Retroperitoneal Hematoma Following Enoxaparin Treatment in an Elderly Woman -A Case Report

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Abstract:

Retroperitoneal hematoma may occur as a result of trauma, rupture of arterial aneurysms (aortic or iliac), surgical complications, tumors and anticoagulation therapy. A life threatening retroperitoneal hemorrhage or hematoma is an infrequent complication of anticoagulation treatment. Enoxaparin is a low-molecular-weight heparin (LMWH) with several advantages over unfractionated heparin. Nevertheless, enoxaparin use is not without risk and severe retroperitoneal bleeding may occur following its use with a potentially fatal outcome. We report a case of sixty six years old female patient who develops a fatal retroperitoneal hematoma two days after enoxaparin treatment for acute coronary syndrome.

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Introduction:

The etiology of retroperitoneal hematoma is mostly as a result of trauma. Other causes of retroperitoneal hematoma include rupture of vascular lesions like aortic or iliac aneurysm, complications from surgical procedures, tumors and anticoagulant therapy. A life threatening retroperitoneal hemorrhage or hematoma is an infrequent complication of anticoagulation medications, and only a few reported cases exist in the world literature of patients with an anticoagulant like enoxaparin, a low molecular weight heparin induced spontaneous retroperitoneal bleeding.[1] The use of enoxaparin in the acute coronary syndrome has been increased over the past decade and incorporated as a class-I recommendation in all guidelines because of its favorable outcomes established by several large randomized trials. [2-7] Enoxaparin is a low molecular-weight heparin (LMWH) and it has several advantages over unfractionated heparin (UFH).[8-9] It has a more predictable anticoagulant response than UFH, and it also has better bioavailability at lower doses than UFH. The anticoagulation monitoring is not necessary in most patients due to the dose-independent clearance mechanism and longer half- life.[10] Furthermore, enoxaparin is more rarely related to major bleeding since it binds less to platelets and inhibit platelet function to a lesser extent. Enoxaperin also has a lower incidence of heparin-induced thrombocytopenia than UFH. Unfortunately, enoxaparin use is not without risk and severe retroperitoneal bleeding has been reported in some cases.[11] We report a patient who had major bleeding episode after enoxaparin use as any other distinct causes for bleeding were not proved.

Case Report:

A 66 years hypertensive, diabetic, dyslipidaemic elderly lady, known case of old stroke (Infarct) with right sided hemiparesis was admitted in C.C.U due to central compressive type of chest pain for one day associated with severe sweating and generalized weakness. Her drug history revealed antiplatelet drug (aspirin and clopidogrel), several antihypertensive drugs and anti diabetic drugs. The patient had no history of coagulopathies. On admission, her pulse was 102 beats /min regular, blood pressure was 140/80 mm Hg, temperature was normal, JVP was not raised. Bilateral coarse crackles were present in both basal lung fields. Her weight was measured as 57 kg.

Electrocardiography (ECG) showed significant ST depression in chest leads.Biochemical tests revealed significantly elevated cardiac enzymes (Troponin-I was 9.58ng/ml,CKMB-99U/L).Bed side echocardiography showed hypokinetic anterior and

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anterolateral wall with mild LV dysfunction (LVEF-50%).

Admission laboratory values were as follows: hemoglobin 10.90 g/dl, platelet count 2,07000/cmm, S.creatinine 1.33mg/dl, S.bilirubin-0.42mg/dl, SGPT-560U/L, SGOT-799 U/L, prothrombin time 16 seconds (patient control 14seconds), INR 1.15, activated partial thromboplastin time (APTT) 35 second (control 30 second). The patient was diagnosed as a case of acute NSTEMI (Non ST elevation myocardial infarction) and treated with loading dose of aspirin and clopidogrel (300 mg aspirin and 300mg clopidogrel) and enoxaparin (subcutaneous injection, 1mg/kg/12 hours) as well as maintenance dose of aspirin 75 mg and clopidogrel 75 mg. After 24 hours of admission patient developed lower abdominal pain radiating to back and left groin. The patient was getting disoriented and hemodynamically unstable. Severe tenderness was present in lower abdomen.

Cardiac enzymes were done again and no significant changes in parameters were evident, SGPT was decreased upto 460U/L. The patient looked pale. Her hemoglobin level decreased up to 5.0gm/dl,S.creatinine was increased up to 4.07mg/dl,SGPT-1671 U/L,SGOT-1830 U/L,Amylase-459U/L,Lipase-149 U/L. Coagulation profile was examined again and revealed prothrombin time 22 second (patient control-14second), INR 1.62 and activated partial thromboplastin time (APTT) 50 second (control-30 second),FDP>20ug/ml.As the patient was disoriented and in impending shock, CT scan of brain was done which revealed small infarct within left deep parietal white matter region involving left capsule-ganglionic area with mild generalized atrophy of brain without any hemorrhage. As the patient had severe abdominal pain and also decreasing hemoglobin drastically without any other focus of blood loss, CT scan of abdomen was done, which revealed a huge well defined mixed density retroperitoneal mass extending from upper quadrant to the left side of the pelvis; Spleen was displaced anteriorly & the left kidney was pushed antero-medially, posterior surface of the spleen could not be separated from the mass. The mass was diagnosed as huge hematoma which had subtle different densities in some regions of retroperitoneum seeming to be due to multiple interval bleeding episodes. But bleeding focus was not well understood by CT scan.

Though antifactor Xa assay is one of the most important predictor of LMWH efficacy in blood and though for this patient, this assay was not measured; other evidences, clinical and laboratory evidences went in favor of retroperitoneal hematoma due to LMWH for this patient. Of course, for our case, deranged liver function test was also a concern to correlate the cause of retroperitoneal hematoma along with enoxaparin use. The patient had raised SGPT and SGOT with normal APTT and INR during admission which may be explained as a sequele of NSTEMI to some extent initially. Just after one dose of

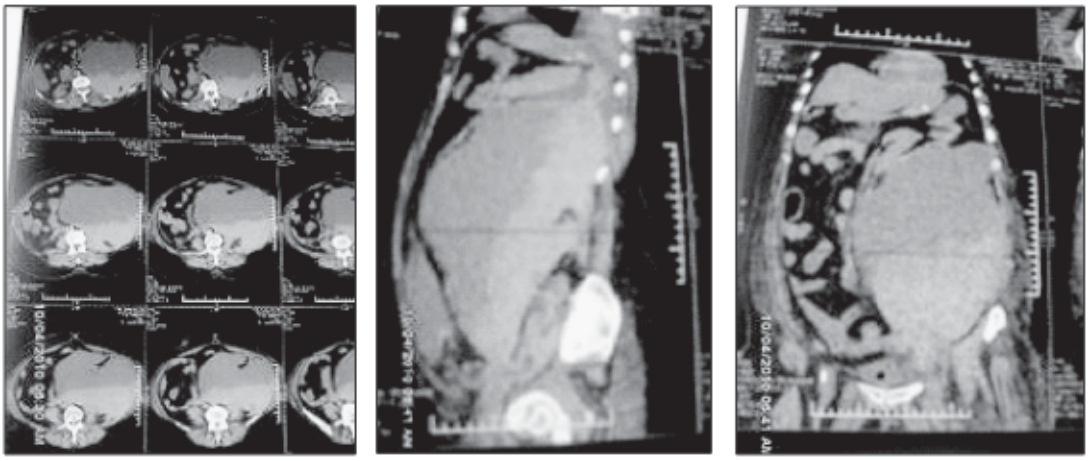

Fig.-1: *CT Scan of Abdomen showed huge well defined mixed density retroperitoneal mass extending from upper quadrant to the left side of the pelvis.*

subcutaneous LMWH , the patient developed retroperitoneal hematoma and just after 12 hours of admission, relook SGPT was rather lower than previous one. So, in our case, very possibly, the deranged liver function test is the subsequent complication rather than a cause or adjuctive factor of hematoma.

Within 36 hours of admission, the patient went to shock and was on ionotropes. From cardiac point of view, coronary intervention couldn't be attempted or considered due to progressive and severe shock with severe anemia. LMWH and antiplatelet drugs were stopped immediately. 4 units of packed RBC cells and 3 units of fresh frozen plasma were transfused. Emergency surgical exploration was also under consideration, but the surgeons and anesthetics couldn't find it favorable for emergency exploration because of the grave homodynamic condition of the patient. No protamine was given since more than 12 hours had elapsed since the last enoxaparin dose. The patient died 72 hours after admission from asystole and cardiogenic shock.

Discussion:

Literature review revealed that apparently the first reported case of a patient with an acute coronary syndrome who died due to enoxaperin induced retroperitoneal hematoma was that by Chan-Tact from the University of Missouri in Columbia.[1] Numerous journal articles and case reports deal with heparin induced retroperitoneal hemorrhage,[10-17] but only a few deals with enoxaparin specifically.

For the last decades, enoxaparin has been demonstrated its advantages over UFHs and has become the commonly used drug for anticoagulation. Because of research data about its efficacy and advantages, we have tendency to use enoxaperin in ACS patients but the debates about safety still remained.[19] For example large clinical studies excluded some diseases such as severe renal impairment, advanced heart failure and used a small sample size of patients with extremely old age(>80 year old),[18,19] although the most part of the patients with ACS are old age and have several comorbidity.

Cohen et al. [2] in their ESSENCE study, showed that enoxaparin was more effective than IV unfractionated heparin in reducing the incidence of death, myocardial infarction or recurrent angina in patients with unstable angina or NSTEMI.Only minor hemorrhage(injection-site ecchymosed) was more common with enoxaperin and benefit was maintained at one-year follow-up. Among 1,578 patients receiving enoxaparin and aspirin for the management of acute coronary syndromes, 17(1%) cases of major bleeding episodes were reported, which included intraocular, retroperitoneal and intracranial hemorrhage, hemoglobin decrease by at least 30g/L, and transfusion requirement of 2 units or more of blood products.

It is recommended that physicians should be extremely observant for the symptoms and sign that suggest retroperitoneal hemorrhage; these include hypotension, decreasing hemoglobin, abdominal distension, increasing bruising, peritoneal signs, flank pain, hip pain, signs of intracranial hemorrhage(neurological deficits, nausea, vomiting, headache, mental status changes), and signs of intraocular hemorrhage (visual changes, nausea, vomiting, photophobia, pain, headache). Enoxaparin should be used very cautiously in elderly patients and in patients with renal insufficiency (creatinine clearance <30ml / min) because of the risk of delayed clearance. A subgroup of high-risk patients requirement close monitoring, including those with bleeding diatheses, thrombocytopenia, uncontrolled hypertension, or recent gastrointestinal bleeding.[10] In these patients, the activity of enoxaparin should be monitored by anti-factor Xa assay. Since enoxaparin is highly active against factor Xa, antifactor Xa values that are within the determined therapeutic range are consistent with adequate drug efficacy and safety. Anti-factor Xa values that are elevated above the determined therapeutic range should alert clinicians to the potential for bleeding complications.[10]

The treatment of patients with retroperitoneal hematoma following enoxaparin should be provided at an intensive care unit. The treatment and supportive care are multifractional and include several steps: discontinuation of enoxaparin, fresh frozen plasma and packed red cells should be administered serially and protamine not given due to NSTEMI.

If these measures fail to stabilize the patient, surgical intervention may needed. Some of these

retroperitoneal hematomas may lead to abdominal compartment syndrome and only prompt surgical approach with exploration and evacuation of the hematoma may offer patient stabilization .Further more, the hematoma may, due to its location, compress surrounding structures and organ to leading to various symptoms, which may also require surgery for resolution.

Conclusion:

The clinical finding of a retroperitoneal hematoma must always lead to thorough evaluation of the patient and search for the etiology. If no other evident causes of retroperitoneal bleeding are found in a patient on anticoagulation therapy, it must be suspected that the anticoagulation agent has caused the bleeding. Heparin and LMWH, either alone or in combination with anti-aggregation medications, may lead to severe retroperitoneal bleeding with a potentially fatal outcome. In these settings, the decision on the surgery is sometimes difficult and must be done with extreme caution. If the patient fail to stabilize with conservative treatment surgical intervention may be required to evacuate the hematoma and if possible, to locate the source of bleeding.

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