CLINICAL VIGNETTE

Arterial Thromboembolism Mimicking Spinal Cord Compression in a Young Woman with Stage IV Gastric Cancer: Case Report and Review of the Literature

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A 46-year-old Hispanic female with metastatic gastric cancer to the peritoneum, ovaries, and ureters presented with 3 hours of acute, sharp, 8/10 lower back pain. She had bilateral percutaneous nephrostomy tubes and was treated with cisplatin and irinotecan 2 days prior. The pain radiated to the posterior right thigh and was associated with numbness and weakness in the right foot, as well as tingling in the left foot. She denied any trauma. There was no incontinence of stool, and urine output through the nephrostomy tubes was stable. The patient had noted mild, achy lower back pain and bilateral flank pain for 2 months, which she attributed to her nephrostomy tubes.

Past medical history was significant for sickle cell trait and enterococcal and candidal urinary tract infection accompanied by septicemia one week ago. She reported a 13 pack-year smoking history, quitting 12 years ago. Medications included amoxicillin, fluconazole, ondansetron, lansoprazaole, oxycontin, docusate, and senna.

On physical examination the patient was writhing in pain, lying on her left side; thus, the initial exam was limited. She was afebrile, with blood pressure 178/84, pulse 88 bpm and regular, and respiratory rate 24 breaths per minute. Lung and cardiovascular exams were normal. Abdomen was without bruits. The patient could not tolerate rectal exam to assess tone. Extremities were warm without trophic changes, and good capillary refill was observed throughout. Femoral pulses were 2+ bilaterally. Because of severe pain, she was unable to tolerate complete examination of the popliteal, dorsalis pedis, and posterior tibial pulses. On neurological exam, there was decreased sensation over the right anterior foot and right calf. Right hip flexion was 3/5, but pain-limited. Dorsiflexion and plantar flexion of the right foot were 3/5. Deep tendon reflexes were 2+ in the upper extremities and 1+ in the lower extremities, except for the left patella reflex, which was 2+. There were no Babinski responses bilaterally. Straight-leg-raising test could not be properly assessed.

The patient received multiple doses of intravenous morphine for pain control and intravenous dexamethasone for presumed spinal cord compression. Immediate MRI of the total spine was performed revealing no significant spinal disease. On return from MRI, the patient reported improved control of the lower back pain; however, she began to complain of worsening right thigh pain, increased pain and numbness below the right knee, and progressive tingling in the left foot. She was then reexamined. Right hip flexion was now 5/5, but the other documented sensorimotor deficits were unchanged. There was slight coolness and pallor of the right lower extremity. Capillary refill was decreased. Pulses confirmed by bedside hand-held Doppler were:

	Femoral	Popliteal	Dorsalis Pedis	Posterior Tibial
Right	2+	0	0	0
Left	2+	2+	1+	1+

Vascular surgery was consulted emergently and IV heparin and oxygen started for acute limb ischemia with an immediately threatened right limb. The patient underwent successful

emergent right superficial femoral artery (SFA) thrombectomy for right SFA and popliteal artery thrombosis, in addition to 4 compartment fasciotomy for intraoperative compartment syndrome.

Further studies were performed to investigate possible sources of the emboli. Antithrombin III deficiency, activated protein C resistance, and lupus anticoagulant were not detected. Transesophageal echocardiogram was negative for intracardiac thrombus, but demonstrated a moderate patent foramen ovale (PFO) with a positive bubble study at rest and with Valsalva. There was no deep venous thrombosis (DVT) on bilateral venous Doppler examination. An inferior vena cava filter was placed for prophylaxis against future DVT-related paradoxical emboli in the setting of a hypercoagulable state and an existing PFO.

Discussion

Spinal Cord Compression

The initial presentation in this patient with stage IV gastric cancer and acute lower back pain with right sided sensory and motor deficits (L4-S1), presumed right hip flexor weakness (L2-L4), and left LLE paresthesias was highly suggestive of malignant epidural spinal cord compression (MESCC), which occurs in 5-10% of cancer patients[1-3]. MESCC is defined as an indentation, displacement, or encasement of the thecal sac surrounding the spinal cord and cauda equina by spinal epidural metastases or locally advanced cancer[4].

Clinical Presentation

Pain, which may be localized, radicular, or referred, is the primary presenting symptom in MESCC, developing in 83% to 95% of patients[4-6] for a median of 8 weeks prior to diagnosis[4,5]. Motor weakness occurs in 60-85% of patients[7]. Paresis is usually observed in the extensors of the upper extremities or the flexors of the lower extremities, based upon the location of the lesion. Upper motor neuron signs (spasticity, hyperreflexia, and Babinski responses) may be evident[8]. While sensory deficits are less common than motor deficits, the former may be seen in 40% to 90% of patients, and the location of sensory loss on examination is one to five levels below the actual anatomic level of spinal cord compression. In addition, patients will frequently report paresthesias of varying degrees[6]. During the diagnostic work-up of MESCC, when the spine is imaged beyond the area of clinically determined cord compression, multiple epidural metastases (MEM) are found in 30% of patients. Since the presence of MEM's may impact the overall treatment strategy, several studies have proposed whole-spine MRI in all patients undergoing neuroimaging[9-11].

After cord compression was excluded by total-spine MRI in our patient, improved control of the patient's severe back pain facilitated thorough reexamination, including a complete vascular exam. Reevaluation revealed new pallor and coolness of the right lower extremity and the absence of right popliteal and bilateral pedal pulses, necessitating a revised diagnosis of acute arterial limb ischemia.

Acute Limb Ischemia

Epidemiology

Acute limb ischemia (ALI) is defined as any sudden decrease in limb perfusion that potentially threatens limb viability[12-14]. The approximate incidence of ALI in the general population is 1.7/10,000 per year. Morbidity and mortality are high with death rates of approximately 15% and amputation rates of 10% to 30%. Approximately 12% of cases of ALI are associated with malignancy[14].

Clinical Presentation

The classical signs and symptoms associated with ALI include the "5 P's": pain, pallor, pulselessness, paresthesias, and paralysis[12-14]. A sixth "P," corresponding to polar[13], perishingly cold[15], or poikilothermia[14] is often added to represent a cold extremity. These factors are optimally assessed by comparing the ischemic and contralateral limbs[13].

Identifying the onset and duration of symptoms and any progression is essential because acute limb ischemia will lead to irreversible tissue

damage within 6 hours unless the limb is revascularized[15]. The severity of these symptoms depends on the location and extent of arterial obstruction, and may be diminished if collateral circulation has developed in the affected territory[13].

The *pain* of ALI may be unrelenting and excrutiating[14]. In contrast to rest pain of chronic limb ischemia, pain in ALI is not well localized to the distal foot[12,13], frequently extends above the ankle, and is unaffected by dependency. Pain may be of sudden onset with arterial embolization to an undiseased vessel, or less abrupt and more longstanding with arterial thrombosis of an atherosclerotic vessel because of the development of collateral perfusion[13,14]. As ischemia progresses, neurosensory loss impairs pain perception, resulting in an apparent reduction in pain intensity[13].

Pallor is caused by intense vasospasm in the distal branches of the occluded vessel. After several hours, the vasospasm subsides, and deoxygenated blood fills the distal arterial tree, resulting in cyanotic and mottled tissue that blanches on pressure, and, thus, remains salvageable. With unchecked ischemia, stagnant blood coagulates, liquefaction and blistering occur, and the tissue becomes nonblanching and unsalvageable[15]. Pallor and coolness typically occur one limb segment below the site of arterial obstruction[13,14]. Decreased capillary refill[13] and low ankle blood pressures[12] reflect the overall state of poor perfusion.

Pulses may be palpated at the level of occlusion early after thrombus formation, but are lost as the thrombus organizes into a dense clot. Hand-held Doppler evaluation is performed on presentation to eliminate the intrinsic inaccuracies of manual pulse palpation. Pulselessness when confirmed by Doppler, strongly correlates with ALI, but does not always represent arterial occlusive disease[12]; for example, the dorsalis pedis pulse may be congenitally absent in either one leg or both legs in 2.9% and 1.8% of the population respectively[16].

Recognition of *paresthesias* is essential because loss of light touch, vibratory sensation, and two-point discrimination, especially in the first dorsal web space of the foot, are the first indicators of tissue loss[14]. Numbness is observed in over half of all patients and signifies persistent, severe ALI[12].

Motor deficits are associated with advanced, limb-threatening ischemia because movement of the foot is controlled by more proximal muscles[13]; since dorsiflexion and plantar flexion of the foot require blood supply from the superficial femoral and popliteal arteries, loss of these functions represents a significant region of ischemic damage.[14] Once frank *paralysis* ensues, the prognosis is poor.[12] Muscle rigor, tenderness, and pain with passive motion represent late manifestations of advanced ischemia predictive of tissue loss[12,13].

Etiology

Acute limb ischemia is caused by *arterial thrombosis* or *embolism*[12-14].

Arterial Thrombosis

Thrombosis develops in either a *bypass graft (native* or *prosthetic) or a native vessel*. In the *native bypass graft*, intimal and valvular hyperplasia initiate arterial thrombosis, whereas in the *prosthetic graft*, the inherent graft thrombogenicity, anastomotic irregularities, and kinking of the graft as it traverses joints serve as the nidus[14].

In the *native vessel*, the primary etiology is peripheral artery disease (PAD) in which atheromatous plaque causes endothelial damage, reactive intimal hyperplasia, luminal stenosis, platelet aggregation, and thrombus formation.[14] Development of collateral vessels over time in PAD mitigates acute symptoms. Patients with arterial thrombosis may report preexisting claudication symptoms and may exhibit absent contralateral pulses. Angiography demonstrates diffuse atherosclerotic disease with a tapered, irregular cut-off at the site of occlusion and well-developed collaterals.[14]

Other etiologies of thrombosis involving *native vessels* include arterial trauma, aortic or arterial dissection, arteritis with thrombosis (giant cell arteritis or thromboangiitis obliterans), thrombosed aneurysm, HIV arteriopathy, popliteal adventitial cyst or popliteal entrapment with thrombosis, vasospasm with thrombosis (as in ergotism), compartment syndrome[12], cocaine abuse (possibly mediated through vasoconstriction)[17], and spontaneous thrombosis associated with hypercoagulable states[12].

Arterial thrombosis has been documented in virtually all thrombophilic states[18]. Most common are antithrombin III deficiency, antiphospholipid syndrome, protein C and S deficiencies, activated protein C resistance, and hyperprothrombinemia[14]; hyperhomocysteinemia is an emerging etiology. Malignancy also represents a hypercoagulable state in which arterial thrombosis may occur. A major pathophysiological mechanism involves factor VII activation by tissue factor, which is expressed by most tumor cells[18]. In addition, cancer procoagulant (CP), a cysteine protease elaborated by some tumor types, directly activates factor X, and mucin procoagulant activates prothrombin. Chemotherapy itself may effect arterial thrombosis by reducing protein C and S levels[19]. Acute aortic thrombosis has been reported in patients receiving cisplatin-based chemotherapy[20] and in gastric cancer patients receiving irinotecan-based chemotherapy[21].

Arterial Embolism

Peripheral arterial embolism leads to sudden onset of extreme ischemia attributed in part to the absence of collateral pathways. A history of claudication is absent and contralateral pulses are usually detected on exam. Angiography shows minimal atherosclerosis, multiple occlusions, and few collaterals[14]. Arterial emboli typically lodge at branch points in the arterial tree where luminal caliber is reduced, most commonly in the femoral bifurcation. Saddle embolus occurs at the aortoiliac bifurcation and may eventuate in bilateral lower extremity ischemia with reversible paraplegia and increased mortality[13].

Spontaneous peripheral emboli originate primarily in the heart. Atrial fibrillation accounts for 66% to75% of all cases, and myocardial infarction may contribute to 20% of cases; however, only 5% of post myocardial infarction associated left ventricular thrombi embolize and cause ischemia. Other sources of cardiac peripheral emboli include prosthetic valves and xenovalves, bacterial and fungal vegetations, and tumors such as atrial myxomas.

Non-cardiac emboli account for 5% to 10% of peripheral emboli[14] and may be generated by plaque or critical stenosis upstream, including cholesterol or atherothrombotic emboli associated with endovascular procedures[12], tumors such as melanoma, and foreign bodies[14]. Paradoxical embolization is a rare cause of arterial embolism, occurring in 2% of patients with peripheral artery emboli[22]. Patients develop venous thromboemboli which gain access to the systemic circulation through a PFO, present in 30% of the adult population[23], or another cardiac septal defect. Multiple filling defects may be detected on arteriography with paradoxical emboli[12].

Another 5% to 10% of peripheral emboli have no identifiable cause, some of which can be attributed to hypercoagulable states[14]. Trousseau's syndrome, a "carcinoma-induced coagulopathy," was first described in 1865 by Armand Trousseau (who himself developed the syndrome 2 years later and subsequently succumbed to gastric cancer). It is associated with arterial emboli from non-bacterial thrombotic endocarditis (in addition to spontaneous recurrent or migratory venous thromboses) in patients with malignancies, particularly mucin-producing tumors such as gastric cancer[24].

Differential Diagnosis

Conditions that mimic ALI include low-flow states such as cardiogenic[14] or septic shock[12,14], phlegmasia cerulea dolens (in which a DVT causes local arterial compression), and acute compressive neuropathy[12].

Staging

The management and prognosis of ALI is based on accurate staging of the affected limb represented by four clinical categories: *Category I* indicates a viable limb that is not immediately threatened. It is well-collateralized with intact sensation and muscle strength and audible arterial Doppler signals. *Category IIa* represents a marginally threatened limb that is salvageable if promptly treated. Minimal sensory loss, if present, is limited to mild forefoot numbness, while muscle strength is intact. Often arterial pulses are inaudible. *Category IIb* signifies an immediately threatened limb that is salvageable if treated immediately. Sensory loss involves the entire foot, and mild to moderate calf muscle weakness and rest pain are evident in the presence of usually inaudible arterial pulses. Category III indicates irreversible ischemia with impending tissue loss and permanent nerve damage, requiring amputation. Profound anesthesia and limb paralysis with muscle rigor are present[14].

Management

Heparin should be administered immediately after arterial thromboembolism is suspected[12-14] to prevent thrombus propagation, which usually occurs proximally in an artery. Distal extension, promoted by the low-flow environment distal to the occlusion, is also arrested by rapid anticoagulation.

Arteriography remains the gold standard in the diagnosis of ALI, but should not be performed if it precludes prompt surgical intervention[14]. Optimal candidates are those who can tolerate a delay before revascularization[14] and in whom catheter-directed treatment is an option[12,14].

Systemic thrombolysis is not effective in ALI[13,14]. However, catheter-directed thrombolysis (CDT) is indicated for patients with categories I and IIa ALI of less than14 days duration[12,13]. Three prospective, randomized trials substantiate the use of catheter-directed thrombolysis (CDT) versus surgery in selected patients.

The Rochester trial demonstrated a one-year mortality benefit for patients with less than 7 days of ischemia receiving CDT versus surgery[14]. The STILE trial (Surgery vs. Thrombolysis for Ischemia of the Lower Extremity) showed lower amputation rates for patients with less than 14 days of ischemia when treated with CDT, and lower amputation rates in patients with greater 14 days of ischemia when treated with surgery[25]. The TOPAS trial (Thrombolysis or Peripheral Arterial Surgery) randomized patients with less than14 days of ischemia to CDT versus surgery. Amputation rates at one year were similar in both groups. The CDT group had higher bleeding rates, but required 40% fewer open procedures at one year than the surgical group[26].

When significant sensory or motor deficits are present, immediate surgery is indicated[14]. After successful revascularization, compartment syndrome, requiring fasciotomy, may develop as a consequence of reperfusion injury, which increases capillary permeability, local edema, and compartment pressures. Untreated, compartment syndrome eventuates in venular and arteriolar obstruction and muscle and nerve infarction[12].

Prognosis

In patients with critical limb ischemia from atherosclerotic disease, the expected survival rate is 80% at one year. However, in a retrospective analysis of patients with malignancy and peripheral artery thrombosis, the outcome was dismal, with survival rates of 50% at 3 months and 17% at one year[27].

Case Commentary

This case describes an unusual presentation of arterial thromboembolism mimicking spinal cord compression in a young woman with stage IV gastric cancer and acute back pain associated with bilateral sensorimotor symptoms. Prompt neuroimaging and continued monitoring and reexamination of the patient, in conjunction with pain management, were crucial in establishing the diagnosis of an immediately threatened right extremity, that enabled thrombectomy and

successful limb salvage. While the source of the thrombus was not identified, the presence of the PFO on TEE suggests paradoxical embolization. Trousseau's syndrome[24] or chemotherapy with cisplatin[20] and irinotecan[21] may have contributed to the hypercoagulable state. The patient's progressive contralateral parethesias confounded the diagnosis of thromboembolism (though paradoxical embolism can cause bilateral peripheral emboli)[28] and may be explained by chemotherapy-induced peripheral neuropathy or possibly from compression neuropathy secondary to preferentially lying on the left side as a consequence of severe right-sided pain.

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