablastic lymphoma (PBL), which has never been described in current literature.

CASE REPORT

In May 2020 a 67-year-old woman with a recent diagnosis of IgG/k PBL was transferred to our Hematology Unit for progressive and severe anemia [hemoglobin (Hb) 6.5 g/dL]. Her medical history revealed the occurrence of diffuse and atraumatic lumbar and rib cage pain six months earlier (November 2019), for which she was referred to the emergency room (ER) of a District-Hospital. Chest X-ray showed a 5th rib fracture and a lumbar Magnetic Resonance Imaging (MRI) scan revealed a ver-

tebral failure of D8. At that time, laboratory investigations did not show abnormalities, yet serum protein electrophoresis was not performed, and the patient started analgesic therapy (ketorolac) with limited benefit. Two months later (January 2020), she consulted both a neurosurgeon and an orthopedic that suggested the use of a corset and she also repeated an X-ray showing a new vertebral failure of D12. In April 2020 back pain worsened further, and the patient was admitted again to the ER, where laboratory tests showed the presence of acute renal failure (creatinine of 14 mg/dL). She immediately started dialysis as an outpatient and developed a large hematoma in the catheter insertion site. Chest X-ray showed lung consolidations in the upper right lobe, while abdominal ultrasound evidenced splenic and hepatic focal lesions and lymphadenopathy. A bone marrow biopsy revealed 80% monoclonal IgG/k plasmablastic plasma cells with t (14;16) by fluorescent in situ hybridization. Suddenly just after the biopsy she developed a large hematoma around the incision site. A staging MRI of the spine and the pelvis showed multiple vertebral lesions (D8, D9, D12 and L4), while 18F-fluorodeoxyglucose (FDG) positron emission tomography revealed increased FDG uptake in dorsal and lumbar spine, pelvis, ribs and stern. Vertebroplasty of D9 was performed for worsening pain, but immediately the patient developed a huge hematoma around the surgical site. A few days later, while she was on dialysis outpatient program waiting to start plasmablastic lymphoma therapy, she was urgently admitted to ER for extreme asthenia and dyspnea. Blood tests showed severe anemia (6 g/dL) and chest Computed Tomography (CT) demonstrated a large hematoma of the left hemithorax with spots of bleeding at the level of the 5th and the 7th rib. Only at this time, she was transferred to our hematology unit. On physical examination, the patient presented a huge purplish hematoma extending from the neck to the hips, also involving the left arm and the left leg (Figure 1). Laboratory tests still showed severe anemia (Hb 6.5 g/dL) despite two packed red blood cell (PRBC) units received while in ER, moderate thrombocytopenia (platelet count 130000/mm^3), increased serum creatinine (5.95 mg/dL) and a monoclonal component IgGk of 2.5 g/dL on serum protein electrophoresis and immunofixation. Serum-free light chain assay demonstrated k 5880 mg/L and λ 3.96 mg/L with a k/λ free light chain ratio of 1458. Thus, induction therapy with bortezomib, PEGylated doxorubicin and dexamethasone (PAD regimen) was started and dialysis continued.

Although the initial screening had shown normal values of PT, aPTT and fibrinogen, we decided to investigate further the coagulation profile considering her recent bleedings and her poor transfusion yield stable Hb of 6 g/dL despite daily transfusions of 2 PRBC units. While laboratory investigations ruled out the presence of platelet dysfunction syndromes and von Willebrand disease, a factor XIII deficiency was detected with a FXIII activity level of 3% by quantitative activity assay (Berichrom Factor XIII test kit, Siemens, Marburg, Germany). The clot solubility assay evaluating the stability of crosslinked fibrin was abnormal and was not corrected by mixing with normal plasma, thus suggesting the presence of FXIII inhibitor which was then confirmed by Bethesda assay at the level of 40 units.[4-6] The patient had no history of bleeding and previous surgeries (cholecystectomy in 2012 and transurethral resection of bladder papillary lesion in 2016) were not complicated by bleeding, so we concluded that the acquired FXIII deficiency was secondary to her recent malignancy. As FXIII concentrates were not available, we used fresh frozen plasma (FFP) daily at the dosage of 15 ml/kg body weight (80 kg) to correct the FXIII deficiency and to continue the PAD-regimen with the aim of eliminating the cause that had triggered the inhibitor (Table 1). However, the patient's clinical condition worsened in three days with increasing dyspnea and decreasing oxygen saturation (SaO2) to 90%. Chest high-resolution CT showed expanding hematoma in the left hemithorax with signs of recent bleeding as well as a bronchopneumonia finding in the upper right lobe associated with pleural effusion (Figure 2). The patient received consequently empiric antibiotic therapy with meropenem and linezolid and a CT angiography was performed revealing minimal blood spread in the arterial phase in the para-costal area in correspondence with the IX left intercostal space without clear evidence of the branch of origin, thus suggesting bleeding secondary to the recent vertebroplasty of D9. The patient immediately underwent embolization of the left intercostal arteries (V to IX) with the sandwich technique, achieving the reso-

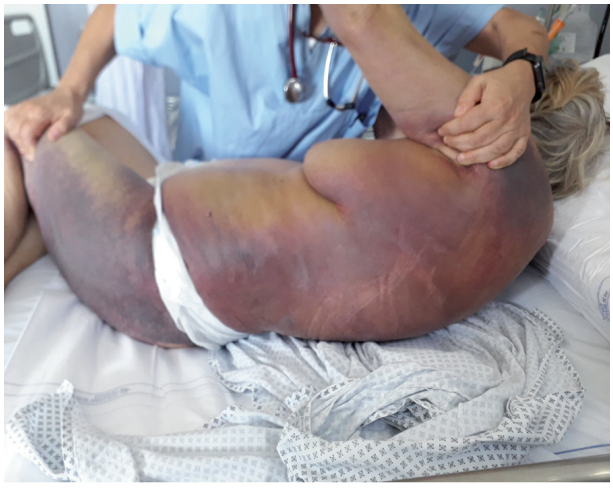

Figure 1. Huge purplish hematoma extending from the neck to the hips, also involving the left arm and the left leg.

lution of the bleeding. Despite an initial rise in hemoglobin levels and a decrease of the monoclonal component (0.44 g/dL), the ventilatory dynamics of the patient were too compromised due to the organized hematoma and the bronchopneumonia pattern in the remaining non-atelectatic lung parenchyma. Our patient died of respiratory arrest five days after embolization.

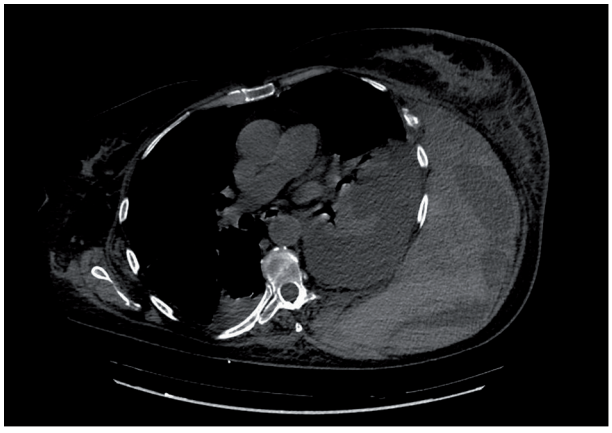

Figure 2. Computed tomography scan: expanding hematoma in the left hemithorax with signs of recent bleeding as well as a bronchopneumonia finding in the upper right lobe associated with pleural effusion.

DISCUSSION AND CONCLUSIONS

Acquired FXIII deficiency is rare and can be classified as non-immune or immune-mediated. The former is caused by FXIII hyper-consumption (such in case of surgery, inflammatory bowel disease or sepsis) or hypo-synthesis (such in case of liver disease or leukemia) and it is typically asymptomatic. Instead, immune-mediated FXIII deficiency is due to the development of anti-FXIII autoantibodies which may develop with concomitant conditions that cause immune dysregulation (such as autoimmune disease, malignancy or Monoclonal Gammopathy of Undetermined Significance (MGUS). Immune-mediated FXIII deficiency often presents with spontaneous or delayed post-operative bleeding, especially in subcutaneous and intramuscular compartments.[1,4,5]

Both congenital and acquired conditions have normal screening coagulation laboratory tests (PT, aPTT and fibrinogen) and no evidence of platelet deficiency/dysfunction.[1,3] Clot solubility assays were traditionally used as the initial screening test, however, they can only detect severe FXIII deficiency. In fact, the International Society on Thrombosis and Haemostasis Scientific and Standardization Committee (ISTH-SSC) recommends a quantitative functional FXIII activity assay as the first-line screening test. As regards autoimmune-mediated acquired deficiency, ISTH-SSC also recommends the detection of neu-

Table 1. Laboratory data.

	T0	T1	T2
Hb (g/dl)	6.5	8	8.3
PLT (1x10^3/µL)	130	152	161
WBC (1x10^3/µL)	7.9	10.4	11.2
PT (%)	96	94	91
INR	1.02	1.03	1.07
PTT (sec$_s$)	29	33	32
PTT Ratio	1	1.13	1.1
Fibrinogen (mg/dl)	325	290	330
vWF:Ag (%)	124	109	136
vWF:RiCof (%)	130	116	124
Factor XIII (%)	3	11	26
FXIII-inhibitor (Bethesda Units)	40		15
ADP-induced platelet aggregation (10 nmol/L) (%)	86		
ADP-induced platelet aggregation (2 nmol /L) (%)	78		
Arachidonate-induced platelet aggregation (1.6 µmol /L) (%)	80		
Collagene-induced platelet aggregation (0.2 mg/ml) (%)	84		
Ristocetin-induced platelet aggregation (1.2 g/L) (%)	78		
Ristocetin-induced platelet aggregation (0.6 g/L) (%)	7		

T0, baseline; T1, five days after beginning of therapy; T2, nine days after beginning of therapy* (day before exitus); Hb, hemoglobin; PLT, platelets; WBC, white blood cells; PT, prothrombin time; INR, international normalized ratio; vWF (Ag: antigen, RiCof: ristocetin cofactor activity); ADP: adenosine diphosphate. *Bortezomib, PEGylated doxorubicin and dexamethasone (PAD regimen). Fresh frozen plasma (FFP) was used daily at the dosage of 15 mL/kg body weight (80 kg) between T0 and T2.*

tralizing antibodies through mixing studies and Bethesda assay and non-neutralizing antibodies through binding assays.[1,6] In 2015 the ISTH-SSC proposed a diagnostic criterion for immune-mediated acquired FXIII deficiency.[5]

The management of immune-mediated FXIII deficiency is dual: hemostatic therapy and autoantibody removal. Since the rarity of this disorder, no guidelines are available. Anti-fibrinolytic administration and FXIII replacement with FXIII concentrates, cryoprecipitate and FFP are used to treat active bleeding. Autoantibody removal can be achieved by immunosuppressive therapies, such as corticosteroids, cyclophosphamide or rituximab, or through plasma exchange. In addition, therapy directed at the underlying etiology is suggested.[1,7]

PBL shares a reported median survival of 10 months and current treatment includes a combination of anti-myeloma agents and chemotherapy.[8]

To date the association between FXIII deficiency and PBL has never been reported in the literature, however, the association between FXIII deficiency and other plasma-cell dyscrasias, such as MGUS and Amyloid Light-chain (AL) amyloidosis, has been described.[9]

Our patient was transferred to our Hematology Unit when the PBL was in a very advanced stage as the diagnosis was made five months after the onset of symptoms. This could be the reason for the poor outcome and, probably, the cause that had triggered the FXIII inhibitor. In fact, a prolonged delay before the diagnosis is associated with a significant negative impact on the clinical course of multiple myeloma, especially in terms of an increased number of complications, Durie-Salmon stage III and reduced disease-free survival.[10] In our case, a common serum protein electrophoresis might have anticipated the diagnosis and, thus, the specific treatment, avoiding further complications or even the exitus. For this reason, we suggest that a blood test comprehensive of full blood cell count, creatinine, calcium and serum and urine protein electrophoresis should be performed in case of bone pain resistant to usual pain medications to rule out a plasma cell disorder, which should be taken in consideration by the physician in every patient with persistent bone pain.

As described, our case was complicated by acquired FXIII deficiency which resulted to be lethal for the patient. Indeed, the first bleeding was considered to be related exclusively to an invasive procedure (catheter insertion) and not a possible underlying bleeding diathesis, despite an uncommon bleeding pattern, especially with normal baseline coagulation tests, as observed in the reported case. Extensive coagulation tests were not investigated, and two other invasive procedures were performed, a bone marrow biopsy and vertebroplasty, the latter responsible for the patient's fatal hematoma. Thus, we suggest that FXIII deficiency should be considered, together with platelet dysfunction syndromes and von Willebrand disease (type 1 and 2), in patients presenting with unexplained bleeding symptoms with normal coagulation profile and platelet count. Even more, rapid recognition of the factor XIII deficiency as the main cause of an important hemorrhagic tendency could allow at least one attempt at correction perhaps by trying to reach circulating levels considered to be at lower bleeding risk for invasive procedures/surgery.[3]

In conclusion, we report here for the first time an association between PBL and acquired FXIII deficiency. Both conditions are rare and require aggressive and prompt management given the life-threatening risk. However, delayed diagnosis is common and can negatively impact the clinical course. Our aim is to increase awareness of both diseases and to highlight the importance of extending coagulation work-up including FXIII deficiency investigation when an unexpected bleeding diathesis is present, avoiding in the meantime every invasive procedure.

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