CASE REPORT

STRANGE RELATIONSHIP BETWEEN CANCER AND HEMOPHILIA

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ABSTRACT

The relationship between cancer and hemostasis, even old, is not sufficiently studied. Intestinal metastases from a lung cancer are rare, mostly found in the advanced stages of the disease. We report the case of a 38 yo man, nonsmoker, with hemophilia A, who presented for cough and hemoptysis since one month. During the last 3 days, the patient had also pain in the hypogastrium. The CT scan diagnosed a left endobronchial tumor. The histopathological exam established the diagnosis of squamous cell lung carcinoma G3. Two months later, he presented again with acute peritonitis and intestinal obstruction. The emergency surgical intervention showed a distal ileum tumoral stenosis. The final diagnosis was: a poorly differentiated left bronchopulmonary adenocarcinoma with peritoneal and terminal ileum metastases, complicated with bowel obstruction and acute peritonitis, in a patient with hemophilia A.

Key words: endobronchial tumor, intestinal metastases, peritonitis.

RÉSUMÉ

Relation étrange entre cancer et hémophilie: rapport de cas

La relation entre le cancer et l'hémostase, même ancienne, n'est pas assez étudiée. Les métastases intestinales dues au cancer du poumon sont rares; elles sont diagnostiquées principalement dans les stades avancés de la maladie. Nous rapportons le cas d'un homme de 38 ans, non fumeur, atteint d'hémophilie A, qui s'est présenté pour toux et hémoptysie depuis un mois. Au cours des 3 derniers jours, le patient avait également des douleurs dans l'hypogastre. Le scanner a diagnostiqué une tumeur endo-bronchique gauche. L'examen histopathologique a établi le diagnostic de carcinome pulmonaire à cellules squameuses G3. Deux mois plus tard, il présentait encore une péritonite aiguë avec obstruction intestinale. L'intervention chirurgicale d'urgence a montré une sténose tumorale de l'iléon distal. Le diagnostic final était: un adénocarcinome bronchopulmonaire gauche peu différencié, aux

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métastases de l'iléon péritonéal et terminal, compliqué d' une obstruction intestinale et une péritonite aiguë chez un patient atteint d'hémophilie A.

**Mots-clés:** tumeur endo-bronchique, métastases intestinales, péritonite.

INTRODUCTION

Due to improvements in the quality of treatment, the life span of patients with hemophilia has increased. With ageing, patients with hemophilia may develop diseases not previously seen in these patients, such as malignant disease, that represent a new challenge for physicians.

CASE PRESENTATION

A 38 yo men, nonsmoker, with hemophilia A, presented to the Emergency Department (ED) for cough and hemoptysis since one month. During the last 3 days the patient had also abdominal pain in the hypogastrium. The physical exam revealed a pale patient, without fever, with symmetrical chest movements and vesicular breath sounds, without crackles, $SatO_2$ 94% while breathing ambient air, rhythmic heart sounds, blood pressure 100/60 mm Hg, abdominal pain in the hypogastrium, without signs of peritoneal irritation, normal liver and spleen, normal intestinal transit. Laboratory tests showed a mild normocytic normochromic anemia and inflammatory syndrome. Chest X-Ray performed in the ED revealed an opacity in the left lung, parahilar,

and right lung hyperinflation (**Figure 1**). Abdominal ultrasonography showed free intraperitoneal fluid, 25 mm, in the lower abdomen. The patient was admitted to the internal medicine clinic and a thoraco-abdominal CT scan was performed, that revealed a left endobronchial tumor, enlarged retroperitoneal and mesenteric lymph nodes (**Figures 2, 3**). Bronchial endoscopy with lavage showed subtotal obstruction of the left primitive bronchus, with congestive and infiltrative appearance. The histopathological exam established the diagnosis of squamous cell lung carcinoma G3. Upper and lower digestive endoscopy were performed, with normal results. The patient was referred to PET-CT scan, from occipital level up to the proximal 1/3 of the thighs, that showed a $T_4N_3M_x$ left pulmonary tumor and colonic tumor T_2-$T_3N_{2b}M_1$ (**Figures 4,5**). The patient was sent for oncological evaluation. Two months later, he presented again to our ED with acute peritonitis and intestinal obstruction (**Figure 6**) and he was admitted to the surgery clinic. The emergency surgical intervention showed a distal ileum tumoral stenosis. At this moment, we have considered the differential diagnosis between two synchronous tumors in a hemophilic patient and a primary lung tumor with intestinal metastases.
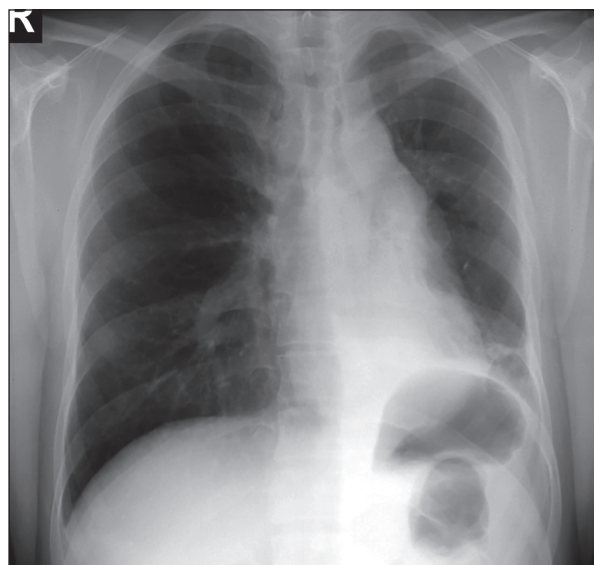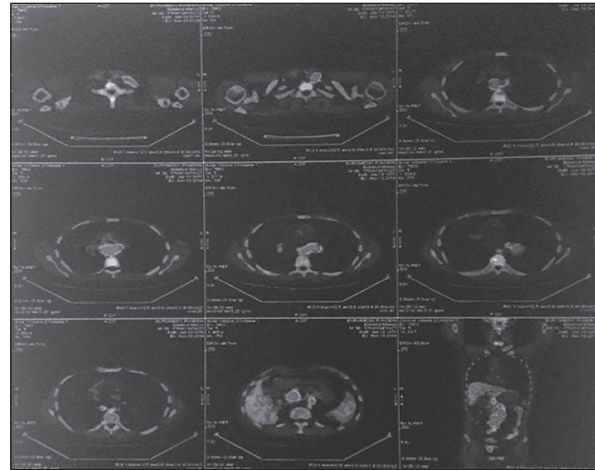

Figure 1. Thoracic X-Ray: opacity in the left lung, parahilar, right lung hyperinflation.
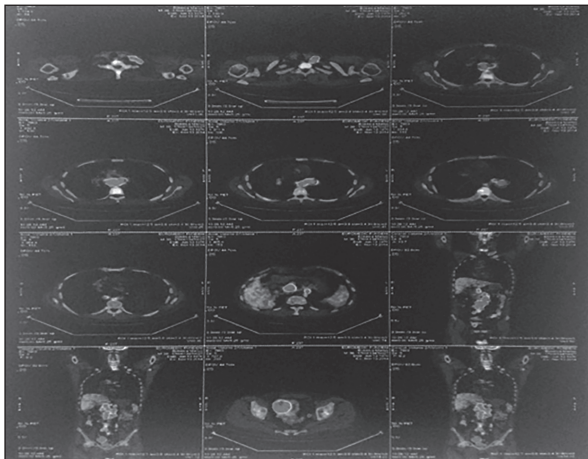

Figure 2. Thoracic CT scan. Left endobronchial tumor and enlarged mediastinal lymph nodes.
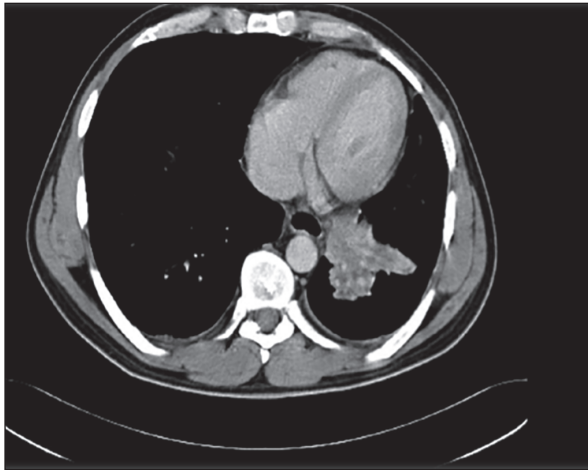
Figure 3. Thoracic CT scan. Left endobronchial tumor.

Figure 4. PET-CT. Left lung tumor and metabolically active metastasis. Stage $T_4N_3M_x$.

Figure 5. PET-CT. Colonic tumor (probably multicentric) with enlarged lymph nodes and peritoneal metastasis, metabolically active. Stage $T_3N_{2B}M_1$.

Figure 6. Abdominal X-Ray showing intestinal obstruction (air levels).

The histopathological exam of the small bowel fragment diagnosed a poorly differentiated carcinoma. Immunohistochemical exam demonstrated CK7 and TTF1 diffusely positive in tumor cells, CEA focally positive in tumor cells, Ck20 and CD X2 negative in tumor cells, positive internal control, P63 negative. Conclusion: the histopathological exam correlated with immunohistochemical tests sustain the diagnosis of an intestinal metastasis from a poorly differentiated adenocarcinoma with bronchopulmonary origin (**Figures 7-10**).

The final diagnosis was: a poorly differentiated left bronchopulmonary adenocarcinoma with peritoneal and terminal ileum metastases, complicated with bowel obstruction and acute peritonitis, in a patient with hemophilia A. The evolution was unfavorable, the patient died 6 weeks later.

DISCUSSION

The case that we presented is rare and has two major particularities:
– the first one is the diagnosis of bronchopulmonary adenocarcinoma in a relatively young hemophilic man, nonsmoker, without exposure to any other risk factors, who presented for cough and hemoptysis;
– the second one is the unusual presence of ileal metastasis from bronchopulmonary adenocarcinoma since the onset of respiratory symptoms. Initially, we took into consideration the diagnosis of two synchronous cancers.

The early diagnosis of ileal metastasis can be very difficult, as in the case presented, due to the unclear clinical symptoms. The initial abdominal CT scan was not able to identify the ileal tumor. PET-CT
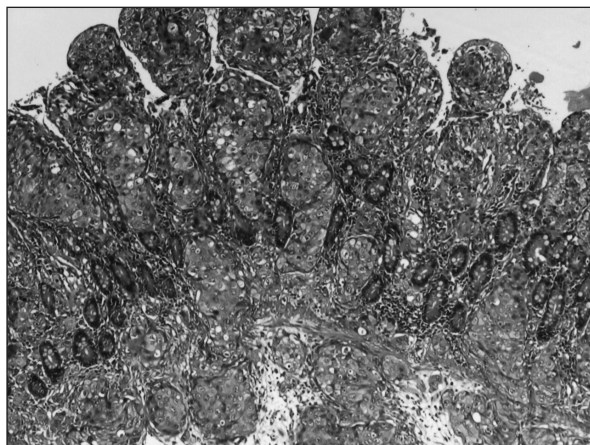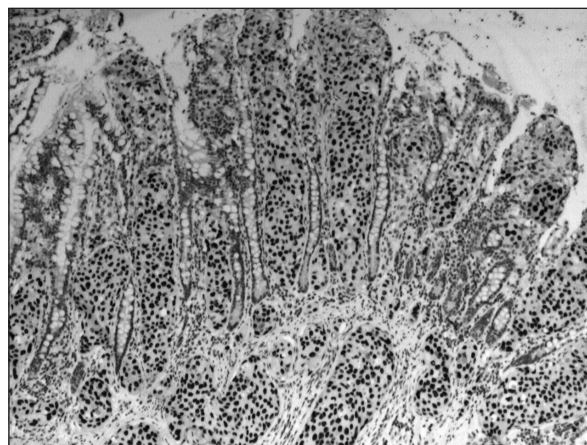
Figure 7. Histopathological exam. HE 100x.
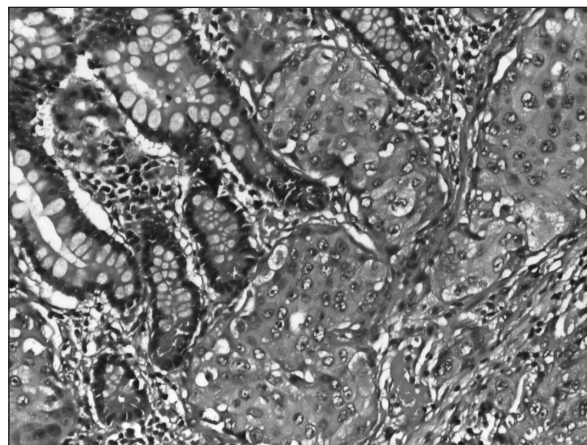
Figure 8. Histopathological exam. HE 200x. Tumoral cells infiltrating intestinal mucosa.

Figure 9. Immunohistochemical exam. CK7, 100x, tumoral cells are diffusely positive; epithelial cells of the intestinal mucosa are negative.

Figure 10. Immunohistochemical exam. TTF1, 100x, tumoral cells are diffusely positive, epithelial cells of the intestinal mucosa are negative.

may be more accurate than CT for the diagnosis of malignant metastasis. In our patient, PET-CT initially diagnosed a colonic tumor. The majority of lung cancer patients with intestinal metastasis present with acute abdomen, emergency surgical intervention being required.

Lung cancer is the leading cause of tumor death worldwide, with 50% of patients presenting metastases at the moment of diagnosis. Most common, lung cancer spreads extrathoracic to supraclavicular and abdominal lymph nodes, liver, adrenal glands, brain, bone and skin[1]. Metastases to gastrointestinal tract from a lung cancer are rare, mostly found in the advanced stages of the disease, their incidence ranging from 0.5% to 10%[2,3]. Metastases of a primary lung carcinoma to the small intestine may cause bleeding, intestinal perforation, malabsorption syndrome, but most often intestinal obstruction is the main consequence. Complications of intestinal metastases from

lung adenocarcinoma are associated with high mortality and a poor short-term prognosis, therefore they must be considered in patients with lung cancer and unexplained anemia and bowel symptoms. In our patient, anemia was not an useful indicator, due to the diagnosis of hemophilia, that could explain the presence of the anemic syndrome.

The relationship between cancer and hemostasis was reported for the first time in 1865, by Armand Trousseau. Endogenous thrombin was identified as a major contributor to tumor implantation, seeding and metastazing[4] by the most important experimental studies related to hemophilia A models, published by Langer et al[5] and Bruggemann et al[6]. Patients with hemophilia are naturally anticoagulated. Due to the great number of transfusions they receive, human immunodeficiency virus (HIV)-associated non-Hodgkin lymphomas and hepatitis C virus-associated hepatocelullar carcinomas are important causes of death

among the virus-infected ageing hemophiliacs[7,8]. A study conducted in Netherlands between 1992-2001 found that the death rate due to neoplasms was 1.5 times higher in hemophiliacs than in the general population[9]. An UK study published in 2007, on behalf of the United Kingdom Hemophilia Centre Doctors Organization, analyzed mortality rates and causes of death in 6018 hemophilic patients uninfected with HIV and concluded that while mortality from liver cancer and Hodgkin disease was increased as compared to general population, there was no evidence of increased mortality for other cancers[10]. Very interestingly, the authors reported a reduction of cancer-related mortality with increasing severity of hemophilia[10]. Moreover, in a review on epidemiological data related to cancer and hemophilia, non-HIV/ HCV-related cancers represented the cause of death in 8-16% of the patients with hemophilia, lower than the mortality rate in the matched general male population[11]. There is an attractive hypothesis in the literature, that hemophilia could confer a kind of protection against cancer, that is only a speculation for the moment. This hypothesis needs further investigation in clinical trials with large populations, followed for many years.

One important problem that physicians face when dealing with hemophilic patients is related to the treatment. Diagnostic and therapeutic procedures in hemophiliacs might be complicated by adverse hemorrhagic events. This concern is the reason why in clinical practice hemophiliacs receive suboptimal anticancer treatment. The literature is scarce in information about cancer treatment in hemophiliacs. The largest study on this subject was published in 2012, on 122 patients monitored in 21 Italian hemophilia centers[12] . In accordance with the previous findings of UK researchers[10], they found that non-virus related cancers were less frequent in patients with severe forms of hemophilia as compared to patients with milder forms of the disease. A very interesting finding was that hemorrhagic events were more frequent in patients receiving chemotherapy or radiotherapy than in those surgically treated, hemophilia experts recommending replacement therapy not only at the time of invasive procedures but also during chemotherapy or radiotherapy[13].

In conclusion, the presence of hemorrhagic events in hemophilic patients should be carefully investigated, especially if they associate other symptoms, in order to not miss a malignant disease. Although rare, intestinal metastasis may appear in the evolution of lung cancer and should be taken into consideration in patients with abdominal symptoms.

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