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Acute Atherothrombotic Disease and Severe Bleeding: A Difficult Clinical Presentation in Medical Practice

CRISTINA CĂLDĂRARU[1], C. POPA[2], ANA FRUNTELATĂ[1], Ș. BĂLĂNESCU[3]
[1]Department of Cardiology, Monza Hospital, Bucharest
[2]Department of Cardiovascular Surgery, Monza Hospital, Bucharest
[3]Department of Angiography and Endovascular Interventions, Monza Hospital, Bucharest

Management of antithrombotic therapy in elderly patients with unstable atherothrombotic disease and increased risk of bleeding is a major clinical challenge. We report the case of a 79 year-old diabetic man with rheumatoid arthritis on both oral corticosteroids and NSAID therapy with mild renal dysfunction, who presented to our hospital because of disabling claudication. Prior to admission he had several episodes of TIA. He also had recurrent small rectal bleeding and mild anemia attributed to his long-standing hemorrhoid disease. Angiography showed a sub-occlusive left internal carotid artery stenosis associated with a significant LAD stenosis and complex peripheral artery disease. Cataclysmic bleeding and hemorrhagic shock occurred in the third day post admission. Withdrawal of all antithrombotic treatment, blood transfusion and emergency sigmoidectomy were performed for bleeding colonic diverticulosis. Subsequently antiplatelet therapy was reinitiated and the patient successfully underwent left carotid artery endarterectomy and LAD stenting. He was discharged from hospital on the 21st day post admission and is doing well at 24 months follow-up.

Key words: unstable atherothrombotic disease, elder, hemorrhagic risk.

CASE REPORT

Mr. M.O. is a 79 year-old man with multiple cardiovascular risk factors (non-insulin dependent type 2 diabetes, hypertension, dyslipidemia and rheumatoid arthritis on low dose corticosteroids and NSAIDs) who was admitted in September 2012 for low claudication index (less than 50m walking on flat). The patient also had multiple episodes of speech disorders and right inferior limb monoparesis, due to transient ischemic attacks (TIAs); the last episode occurred 4 days prior to admission.

When admitted the patient was pale and mentioned he had minimal recurrent rectal bleeding, which he attributed to his long-standing hemorrhoids. Previous medical history included a PCI with a DES on the right coronary artery in 2004.

Drug therapy included candesartan 16 mg od, amlodipine 5 mg od, metoprolol 50 mg od, clopidogrel 75 mg od, solumedrol 8 mg od and diclofenac 25 mg bid; anti-inflammatory drugs were stopped on admission due to increased athero-thrombotic risk. Type 2 diabetes was treated with metformin 500 mg bd. Enoxaparin 60 mg bid was started by the treating cardiologist due to the perceived global vascular risk.

Physical examination on admission revealed a pale patient with joint changes due to rheumatoid arthritis. A left cervical and bilateral common femoral artery murmur could be heard. There was no popliteal pulse in both inferior limbs.

His 12 leads ECG on admission showed sinus rhythm, an isolated Q wave in DIII and no ST segment changes (Fig. 1A).

The blood count showed hyposideremic anemia (Hb = 8.9 g/dL, MCV = 81.2 μm^3). Systemic inflammation was found (ESR = 50 mm/h; CRP = 15 mg/L); total cholesterol was 230 mg/dL with an LDL = 130 mg/dL; serum triglycerides were 220 mg/dL. A serum creatinine of 1.2 mg/dl and an eGRF 60 mL/min confirmed mild renal dysfunction.

Echocardiography revealed preserved systolic function (LVEF = 50%), inferior wall hypokinesia, and aortic valve sclerosis with a maximum systolic gradient of 15 mmHg.

Carotid ultrasound revealed a sub-occlusive stenosis of 95% on the left internal carotid artery (Fig. 2).

On the first day after admission the patient had recurrent speech disorders lasting a few minutes on treatment with clopidogrel and enoxaparin.

DOI: 10.1515/rjim-2015-0045

On the second day from admission we performed carotid, coronary and inferior limbs angiography to diagnose precisely the extension of atherothrombotic disease. A high grade stenosis of the left internal carotid artery was confirmed; the left common carotid artery originated in the innominate artery (“bovine arch”) (Figs. 3A, 3B). A long significant stenosis of the LAD was observed (Fig. 4A). Critical stenosis on both superficial femoral arteries was noted (Fig. 4B).

One hour after angiography the patient had a massive rectal bleeding while on clopidogrel alone (enoxaparin was stopped on the day of the angiogram); digital rectal examination revealed the presence of fresh blood. At that time blood pressure was stable. Clopidogrel was stopped and enoxaparin further given at a lower dose (40 mg SC od, although not sustained by guidelines for recurrent TIAs) in a patient in need of surgical carotid artery revascularization and possible major bowel surgery due to major bleeding.

Emergency colonoscopy revealed bleeding from multiple colonic diverticulosis. Adrenaline was locally injected to control bleeding; blood transfusion was given because of an initial hemoglobin loss of 1.6 g/dL. Abdominal surgery was initially not considered due to high risk of surgery in a patient with recurrent TIAs.

After 2 days, while neurologically stable, the patient repeated a massive rectal bleeding (about 700-800 mL of fresh blood) with blood pressure reduction and angina with ST segment depression (Fig. 1B). This time we decided to urgently perform abdominal surgery for hemostasis. The patient accepted surgery when explained it was the only option to efficiently stop the bleeding, despite the risk of permanent neurological damage. Surgical hemostasis was achieved on no antithrombotic treatment by sigmoid colectomy and left iliac colostomy. Enoxaparin 40 mg bid was reintroduced and aspirin 75 mg od was started 12 hours after surgery. Seven units of blood were given to maintain hemoglobin above 10 g/dL.

Eight days after abdominal surgery with no obvious blood loss, left internal carotid endarterectomy was performed on aspirin alone. The patient was brought from the operating theater to the cathlab and treated by PCI with a drug-eluting stent on the left anterior descending artery (Figs. 5A, 5B).

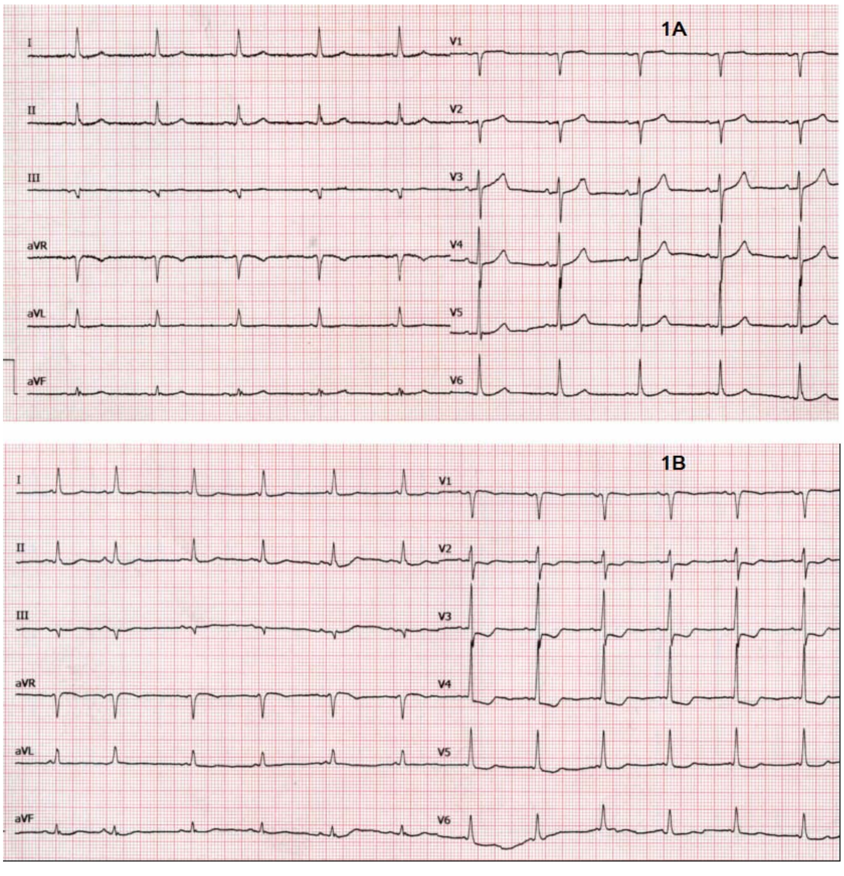

Figure 1. 12 leads ECG on admission (Fig. 1A). ECG with ST segment depression after bleeding and with a low hemoglobin (Fig. 1B).

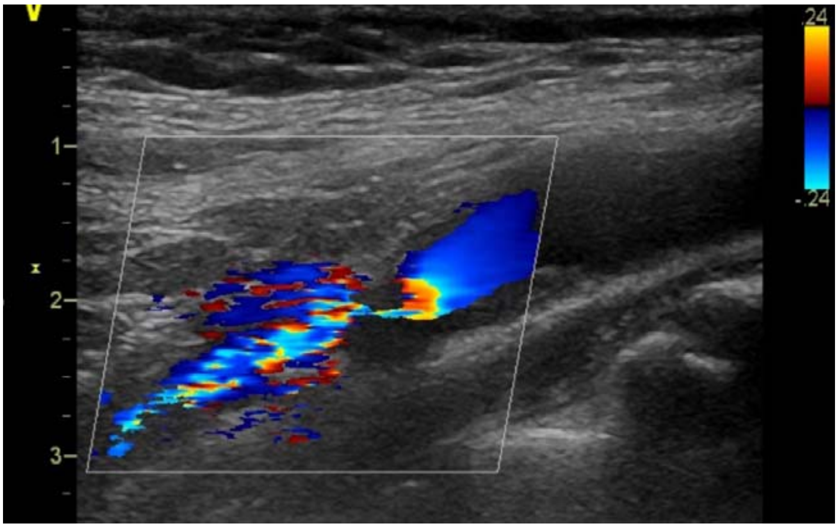

Figure 2. Carotid color Doppler ultrasound of the bifurcation of left common carotid artery demonstrating the sub occlusive stenosis of the internal carotid artery.

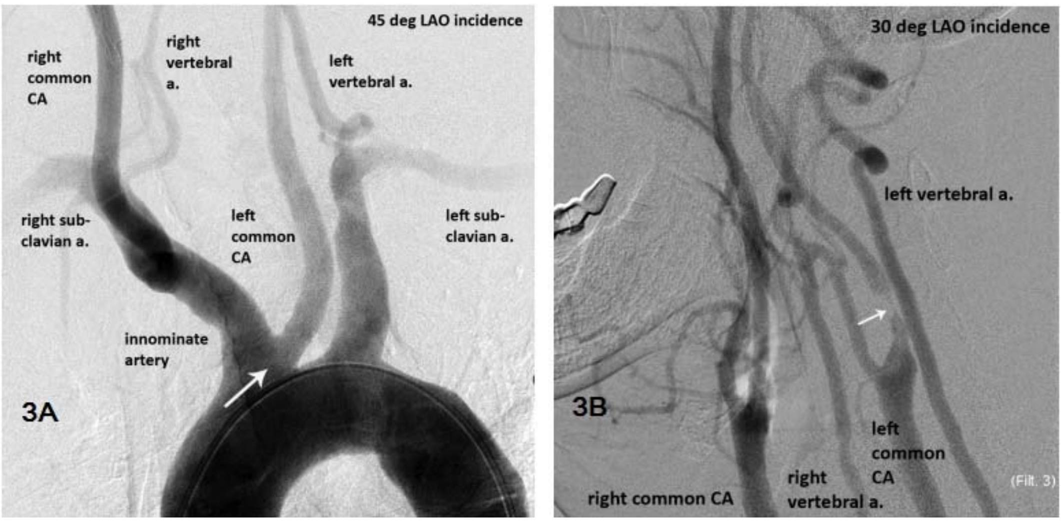

Figure 3. Bovine-type aortic arch with the origin of left common carotid artery in the innominate artery (white arrow in Fig. 3A). Left ICA high grade stenosis at angiography (white arrow in Fig. 3B).

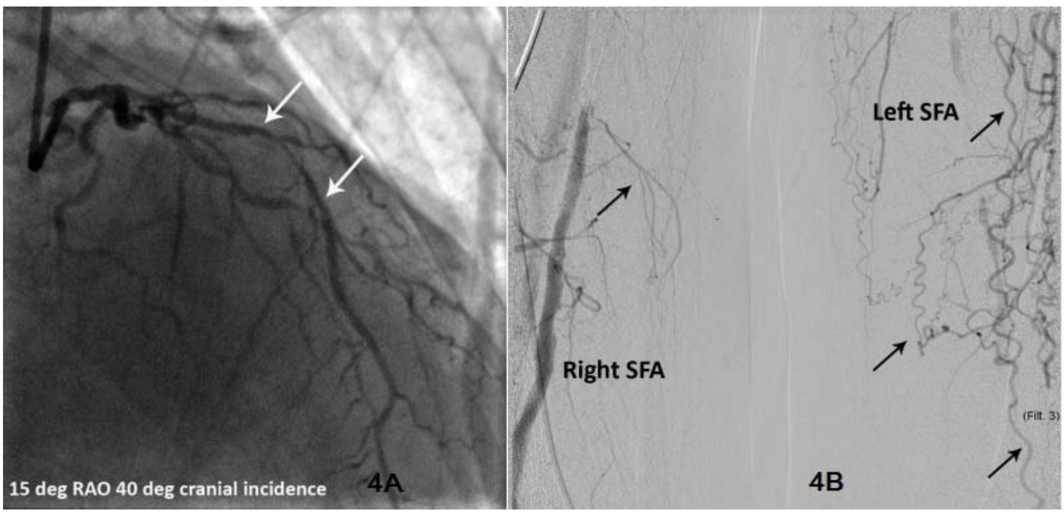

Figure 4. The long significant stenosis of the mid-LAD, on a vessel less than 3 mm in a diabetic patient (white arrows in Fig. 4A). Chronic occlusion of both SFA at angiography (Fig. 4B); black arrows point to abundant collateral vessels.

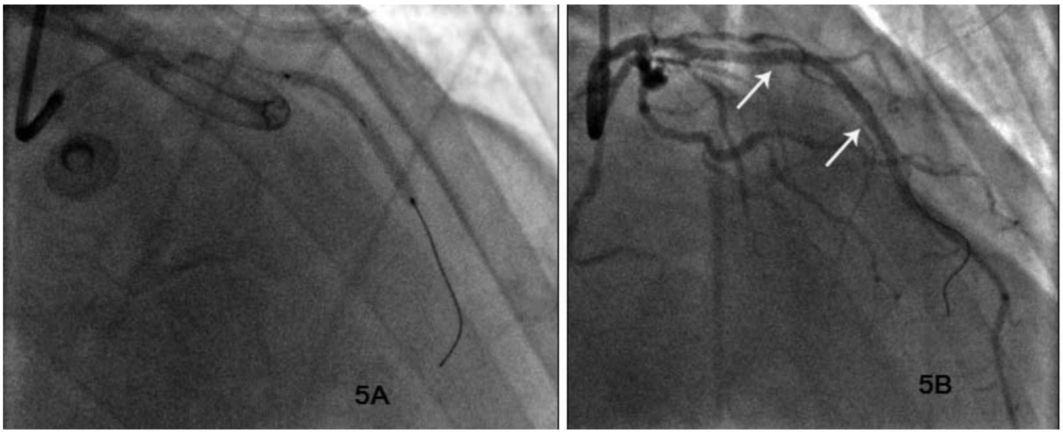

Figure 5. LAD stenting with 2.75×33 mm drug-eluting stent (Fig. 5A) with optimal angiographic result (Fig. 5B); white arrows show the segment of stented vessel.

The patient had an uneventful recovery without recurrent speech disorders, no angina and no bleeding events. The ECG showed no new ST segment changes and hemoglobin remained stable.

He was discharged on clopidogrel, aspirin, metoprolol, atorvastatin, amlodipine, pentoxifylline and metformin. Clopidogrel was given for 6 months after a limus DES implantation and subsequently the patient was left on aspirin alone. Anti-inflammatory treatment on discharge included leflunomide alone, that efficiently controlled joint pain and systemic inflammation.

Subsequent bowel reintegration was successfully performed in our hospital in September 2013, one year after the initial procedure.

DISCUSSION

We present the case of a 79 year-old patient with severe peripheral artery disease, recurrent TIA's, coronary disease and multiple comorbidities. Initial treatment of atherothrombotic disease with enoxaparin and clopidogrel was complicated by life threatening bleeding from colonic diverticulosis. Local injection of adrenaline failed to control bleeding. Despite high surgical risk, antithrombotic treatment was withheld and emergency sigmoidectomy was performed to control bleeding. Subsequently low molecular heparin was restarted and aspirin was given; the patient underwent successful carotid TEA and LAD stenting on the same day. His PAD was conservatively treated as no tissue damage could be observed.

Several risk scores have been developed in order to facilitate clinical decisions in the setting of acute coronary syndromes. The most used in clinical practice are the GRACE score for ischemic risk and CRUSADE for major bleeding [1]. None of these, however, was validated in a patient with TIA and associated CAD and PAD and none can replace clinical judgement. The following observations characterize the outcome of our patient:

1. When massive bleeding occurred in our patient we initially suspected malignancy or some other pattern of colonic proliferation (i.e. multiple polyposis, telangiectasia). NSAIDs and corticosteroids given for rheumatoid arthritis could be responsible for peptic ulcer or erosive gastritis. However, acute diverticulitis may occasionally be responsible for massive bleeding, as in our patient.

2. Combination therapy (antiplatelet agents and an anticoagulant) is associated with a significantly increased risk of major bleeding, mostly from the upper GI tract. There is general agreement that this combination should be used with established vascular, arrhythmic, or valvular indication [2]. In some clinical settings, the combination of anticoagulant and antiplatelet therapy is superior to antiplatelet therapy alone [3] but it is associated with a substantial increase in gastro-intestinal bleeding. A meta-analysis of unfractionated heparin plus ASA *versus* ASA alone in acute coronary syndromes demonstrated a 50% increase in major bleeds [4]. Low-molecular-weight heparin with ASA also increases major bleeding, as demonstrated in the FRISC-1 [5] and CREATE trials [6]. The thin border between bleeding risk and anti-ischemic benefit is most obvious in old patients with unstable disease and also predisposed to bleeding.

3. The decision to stop anti-thrombotic treatment in our patient was taken by the Heart Team and the general surgeon [7]. The patient was informed about the risk of bleeding *versus* stroke, myocardial infarction or acute inferior limbs ischemia. Accordingly we decided first to control bleeding by

sigmoidectomy and promptly resume antiplatelet and anticoagulant treatment to perform carotid TEA and LAD stenting. Fortunately our patient did not experience any acute ischemic complication and this should be attributed to pure play of chance.

4. After surgical control of colonic bleeding, we decided to perform carotid TEA. The Heart Team also decided to revascularize the LAD lesion by PCI. Coronary by-pass surgery was considered as too high risk (Euro SCORE = 21.64%). As far as coronary stenting was decided and the necessity of DAPT was obvious thereafter, carotid stenting could be another option to treat the left internal carotid artery. However, because of the anatomy of the aortic arch and the sub-occlusion of the carotid artery, stent implantation carried a high risk of neurological complications [8]. TEA was considered the safest way to treat carotid disease.

5. Another difficult decision was related to the type of stent that should be used to treat the LAD stenosis. In patients with high risk of bleeding current guidelines recommend BMS implantation because of shorter DAPT duration. However, we decided to implant a DES in the mid-LAD because the patient was diabetic, he had a long stenosis in a vessel smaller than 3.0 mm [9]. Previous accurate control of bleeding by surgery gave us confidence to use a DES in this patient.

6. Finally severe PAD in this patient was left on medical therapy and no revascularization was considered, despite this was the main complaint on admission. As far no severe tissue damage and no symptoms occurred at rest, we decided that antiplatelet therapy, statins and vasodilators should be used to treat PAD.

CONCLUSIONS

In the setting of an acute atherothrombotic event complicated by bleeding the latter should be addressed first to allow proper treatment by surgery or stents and consequent antiplatelet drugs or oral anticoagulation.

When an elderly patient presents with mild anemia and needs anti-thrombotic treatment a thorough search for the cause avoids subsequent hemorrhagic complications.

The management of such complex morbid associations can be performed only by complex medical teams including clinicians, radiologists, surgeons, anesthesiologists and interventional cardiologists.

Disclosure. There are no potential conflicts of interest that relate to the manuscript, as declared under signature by all authors above; it has not been supported by any grant from the industry. The requirements for authorship are met for all authors, and each author states the manuscript represents honest work. All authors have read and approved submission of the manuscript, and this has not been published and is not being considered for publication elsewhere in any language.

Managementul terapiei antitrombotice la pacientul vârstnic cu boală aterotrombotică instabilă şi cu un risc major de sângerare este o provocare pentru clinician. Prezentăm cazul unui pacient în vârstă de 79 de ani cu artrita reumatoidă şi cu disfuncţie renală uşoară ce urma terapie cu corticoizi orali şi AINS, care se prezintă pentru claudicații severe. Anterior internării pacientul a suferit mai multe episoade de AIT (atacuri ischemice tranzitorii). El prezenta rectoragii recurente asociate cu un sindrom anemic uşor datorat bolii hemoroidale. Angiografia a relevat stenoză subocluzivă a arterei carotide interne stângi ce se asocia cu o stenoză semnificativă pe LAD şi cu o boală arterială periferică complexă. În a treia zi de la internare pacientul suferă o hemoragie cataclismică ce a asociat şoc hemoragic. Imediat s-a oprit tratamentul antitrombotic şi s-au administrat transfuzii, realizându-se o sigmoidectomie de urgență pentru diverticuloza cronică. Ulterior, s-a reintrodus terapia antiplachetară şi pacientul a fost supus cu success endarterectomiei arterei carotidiene stângi alături de stentarea LAD. A fost externat în cea de-a 24-a zi de la intrenare şi starea sa la 24 de luni este satisfăcătoare.

Correspondence to: Cristina Căldăraru, Department of Cardiology, Monza Hospital –Cardiovascular Centre
27, Tony Bulandra Str, Postal Code: 021968, Sector 2, Bucharest, Romania
Tel: +40-31-2252500.
E-mail: cristina.caldararu@spitalulmonza.ro

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Received February 23, 2015