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Case Report

A Case Report on Paradoxical Emboli

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Abstract

Venous Thromboembolism (VTE) is a major public health concern, affecting approximately 900,000 people annually in the United States. In rare cases, a Patent Foramen Ovale (PFO) may allow a venous thrombus to cross into the arterial circulation, causing a paradoxical embolism. This case report presents a 46-year-old male who developed left renal artery stenosis after a paradoxical embolism, likely triggered by a prolonged flight and binge alcohol consumption. The patient was found to have a moderate-sized PFO and renal infarction, confirmed by imaging studies. Despite initial anticoagulation therapy and a planned stenting procedure, intraoperative findings revealed only mild stenosis, leading to cancellation of the stent placement. The patient ultimately underwent PFO closure with an Amplatzer Talisman device. This case underscores the diagnostic challenges in managing paradoxical embolism and the need for individualized treatment, particularly concerning anticoagulation duration, the decision for PFO closure, and post-procedural antithrombotic therapy. Further research is required to establish optimal management strategies for cryptogenic embolic events.

More Information

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Introduction

In 2024, Venous Thromboembolism (VTE) continues to be a significant public health concern in the United States, affecting approximately 900,000 individuals annually, according to the Centers for Disease Control and Prevention (CDC) [1]. VTE remains one of the leading causes of preventable hospital deaths, particularly affecting patients who have recently undergone surgery, been hospitalized, or experienced prolonged immobility. Normally, venous thrombi do not cross into the arterial circulation due to the pulmonary capillary network, which acts as a barrier. However, in rare cases, individuals with a Patent Foramen Ovale (PFO) may develop a paradoxical embolism, where emboli pass from the right atrium to the left atrium, entering arterial circulation. This can lead to cerebrovascular blockages causing strokes or infarctions in other organs. Despite extensive testing, the origin of emboli remains unclear in some cases. Notably, an estimated 20% - 40% of ischemic strokes are classified as cryptogenic, meaning no clear source of the embolism is identified after comprehensive evaluation. From a vascular medicine perspective, the optimal type and duration of anticoagulation for preventing future events in these patients remain areas of uncertainty.

We present a case of paradoxical embolism leading to left renal artery stenosis in a 46-year-old male with PFO.

Case presentation

A 46-year-old male with no significant medical history presented to the emergency department with abdominal pain. He had just returned to the United States from a long flight from Europe, during which he consumed 12-14 alcoholic drinks per day over five days. The abdominal pain gradually worsened during a morning walk and localized to his left flank. He was afebrile but tachycardic. Initial lab results revealed a creatinine level of 1.16 mg/dL (baseline of 1.24 mg/dL), mildly elevated liver enzymes, and leukocytosis with a white blood cell count (WBC) increase from 6,000 to 12,000. A CT scan showed a left renal infarct affecting approximately 30% of the upper renal pole and interpolar region, initially read as “probably chronic.” The patient had a recent upper respiratory infection two weeks prior, a remote history of microscopic hematuria, and a past fall that resulted in a left humerus fracture. He denied any history of arrhythmia, palpitations, clotting disorders, or prior thrombotic events.

Two days into his hospital stay, his creatinine level increased to 1.5 mg/dL, and urinalysis revealed 3+ blood and protein. WBC further increased to 15,000, lactate dehydrogenase (LDH) was elevated at 588, and procalcitonin was 0.38 ng/mL. A repeat CT scan showed an evolving renal infarct and an echocardiogram with agitated saline demonstrated a moderate-sized PFO, with 10-30 bubbles crossing from the right to the left atrium. Magnetic Resonance Angiography (MRA) confirmed a high-grade stenosis in the mid-left renal artery, corresponding to a large infarct.

On day five, a venous ultrasound ruled out deep vein thrombosis, and a CT pulmonary embolism study was negative, albeit limited by suboptimal contrast. The patient was discharged on apixaban (Eliquis) 5 mg twice daily with a two-week Holter monitor. He was advised to follow up with cardiology for PFO evaluation and intervention, nephrology for acute kidney injury management, and hematology for a hypercoagulability workup. (Table 1).

Three months later, repeat testing for lupus anticoagulant was negative. Further hypercoagulability testing, including beta-2 glycoprotein antibodies and anticardiolipin levels, were all negative. Hematology recommended a six-month course of anticoagulation followed by lifelong aspirin (81 mg daily).

Vascular surgery was consulted for stenting due to the high-grade renal artery stenosis, but intraoperative findings revealed only 20% - 30% stenosis and the procedure was canceled.

Eight weeks after his initial presentation, the patient underwent PFO closure with a 25 mm Amplatzer Talisman device. He was prescribed dual antiplatelet therapy (DAPT) for six months, followed by single antiplatelet therapy for at least five years, with continuation of apixaban in the interim.

Discussion

This case of paradoxical embolism leading to left renal artery stenosis in a 46-year-old male with a Patent Foramen Ovale (PFO) highlights several critical aspects of PFO management, particularly in patients with cryptogenic embolic events. The role of imaging, the decision between medical and surgical management, and the use of anticoagulation therapy all require careful consideration. The complexities surrounding PFO and paradoxical embolism necessitate a better understanding of current literature and evidence-based guidelines.

Imaging for detecting renal artery stenosis

Imaging plays a crucial role in diagnosing Renal Artery Stenosis (RAS), particularly in patients with embolic events. Multiple modalities are available, each with unique sensitivities and specificities. Computed tomographic angiography (CTA) has demonstrated sensitivity ranging from 88% to 96% and specificity between 77% and 98% in detecting significant stenosis (greater than 50% narrowing). In diagnosing stenosis of the main renal arteries, the sensitivity and specificity approach 100% and 98%, respectively, making CTA a highly reliable tool in ruling out RAS [2].

Magnetic Resonance Angiography (MRA), particularly when gadolinium-enhanced, has also shown excellent diagnostic capability, with studies reporting sensitivity from 88% to 100% and specificity from 71% to 100%. A meta-analysis of 39 studies involving gadolinium-enhanced MRA reported an overall sensitivity of 97% and specificity of 85%, further solidifying its role in the diagnostic workup for renal artery stenosis. Given its utility in patients with suspected renovascular disease and diminished renal function, MRA can be particularly valuable in cases where CTA is contraindicated due to contrast nephropathy risk [2].

Ultrasound, though less commonly used in recent years, still plays a role in certain clinical settings. Using parameters such as a peak systolic velocity exceeding 1.8 or 2.0 m/s and a renal artery-to-aortic velocity ratio exceeding 3.5, ultrasound demonstrates sensitivities from 85% to 90%, with specificity similarly high at around 90%. However, the reliance on operator skills and the potential for incomplete visualization in obese patients limit its broader application [2].

In this case, the imaging confirmed a high-grade focal stenotic lesion involving the mid-left renal artery, associated with a large infarct of the left upper renal pole. This finding, combined with the patient's recent long-haul flight, positive lupus anticoagulant (later negative on repeat testing), and PFO, underscores the importance of thorough diagnostic workup in embolic events involving unusual sites such as the renal arteries.

Surgical *vs.* medical management

The decision between surgical PFO closure and medical management with anticoagulation or antiplatelet therapy is complex and has been the subject of multiple large trials. The CLOSURE I, PC, CLOSE, RESPECT, and REDUCE trials offer varying insights into the efficacy of PFO closure versus medical therapy.

Table 1: Timeline of patient's clinical course. Sensitivities and Specificity reference [2,3].

Date	Modality	Finding	Sensitivity %	Specificity %
2/18/2024 (admission)	CT ABD/PEL	Left renal infarct involving approx 30% of left renal parenchyma, probably chronic	88-96	77-98
2/22/2024	CT ABD/PEL	Left renal infarct appears progressed in the interval. Left retroperitoneal lymphadenopathy, which may be reactive.	88-96	77-98
2/23/2024	US DVT	NO DVT		
2/25/2024	MRA ABD WO/W IVCON	High-grade focal stenotic lesion involving the mid-left renal artery. There is an associated large infarct (diminished enhancement) affecting the upper lobe laterally.	88-100	71-100
3/6/2024	Renal US artery (left)	Left renal artery 70% - 99% stenosis	85-90	90
4/3/2024	Renal angiogram	Estimated 20% - 30% stenosis intraoperatively, a decision not to insert stent was made.	68.30%	80.00%

The PC Trial (2013) enrolled 414 patients across 29 sites and compared PFO closure with medical therapy [4]. The primary outcome occurred in 7 patients in the closure group and 11 in the medical therapy group, with a hazard ratio (HR) of 0.63 (95% CI, 0.24 – 1.62; $p = 0.34$). However, this difference was not statistically significant, and the trial did not achieve its pre-specified endpoint for efficacy. Similarly, the CLOSURE I trial failed to demonstrate a significant reduction in recurrent stroke rates between closure and medical therapy, leading to a period of reduced enthusiasm for PFO closure in the United States.

However, subsequent trials such as the CLOSE and RESPECT [5] trials reinvigorated interest in PFO closure. The CLOSE trial [6,7] enrolled 663 patients with cryptogenic stroke, comparing PFO closure plus antiplatelet therapy versus medical management alone. The study found that PFO closure significantly reduced the risk of recurrent stroke, with an HR of 0.03 (95% CI, 0 – 0.26; $p < 0.001$), suggesting a profound benefit of closure in preventing recurrent events. However, the trial also noted an increased risk of Atrial Fibrillation (AF) in the closure group, with rates of 4.6% compared to 0.9% in the medical therapy group ($p = 0.02$).

The RESPECT trial [5] further supported the use of PFO closure. In this study, 980 patients with cryptogenic stroke were randomized to either PFO closure using the Amplatzer PFO Occluder or medical therapy with antiplatelet agents or warfarin. After a mean follow-up of 2.6 years, the closure group had a recurrence of stroke in 9 patients, compared to 16 in the medical therapy group (HR, 0.49; 95% CI, 0.22 – 1.11; $p = 0.08$). Although the difference did not reach statistical significance in the initial study, an extended follow-up (mean of 5.9 years) demonstrated a significant reduction in recurrent ischemic strokes in the closure group (HR, 0.55; 95% CI, 0.305 – 1.0; $p = 0.046$). This study ultimately led to the FDA approval of the Amplatzer PFO Occluder.

In the REDUCE trial [7], 664 patients with cryptogenic stroke were randomized to PFO closure with either the Helex Septal Occluder or Cardioform Septal Occluder, plus antiplatelet therapy, versus medical therapy alone. The trial reported a significantly lower rate of recurrent ischemic stroke in the closure group (1.4%) compared to the medical therapy group (5.4%) with an HR of 0.23 (95% CI, 0.09 – 0.62; $p = 0.04$). Additionally, the trial demonstrated a significant reduction in new silent brain infarcts on imaging. However, the rate of AF was significantly higher in the closure group (6.6% *vs.* 0.4%; $p \leq 0.001$), underscoring the procedural risks associated with device implantation.

Anticoagulation *vs.* antiplatelet therapy

In patients who are not candidates for PFO closure or decline surgical intervention, the choice between anticoagulation and antiplatelet therapy is another critical decision. A Rapid Recommendation Panel by the *BMJ* [8] suggests that for patients who are open to all options, PFO closure combined with antiplatelet therapy is preferred over anticoagulation. For those who decline or are contraindicated for PFO closure, anticoagulation is recommended over antiplatelet therapy alone. These recommendations underscore the nuanced approach required in treating PFO-related embolic events.

The CLOSE trial's findings support the use of antiplatelet therapy post-PFO closure, though the trial also indicated that anticoagulation might have a trend toward superiority in preventing stroke, though not statistically significant (HR, 0.43; 95% CI, 0.1 – 1.5; $p = 0.17$). De Caterina, et al. recommend Dual Antiplatelet Therapy (DAPT) with aspirin and clopidogrel for 1 – 6 months post-closure, followed by single antiplatelet therapy for up to 5 years [9]. In contrast, oral anticoagulation is recommended for patients with PFO-related ischemic strokes who are not candidates for transcatheter closure [9].

Duration of therapy

The optimal duration of antithrombotic therapy following PFO closure remains a point of debate. In a retrospective cohort study involving 259 patients undergoing PFO closure for cryptogenic stroke, short-term (6 months) versus extended (> 6 months) antithrombotic therapy showed no significant difference in clinical outcomes over a median follow-up of 10 years [10]. The study reported a low recurrence rate of stroke (0.3% per patient-year) and device thrombosis (0.2% per patient-year), suggesting that short-term antithrombotic therapy may be sufficient in many cases.

However, guidelines generally recommend at least 6 months of DAPT followed by single antiplatelet therapy for 5 years. The balance between preventing recurrent embolic events and minimizing the risk of AF and bleeding complications continues to be a subject of ongoing research.

Conclusion

This case of paradoxical embolism resulting in left renal artery stenosis in a 46-year-old male with a PFO highlights the complexities of managing cryptogenic embolic events. While PFO closure reduces the risk of recurrent stroke, it carries risks, particularly atrial fibrillation. The choice between anticoagulation and antiplatelet therapy, the decision to opt for surgical versus medical management, and the duration of treatment remain topics of ongoing research. Further studies are necessary to clarify the long-term outcomes of various treatment approaches and to refine therapeutic strategies for patients with PFO-related embolism.

Ethical consideration

The patient's informed consent was obtained verbally for this case of paradoxical emboli.

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