CASE REPORT

UDC: 615.03::[616.151.5-08:615.065
DOI: 10.2298/VSP130924012S

Massive retroperitoneal hematoma as a complication of anticoagulation therapy in a patient treated in a pulmonary intensive care unit

Masivni retroperitoneumski hematom kao komplikacija antikoagulantne terapije kod bolesnika lečenog u pulmološkoj jedinici intenzivne nege

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Abstract

Introduction. Retroperitoneal hematoma may occur as a result of trauma, but also from rupture of arterial aneurysms (aortic or iliac), surgical complications, tumors or anticoagulation therapy. **Case report.** We presented a patient on permanent anticoagulation therapy. On the day of admission to our institution, the patient had the value of his INR 5.57 which required immediate suspension of the therapy. The main symptom in this patient was pain in the right inguinal canal with propagation along the right leg, which was indicated in clinical picture of spontaneous retroperitoneal haematoma. After three days the fall of hemoglobin occurred, so the additonal diagnostics was done. A computed tomography of the abdomen was performed showing well limited, large retroperitoneal hematoma (213 × 79 × 91 mm). Transfusion of concentrated red blood cells was performed twice with satisfactory correction of hemoglobin level, and four units of fresh frozen plasma. The patient was hemodynamically stabilized and discharged after a two-month long intensive care unit treatment, with the advice to use low-molecular weight heparin 2 × 0.4 mg subcutaneusly, due to persistent arrhythmia. **Conclusion.** In patients on anticoagulation therapy regular monitoring of the anticoagulant status is extremely important, because of the possibility of fatal complications development, such as retroperitoneal hematoma.

Key words:
anticoagulants; drug toxicity; hemorrhage; hematoma; retroperitoneal space; treatment outcome.

Apstrakt

Uvod. Retroperitoneumski hematom može nastati kao rezultat traume, rupture aneurizme arterije (aortne ili ilijačne), hirurške komplikacije, tumora ili antikoagulantne terapije. **Prikaz bolesnika.** Prikazali smo bolesnika na trajnoj antikoagulantnoj terapiji koji je na dan prijema u našu ustanovu imao vrednost INR 5,57. Odmah je obustavljena antikoagulantna terapija. Bolesnik je od tegoba navodio i bolove u desnom ingvinalnom kanalu koji su zračili duž desne noge, što se uklapalo u kliničku sliku spontanog retroperitonumsku hematoma. Posle tri dana došlo je do sniženja nivoa hemoglobina, tako da je primenjena dopunska dijagnostika. U nalazu dobijenom kompjuterizovanom tomografijom abdomena opisan je dobro ograničen retroperitoneumski hematom velikih dimenzija (213 × 79 × 91 mm). Primenjena je transfuzija koncentrovanih eritrocita koja je dovela do zadovoljavajuće korekcije nivoa hemoglobina. Bolesnik je dobio i četiri jedinice sveže smrznute plazme. Nakon što je hemodinamski stabilizovan, otpušten je iz jedinice intenzivne nege, posle dvomesečnog lečenja. Savetovano mu je da zbog perzistentne artimije koristi niskomolekulski heparin 2 × 0,4 mg potkožno. **Zaključak.** Kod bolesnika na antikoagulantnoj terapiji izuzetno je značajno redovno praćanje njihovog antikoagulantnog statusa, upravo zbog razvoja ponekad i fatalnih komplikacija, kao što je spontani retroperitonealni hematom.

Ključne reči:
antikoagulansi; lekovi, toksičnost; krvarenje; hematom; retroperitonealni prostor; lečenje, ishod.

Introduction

Retroperitoneal hematoma (or retroperitoneal bleeding) refers to accumulation of blood in the retroperitoneal space. It is most frequently seen after femoral artery catetherisation or pelvic and lumbar trauma [1]. Also, retroperitoneal hemorrhage can be the result of ruptured abdominal aortic aneurysm or some kidney or adrenal gland conditions. Spontane-

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ous retroperitoneal hemorrhage refers to bleeding without trauma or retroperitoneal pathology. Spontaneous retroperitoneal hematoms is rare but potentially life threatening condition and it is almost always seen in association with anticoagulation therapy, coagulopathies and in patients on hemodialysis [2].

The incidence of retroperitoneal hematoma has been reported to be 0.6–6.6% in patients on oral anticoagulant therapy [3].

Coumarins are vitamin K antagonists that produce their anticoagulant effect by interfering with the cyclic interconversion of vitamin K and its 2,3 epoxide (vitamin K oxide). Vitamin K antagonists inhibit carboxylation of the regulatory anticoagulant protein C and S and therefore have the potential to exert a procoagulant effect [4].

Drugs may influence the pharmacodynamics of warfarin by inhibiting synthesis or increasing clearance of vitamin K-dependent coagulation factors or by interfering with other pathways of hemostasis.

Drugs such as aspirin, nonsteroidal anti-inflammatory drugs, high doses of penicillins and moxolactam increase the risk of warfarin-associated bleeding by inhibiting platelet function. The mechanisms by which erythromycin and some anabolic steroids potentiate the anticoagulant effect of warfarin are unknown. Sulfonamides and several broad-spectrum antibiotic compounds may augment the anticoagulant effect of warfarin by eliminating bacterial flora and aggravating vitamin K deficiency in patients whose diet is deficient of vitamin K [4].

It would be reasonable to monitor the prothrombin time (PT) more frequently when any drug therapy is added or withdrawn from the regimen of a patient treated with an oral anticoagulant drug.

According to the literature when the value of international normalised ratio (INR), that is standardized measure of protrombin time, ≥ 5, the risk of bleeding increases 3.6 times compared to the referent range of 2.0–3.0 [5]. Patients on oral anticoagulant therapy with INR ≥ 6 are faced with the risk of major, life-threatening bleeding [6].

We presented a patient treated in the pulmonary intensive care unit, with a large retroperitoneal hematoma, as the result of complication of anticoagulant therapy.

Case report

A 73-year-old male patient was transferred to the Pulmonary Intensive Care Unit from the Coronary Care Unit, Clinical Center of Serbia, because of acute partial respiratory insufficiency. He complained of exertional fatigue lasting for the last year and ten days before admission he got tired in peace. During the last five days the patient also felt pain in the right inguinal canal emitting in the right leg. The day before admission at the Coronary Care Unit strong fever, chills and dyspnea appeared and on the day of admission, his general condition deteriorated and the patient became drowsy and was hospitalized in the Coronary Care Unit with suspected pulmonary embolism. Computed tomography (CT) scan of the thorax had not comfirmed the existence of pulmonary embolism or other pathological processes in the chest. At the Coronary Care Unit echocardiography of the heart was made: dilated aortic root was found (4.0 cm), normal size of the left ventricle, thick concentric walls, ejection fraction rate of 50%, enlarged left atrium (4.6 cm), enlarged right ventricle (3.3 cm) while without free wall motion abnormalities with tricuspid regurgitation 2–3 +; indirectly measured systolic pressure in the right ventricle was 46 mm.

In his personal history we found that the patient had myocardial infarction 15 years ago, triple coronary artery bypass grafting (ACBG) was made and in February 2007 redo triple ACBG was performed and also a biological valve was implanted because of aortic valve insufficiency. The patient also had diabetes for about five years, then permanent absolute arrhythmia and was treated from gout, and was on continuous oral anticoagulant therapy. In the Coronary Care Unit the patient was treated with warfarin sodium 3.75 mg and 5 mg alternately, isosorbid-5-mononitrate 2 × 20 mg, metformine 1,000 mg 2 × 1, enalapril 10 mg, furosemid 40 mg, spironolacton 50 mg and bisoprolol 5 mg.

On the day of admission the patient was conscious, oriented, somnolent, afebrile with cyanosis and dyspnea, and decompensated heart failure with pedal edema, without sings of hemorrhagic syndrome. Through auscultation of the lung we found bilateral lower breath sounds and arrhythmic heart rate, clear tones, systolic ejection murmur of intensity grade 2. Chest radiography showed enlarged cardiac silhouette and the voluminous hilum (Figure 1). Electrocardiogram described atrial fibrilation with absolute arrhytmia of ventricules, negative T-waves in V2-V6. Blood presure was 140/90 mmHg, while the heart frequency was 125/beats *per* minutes. Arterial blood gas reflected significant partial respiratory insufficiency (pH 7.40, pO_2 5.5 kPa, pCO_2 4.9 kPa, saturation 83%).

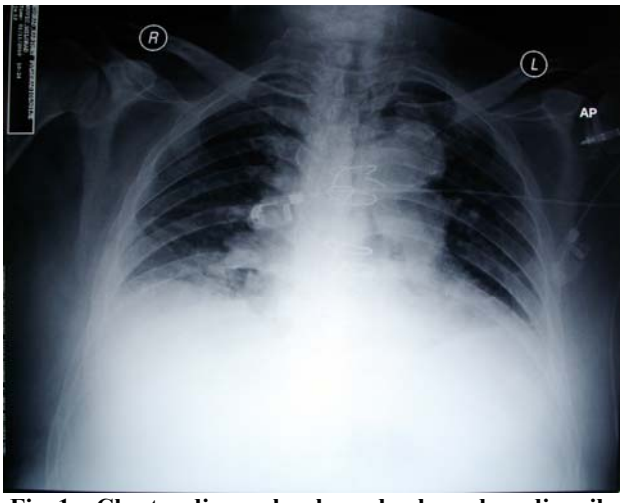

Fig. 1 – Chest radiography showed enlarged cardiac silhouette and the voluminous hilum.

Laboratory analyses were: leukocytes (Le) 14.5 × 10^9/L, sedimentation rate (SE) 84 mm/h, C-reactive protein (CRP) 120 mg/L, fibrinogen 7.0 g/L, urea 13.3 mmol/L (normal range 2.5–7.5 mmol/L), creatinine 169 umol/L (normal range 59–104), aspartate aminotransferase (AST)

108 U/L (normal range 0–37), alamine aminotransferase (ALT) 96 U/L (normal range 0–41), laetate dehydrogenase (LDH) 601 U/L (normal range 220–400), d-dimer 2.56 mg/L (normal range 0–0.55), INR 5.57. Other laboratory values were in the reference range. All the therapies prescribed by cardiologist were continued. Because of high INR values oral anticoagulant therapy was immediately discontinued and anticoagulant status of the patient was monitored every day.

Somnolence with hypoxemia despite oxygen therapy was a dominant sign of clinical features at the beginning of hospitalization, so non-invasive mechanical ventilation was applied which corrected arterial blood oxygenation. Three days later in blood analyses we registered the fall of hemoglobin level (123...94...82...68 g/L) and, at the same time, the occurrence of a large hematoma in the soft tissue of the lateral side of the right hemothorax. Ultrasound examination of the lateral chest soft tissues described hematoma in organization, with the dimension of 25 mm and the length of 35–40 mm. As there was no evident bleeding in the chest and the Adler-Weber test was negative, we decided to make the scan of abdomen. CT of the abdomen described: retroperitoneal hematoma localized between the liver ant the pelvis, size 213 × 79 × 91 mm, density 24–56 HU. The right *musculus iliopsoas* and right *musculus iliacus* were edematous with signs of intramuscular hematoma, hematoma in the soft tissues of the right abdominal wall. In the infrarenal part of the abdominal aorta the aortic wall had sclerotic aneurysm of the segment length 50 mm and wide 48 mm, with no signs of extravasation of blood (Figure 2).

Transfusion of concentrated red blood cells was performed twice with a satisfactory correction of hemoglobin level, and four units of fresh frozen plasma. After the consultation with the abdominal surgeon, he did not indicate surgical treatment. We also consulted the hematologist, who concluded that it was spontaneous hemorrhage as a complication of anticoagulant therapy in the application of standard dose of medication and for future treatment he sugested low-molecular weight heparin which should be suspended at INR higher than 3.

Two control scan examinations of the abdomen described a slightly lower retroperitoneal hematoma. A month later the dimesion of hematoma was 143 × 70 × 78 mm. Because of altered state of consciousness and the present long-term sleep disorders, a neurologist was consulted and he suggested endocranial CT scan which showed notable degenarative changes with no pathological density and polysomnographic testing.

After applying the therapy, the patient was hemodynamically stabilized, The INR value was within the referent range, with satisfactory gas exchange. The patient was discharged after two months of hospital treatment in the Intensive Care Unit, with the advice to use anticoagulant therapy (low molecular weight heparin, nodroparin calcium 2 × 0.4 mL *sc*) because of the persistence of arrhythmia and due to hematoma transition, oral anticoagulants were delayed because of difficult dosing. Frequent monitoring of INR values was adviced, to.

Discussion

Anticoagulant therapy such as warfarin, unfractionated heparin and low-molecular weight heparin are widely used in everyday practice in prevention and therapy of deep vein thrombosis, pulmonary embolism, acute ishemic stroke, valvular heart disease and atrial fibrilation. Bleeding is the most common complication, but literature recognises many other complications like subcapsular renal hematoma, retroperitoneal and intraperitoneal hemorrhage, hemothorax, spinal epidural hematoma, gastrointestinal and cutaneous hematoma [7, 8].

An individual patient's risk for major anticoagulant-related bleeding can be estimated on the basis of specific risk factors

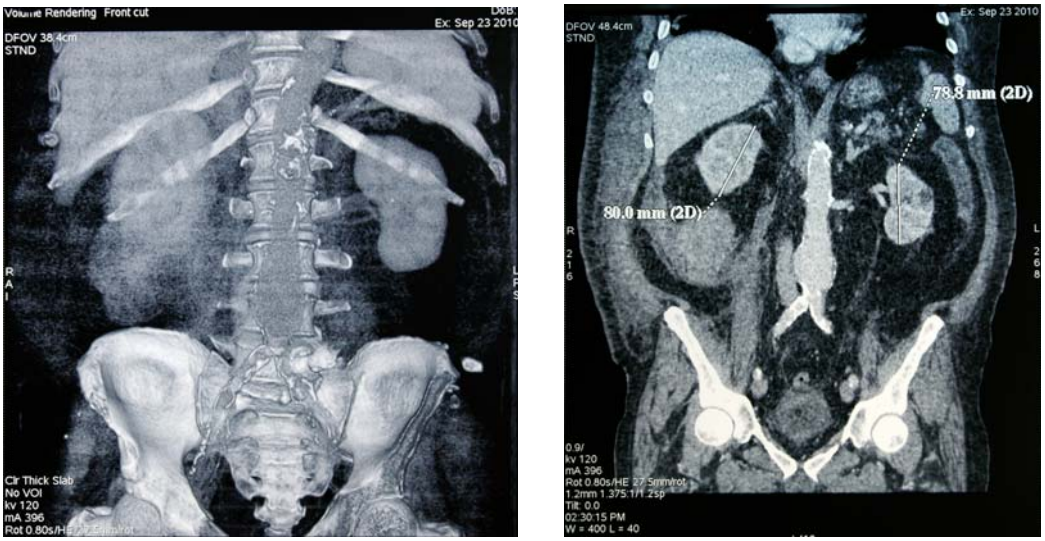

Fig. 2 – Computed tomography of the abdomen: retroperitoneal hematoma localized between the liver and the pelvis.

such as the intensity of the anticoagulant effect achieved and the presence of serious comorbid diseases, especially cerebrovascular, kidney, heart, and liver disease; older age and concurrent medicines may also be independent risk factors. The frequency of bleeding during warfarin therapy is reduced by less intense therapy achieving the prothrombin time with an INR of 2.0 to 3.0, which is efficacious for most indications [9].

A large study of Sasson et al. [10] showed that patients on anticoagulant therapy, even in therapeutical doses, should be monitored and checked regularly because of the possibility of complications of this therapy such as the development of spontaneous retroperitoneal hematoma. The most common symptoms are acute onset, persistent pain in the upper quadrant of the abdomen, in the groin or lumbal region with radiation to the scrotum. Pain and paresthesia are the result of pressure on the femoral nerve, the largest branch of the lumbal plexus.

We presented the patient who permanently used anticoagulant therapy. On the day of admission to our hospital he had the value of INR 5.57, so we immediately stopped this therapy. According to Naranjo et al. [11] adverse drug reaction probability scale, adverse event was definitely related to the drug.

The main symptom was the pain in the right ingvinal canal radiating down the right leg, which is comparable to the clinical features of spontaneous retroperitoneal hematoma.

The diagnosis of spontaneous retroperitoneal hematoma is a challenge even on high-resolution CT or nuclear magnetic resonance, because many benign and malignant lesions can mimic this condition. CT is superior to ultrasound in localization, extension and evaluation of the size of hematoma.

Good limited and large-scale retroperitoneal hematoma was described on CT in our patient [12].

Treatment of spontaneous retroperitoneal hematoma includes surgery and conservative treatment of anemia and correction of warfarin-associated coagulopathy [13]. Conservative treatrement depends on severity and location of hemorhage and the INR when bleeding occurs. Warfarin therapy should be withheld in all patients with bleeding during oral antigoagulant therapy. Patients should be treated with coagulation factor replacement and intravenous vitamin K [14]. Fresh frozen plasma provides rapid but partial reversal of coagulopathy providing replacement of coagulation factors II, VII IX and X. The usual dose of fresh frozen therapy is 15 mL/kg, although the optimal dose has not been established [15].

Vitamin K reverses the action of warfarin partially or wholly depending on the route of administration and the dose used. The most effective way of treatment is intravenous administration of vitamin K. Usual dose is 2–5 mg. Reduction of INR begins within 2 hours, and correction to normal range is expected within 24 hours [16].

Prothrombin complex concentrate depending on recommended doses ranges from 25 to 100 U/kg product used. Three-factor concentrates may not adequately correct the INR [9].

Recombinant factor VIIa, in usual dose of 10 to 90 μg⁄kg, has immediate effect [9].

A small hematoma with mild symptoms of neuropathy, without compression to surrounding structures and the need for transfusion and no signs of infection can be treated conservatively. On the other hand, surgical treatment is necessary when patients cannot be stabilized with conservative treatment, in unstable patients or due to constant compressive syndrome (femoral or ischiadical neuropathy) [17, 18].

The presented patient was successfully treated with the application of fresh frosen plasma and blood transfusion.

Conclusion

Spontaneous retroperitoneal hematoma as a rare complication is still a diagnostic challenge even for experienced clinicians. Acute abdominal pain, parestesia and laboratory signs of anemia in patients receiving oral anticoagulant therapy, should raise suspicion for intraabdominal bleeding. The early diagnosis is crucial because patients can be treated conservatively with good outcome. In patients who are on anticoagulant tretment it is extremely important to follow their status regularly, because of development of sometimes fatal complications such as spontaneous retroperitoneal hematoma

REFERENCES

1. *Panetta T, Sclafani SJ, Goldstein AS, Phillips TF, Shaftan GW*. Percutaneous transcatheter embolization for massive bleeding from pelvic fractures. J Trauma 1985; 25(11): 1021−9.
2. *Danaci M, Kesici GE, Kesici H, Polat C, Belet U*. Coumadin-induced renal and retroperitoneal hemorrhage. Ren Fail 2006; 28(2): 129−32.
3. *Pallea EX, Domingo P, Fontcubertta J, Felez J*. Spontaneus tertoperitoneal haemorrhage during oral anticoagulant therapy. Arch Inrern Med 1985; 145(8): 1531−4.
4. *Hirsh J, Dalen JE, Anderson DR, Poller L., Bussey H, Ansell J,* et al. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. Chest 2001; 119: 8S−21S.
5. *The European Atrial Fibrillation Tril Study Group*. Optimal oral anticoagulant therapy in patients with nonrheumatic atrial fibrillation and recent cerebral ischemia. N Engl J Med 1995; 333: 5−10.
6. *Hylek EM, Chang YC, Skates SJ, Hughes RA, Singer DE*. Prospective study of outcomes of ambulatory patients with excessive Warfarin anticoagulation. Arch Inter Med 2000; 160(11): 1612−7.
7. *Balci NC, Sirvanci M, Tüfek I, Onat L, Duran C*. Spontaneous retroperitoneal hemorrhage secondary to subcapsular renal hematoma: MRI findings. Magn Reson Imaging 2001;19(8):1145-8.
8. *Kirazli Y, Akkoc Y, Kanyilmaz S*. Spinal epidural hematoma associated with oral anticoagulation therapy. Am J Phys Med Rehabil 2004; 83(3): 220−3.
9. *Crowther MA, Warkentin TE*. Bleeding risk and the management of bleeding complications in patients undergoing anticoagulant therapy: focus on new anticoagulant agents. Blood 2008; 111(10): 4871−9.
10. *Sasson Z, Mangat I, Peckham KA*. Spontaneous iliopsoas hematoma in patients with unstable coronary syndromes receiving

intravenous heparin in therapeutic doses. Can J Cardiol 1996; 12(5): 490−4.
11. *Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA,* et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981; 30(2): 239−45.
12. *Pless T, Loertzer H, Brandt S, Radke J, Fornara P, Soukup J.* Atraumatic retroperitoneal hemorrhage: interdisciplinary and differential diagnostic considerations based on a case report. Anaesthesial Reanim 2003; 28(2): 50−3. (German)
13. *Quartey B, Nelson J.* Massive spontaneous retroperitoneal hemorrhage induced by enoxaparinand subsequent abdominal compartment syndrome requiring surgical decompression: a case report and literature review. IJCRI 2011; 2(10): 14−8.
14. *Dentali F, Crowther M.* Management of excessive anticoagulant effect due to vitamin K antagonists. Hematology Am Soc Hematol Educ Program 2008; 2008: 266−70.
15. *Baglin T.* Management of warfarin (coumarin) overdose. Blood Rev 1998; 12(2): 91−8.
16. *Lubetsky A, Yonath H, Olchovsky D, Loebstein R, Halkin H, Ezra D.* Comparison of oral vs intravenous phytonadione (vitamin K1) in patients with excessive anticoagulation: a prospective randomized controlled study. Arch Intern Med 2003; 163(20): 2469−73.
17. *Ivascu FA, Janczyk RJ, Bair HA, Bendick PJ, Howells GA.* Spontaneous retroperitoneal hemorrhage. Am J Surg 2005; 189(3): 345−7.
18. *Daliakopoulos SI, Bairaktaris A, Papadimitriou D, Pappas P.* Gigantic retroperitoneal hematoma as a complication of anticoagulation therapy with heparin in therapeutic doses: a case report. J Med Case Rep 2008; 2(1): 162.

Received on September 24, 2013.
Revised on April 17, 2014.
Accepted on June 9, 2014.
Online First March, 2015.