Missed, misinterpreted and amended: Methyldopa-induced anemia presenting as ischemic heart disease

Consultation with cardiologist

A 47-year-old moderately built woman consulted a cardiologist in the last week of August 2003, with complaints of retrosternal burning pain and dyspnea on exertion, of one-month duration. The pain radiated to both the shoulders and arms and was not associated with sweating, syncope or palpitation. She reported no fever, chills, weight loss, or night sweats. She had no dizziness, cough, orthopnea, paroxysmal nocturnal dyspnea, or lower-extremity edema.

She has been a hypertensive for the past 6 years, with poor drug compliance, and was on several drugs at different periods by various practitioners, but finally was on tablet methyldopa 250 mg thrice a day.

She gave a h/o mild chest pain since 6 months. She was an asthmatic (seasonal, relieved by injections and tablets) but not a known diabetic.

Her past history included burns 20 years back, gastritis, abdominal surgeries for hysterectomy, ovarian cystectomy, appendectomy, and incisional hernia (three surgeries in the past five years and the last done about one year back). No relevant personal habits was reported.

Family history: Mother was a known hypertensive, No F/H of coronary heart disease (CHD).

O/E: She weighed 67 kg, bilateral conjunctival pallor present, BP 150/100, other systems were normal.

Echocardiogram- normal LV size, ejection fraction (EF) 63% with no regional wall motion abnormality

ECG: normal rate (92 BPM) and rhythm, with non-specific T wave abnormalities in leads I, avL, V5 and V6.

She was prescribed a combination of tablet losartan 50 mg + hydrochlorothiazide 25 mg, od, extended release metoprolol 150 mg, od, enteric coated aspirin 150 mg, od, simvastatin 10 mg, od and nimesulide 100 mg, bid.

On Day 2, treadmill test (TMT) was done with a modified Bruce protocol, stress analysis was positive for inducible myocardial ischemia at low METS and 72% of maximum heart rate response. The test was stopped in Stage 4 because of angina. Blood pressure (BP) response was normal and there were no arrhythmias. Effort tolerance was poor.

She was diagnosed as a case of Class III chronic stable angina with positive TMT and hypertension and was advised to undergo coronary angiogram. The patient refused and came back home without a review of the following investigation results: Hb 7.6 g/dL, blood glucose (fasting and postprandial), thyroid (T3, T4 & TSH), serum CPK, LDH, AST, Trop T were all within normal range.

Consultation with the author

On Day 3, because of worsening symptoms, she consulted her family friend (the first author) whether to undergo an angiogram. O/E, she had a BP of 150/100 mm Hg, resting heart rate 92 BPM, and respiratory rate 20/min. She had no fever, orthostatic changes in the BP, jugular venous distention or lymphadenopathy. Both the palpebral conjunctivae were pale. The remainder of the physical examination, including the heart and lungs, was normal. She gave no history of bleeding per rectum. A stool sample was negative for occult blood. There was no evidence of malabsorption from the history or clinical findings. Based on the earlier mentioned results, it was suggested that her anemia needed to be corrected since the present symptoms could be due to it or at least could synergize with any coronary problem she had been diagnosed of. She was advised that there was no harm in having a coronary angiogram but the anemia part needed a detailed investigation at the very earliest. However in the meantime because of the very low Hb level, she was started on iron sorbitol injection (100 mg of elemental iron) intramuscular after a test dose, (pending a detailed work-up) and tab B complex 1od. On Day 4 her symptoms further worsened and she was taken to the cardiologist again.

Consultation with cardiologist and hematologist

The patient was readmitted and readied for coronary angiogram, at which time the patient’s husband reminded the cardiologist about the anemia part. Immediately, the patient was referred to a hematologist. After confirming that there was no h/o bleeding diathesis and hemorrhoids, but h/o burns 15-20 years back, the case was worked up further. The results of the investigations ordered by the hematologist were as follows: Hb 5.3 g/dL (11.5-16.5), PCV 16% (37-47), reticulocytes 8.2% (0.2-2), stool occult blood negative, abnormal Hb absent, fetal Hb <1%, Hb A2 2.3% and a normal Hb electrophoresis pattern. Bilirubin total 3.7 (0.5-1), Bilirubin direct 1.0 (0.2 – 0.6), Bilirubin indirect 2.7 (0.3 – 0.5) mg/dL respectively.

Thyroid profile was normal. HBs Ag -EIA and HIV1/II –EIA
were negative. Coomb’s ID Gel method - direct and indirect were both positive. Blood group was A, Rh +ve.

Bone marrow aspiration cytology revealed hypercellular aspirate; erythroid hyperplasia with mild megaloblastic change, myeloid maturation, megakaryocyte and lymphoid number and morphology were normal. There was a mild eosinophilia. Stain for reticulin showed no increase in reticulum fibers but stainable iron could be seen.

Now the patient’s drug history was elicited. She was on methyldopa for the past 6 months and had stopped since 2 weeks. Before six months she was on losartan. Based on drug history, results of bone marrow cytology, serum bilirubin and Coomb’s test results she was diagnosed as a case of ‘Drug (methyldopa)-induced hemolytic anemia’. She was started on tablet methyl prednisolone 20 mg, bid X 1wk, 30 mg, od X 1wk along with diltiazem (sustained release) 120 mg, od, isosorbide mononitrate (sustained release) 60 mg, od, aspirin (enteric coated) 150 mg, od, pantoprazole 40 mg, od and isosorbide dinitrate 5 mg, SL sos.

After 15 days the results showed Hb% 9.8 g/dL, PCV 28%, bilirubin total 1mg/dL, RBC 4.7, with nil complaints. Presently the patient has been weaned gradually from steroids and is on losartan with a good control of her hypertension. Hb of 11.6 g/dL (on 19th March, 2004), normal ECG and is free of chest symptoms.

**Discussion**

Complaints of retrosternal pain and dyspnea on exertion in a known hypertensive adult would in all probability lead to a suspicion of IHD. A stress ECG near confirms the same and an angiogram would seal the diagnosis. However, severe anemia could also present with symptoms suggestive of IHD. While this part was missed by the cardiologist, it was misinterpreted as any other usual case of anemia by the author.

In the usual circumstances a rapidly progressive anemia arouses a suspicion of ongoing hemorrhage. In the present case there was no evidence for the same, however; the next suspect should be other causes like hemolytic anemia.

Autoimmune hemolytic anemia typically produces an anemia of rapid onset that may be life-threatening in severity. Patients complain of fatigue and may present with angina or congestive heart failure. The amendment came when the hematologist intervened. A detailed work-up (including Coomb’s test) along with the drug history (though the patient has stopped methyl-dopa two weeks prior to presentation), clinched the cause. Case reports of methyldopa-induced hemolytic anemia presenting in different ways (as SLE-like syndrome, near syncope, as CCF and respiratory arrest) have been reported in the literature. It has been suggested aptly that every case prescribed with methyldopa be subjected to Coomb’s test.

This case highlights the importance of not dismissing incidental findings as trivial without thoughtful consideration of how they may be related to other abnormalities. Also, not to stop short with current drug history since a recently stopped medication may also be the cause of the present problem.

**G. Sivagnanam,
P. Thirumalaikolundhusubramaniam*  
Department of Pharmacology, Chengalpattu Medical College, Chengalpattu - 603 001. *Department of Medicine, Madurai Medical College, Madurai, India.  
Email: drsivagnanam@rediffmail.com

**References**