Diagn Interv Radiol 2010; 16:165–167

Ergotamine-induced lower extremity arterial vasospasm presenting as acute limb ischemia

Şenay Demir, Şule Akın, Fahri Tercan, Anis Arıboğan, Levent Oğuzkurt

ABSTRACT
Ergotamine-induced limb ischemia is rare and usually results from an accidental overdose. Several agents, including erythromycin and tetracycline, raise serum ergotamine levels and augment its effect. We present a case of acute lower limb ischemia with characteristic angiography findings of diffuse arterial spasm resulting from use of ergotamine and an erythromycin derivative, clarithromycin. The history of the patient and classic features seen on angiography helped us establish the diagnosis. The patient was successfully treated with low molecular heparin and epidural infusion of bupivacain. Since ergot vasospasm is a self limited and medically treatable condition, interventional radiologists must be aware of ergotamine-induced acute limb ischemia to avoid any unnecessary interventional procedures, unless necrosis and gangrene are imminent.

Key words: • *ergotism* • *vasoconstriction* • *angiography*

Ergot and its derivatives are commonly used in the treatment and prophylaxis of vascular headaches. These drugs have a long history of toxicities not easily recognized (1). Vasospasm, most commonly involving the lower limbs, is a rare complication of ergotamine tartrate therapy, usually resulting from an accidental overdose. Involvement of the systemic vasculature including the mesenteric, coronary, carotid and renal circulations has also been reported (1). Several agents, including erythromycin and tetracycline raise serum ergotamine levels and augment its effect (2). Because all these agents are used in certain patients, ergotamine-induced clinically significant vasoconstriction leading to vascular insufficiency can occur and should be suspected in certain patient populations (3).

In this report, we present the case of acute lower limb ischemia with characteristic angiography findings resulting from the use of an erythromycin derivative, clarithromycin, in a patient who had been taking ergotamine preparations for 3 years.

Case report

An 18-year-old female was referred to the emergency department of our hospital with the complaint of pain during rest and mild cyanosis in both legs. The symptoms had started two days before and had been worsening. The pain was significant and necessitated narcotic analgesics. On physical examination lower extremities were cool, cyanotic and tender on palpation. Femoral pulse was weak and distal pulses could not be palpated. Past medical history revealed that the patient had been on clarithromycin for 3 days for upper respiratory infection. Color Doppler ultrasound examination revealed that the arteries from both iliac to the popliteal regions were very thin and flow velocity was increased. However, normal triphasic flow pattern was preserved. Flow spectrum could not be obtained at the ankle level. Laboratory studies revealed normal hemoglobin, hematocrit, white blood cell count, platelet count, blood chemistry, coagulation studies and urinalysis. A chest radiograph was also normal. Because of worsening symptoms and cyanosis, angiography was undertaken to rule out thromboembolism.

The right common femoral artery was punctured and a 5 F vascular sheath was placed. A 5 F pig-tail catheter was placed in the aorta to visualize the arteries from the renal arteries to the arch of both feet. Angiograms demonstrated unusual threadlike, very thin arteries starting from the iliac down to the tibial arteries (Figure). All the arteries were patent without thromboemboli. This was regarded as diffuse spasm; however, repeat intraarterial 100 µg nitroglycerine injections (a total of 500 µg) did not change the angiographic appearance. Ergot-induced arterial spasm, not considered at the beginning, was then contemplated. The history of the patient after the angiography revealed that she has had

From the Departments of Radiology (Ş.D. ✉ *drsenaydemir@hotmail.com*, F.T., L.O.), and Anaesthesiology and Reanimation (Ş.A., A.A.), Başkent University Adana Medical and Research Center, Adana, Turkey.

Received 8 July 2008; revision requested 19 July 2008; revision received 23 July 2008; accepted 26 July 2008.

Published online 9 October 2009
DOI 10.4261/1305-3825.DIR.1931-08.2

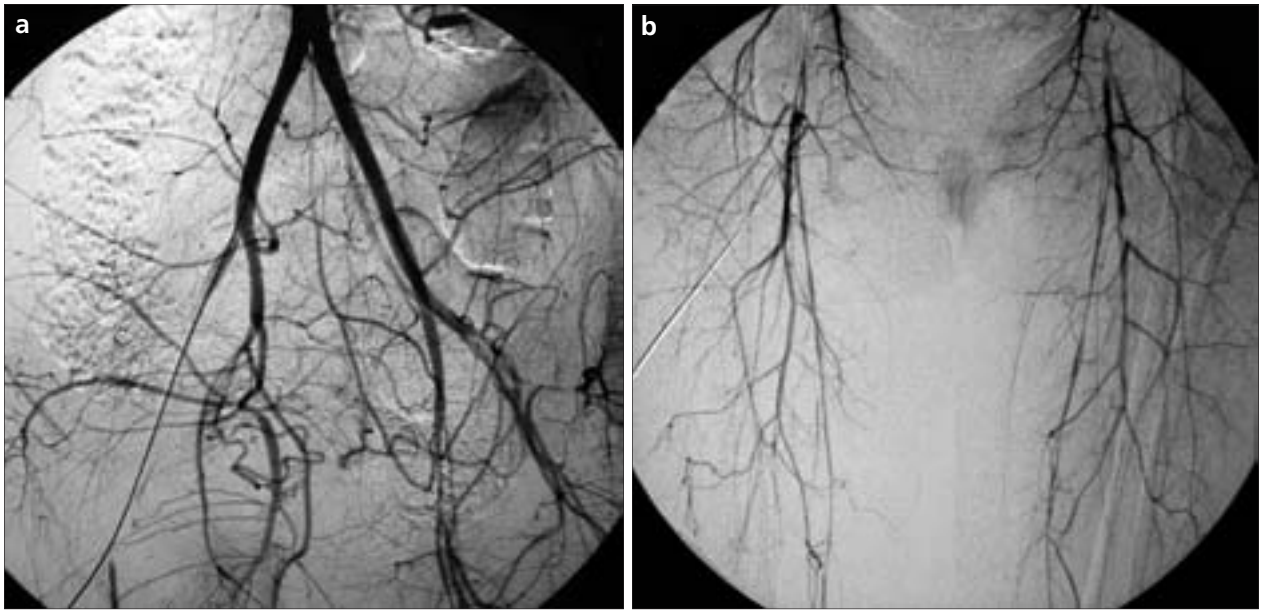

Figure. a–c. Angiograms showing a very thin external iliac artery on the right **(a)**, and thin femoral, popliteal and crural arteries on both sides **(b, c)**. This appearance of the arteries is consistent with diffuse vasospasm (the asymmetric thinning of the right external iliac artery might have also resulted from guide-wire or catheter manipulation of the artery).

migraine and was on ergotamine for three years in addition to clarithromycin for 3 days. She did not explain this before angiography because reportedly she did not remember due to the severe pain she had had. The complaints started one day after she had begun using clarithromycin. She denied any other episodes of leg pain before.

The diagnosis of ergotamine-induced vasospasm was established. Both clarithromycin and ergotamine were discontinued. Both lower extremities were kept warm. Low molecular weight heparin was administrated to prevent possible thrombotic complications. Then, an epidural catheteher was placed (Epidural Minipack System, Portex Ltd, Hythe, Kent, UK) and infusion of bupivacain 0.125% (Marcaine, AstraZeneca Ltd., King's Langley, Herts, UK) at a rate of 4–6 mL/h was initiated. The patient's condition gradually improved and resolved at the end of 4 days, and she was discharged. She was informed on all the medications that can augment the effect of ergotamine. The patient was free of symptoms at 1 month follow-up.

Discussion

Ergotamine is an alkaloid produced by a fungus, *Clariceps purpura*. Ergotamine has been widely used for the treatment and prevention of migraine headaches (4). Vasospasm is a rare but well recognized complication of ergotamine tartrate therapy. The lower extremities are most commonly involved. Involvement of the systemic vasculature including the mesenteric, carotid and renal circulations has also been reported (5). Ergot alkaloids and their derivatives have alpha adrenergic blocking and antiserotonin activity with a direct stimulating action on smooth muscle, especially of the medium sized arteries and arterioles and the uterus. Medical applications include the treatment of vascular headaches, postpartum hemorrhage and thromboembolic prophylaxis (5).

Patients with peripheral vascular insufficiency from ergotism are described as having cool pale limbs, diminished or absent peripheral pulses, and intermittent or chronic pain in the involved extremity. Angiographic findings in ergotism are described as a diffuse and segmental vasospasm seen as a smooth narrowing of the vessels. The changes are usually symmetric with both lower extremities equally involved (3). Unfortunately, clinical signs of ergot toxicity do not correlate with the blood ergotamine level. Presence of ergotamine in the patient's blood demonstrates that ergotamine was present in his or her system. However, toxicity can occur despite undetectable blood levels (3).

Although toxic ergot reactions occur more frequently in chronic usage of the drug, acute toxicity may also occur from a one-time excessive dose ingestion of the drug. A number of conditions are known to potentiate the vasospastic effects of ergotamine like, fever, sepsis, malnutrition, thyrotoxicosis, pregnancy, liver and renal insufficiency, coronary artery disease, and peripheral vascular disease. Drugs, including oral contraceptives, xanthine derivatives, antiviral agents, antibiotics interfering with the liver metabolism of ergotamine (i.e. clarithromycin, ampicillin, erythromycin, and troleandomycin), may also be

responsible to potentiate the effects of ergotamine (6, 7). More recently, Baldwin and Ceraldi described a case of ergotamine toxicity in a human immunodeficiency virus infected patient treated with antiviral protease inhibitor (8). Ergotamine and propranolol may be synergistic for severe ischemic coronary vasospasm (3).

The optimum means of therapy for ergotamine poisoning has not been established. Complete withdrawal of the ergot compound is indicated along with efforts to prevent ischemic damage by maintaining inadequate circulation in the affected parts (5). If symptoms of ergotism are not relieved by withdrawal of the drug, pharmacologic or interventional therapies may be instituted. Pharmacologic interventions include nitroprusside, prazosin, thymoxamine hydrochloride, i.v. streptokinase, calcium channel blockers, intra-arterial infusion of prostaglandin E1, i.v. heparin, nitroglycerin, or intra-arterial nifedipine. Other measures include intra-arterial balloon dilatation and surgical or chemical sympathectomy. The need for arteriography and the course of treatment depend on the location and severity of symptoms (9). Occasionally, treatment includes vascular surgery, hyperbaric oxygen therapy, and peritoneal dialysis as needed (3).

Since ergot-triggered arterial spasm is a transient and self limited disease which usually responds to aggressive medical treatment, caution must be exercised before any intervention is considered. Peripheral balloon angioplasty, atherectomy and other interventions may relieve the arterial spasm, but they increase the risk of permanent anatomic damage to otherwise normal arteries and, therefore, must be avoided when ergot toxicity is suspected, unless necrosis and gangrene are imminent (3).

The present case emphasizes the importance of acquiring a detailed medication history and knowledge of medication-induced arterial disease. Acute limb ischemia due to ergot toxicity is unexpected but may occur. The angiographic features are very characteristic with bilateral diffuse but smooth narrowing of all lower extremity arteries. Our patient was young and did not have angiographic signs of atherosclerosis, so, in retrospect, the diagnosis was straightforward. But it may be difficult when there is atherosclerosis together with ergotamine-induced vasospasm. Color Doppler ultrasound examination actually revealed diffuse thinning of the arteries with increased velocities, a suggestive sign for diffuse spasm, but the condition could not be considered in the differential diagnosis because of its rarity. The patient was urgently sent for angiography because of acute limb ischemia; however, computed tomography or magnetic resonance angiography could have been sufficient for the diagnosis in the setting of familiarity with the condition. Withdrawal of the causative medication and epidural infusion of bupivacaine relieved the symptoms. An understanding of the clinical features and angiographic findings of ergotamine-induced ischemia is essential in early diagnosis and treatment to avoid angiography and prevent irreversible complications (4).

Buerger disease and Raynaud phenomenon can be included in the differential diagnosis according to angiographic appearance, but they have clinical and angiographic features distinct from ergotamine-induced diffuse spasm (10). Buerger disease causes occlusion of the crural arteries and features screw-like collaterals along the occluded arteries. Arteries proximal to the occlusion are usually normal and do not show diffuse spasm. Raynaud phenomenon is mostly seen in the upper extremity arteries, mostly responds to intraarterial vasodilator administration, and usually does not cause acute worsening of symptoms (11).

In summary, ergotamine poisoning remains a rare but important and potentially reversible condition, and the presence of diffuse arterial spasm on angiography should raise the possibility of drug-induced vasotoxicity. Interventional radiologists, who are active in the treatment of peripheral vascular disease, must recognize this condition as it may present as an acute limb threatening situation which may require consideration for endovascular intervention.

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