Paraneoplastic factor XIII deficiency in a pregnant female with colon cancer: a case report

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ABSTRACT

Background: Factor XIII deficiency, which can be congenital or acquired, is a rare disorder. It can cause life-threatening bleeding. It cannot be diagnosed by usual hemostasis tests; only by specific screening tests.

Case Presentation: We report the case of a young pregnant woman whom we discovered a paraneoplastic factor XIII deficiency with the underlying cause of colorectal cancer.

Conclusion: A paraneoplastic context concerning hematologic malignancies as well as solid tumors must not be ignored. No other case of paraneoplastic factor XIII deficiency resulting from colorectal cancer is previously reported in the literature.

Keywords: Factor XIII, pregnancy, paraneoplastic syndrome, colorectal cancer, case report.

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Background

Factor XIII, also known as the fibrin stabilizing factor, is a transglutaminase that circulates in the blood as a tetramer. This tetramer comprises two alpha subunits and two beta subunits. The alpha subunit is produced by the bone marrow, however, the beta subunit is produced by the liver.

Patients can develop antibodies against the alpha or beta subunit in autoimmune diseases, cancers, or after consumption of certain drugs [1].

Factor XIII deficiency is seen mostly in rheumatoid arthritis, certain liver diseases, systemic lupus erythematosus, and lymphoproliferative disorders [2].

Only limited data on acquired factor XIII deficiency and disseminated intravascular coagulation in cancer patients are available so far [3].

Case Presentation

A 33-year-old female, 18 weeks pregnant was admitted to the emergency room with a complaint of severe epistaxis for which she needed the transfusion of three units of red blood cells.

During a hemostasis check-up, an isolated factor XIII deficiency was diagnosed, with a factor XIII activity of 50%, which cannot explain the epistaxis. Prothrombin time, international normalized ratio, as well as the activated partial thromboplastin time were normal.

The medical history of the patient accounts for surgery for stenosis of the aorta, two left knee surgeries, and one childbirth by vaginal delivery. None were accompanied by hemorrhagic complications. No previous history of bleeding is known.

The epistaxis was controlled by a surgical intervention which included ligation of ethmoidal and sphenopalatine arteries under general Anesthesia.

Shortly after the epistaxis problem, the patient developed pain in the lower left limb. Venous ultrasound of the lower left limb revealed a deep vein thrombosis of the saphenous vein. Curative anticoagulation was not an option due to the recent discovery of a hemostasis anomaly. The saphenous vein was ligated surgically.

The patient checked back into the emergency room 7 days later due to abdominal pain mainly in the right hypochondrium and constipation.

At this moment, another hemostasis check-up was done and showed further reduced factor XIII activity (36%).

An ultrasound of the abdomen is performed and showed two hyperechoic lesions of the right hepatic lobe and one hyperechoic lesion of the left hepatic lobe.

A Magnetic resonance imaging of the liver confirmed the presence of multiple suspect lesions in both lobes. A positron emission tomography - computed tomography (PET-CT) with significant dose reduction due to pregnancy shows infiltration of the left and right hepatic lobes by multiple secondary lesions (Figure 1). Furthermore, it shows para-aortic adenopathy in regard to L2 and a probable primary lesion in the left colon (Figure 1).

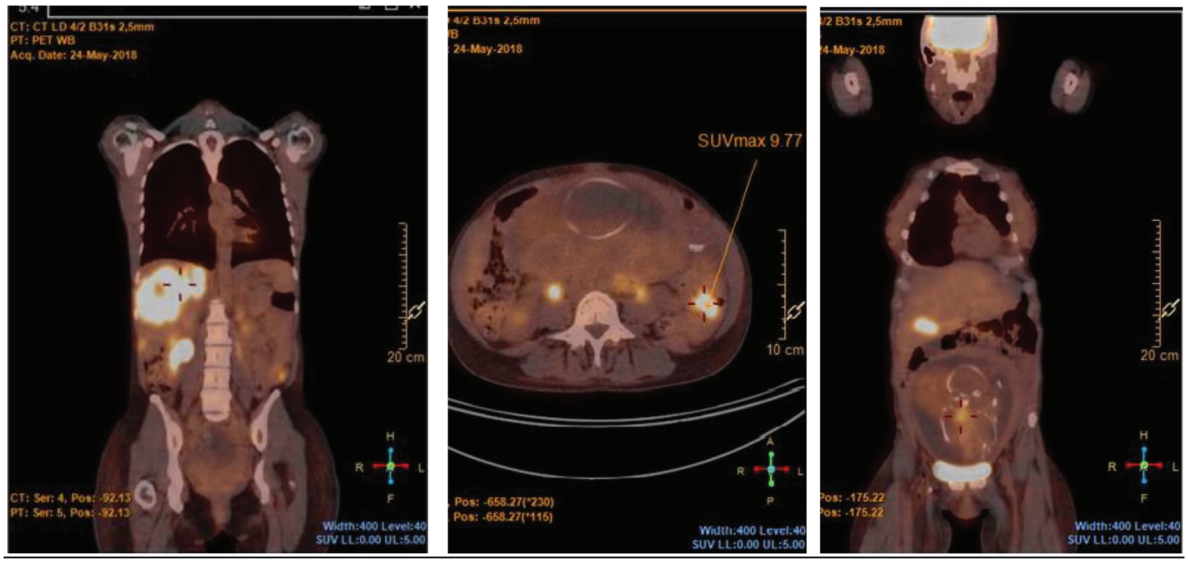

Figure 1. *PET-CT WITH 18-FDG: injection of 2.7 mCi of 18F-FDG (dose reduction in order to reduce fetal irradiation). Results: Right and left hepatic lobes are infiltrated by multiple tumour-like lesions which are intensely hypermetabolic, probably secondary lesions. Lesion on the left colon which might correspond to the primitive tumour. Left para-aortic adenopathy in regard of L2. Technique: The FDG PET-CT was performed with adequate hydration and a lower radiation dose. The total estimated dose of maximum 7.4 mGy was administered to the fetus. Regardless of the uncertainties the dose is still well below the threshold for deterministic risks from radiation. Nevertheless cancer induction is believed to be a probabilistic risk (there is no threshold for adverse events) but the risk increases with increasing the dose. For example, the background risk of leukaemia is estimated to be 1/3,000, and this risk is thought to increase by a factor of 1.5-2.0 per 10-20 mgy fetal exposure [12].*

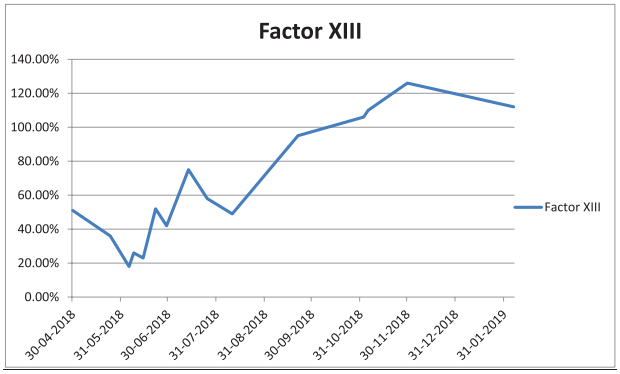

Figure 2. *Evolution of Factor XIII during anti-cancer therapy. After chemotherapy administration, factor XIII is increasing to normal levels.*

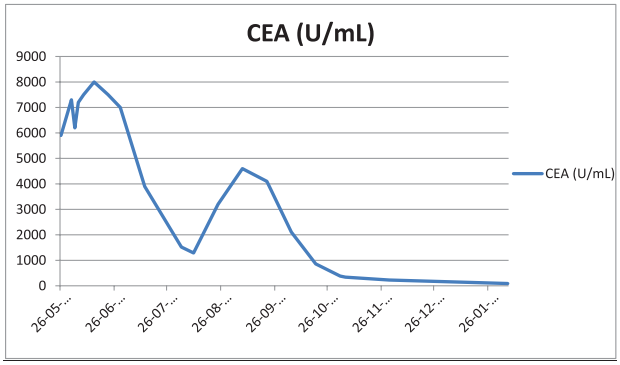

Figure 3. *Evolution of the tumour marker "carcinoembryonic antigen" during anti-cancer therapy. The CEA is decreasing after every chemotherapy administration.*

After this discovery, a colonoscopy is performed and showed a suspect colic lesion at 35 cm from the anal margin. Multiple biopsies confirmed the presence of a moderately differentiated colorectal adenocarcinoma with a Kirsten rat sarcoma viral oncogene homolog gene mutation. Neuroblastoma RAS viral oncogene homolog and B-Raf proto-oncogène genes are not mutated. The tumor is microsatellite stable.

No further hemorrhagic complications occurred during the biopsies, however, two transfusions of fresh frozen plasma were administered before the procedure.

Tumor markers were very high with a carcinoembryonic antigen at 5,900 U/ml and a Ca19.9 at 80.800 U/ml.

The decision to start a chemotherapy treatment despite the pregnancy was made and a first Folinic acid-fluorouracil-oxaliplatin (FOLFOX) cycle was administered.

The Factor XIII was found to be progressively increasing during the chemotherapy treatment. (Figure 2)

In parallel, tumor markers are decreasing (Figures 3 and 4) with significant regression of the hepatic metastases.

A cesarean section was planned for the 32nd week of the pregnancy with factor XIII activity of 58%. Fresh frozen plasma and blood transfusions were available for an emergency but were not needed. Cesarean section was performed without complications for mother and child.

A total of six FOLFOX (Folinic acid-fluorouracil-oxaliplatin) cycles of normal regimen and with 14-days gaps partially during pregnancy, 4 Folinic acid-fluorouracil-irinotecan-oxaliplatin (FOLFIRINOX) cycles, and 2 FOLFIRINOX + Bevacizumab cycles were administered in total. As bevacizumab and irinotecan are contraindicated during pregnancy, they were added to the regimen

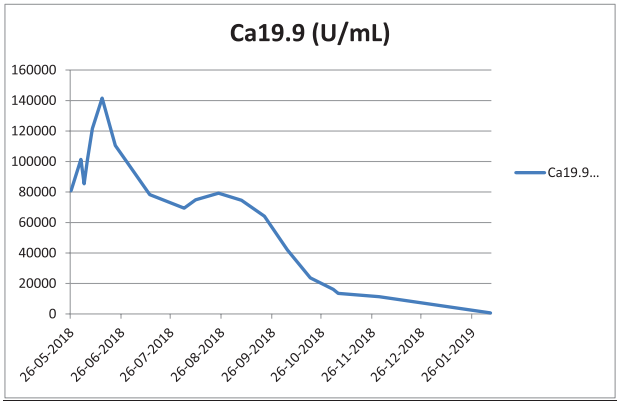

Figure 4. *Evolution of the tumour marker "Cancer antigen 19.9" during anti-cancer treatment. The Ca19.9 is decreasing after chemotherapy administration.*

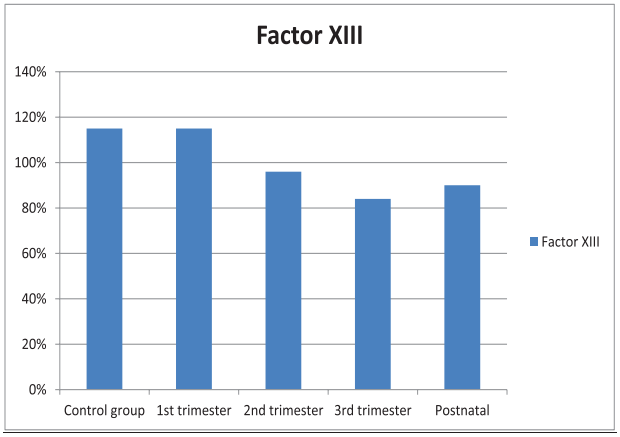

Figure 5. *"Mean factor XIII activity among control, First, Second and Third trimester of pregnancy, and postnatal period [10]."*

after delivery. A significant decrement in the size of hepatic metastatic lesions was observed. Surgical removal is indicated and performed.

Furthermore, a right extended hepatectomy of the segments IV and VIII, a partial hepatectomy of segment II and segment IVb are done without bleeding complications.

Hemicolectomy and lymph node surgery weren't performed as there was a complete remission observed on multiple imaging techniques.

Discussion

Factor XIII deficiency diagnosis is difficult given the rarity of this disorder and the necessity of specific screening tests. Usual coagulation tests including prothrombin time, partial thromboplastin time, platelet count, thrombin time, and bleeding time, are normal. Factor XIII deficiency remains the most under-diagnosed coagulopathy. Regarding the screening tests, the quantification of the activated form of factor XIII is recommended first. The screening of the anti-factor XIII antibodies is necessary for the factor XIII deficiency classification [4].

Research on acquired factor XIII deficiency is mainly based on case reports [3]. Patients can develop antibodies against the alpha or beta subunit in case of autoimmune disorders, cancers, or after consumption of certain drugs. Concerning the neoplastic context, an acquired factor XIII deficiency has been discovered among children suffering from acute myeloid leukemia, acute lymphoid leukemia, and non-Hodgkin lymphoma as well as in solid tumors like neuroblastoma and rhabdomyosarcoma [1].

In the case of colorectal cancer, a study was screening activated factor XIII in sick patients and a control group. Despite the size limitation of the two cohorts, they concluded that the screening of factor XIII would have a potential of distinction between healthy patients and patients suffering from colorectal cancer that presented a decrease of factor XIII [5].

In the case of acute myeloid leukemia, factor XIII-A is a sensitive marker of blast cells in which the expression of factor XIII is increased compared to normal cells. It may be a marker of promyelocytic leukemia. Factor XIII-A might be considered as an immunophenotype associated with leukemia, interesting for the diagnosis and follow-up of the disease [6].

Leukemias, on the other hand, are also associated with plasma factor XIII consumption.

Concerning a child with acute lymphoblastic leukemia, the discovery of a factor XIII activity of 56% preceded the diagnosis of leukemia. Factor XIII activity was normalized when the child was in complete remission [7].

In a young female with a retrobulbar hematoma, a factor XIII activity of 7.6% was discovered, 3 weeks preceding the diagnosis of acute promyelocytic leukemia [8].

Concerning breast cancer, in a study of 11 patients, factor XIII was found to be significantly decreased in the cancerous tissue compared to the healthy breast tissue [9].

Factor XIII might play a part in m*etastasization*. In a study, cancer cells of pulmonary carcinoma and melanoma were injected into rats. The metastatic potential is significantly decreased in rats having a factor XIII deficit compared to the control group [10].

The treatment of factor XIII deficiency remains the treatment of the underlying cause.

In the case of bleeding or prevention of bleeding, administration of human factor XIII concentrate, if available, is recommended. If not available, fresh frozen plasma can be used [2].

Concerning the pregnancy, one study showed the progressive decrease of factor XIII during pregnancy with significantly lower plasma levels during the 3rd trimester compared to the control group (Figure 5) [11].

In our patient, factor XIII increased during pregnancy as the size of the liver metastases decreased.

Conclusion

Acquired factor XIII deficiencies are rare disorders and are likely to induce severe hemorrhagic complications. Diagnosis is difficult because a specific screening test is

necessary. A paraneoplastic context concerning hematologic malignancies as well as solid tumors must not be ignored.

The treatment of acquired factor XIII deficiency remains the treatment of the underlying cause. In the case of bleeding or prevention of bleeding, administration of human factor XIII concentrate, if available, is recommended, and/or fresh frozen plasma.

What is new?

Acquired factor XIII deficiency is a rare disorder and underdiagnosed. We never heard of a paraneoplastic in context before.

List of Abbreviations

BRAF	B-Raf proto-oncogène,
Ca 19.9	Cancer antigen 19-9
CEA	Carcinoembryonic antigen
DIC	Disseminated intravascular coagulation,
FDG PET/CT	Fluorodeoxyglucose (FDG)-positron emission tomography (PET) / computed tomography (CT)
INR	International normalized ratio
KRAS	Kirsten rat sarcoma viral oncogene homolog,
MSS	Microsatellite stable,
NRAS	Neuroblastoma RAS viral oncogene homolog,
PET-CT	Positron emission tomography - computed tomography

Funding

None.

Conflict of interests

The authors declare that there is no conflict of interest regarding the publication of this article.

Consent for publication

Consent of patient was received.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

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Summary of the case

1	**Patient (gender, age)**	Female, 33
2	**Final diagnosis**	Colorectal cancer
3	**Symptoms**	Epistaxis
4	**Medications**	Blood transfusion
5	**Clinical procedure**	ligated arteries
6	**Specialty**	oncology