An unusual case of upper limb ischemia in a marathon runner

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ABSTRACT

Acute limb ischemia in young adults warrants thorough investigation to determine the underlying cause. Here, we present a case of acute upper limb ischemia in a marathon runner secondary to paradoxical embolism. The patient had associated deep venous thrombosis of the lower limb with multiple pulmonary emboli and patent foramen ovale. This case report emphasizes the under-recognition of intense endurance exercise as a risk factor for venous thromboembolism and highlights the potentially debilitating embolic sequelae of venous thromboembolism in patients with patent foramen ovale. (J Vasc Surg Cases and Innovative Techniques 2020;6:160-4.)

Keywords: Venous thromboembolism; Marathon runner; Paradoxical embolism; Patent foramen ovale

Paradoxical embolism is an important clinical entity in patients with venous thromboembolism (VTE) and intracardiac or intrapulmonary shunts. The clinical presentation is diverse and potentially life-threatening. Intense endurance exercise is an under-recognized risk factor for VTE, and a diagnosis of VTE should be considered in atypical populations, particularly young, healthy, and athletic patients, with concerning symptoms.[1] Here, we present a case of a patient with deep venous thrombosis (DVT) of the lower limb associated with multiple pulmonary emboli and suspected paradoxical embolization causing acute upper limb ischemia after a marathon. The patient has consented to publication of the details and images pertaining to the case.

CASE REPORT

A 42-year-old woman presented to our institution with symptoms consistent with acute right upper limb ischemia. There were no neurologic abnormalities on presentation to suggest a neurovascular event. She described a 2-week history of exertional right upper limb pain and associated coolness. One week before the onset of these symptoms, she had completed a 42-km marathon, of which the final 5 km was marred by severe calf myalgia extending 3 days into the subsequent post-marathon recovery period. On examination, she had absent right arm brachial and radial pulses. Computed tomography angiography confirmed a long brachial artery occlusion in the cubital fossa (Fig 1). Furthermore, at the time of upper limb symptoms, the patient had right calf tenderness; an outpatient venous duplex ultrasound study had demonstrated right lower limb DVT within the tibial and soleal veins (Fig 2). No iliofemoral DVT was noted on this study.

The patient was a long-standing endurance runner who had completed several half-marathons, running variable long distances thrice weekly and cycling 10 km twice daily to work for several years. The training period was uneventful, spanning a period of 4 months with progressively increasing running distances culminating in the target marathon distance. Hydration throughout the marathon was optimized by a mobile hydration pack.

Her past medical history was unremarkable. She denied having any history of previous malignant, vasculitic, autoimmune, or thromboembolic diseases, and she had no family history of these. She also denied any recent surgery, long-haul travel, or local trauma. She does not smoke or consume alcohol. Her only regular medication was the combined ethinylestradiol/levonorgestrel (30/150 μg) oral contraceptive pill.

Complete thrombophilia and vasculitic screens were negative. Given the suspicion of paradoxical embolism, computed tomography pulmonary angiography undertaken to assess for any additional clot burden showed bilateral segmental and subsegmental pulmonary emboli in the absence of any symptoms or hemodynamic compromise. Subsequent transthoracic bubble echocardiography was positive, suggesting a right-to-left atrial-level shunt consistent with patent foramen ovale (PFO; Fig 3). Transesophageal echocardiography similarly showed a small PFO with a highly mobile interatrial septum. Pulmonary artery pressures were estimated to be 25 mm Hg; 24-hour electrocardiography monitoring found no abnormalities. Magnetic resonance imaging of the brain excluded any acute or subacute infarcts.

Subsequently, a brachial arteriotomy was performed with a transverse arteriotomy. Good arterial inflow and outflow were established by embolectomy with 4F and 3F Fogarty catheters, respectively. Subsequent on-table angiography demonstrated

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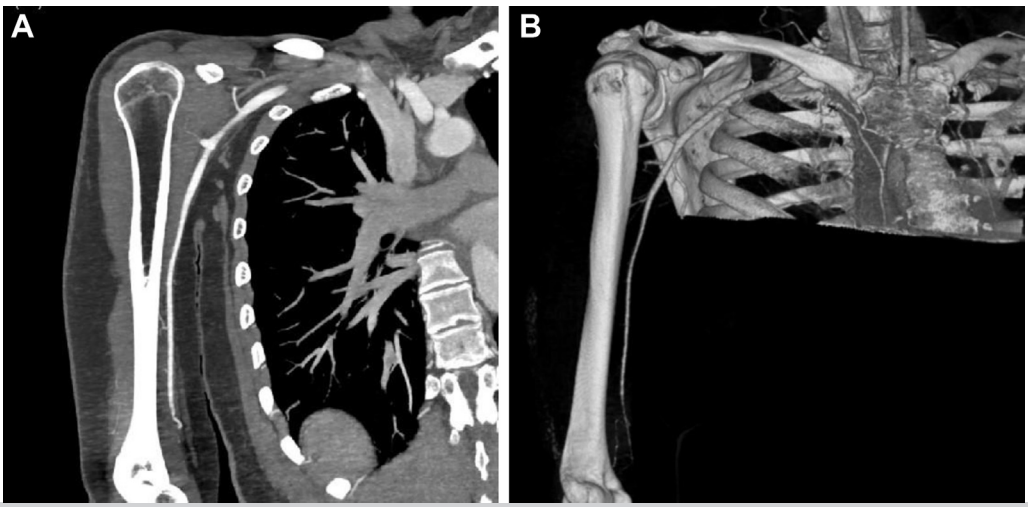

Fig 1. Occlusion of the right brachial artery on **(A)** computed tomography angiography and subsequent **(B)** three-dimensional reconstruction.

ulnar spasm with residual thrombus in the radial artery, for which another embolectomy was performed (Fig 4); 100 μg of glyceryl trinitrate was instilled intra-arterially to reduce spasm. No intra-arterial thrombolysis agents were used. There were no intraoperative complications, with minimal blood loss. The patient had an unremarkable recovery and was discharged on postoperative day 2. The patient was prescribed therapeutic intravenous heparin anticoagulation in the postoperative period before being transitioned to a direct oral anticoagulant, which was continued until her PFO was closed. The oral anticoagulant used was apixaban because of its established dosing. The combined oral contraceptive pill was ceased, and a progestin intrauterine device was inserted for alternative contraception. Her PFO was closed successfully with a 25-mm Amplatzer PFO Occluder (Abbott Laboratories, Abbott Park, Ill) 8 months from her original presentation. Her anticoagulation was subsequently ceased, and she was prescribed dual antiplatelet therapy for 3 months.

DISCUSSION

Given the poor specificity of symptoms, VTE can be difficult to diagnose in high-intensity endurance athletes. Although rare, several cases describing such patients with severe and potentially fatal sequelae, including pulmonary embolism with critical right-sided heart strain, have been described in the literature.[2-4] Intense endurance exercise is associated with VTE by endothelial injury due to exercise-related vessel microtrauma, hypercoagulability due to hemoconcentration as a result of dehydration, and venous stasis as a result of the compensatory basal bradycardia seen in athletes.[5] Another consideration in this case is the limited mobility secondary to lower limb pain in the post-marathon recovery period contributing to venous stasis. The use of estrogen-based oral contraception for menstrual cycle manipulation might also be a predisposing factor in female athletes.[5] Although the conferred risk varies by the included progestogen component, the annual incidence of VTE in women taking the combined oral contraceptive pill is 7 to 12 per 10,000 women (a fourfold to sixfold increase in relative risk[6]).

Although there are several case reports highlighting the risks of VTE in marathon runners, the prevalence remains undocumented. Pulmonary embolism in isolated calf DVT itself is rare. Although a recent systematic review has reported an incidence of up to 6.2%, this is thought to be largely inflated because of the number of embolized proximal lower limb DVTs presenting as isolated calf DVT, which may be a further consideration in this case.[7] There is currently no strong evidence to guide long-term anticoagulation or return to activity in this population.[1] Preventive measures to reduce the likelihood of DVT and pulmonary embolism in athletes should be individualized but are overall similar to those recognized for the general adult population. Most institutions advise a gradual return to activity with close monitoring for thromboembolic events, whereas some consider anticoagulation after risk-benefit counseling with the patient.[1,8] Otherwise key recommendations would be to mitigate reversible risk factors, for example, ensuring adequate hydration or the use of non-estrogen-containing contraceptives.

The most common intracardiac shunt is a PFO, which is between the left-sided interatrial septum primum and the right-sided interatrial septum secundum. A patent connection between the atria may be found in up to 27% of otherwise normal hearts, and the prevalence of a PFO appears to decrease with increasing age.[9] Under physiologic conditions, a pressure gradient is maintained between the left and the right atrium, which results in passive closure of the PFO. In the case of increased right atrial pressure exceeding left atrial pressure (as observed

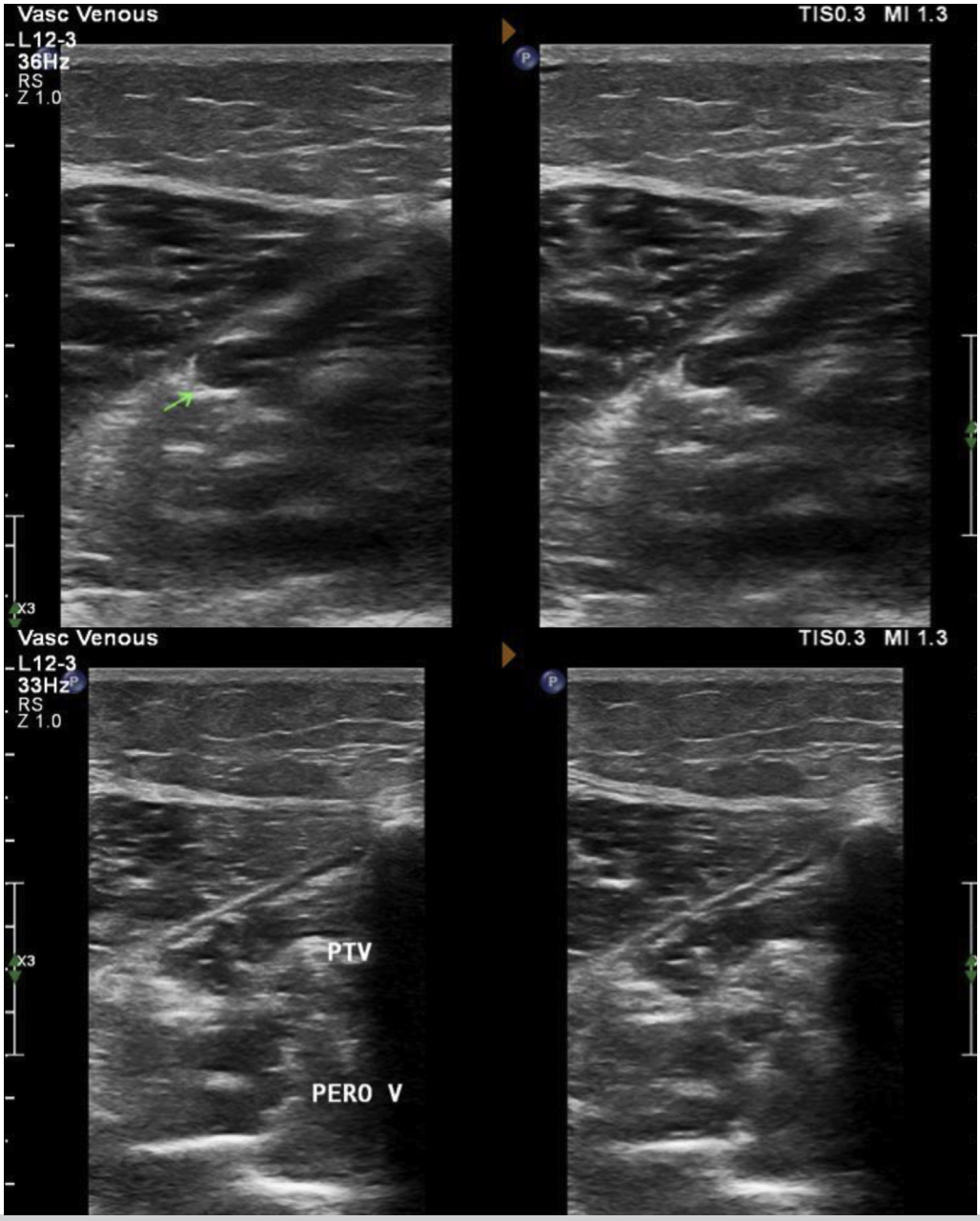

Fig 2. Dual screen ultrasound B-mode images of the tibial and calf veins were captured, with the right-side image demonstrating active compression. Noncompressibility of calf and tibial veins is suggestive of deep venous thrombosis (DVT).

at the end of Valsalva maneuvers, such as coughing, sneezing, squatting, defecation, or micturition), a transient right-to-left shunt may occur, carrying particulate matter such as thrombi into the systemic circulation. A permanent increase in right-sided cardiac pressures, as observed after pulmonary embolism or other causes of pulmonary arterial hypertension, can result in a more significant right-to-left interatrial shunt, thereby increasing the risk of paradoxical embolism.

In this case, the presenting complaint of the patient was acute upper limb ischemia. Neurovascular events, however, constitute the most frequent relevant clinical manifestations of presumed paradoxical embolism. Strokes with no clear cause, also known as cryptogenic strokes, have long been associated with PFO. Up to 46% of patients with cryptogenic stroke have been demonstrated to have PFO.[10] Three large randomized controlled trials have recently been published to support the role of PFO closure in preventing recurrent cryptogenic stroke. The Closure of Patent Foramen Ovale or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence (CLOSE) trial comparing transcatheter

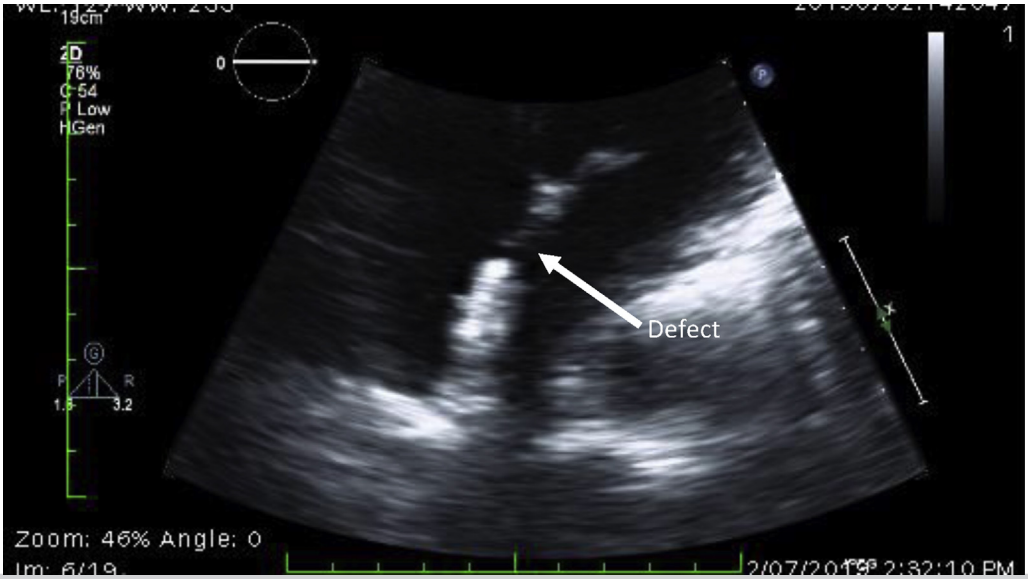

Fig 3. Transthoracic echocardiography highlighting patent foramen ovale (PFO).

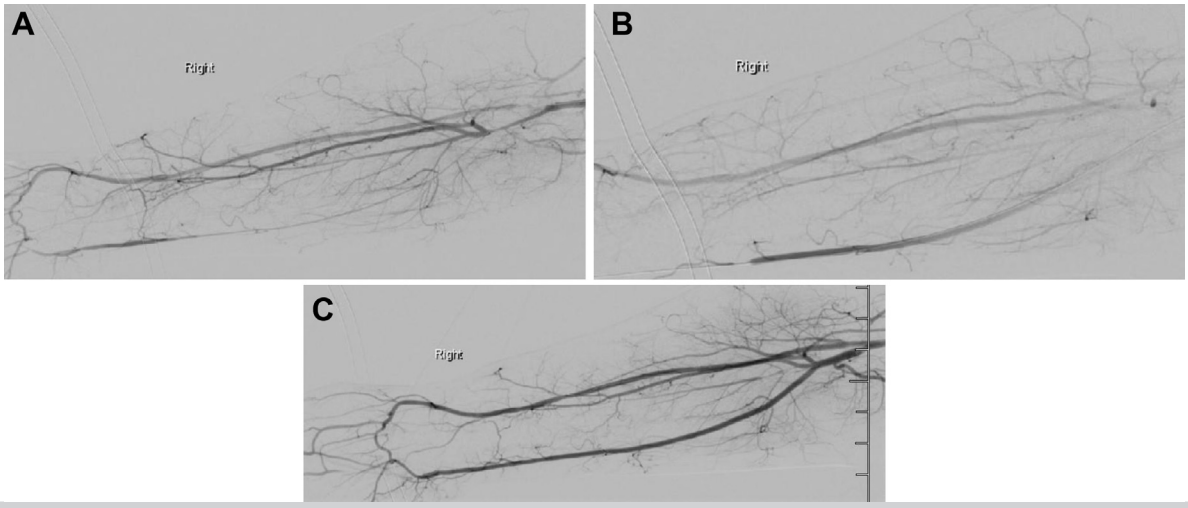

Fig 4. Digital subtraction angiography. **A,** Thrombus proximal to the bifurcation of the brachial artery with poor outflow into both radial and ulnar arteries. **B,** Ulnar spasm and residual radial artery thrombus follow embolectomy of the brachial artery. **C,** Final digital subtraction angiogram after embolectomy.

PFO closure and long-term antiplatelet therapy with antiplatelet therapy alone found significantly decreased occurrence of recurrent stroke in the patients assigned to PFO closure combined with antiplatelet therapy at 3-year follow-up after a 2-year inclusion period (hazard ratio [HR], 0.03; 95% confidence interval [CI], 0-0.26; $P < .001$) but a significantly higher rate of atrial fibrillation or flutter (11% vs 2%; $P = .02$).[11] In addition, the GORE Septal Occluder Device for Patent Foramen Ovale Closure in Stroke Patients (REDUCE) trial comparing similar groups also found a decrease in recurrent stroke (HR, 0.23; 95% CI, 0.09-0.62; $P = .002$) but a serious device-related adverse event in 6% of patients and a similarly increased risk of atrial fibrillation or flutter (6.6% vs 0.4%; $P < .001$).[12] Last, the findings of the Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT) trial comparing PFO closure with medical therapy demonstrated significantly reduced rate of recurrent stroke over a considerable median follow-up period of 5.9 years (HR, 0.55; 95% CI, 0.31-0.999; $P = .046$).[13] In light of these recent findings, our patient's PFO was closed successfully on the completion of her period of therapeutic anticoagulation.

CONCLUSIONS

Intense endurance exercise is an under-recognized risk factor for VTE. The embolic sequelae of VTE can be debilitating and life-threatening, especially in patients with PFO. In suitable cases, evidence continues to emerge to support the closure of PFO to prevent recurrent stroke or other systemic embolization.

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