

Received: 2016.09.19
Accepted: 2016.11.23
Published: 2017.01.25

ISSN 1941-5923
© Am J Case Rep, 2017; 18: 85-89
DOI: 10.12659/AJCR.901622

Antiplatelet Therapy and Spontaneous Retroperitoneal Hematoma: A Case Report and Literature Review

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Conflict of interest: None declared

Patient: Male, 66
Final Diagnosis: Spontaneous retroperitoneal hematoma secondary dual antiplatelet therapy
Symptoms: Anemia • knee joint pain
Medication: —
Clinical Procedure: None
Specialty: Cardiology

Objective: Rare disease
Background: Dual antiplatelet therapy has proven efficacy in primary and secondary prevention of coronary artery disease with a relatively good safety profile. Review of the literature revealed 8 cases of spontaneous retroperitoneal hematoma secondary to antiplatelet treatment.

Case Report: We report the case of a 66-year-old male with a flare of acute gout secondary to uncontrolled chronic myeloid leukemia. The patient was started on dual antiplatelet treatment following a drug-eluted stent placement for symptomatic coronary artery disease. He suffered from an unexplained acute drop of five grams of hemoglobin from 10.4 to 5.8 g/dL and symptomatic anemia. The initial labs excluded occult GI bleeding, hemolysis, and bone marrow suppression. However, an abdominal CT scan showed an approximately 7.2×4.7×6.7 cm spontaneous retroperitoneal hematoma involving the left iliacus muscle. The patient was successfully treated conservatively by discontinuing antiplatelet therapy and supportive measures.

Conclusions: A spontaneous retroperitoneal hematoma often presents without localizing signs and symptoms and therefore should be considered in any case of unexplained blood loss in patients on antiplatelet therapy. CT without contrast is the modality of choice to diagnose retroperitoneal hematoma.

MeSH Keywords: Aspirin • Hematoma • Platelet Aggregation Inhibitors • Retroperitoneal Space

Full-text PDF: <http://www.amjcaserep.com/abstract/index/idArt/901622>



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Background

The benefits of antiplatelet therapy in patients with atherosclerotic disease as both primary and secondary preventive measures for myocardial infarction and stroke are well established. Dual antithrombotic therapy including aspirin and clopidogrel is currently recommended for at least 1 year following a confirmed acute coronary syndrome (ACS) and/or stent placement. Clopidogrel is used as a secondary prevention therapy in addition to aspirin in patients at high risk of thrombotic events as a result of recent myocardial infarction or stroke [1]. Clopidogrel reduces ADP-induced activation of membrane Gp IIb/IIIa complex, leading to irreversible inhibition of ADP-induced binding of platelets to fibrinogen [2]. Adverse effects reported are rash, pruritus, gastrointestinal bleeding, and diarrhea [3]. Bleeding (major or minor) has been reported as a complication of dual antiplatelet therapy with aspirin and clopidogrel, and the addition of clopidogrel was associated with an increase in risk of major gastrointestinal bleeding [4].

There are but few case reports describing spontaneous retroperitoneal bleeding associated with dual antiplatelet therapy [5].

In addition to antithrombotic therapy, other causes of retroperitoneal hematoma include trauma, benign and malignant renal tumors, inflammatory disorders (periarteritis nodosa, Wegener angitis), severe portal hypertension, vascular aneurysm, ureteral calculi, iatrogenic (complication of coronary angioplasty) disorders, and bleeding disorders (hemophilia).

Retroperitoneal bleeding itself is difficult to diagnose and can present with non-specific symptoms including abdominal pain or mass, groin or hip pain, anemia, hypotension, or leg paresis [6], and can even mimic appendicitis [7].

Even in the absence of localizing symptoms, spontaneous retroperitoneal bleeding should be included in the differential diagnosis in the setting of acute blood loss without an identified source. The signs and symptoms can be subtle or often obscure. We report a case of spontaneous retroperitoneal hematoma (SRH) secondary to dual antiplatelet therapy with almost no local abdominal clue and provide a review of the literature on similar presentations.

Case Report

A 66-year-old African American male known to have chronic myeloid leukemia (CML) who was noncompliant with imatinib, coronary artery disease status post percutaneous coronary intervention (PCI) with a drug-eluting stent (DES) placed 7 months prior to his presentation, and taking aspirin 81 mg and Plavix 75 mg daily presented to the hospital complaining of left knee pain and swelling for three days.

The exam revealed stable vital signs, an erythematous left knee that was tender to palpation, and a palpable suprapatellar effusion. His left hip and knee ROM was limited to both active and passive flexion and extension. He had splenomegaly 2 cm below the costal margin without ascites. Initial laboratory investigations showed a hemoglobin (Hgb) of 10.4 mg/dL, which was at baseline, but otherwise unremarkable.

His knee pain was confirmed to be acute gout via arthrocentesis showing intracellular monosodium urate crystals. It was subsequently treated with an intraarticular corticosteroid injection.

Despite the treatment, his knee pain worsened and a repeat arthrocentesis revealed a hemarthrosis. The patient also complained of pain affecting the entire lower extremity including his hip. Over 5 days of admission, he also developed generalized weakness, dizziness, and palpitations. However, he denied any passing of fresh blood per rectum, melena, or bleeding from any other sites.

Repeat laboratory studies showed a Hgb of 5.8 g/dL, normal MCV, leukocytosis of 321.8×10^3 per mm^3 (which improved after restarting CML treatment), reticulocytes 3.5%, platelets of 73×10^3 per mm^3 , INR 1.17, and APTT 30 s. Platelet function tests COL/EPI and COL/ADP were prolonged. His electrolytes, creatinine, and liver function studies with the exception of hypoalbuminemia of 3 g/dL were normal. Uric acid level was elevated at 14 mg/dL (which responded to Rasburicase treatment, falling to 1.4 mg/dL during admission). A hemolytic panel was also normal.

During admission, he required transfusion of 7 units of red cells and 5 units of platelets. His abdominal CT scan showed a hypodense area measuring approximately $7.2 \times 4.7 \times 6.7$ cm involving the left iliacus muscle that was suggestive of a retroperitoneal hematoma (Figure 1). The initial treatment strategy included an unsuccessful embolization by interventional radiology (IR), as no extravasation of the contrast was identified following catheterization of both the infra-renal abdominal aorta and the culprit left iliac artery (Figures 2, 3).

His dual antiplatelet therapy was also discontinued, and with supportive treatment as above his hemoglobin eventually stabilized, and he was discharged to a rehabilitation facility in good condition with hemoglobin 7.9 g/dL.

Discussion

Evidence suggests that continuing dual antiplatelet therapy beyond one year after DES PCI reduces the risk of major adverse cardiac events [8]. However, the gap between cardiovascular benefit and bleeding risk shrinks following the initial year of dual antiplatelet therapy.

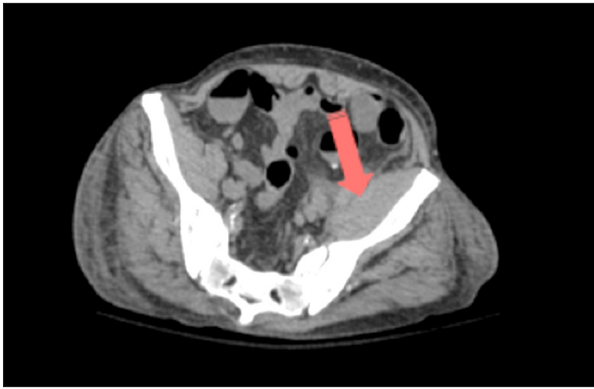


Figure 1. Hypoattenuating area involving the left ilioc muscle measuring approximately 7.2×4.7×6.7 cm, with varying degrees of attenuation and some increase in density that was suggestive of retroperitoneal hematoma.

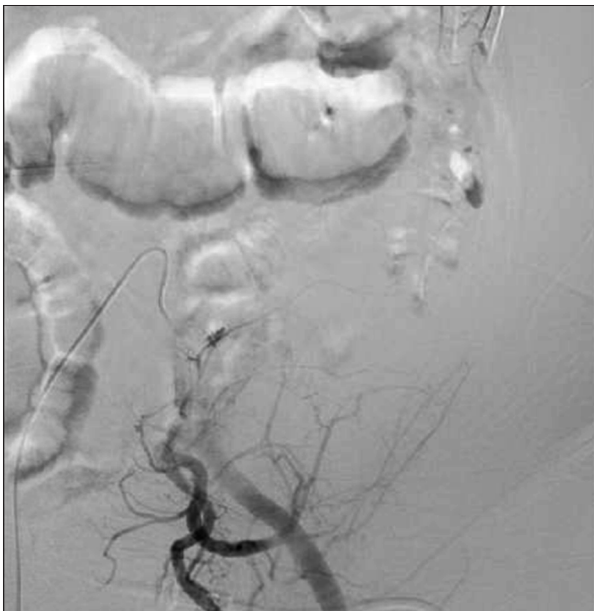


Figure 2. Intra-renal abdominal aorta angiogram with no extravasation of the contrast.

A meta-analysis of 338,191 patients revealed that the risk of major bleeding associated with high-dose aspirin (>325 mg) and thienopyridines was estimated as 2.5% and 2.1%, respectively [9]. Of the patients who presented with SRH, 30.3% cases were related to antiplatelet therapy [10].

Table 1 describes the various presentations and frequency of SRH related to antiplatelet therapy. Although SRH is not a common complication of dual antiplatelet therapy, it has been reported.

A careful review of the literature revealed eight reported cases of SRH related to antiplatelet therapy. The indications for antiplatelet therapy in these cases were secondary prevention



Figure 3. Left iliac angiogram with no extravasation of the contrast.

of ACS and/or following cardiac revascularization therapy, as well as secondary prevention of stroke.

We found 9 cases including our case: the mean age was 69 (\pm SD 9.6) years, 77.7% were males, and 2 out of the 9 cases were on dual antiplatelet therapy (aspirin and clopidogrel). Of the two drugs, clopidogrel (44%) has been reported more often than aspirin (33%) in association with SRH.

Presentation varied, with abdominal pain being the most frequently reported. Mean Hb on presentation was 9.8 (SD \pm 2.5 g/dL). Most patients did not require transfusion at the time of initial assessment; however, when transfusion was required, they required an average of 6.6 units of packed red blood cells (PRBCs).

In our set of reviewed patients, no intervention was needed and only RBC transfusion was needed in 33% of the patients, which is in concordance with the findings in the study post cardiac catheterization by Trimarchi et al. [11]. This is in contrast to the findings of Sunga et al., where among the mixed population of patients on antiplatelet or anticoagulation treatment, 75.3% required RBC transfusion [10]. The requirement for volume support has not been documented in any of the cases reviewed; we are not able to comment on that.

SRH has been reported as early as 2 months after initiation of antiplatelet therapy and as late as 10 years after initiation, which emphasizes that the duration of antiplatelet therapy has minimal impact on the occurrence of SRH.

Table 1. Demographics and presentations of antiplatelet-related spontaneous retroperitoneal hematoma, reported in the English literature.

Age	Gender	Antiplatelet therapy		Symptoms on presentation	Time since starting AP	Initial Hb g/dL/HCT	Platelet count on admission 10 ³ /μL	Transfusions		Modality of diagnosis	Author and year of publication
		Aspirin	Clopidogrel					PRBC units	Platelet units		
66	M	Yes	Yes	N/V, right flank pain	2 Months	7/23%	Normal	9	12	CT	Zaher et al. 2006
77	M	Yes	No	N/V, right flank pain	Unknown	11.4	Unknown	0	0	CT	Abdulmuttalip Simsek et al. 2014
49	M	No	Yes	Pain right lower quadrant, tenderness and nausea for 3 days	6 Years	110/65	Normal	Unknown	Unknown	CT	Darko Jurisic et al. 2006
81	F	No	Yes	Purple discoloration and tenderness of the chest wall and back	10 Years	10.3/31.6%	Normal	0	0	CT	Mehmet Akif Cakar et al. 2012
70	F	No	Yes	Abdominal wall swelling and skin discoloration	1 Year	12.7/36.2%	Normal	0	0	CT/US	Guyen et al. 2004
64	M	Yes	No	Pain, weakness, and dizziness	Unknown	10	Unknown	4	Yes	CT	Abdulmuttalip Simsek et al. 2014
71	M	Yes	No	Sudden left flank colic	1 Year	35%	Normal	0	0	CT	Keisuke Yamamoto et al. 2005
78	M	No	Yes	Low abdominal and back pain	4 Years	Normal	Normal	0	0	CT	Atsunori Nakao et al. 2001
66	M	Yes	Yes	Left hip pain	7 Months	5.8	73	7	5	CT	Our case

N/V – nausea and vomiting; CT – computed tomography; US – ultrasound study; PRBC – packed red blood cells; Hb – hemoglobin; AP – antiplatelet.

In our patient another hypothetical contributor was the uncontrolled CML, which is rather difficult to eliminate based on the available data.

Chronic myeloid leukemia has been reported rarely as a cause of spontaneous hematoma in various sites, i.e., chest wall [12], soft tissue [13], retroperitoneal spontaneous iliac psoas muscle [14], mediastinal hematoma and hemothorax [15], spontaneous epidural hematoma [16], and following bone marrow biopsy [19].

In those cases, thrombocytosis and non-functioning platelets appear to be the hypothesized mechanism of the encounter bleeding.

Improvement of platelet function is also described following initiation of CML treatment [17].

In our patient, platelet function tests COL/EPI and COL/ADP were both prolonged, which may be due to either the effect of aspirin and clopidogrel or the CML effect on platelets. However, the fact that the patient improved and clinically stabilized within 10 days of the stopping the dual antiplatelet therapy with supportive treatment and imatinib therapy favors the theory of anti-platelets as the major cause of the non-functional platelets rather than improvement of CML following treatment, which usually takes months to show this desirable effect.

The appearance of retroperitoneal hematoma with CT imaging has been well described [18]. CT without contrast is the modality of choice to diagnose retroperitoneal hematoma; this is in concordance with Sunga et al. making plain that a CT scan is the quickest, safest, and most accurate modality for diagnosis [10].

Surgical intervention and IR embolization have a minimal role in the management of SRH, and the majority will stop alone, as evident in previous studies such as those of Sunga et al. [10] and Ekici et al. [19], probably because of the tamponade effect of the ongoing bleeding after stopping the offending factors.

The SRH seems to happen in a wide oozing base of the affected side where no specific vessels can be found as a source of bleeding. This explains the limited use of IR in stopping the bleeding noted by Sunga et al. [10] and Ekici et al. [19], and IR has the disadvantage of exposing the patient to the risk of contrast without helping in controlling the bleeding.

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Conclusions

Spontaneous retroperitoneal hematoma is a complication of dual antiplatelet therapy that often presents with the absence of localizing signs and symptoms, thus making it a diagnostic challenge. Our review suggests that in the right clinical picture, diagnosis of SRH should always be in the differential, and there should be a low threshold to screen at-risk patients to ensure early diagnosis and initiation of supportive therapy, both of which lead to better outcomes.