Hemorrhage due to warfarin overdose
Hemotórax secundário a intoxicação varfarínica

Alberto Pereira Ferraz1, Fabio Freire José2

Received from Division of Internal Medicine. Escola Paulista de Medicina. Universidade Federal de São Paulo – EPM/UNIFESP – São Paulo, SP, Brasil.

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INTRODUCTION
Non-traumatic hemotorax is a well reported phenomenon that is relatively uncommon in clinical practice. The diagnostic
of hemothorax requires the evidence of a bloody pleural effusion in which the pleural fluid hematocrit is 50% or more of the peripheral blood hematocrit. Causes of non-traumatic hemothorax include malignancies, anticoagulant medications, vascular ruptures (aortic dissection, arteriovenous malformations), endometriosis, pulmonary infarctions, adhesions with pneumothorax, hematologic abnormalities such as hemophilia and tuberculosis.

**CASE REPORT**

A 58-year-old black woman, was admitted with a history of intermittent transvaginal bleeding of moderate intensity. She also complained of asthenia and dry cough for 1 month. In her past medical history, rheumatoid arthritis of 5 years duration and one episode of deep venous thrombosis in his left leg 1 year ago was reported. There was no major risk factors such as surgery, diagnosis of malignancy or immobilization related to the episode of deep venous thrombosis. Her medications were 20mg of prednisone, methotrexate 75 milligrams and 10 milligrams of warfarin. She is a heavy smoker and her family history was negative for cancer or thrombosis. Regarding to her international normalized ratio (INR) monitoring, there were no recent medication changes, diet changes or infections, but she did not attend medical visits to check levels of INR.

On physical examination the patient was drowsy but cooperative. Vital signs were as follows: The heart rate was 145bpm, the blood pressure 90x60mmHg, respiratory rate of 26 incursions per minute, pulse oximetry of 86% in room air and 93% while receiving oxygentherapy of 3 litres per minute. The pulmonary auscultation revealed no lung sounds in the lower third of the right hemithorax. The remainder of her physical examination was unrevealing.

On admission laboratory evaluation, the hemoglobin was 7,2 grams per deciliter, hematocrit was 21,7 percent; the mean cell volume (MCV) was 93,9 fentoliter, mean cell hemoglobin (MCH) 31,2 picogram, mean corpuscular hemoglobin concentration (MCHC) 32,2 gram per deciliter, red blood cell distribution width (RDW) 14,9 percent; the white-cell count was 21800 per cubic millimeter, with 82 percent neutrophils, 12,8 percent lymphocytes, 4,4 percent monocytes. The platelet count was 400.000 per cubic millimeter. The international normalized ratio was greater than 9.

After intravenous hydration with crystalloid solution, administration of vitamin K and transfusions of blood products (2 units of red blood cells and 20ml/kg of fresh plasma), the patient improved hemodynamic parameters and had complete resolution of transvaginal bleeding.

Chest x-ray showed opacity in all the right hemithorax. The tomographic study for the assessment of pulmonary infarct, a known risk factor for hemothorax in patients on oral anticoagulation, showed the presence of bilateral pleural effusion, extensive in right hemothorax, atelectasis of the lower and medium lobes in the right hemithorax and failure of filling of contrast in the left pulmonary artery with chronic characteristics (Figure 1). Signs of thrombosis with recanalization were found in left leg (Figure 2).

When the INR reached the range of 1.8, the thoracentesis was performed and demonstrated presence of hemothorax. The parameters of the fluid by thoracocentesis were: total cells of 820/mm³, 1 064 000 red blood cells/mm³. The differential count was: Neutrophils 63%, lymphocytes 10%, monocytes 0%, macrophages 22%, mesotheliocytes 5%. Glucose was 130 milligrams per deciliter, total proteins dosage’s of 3.7 grams per deciliter. Drainage of 2600 milliliters of hematic fluid was then performed. After recovery and hospital discharge, the patient underwent an elective pleural biopsy, which reveals pleural tissue without histological changes, subpleural alveolar parenchyma with signs of former hemorrhage and no signs of malignancy. At follow-up at 8 months patients is currently doing well.
DISCUSSION

For more than 50 years, oral anticoagulants has promoted effective primary and secondary prevention of arterial and venous thromboembolism. Deep vein thrombosis, pulmonary embolism, atrial fibrillation and prosthetic heart valves are the most common clinical indications for anticoagulation. Despite its unquestionable benefits, as well as most of the drugs in clinical practice, they are not free from side effects. The major complication of anticoagulant therapy is bleeding. The novel oral anticoagulants as dabigatran and rivaroxaban have lower risk of bleeding and easier clinical management. However, coumarins, the vitamin K antagonists (VKAs), especially warfarin, are still the drug widely use.

Studies vary in the definition and classification of bleeding complications, making it difficult to compare them. Fihn et al., had proposed the following three categories of bleeding: 1- minor (reported, but not requiring additional testing, referrals, or visits - include mild nosebleeds, bruising, mild hemorrhoidal bleeding, and microscopic hematuria); 2- major (requiring treatment, medical evaluation - include overt gastrointestinal bleeding, occult gastrointestinal bleeding if endoscopic studies were done, gross hematuria that prompted cystoscopy or intravenous urography and hemoptysis); 3- life threatening (leading to cardiac arrest, surgical/angiographic intervention, irreversible sequelae - such as myocardial infarction, neurologic deficit consequent to intracerebral hemorrhage-, massive hemothorax, loss of 3 or more units of blood, systolic blood pressure less than 90mmHg, critical anemia).

In 2005 The International Society on Thrombosis and Hemostasis issued a recommendation for definition of major bleeding in studies on antithrombotic products in nonsurgical studies, requiring at least one criterion of three: 1- Fatal bleeding, 2- Symptomatic bleeding in a critical area or organ (such as intracranial, intraspinal, intraocular, retropitoneal, intrarticular or pericardial) or intramuscular with compartment syndrome, 3- Bleeding causing a fall in hemoglobin level of 2g/dL or more, or leading to transfusion of two or more units of whole blood or red cells. In the case report presented here it was a major bleeding according to both definitions but also a life threatening according to Fihn. Due to the existence of different definitions, the reader should be aware of the definition used in clinical studies.

The major determinants of oral VKA-induced bleeding are the intensity of the anticoagulant effect, patient characteristics, the concomitant use of drugs that interfere with hemostasis, and the length of therapy. Although the intensity of the anticoagulant effect is one of the most important risk for bleeding, it also can happens in a patient with INR in the therapeutic range. It can be explained by other risk factor such as hypersensitivity to VKA due to a genetic mutation of anticoagulants factors. Among others patient’s characteristics age, renal insufficiency, heart failure, cancer, cerebrovascular disease are common factors that increase the risk of bleeding.

An assessment of bleeding risk should be part of the patient assessment before starting anticoagulation. Various bleeding risk scores have been validated to assist the attending physician in decision-making. The most simple and widely used bleeding risk score is the HAS-BLED, which has been validated for patients with atrial fibrillation. It takes into account the diagnosis of hypertension, of stroke, abnormal renal function, abnormal liver function, bleeding history or predisposition, labile INR, elderly >65, alcohol abuse or use of drugs. A score of ≥3 indicates high risk for bleeding, and some caution and regular review of the patient is needed following the initiation of antithrombotic therapy. Specifically for the cases of deep venous thrombosis and pulmonary emboli, we usually did not assess an individual patient’s risk of bleeding by clinical prediction rules because its considered that most recommendations would be unlikely to change based on differences in risk of bleeding, although risk factors for this event should be recognized in all patients for more careful follow up.

For all of these cases, none of the available clinical prediction rules exhibit sufficient predictive accuracy or they have trials evaluating the impact of their use on patient outcomes.

The patient reported had none of the risk factors previously listed, except the intensity of the anticoagulant effect, and had a HAS-BLED score of 0. She had therefore low risk of bleeding, but the inappropriate ambulatory control of INR should have been considered in the indication and maintenance of anticoagulation treatment.

Overall, hemothorax is very rare in the setting of anticoagulation (3% of all hemorrhagic complications due to warfarin therapy), and most cases occur within the first week of therapy. In the case described here, the patient presented a hemothorax one year after initiation of anticoagulation. In the literature review, many of the reported cases of hemothorax related to anticoagulation were associated with an underlying lung disease, although few other cases failure in finding such association. In our case, due to the hemothorax match the contralateral hemothorax of the cronic pulmonary embolus, predisposing cause investigation was conducted, but no pleural disease or parenchymal structural alteration that could predisposes the patient to bleeding were identified. Importantly, however, one should consider the sensitivity and accuracy of the biopsy. Although it has better results than blind biopsies, the imaged-guided biopsy cannot safely discard false negatives (sensitivity around 70-76% for malignancy by biopsy guided by ultrasound).

REFERENCES

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