



# Acquired Factor XIII Deficiency in a Patient with Metastatic Lung Cancer

Ana Sofia Mendes\*, Marco Dias, Sara Morais, Raquel Romão, Bernardo Teixeira, Cláudia Pedrosa, Isa Peixoto, Paula Fidalgo and António Araújo

Department of Medical Oncology, Porto University Hospital Center, Portugal

## Abstract

**Introduction:** Acquired Factor XIII (FXIII) deficiency can result in life-long bleeding tendency and can be caused by enhanced consumption, impaired synthesis, or as an immune-mediated process. The latter can be related with solid neoplasms, through neutralizing or non-neutralizing antibodies. The relationship between FXIII activity and Non-Small Cell Lung Cancer (NSCLC) is not well established. This case report is about a patient with NSCLC and acquired FXIII deficiency.

**Materials and Methods:** Clinical records were obtained through the electronic process analysis, and the confidentiality of the patient was always assured.

**Results and Discussion:** A 70-year-old male with no relevant past medical history and a recently diagnosed metastatic NSCLC was admitted for priapism. Five days later, he developed a bleeding disorder, with slightly elevated coagulation times and normal fibrinogen levels and platelets count. FXIII level was found to be decreased (0.24 IU/mL) and FXIII plasma mixing studies did not confirm the presence of a neutralizing inhibitor. The FXIII level correction with standard plasma mixing studies was in favor of a non-neutralizing antibody. Despite treatment, hemorrhage control was not achieved and the patient died.

**Conclusion:** This clinical report describes a rare case of a patient with metastatic NSCLC presenting a severe hemorrhagic event caused by FXIII deficiency immune-mediated by non-neutralizing antibodies and subsequent increased clearance.

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### \*Correspondence:

Ana Sofia Mendes, Department of Medical Oncology, Porto University Hospital Center, Largo Professor Abel Salazar, 4099-001 Porto, Portugal, Tel: +351-222-077-500;

E-mail: [u12649@chporto.min-saude.pt](mailto:u12649@chporto.min-saude.pt)

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## Introduction

Factor XIII (FXIII) is a pro-coagulant plasma protein, essential in the primary stabilization of the clot by cross-linking fibrin strands [1]. Its deficiency, resulting from inherited or acquired causes, can result in life-long bleeding tendency [2]. Acquired FXIII deficiency can occur secondary to either enhanced consumption, impaired synthesis, or as an immune-mediated process [3]. It usually occurs in elderly patients, with a median age of 70 years, and may be related to comorbidities such as solid neoplasms [4,5]. When this disorder is related to solid neoplasms, the underlying etiology is usually immune-mediated either through inhibitory antibodies (neutralizing) or accelerated clearance (non-neutralizing antibodies) [6].

The relationship between FXIII and Non-Small Cell Lung Cancer (NSCLC) is controversial, with some authors describing an increased activity of FXIII in such cases [7,8].

This is a case report of a male patient with metastatic NSCLC and FXIII deficiency, which is a challenging diagnosis that requires a high index of clinical suspicion in the presence of normal routine coagulation tests (APTT, PT and fibrinogen).

## Materials and Methods

Case report of a man with metastatic NSCLC and a hemorrhagic pattern due to FXIII deficiency. Clinical records were obtained through the electronic process analysis, and the confidentiality of the patient was always assured.

## Results and Discussion

We describe a case of a 70-year-old male with a good performance status and a past medical history of arterial hypertension, post-traumatic stress disorder and prior smoking history. He had no personal or family history of hemorrhagic or hematologic disorders.

The patient was previously evaluated at another institution due to pain in the right buttock, radiating along the ipsilateral lower limb. Computed Tomography (CT) scan revealed a lytic lesion on the right ischiopubic ramus associated with a pathological bone fracture. A biopsy of the lesion was performed and histopathological and immunohistochemistry analysis identified a non-small cell carcinoma, adenosquamous type. Chest CT confirmed the presence of a subpleural pulmonary nodule in the upper segment of the right lower lobe, suspicious of primary lung cancer, as well as mediastinal enlarged lymph nodes.

Three months later he was admitted at our institution due to a one week-long cryptogenic ischemic priapism, causing an acute urinary retention, with fever and increased inflammatory parameters. He was referred for an observation by Urology, who performed a corporal aspiration and irrigation, with complete detumescence. A broad-spectrum antibiotic was initiated.

The pelvic CT performed at admission showed the presence of multiple large lymph nodes (right iliac and obturator), the known lytic lesion with soft tissue involvement infiltrating the ipsilateral obturator muscle and a pelvic collection with a necrotic centre suggestive of superinfection.

After 5 days of hospitalization, the patient developed an extensive left lumbar hematoma, associated with significant hemoglobin decrease (3 g/dL) and hemodynamic instability. The study revealed a slightly elevated activated Partial Thromboplastin Time (aPTT) (32.3 s) and prothrombin time (16.8 s), without alterations in fibrinogen levels (2.25 g/L) or platelets count (215000/ $\mu$ L). After 48 h, mucocutaneous bleeding increased and a newly performed CT scan revealed *de novo* multiple intra-pelvic and right thigh hematomas. At this time, coagulation and platelet study was repeated and no significant alterations were observed. Due to the bleeding progression in a patient with a NSCLC and minimal changes on routine screening coagulation tests, the suspicion of FXIII deficiency was raised. A FXIII level was found to be decreased (0.24 IU/mL) and FXIII plasma mixing studies did not confirm the presence of a neutralizing inhibitor [9,10]. The patient immediately started FXIII supplementation with fresh frozen plasma and intravenous prednisolone 1 mg/kg/day, but died within 24 h. Given the patient's recent cancer diagnosis and this bleeding condition, therapy directed to the oncological disease was never initiated.

An unrecognized coagulation disorder can have serious consequences. The differential diagnoses of a bleeding disorder with normal coagulation testing are limited but challenging. FXIII deficiency, as shown in our case report, is one of those diagnoses.

Causes of FXIII deficiency, other than congenital, can be either immune (through inhibitory antibodies - neutralizing, or accelerated clearance - non-neutralizing antibodies) or non-immune mediated (reduced synthesis or increased consumption) [3]. In the present case, congenital FXIII coagulation deficiency was ruled out based on patient's age and absence of personal or familiar history of bleeding tendency.

When FXIII levels are lower than 10%, the cause is usually immune-mediated, and patients present with significant bleeding symptoms. At superior levels, the bleeding tends to be milder and the cause non-immune mediated. If the etiology of the disorder is a solid neoplasm, the most likely pathophysiology will be immune-mediated [6]. The treatment of the immune-mediated cause involves

high-dose corticosteroids and/or cyclophosphamide [11] and the treatment of the bleeding event involves replacement of FXIII through concentrate, cryoprecipitate, or fresh frozen plasma [12]. The FXIII level correction with standard plasma mixing studies was in favor of a non-neutralizing antibody.

Coagulation abnormalities are common in patients with metastatic oncological disease [13]. The relationship between FXIII and NSCLC is controversial, with some authors describing an increased activity of FXIII in patients with this neoplasm [7,8]. Given the initial picture of priapism in a patient with NSCLC, there was a suspicion of Disseminated Intravascular Coagulation (DIC). Nevertheless, the APTT and PT were only slightly elevated, and the fibrinogen and platelet counts were normal and stable over time, which argues against DIC.

To the best of our knowledge, this is the first reported case of acquired FXIII deficiency in a patient with metastatic NSCLC.

## Conclusion

Many patients with metastatic solid neoplasms have coagulation study abnormalities. Acquired FXIII deficiency is a rare condition and in cancer patients it is usually immune-mediated. This report represents a rare case of a patient with metastatic NSCLC and a severe hemorrhagic event caused by FXIII deficiency immune-mediated by non-neutralizing antibodies and subsequent increased clearance.

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