Testosterone use causing erythrocytosis

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A 60-year-old man with a medical history of depression, seasonal allergies, remote appendectomy and cholecystectomy presented to the emergency department with a sudden headache. Upon examination, his blood pressure was elevated (190/112 mm Hg) and he had erythrocytosis (hemoglobin 196 [normal 130–180] g/L and hematocrit 58% [normal 40%–54%]). Results for a complete blood cell count that was obtained six months before the patient’s visit to the emergency department were normal (hemoglobin 154 g/L and hematocrit 46%). Our patient was discharged from the emergency department with a prescription for amlodipine (5 mg once daily) for management of his hypertension. After follow-up with his family physician, he was referred to our general hematology clinic for evaluation of erythrocytosis.

We noticed that the patient was using a topical formulation of testosterone at two pumps (125 mg per pump) twice daily for fatigue and perceived androgen deficiency, although his pre-treatment level of total testosterone was within normal range at 17 (normal 7.6–31.4) nmol/L. He was also taking citalopram and, on occasion, lorazepam. He reported intermittent facial flushing, but he had not experienced focal neurologic deficits to suggest stroke, tinnitus, vertigo, abdominal pain, cardiac symptoms or other symptoms consistent with hyperviscosity syndrome.

There was nothing on history or physical examination to suggest a primary hematologic cause for erythrocytosis. Upon inquiry, the patient did not have constitutional symptoms, erythromelalgias (e.g., pain, redness and elevated temperature of extremities), aquagenic pruritus (e.g., itching that occurs upon contact with water, without visible lesions), or early satiety or abdominal bloating suggestive of splenomegaly. In addition, his cardiac and respiratory examinations were unremarkable. He had no risk factors for chronic hypoxia, such as a smoking history, lung or cardiac pathology.

Results for peripheral blood testing for the JAK2 mutation, which is present in about 97% of patients with polycythemia vera, were negative. Moreover, our patient’s serum erythropoietin level was inappropriately normal at 9.6 (normal 3.8–16.9) IU/L, which further supported that a secondary process was causing elevated hemoglobin and hematocrit through an erythropoietin-dependent mechanism. Renal ultrasonography to exclude the presence of an erythropoietin-secreting tumour was unremarkable.

Because of the negative result for JAK2 testing, inappropriately normal serum erythropoietin level and temporal association with onset of androgen replacement therapy in our patient, we diagnosed erythrocytosis secondary to testosterone supplementation, and we recommended that he discontinue treatment with testosterone. Because his hematocrit was 58% in the setting of new onset hypertension, we also suggested urgent phlebotomy, after which his hemoglobin level and hematocrit normalized (154 g/L and 45%, respectively) (Figure 1).

Discussion

The Canadian Men’s Health Foundation Multidisciplinary Guidelines Task Force on Testosterone Deficiency and the American Endocrine Society recommend testosterone for men with symptomatic androgen deficiency and low levels of serum testosterone. Erythrocytosis is a predictable yet underrecognized effect of testosterone.

Erythrocytosis is an increase in the number of erythrocytes and is defined as a hemoglobin level above 185 g/L and hematocrit percentage over 49% in men, or 165 g/L and 48%, respectively, in women. An approach to erythrocytosis includes distinguishing a primary bone marrow disorder (e.g., polycythemia vera or other myeloproliferative neoplasm) from possible secondary causes. Primary erythrocytosis is characterized by a low level of serum erythropoietin and secondary causes by normo or high erythropoietin (Figure 2).

Secondary erythrocytoses are further subdivided into congenital and acquired. Congenital causes include germline mutations resulting in high oxygen affinity haemoglobinopathies, altered intracellular oxygen sensing pathways or enhanced erythropoietin receptor signalling. More commonly, erythrocytosis is acquired. Erythropoietin stimulation can be physiologically appropriate in the setting of chronic hypoxic states such as lung disease, heavy smoking, intracardiac shunting, hypoventilation syndromes and local renal hypoxia (e.g., in renal artery stenosis). Drugs to stimu-
late erythropoietin, including darbo-
poeitin, thiazide diuretics or androgen
therapy (i.e., testosterone or anabolic
steroids) are also common acquired
causes for erythropoiesis. Alterna-
tively, erythropoietin secretion can be
pathologic in erythropoietin-produc-
ing malignant diseases such as renal
cell carcinoma, hepatocellular carci-
noma and pheochromocytoma.4

Erythrocytosis can result in symp-
toms of hyperviscosity, including chest
and abdominal pain, weakness, fatigue,
headache, blurred vision and paresthe-
sias. Thrombosis is also an important
consequence of erythrocytosis. A
34-year follow-up of the cohort of the
Framingham study found an associa-
tion between higher hematocrit and
risk of cardiovascular mortality and
morbidity.5 In addition to arterial
thrombosis, an association between
elevated hematocrit and venous throm-
boembolism has been recognized
among patients with primary and sec-
dary polycythemia, and even
patients with an elevated baseline
hematocrit who do not meet criteria for
the classical definition of erythrocyto-
sis.6 Although this relation has not been
investigated in prospective randomized
controlled trials, the US Food and Drug
Administration has warned about the
risk of venous thromboembolism, heart
attack and stroke in patients using tes-
tosterone products.7

Testosterone-induced
erythrocytosis
Interestingly, exogenous testosterone
was used initially as a treatment for
anemia. Recent understanding of
hematopoiesis shows that estradiol, an
aromatized form of testosterone, is
responsible for an increase in hematopo-
ietic stem cell proliferation and
survival. In addition, testosterone
increases erythropoiesis by increasing
iron availability via reduced hepcidin
levels, a hormone responsible for iron
sequestration.8

An American study that evaluated
the effects of graded doses of testos-
terone on erythropoiesis found that
the percentage of hematocrit started
to increase within one month of the

Figure 1: Trends for hemoglobin level (red line) and hematocrit percentage (blue line) in a 65-year-old man receiving testosterone supplementation for perceived androgen deficiency. Shaded section indicates duration of time that the patient was taking testosterone, and black arrows indicate when phlebotomy was conducted. Broken black line indicates a hematocrit of 54%.

Figure 2: A generalized approach to erythrocytosis.4 EPO = erythropoietin, ESRD = end-stage renal disease, Hb = hemoglobin, Hct = hematocrit.
The American practice guideline on testosterone therapy recommends against the use of testosterone in patients with hematocrit above 50% or untreated obstructive sleep apnea, whereas the European guideline on male hypogonadism suggests that testosterone therapy is contraindicated at a hematocrit greater than 54%. Although the most recent Canadian guideline does not advise on a hematocrit threshold above which testosterone therapy should be avoided, it recommends that hematocrit be measured at baseline, three to six months and annually, which is in keeping with the American guideline.

In addition to monitoring of hematocrit percentage during testosterone replacement, physicians should reevaluate indications for testosterone to ensure that patients are receiving clinical benefit, warranting ongoing treatment. In addition, initiation of testosterone therapy should be limited to those patients who show both clinical and biochemical evidence of androgen deficiency to avoid complications caused by unnecessary drug exposure.

Evidence-based guidelines on the management of erythrocytosis secondary to testosterone are lacking, and current guidelines based on expert consensus are variable. At a hematocrit percentage above 54%, stopping testosterone is advised by the American guideline, whereas the European guideline suggests that phlebotomy should be considered at this level. This hematocrit value was derived from the Framingham cohort study. If the hematocrit percentage drops to less than 50%, and no other secondary causes of erythrocytosis are found, testosterone can be restarted at lower doses.

Although dose reduction or discontinuation may be appropriate for some patients, patients with symptoms of hyperviscosity may benefit from phlebotomy. For patients requiring ongoing testosterone treatment, transdermal formulations (with appropriate monitoring) may be a reasonable alternative to parenteral formulations, which are associated with higher hematocrit percentages.

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