Case Report

Massive Pulmonary Embolism in Oncological Patient with Cetuximab Treatment: Hipercoagulability Status in Cancer Patients - A Case Report and a Review of Scientific Literature

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Abstract
Paraneoplastic hypercoagulable status is a cancer entity that affects one of every two hundred patients with cancer. We have reviewed scientific literature about this paraneoplastic syndrome. Also, there are described many cytostatic drugs that promotes thrombotic phenomena.

We presented an oncologic patient with massive pulmonary thromboembolism in the context of tumor hypercoagulable status and cetuximab treatment.

The presence of cancer cells in the systemic circulation generates and activates procoagulant and antifibrinolytic state, with production of pro-inflammatory cytokines (IL-1, TNF, VEGF) and interaction of cancer cells with other vascular cells (endothelial cells, platelets and monocytes).

The relative risk of thrombosis in cancer patients is between 2 and 6. The diagnosis must be established with clinical suspicion, imaging tests and predictive scales such as Wells, Geneva and Khorana in the case of venous thromboembolic disease. On the other hand, among Cetuximab toxicities, even it’s rare; it has been described pulmonary embolism.

In the treatment of thrombosis in cancer patients the use of LMWH is recommended in order to present less drug interactions with cytostatic and other drugs, and be easier to handle, than oral anticoagulants.

The duration of the anticoagulation treatment if there is any potential reversible cause (curable cancer) is at least 6 months (range between 6 and 9 months is acceptable); in case of advanced malignancies or patients receiving palliative chemotherapy, maintenance anticoagulation should be indefinite.

CASE PRESENTATION

We report the case of a woman of eighty-three years old with the following oncologic history:

In 2009 partial glossectomy and neck dissection were performed due to a tongue squamous cell carcinoma, receiving no additional treatment. Between March 2013 and January 2014 she presented two local recurrences, being necessary cervical right lymphadenectomy (negative for malignancy) and another partial glossectomy.

She presented new local recurrence in March 2016. The neck scan reported these findings: the presence of an excrescence irregular tumor from soil mouth adjacent to left mandibular branch with dimensions of 33 mm x 46 mm transverse diameter larger cranio-caudal diameter; in addition, there were metastatic lymphadenopathy in both yugulocarotides chains.

The clinical case was presented in the head and neck tumors committee, determining its unrepeatability. So, it was decided in committee radical treatment with Cetuximab and concomitant radiotherapy. She had completed twenty daily sessions of external radiation therapy and received five weekly intravenous infusions of Cetuximab.

The patient was brought in May 2016 to the emergency department for having two pre-syncope episodes at home, accompanied by dyspnea, without chest pain, and spontaneous recovery. At arrival in the emergency service, the physical
examination revealed bad general condition, tachypnea, apiretic, basal saturation of O2 97%, 80/50 blood pressure and heart rate 140 bpm.

Analytically, highlighted elevated D-dimer (of 7466), and proBNP cardiac enzymes. Venous blood gas analysis discovered pH 7.23, PCO₂ 47 mmHg, PO₂ 49mmHg, HCO₃ 8.2 mmol/L, lactic acid 19.7mmol/L. ECG described sinus tachycardia, SI QII QIII EKG pattern. Given the clinical-analytically situation, a thoracic computed tomography (CT) was requested.

The CT was reported with the presence of thrombus image between the two pulmonary arteries and wide extension lobar arteries, segmental and sub segmental both lungs. It was compatible with extensive pulmonary embolism (Figure 1).

Treatment was established with subcutaneous low molecular weight heparin (LMWH), specifically enoxaparin in therapeutic doses.

We transfer the patient to the Intensive Care Unit. Given the situation of the patient, fibrinolysis was performed improving hemodynamic parameters. In addition she required endovenous fluidtherapy and close hemodynamic monitoring. During that period, the patient presented self-limited episode of rectal bleeding without hemodynamic impact. The patient spent 24 hours in the Intensive Care Unit (ICU), with suitable evolution of laboratory findings leaving ICU to hospitalization area.

She was diagnosed of oral mucositis grade IV and poor pain control, managed with parenteral nutrition, intensive fluidtherapy, intravenous antifungal drugs and morphine endovenous infusion. The patient was discharged in June 2016, with appropriate clinical and analytical evolution.

After the situation described before, the clinical case was again presented in the head and neck tumors committee, deciding stopping chemoradiotherapy. Then, continued revisions at Medical Oncology department. Assessment of Palliative Care Unit of our hospital was requested, performing setting medication and symptom control.

In September 2016, the patient passed away after an episode of massive bleeding oral cavity.

### DISCUSSION

As we explained in the lines above, we have presented an oncologic patient with massive pulmonary thromboembolism in the context of tumor hypercoagulable status and Cetuximab treatment.

The association between thrombosis and cancer has been showed throughout decades in the scientific literature.

Trousseau was the first physician who described this connection. In the XIX century he described the association between migratory thrombophlebitis and cancer, known as Trousseau’s syndrome. The singularity of this is that he diagnosed himself a deep vein thrombosis of the left upper limb and was the first step to diagnose himself a neoplasia. He died of gastric cancer years later.

Virchow studied the predisposition for thrombus formation in cancer patients; it was based in the interaction of endothelial lesion [1], hypercoagulability, ecstasy and turbulence.

As reported in the scientific literature, paraneoplastic hypercoagulable status [2-6] affects one of every two hundred cancer patients [2], and implicate a worst prognosis and lower survival[7]. The relative risk of thrombosis in cancer patients is between 2 and 6; some authors explain that the treatment with chemotherapy increases the risk up to 6.5 times. In fact, chemotherapy is an independent risk factor for the development of ETV.

Cancer cells can produce and activate procoagulant and antifibrinolytic state [3]. It can be explained by pro-inflammatories cytokines (IL-1, TNF, and VEGF) and the interaction of cancer cells with other vascular cells (endothelial cells, platelets and monocytes). Another factors contributing to hypercoagulable status in cancer patients are alteration of protein metabolism, necrosis, acute phase reactions and changes in hemodynamic state. Many procoagulant factors are secreted by or are expressed at the cell surface of many tumours. Platelet turnover and activity are also involved [7-11].

In scientific literature, is reported that the risk of thrombosis related to cancer is higher with certain tumour types-gastrointestinal cancers, especially gastric and pancreatic disease, also with lung cancer and a few others (ginecological..) [12]. Risk is increased in the first 3 months after diagnosis and accumulates over time. Bleeding complications are also increased in cancer patients, both with treatment and with the use of thromboprophylaxis. The suspected diagnosis in the hypercoagulability syndrome must be based in analytical-clinical data [1-4], using the predictive scales such as Wells, Geneva and Khorana in the case of venous thromboembolic (VTE) disease; the clinical presentation of pro-thrombotic state in cancer range from asymptomatic, basic abnormal coagulation tests, to massive clinical thromboembolism. The confirmation is based on imaging studies [9,14] (Figure 2).

Relative the Khorana predictive model of thromosis in cancer patients [5,15], it is a predictive tool that allows the classification of patients who receive active chemotherapy in three risk groups (mild, moderate and high) according to five items: primary tumour, pre-chemotherapy platelet count> 35000 / mm3, Hb<10 g / dl, use of erythropoietic progenitors, pre-chemotherapeutic leukocyte counts> 11000 / mm3, 35 kg / m².
The patients were classified in three different risk groups: low risk (score=0): VTE incidence 0.3-0.8%; intermediate risk (score=1-2): VTE incidence 1.8-2.0%; and high risk (score >/= 3): VTE incidence 6.7-7.1%.

According to the Spanish Society of Medical Oncology (SEOM), clinical trials have been designed (PROTECHT and SAVE ONCO in different cancer populations and FRAGEM-UK and CONKO-004 in patients with pancreatic cancer) that demonstrate a significant decrease [8,16] in incidence of venous thromboembolic disease greater than 50% compared to placebo with no increase in bleeding rate and with no impact on overall survival. In these studies, it was reached a number of patients to be treated to avoid an event (NNT) of 46-60. And, this challenge of identify cancer patients who could be benefited with primary thromboprophilaxis, is higher in cancer outpatients who are receiving chemotherapy. It represents the relevance of developing more studies in this way.

That is why international guidelines (NCCN¹ [6], SEOM and ISTH) recommend primary thromboprophilaxis in all patients with high risk of venous thromboembolism and low risk of bleeding who are receiving chemotherapy.

In addition, the incidence of thrombosis varies widely depending on chemotherapy regimens used reaching the highest incidence with cisplatin-based, lenalidomide and thalidomide, and angiogenesis inhibitors treatments. Also, Cetuximab, widely used in head and neck tumors area, as seen in some international guides of clinical practice. Although the profile of Cetuximab is currently recruiting participants.

In the treatment of new thrombosis in cancer patients the use of LMWH dalteparin in a randomized trial [5] of 98 outpatients deemed at very high risk, with Khorana scores ≥ 3 [2]. Venous thromboembolic events occurred in 12% on the dalteparin arm and 21% in the control arm, showing a 9% absolute risk reduction and a 42% relative risk reduction with Major bleeding was similar in each arm, but clinically relevant bleeding was higher with dalteparin. In the 6-month study period, 27 of 336 patients in the dalteparin group had recurrent venous thromboembolic events, as compared with 53 of 336 patients on warfarin (hazard ratio [HR] = 0.48; P = .002). The probability of recurrent venous thromboembolism was 9% and 17%, respectively, with a risk reduction of 52%.

The duration of the anticoagulation treatment if there is any potential reversible cause (curable cancer) is at least 6 months (range between 6 and 9 months is acceptable); in case of advanced malignancies or patients receiving palliative chemotherapy, maintaining anticoagulation should be indefinite. Referred of this long-term anticoagulation, the RIETE Registry, compared 6 months of low–molecular-weight heparin, then either continued low–molecular-weight heparin or switched to warfarin at the treating physician’s discretion, without being founded statistically significant difference in recurrent venous thromboembolism between these groups (HR = 0.67, 95% CI = 0.44–1.02, P = .06) and no difference in major bleeding or total bleeding.

Data from the CATCH trial also found no statistically significant difference between tinzaparin (not available in the United States) and warfarin in the upfront treatment of venous thromboembolism in cancer patients.

Currently, the newer oral anticoagulants represent a therapeutic option in thrombotic patients. And in patient cancer? There are very limited data of their safety and efficacy. In a recent trials [EINSTEIN-DVT and EINSTEIN-PE] [17], rivaroxaban demonstrated similar efficacy to prevent recurrence of venous thromboembolism [8], decreasing the number major bleeding events compared with treatment with enoxaparin and a vitamin K antagonist. It is important to mark that there was no difference between groups for clinically relevant bleeding.

In our country, is pending opening a prospective clinical trial (CARAVAGGIO TRIAL) to evaluate the efficacy and safety of apixaban in the venous thromboembolism treatment.

In otherhand, it has been designed a study of rivaroxaban in the treatment of venousthromboembolism in cancerpatients, that is currently recruiting participants.

Finally, referred to the economic point of view, it must be highlight that while LMWL is an effective treatment, it offers only a small gain in quality-adjusted life-years (QALYs) compared to warfarin, and this advantage is associated with an important increase in cost.

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