Case of Atheroemolic Renal Disease

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Abstract

The exact incidence of AERD is not known. The clinical experience is limited to isolated case reports and clinicopathologic case discussions. There have been no prospective studies that systematically focused on this problem. Panum first described this entity in 1862. The reported incidence of AERD varied in the literature because of the differences in study design. However, during the past few years, the observed incidence of AERD in clinical practice seems to have increased. The possible reasons include increased clinical awareness, increased longevity of patients with atherosclerotic vascular disease, improved invasive vascular procedures, routine use of thrombolytics and anticoagulants in clinical practice, and different criteria used for making the diagnosis.

Keywords: AERD • Coronary angiography • Cardiology • Nephrology • Inflammatory markers

Introduction

Atheroembolic Renal Disease (AERD), also called atheroembolism, cholesterol embolism, cholesterol atheroembolic renal disease, or cholesterol crystal embolization, often is an underdiagnosed clinical illness. Atheroembolic renal disease is caused by the occlusion of small arteries in the kidneys by cholesterol crystal emboli from ulcerated atherosclerotic plaques and is a part of systemic atheroembolism disease. The proximity of the kidneys to the abdominal aorta and high renal blood flow makes them the most frequent target organ [1-4].

Etiology

AERD occurs in patients with significant atherosclerotic plaques, particularly in the aorta and large to medium-sized vessels. These plaques have a lipid-rich core and thin fibrous cap.

Mechanical and hemodynamic stresses can rupture the fibrous cap and release the cholesterol-rich matrix, which enters circulation and lodges a distal site causing vascular occlusion.

Iatrogenic disease: Follow surgical procedures like:

- Coronary artery bypass grafting.
- Abdominal aortic aneurysm repair.
- Vascular procedures like angiography, angioplasty, or endovascular grafting.
- It May be related to anticoagulation with warfarin, heparin, and antiplatelet agents or to thrombolytic therapy.
- A small number of patients may occur spontaneously without any inciting or triggering factors.

Epidemiology

AERD occurs in patients with systemic generalized atherosclerosis.

Risk factors include:

- Older age
- Male gender
- Diabetes
- Hypertension
- Hyperlipidemia
- Smoking

These patients frequently have coronary artery disease, congestive heart failure, cerebrovascular disease, renal artery stenosis, renal insufficiency, and aortic aneurysm.

Physiology

Angiography or angioplasty:

- Catheter manipulations disrupt the plaques, exposing the soft, cholesterol-laden core of the plaque to the arterial circulation.

Anticoagulants or thrombolytic therapy:

- Prevent the formation of a protective thrombus overlying an ulcerated plaque
- Could initiate the disruption of a plaque by causing hemorrhage it exposing them to the hemodynamic stress of circulating blood.

Pathophysiology

Once in circulation, cholesterol crystal emboli lodge in small arteries, 150 mm to 200 mm in diameter. These cause partial occlusion of the vessel and distal ischemia. This is followed by an inflammatory reaction, intimal proliferation, and intravascular fibrosis.

Histopathology

Emboli typically lodge in the arcuate and interlobar arteries. It is seen on light microscopy as elongated biconvex transparent needle-shaped clefts. The blood vessel is partially occluded initially [5]. Endothelial inflammatory response ensues and eventually leads to complete obliteration of the flow of blood within weeks or months. Glomeruli may appear normal in the initial stages, but eventually, there may be glomerular collapse or shrinkage [6]. Other changes in histology may include acute tubular necrosis, interstitial fibrosis, and tubular atrophy (Figures 1 and 2).

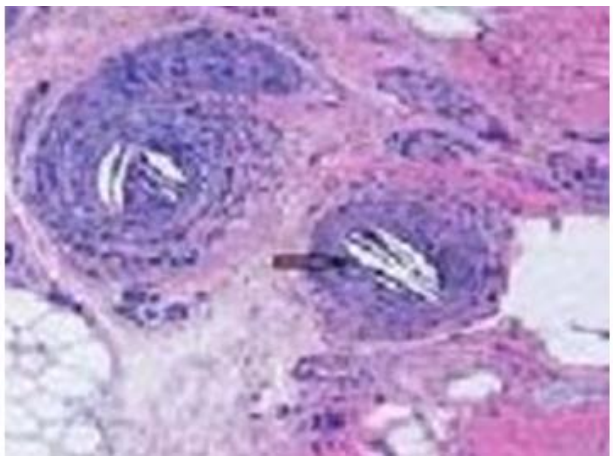

Figure 1. Skin biopsy showing bi-convex cholesterol emboli on the small blood vessels.

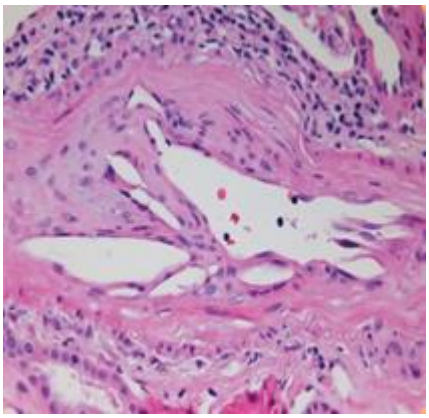

Figure 2. Cholesterol atheroemboli in renal interlobular arteries.

Signs and symptoms: AERD is most commonly part of generalized Atheroembolic disease.
The 5 most commonly affected organs are:

- Skin
- Lower extremity skeletal muscles
- Gastrointestinal tract
- Kidneys
- Brain.
- Clinical manifestations include:
- Livedo reticularis
- Blue toe/purple toe syndrome
- Abdominal pain
- Neurological deficits (Figures 3 and 4)

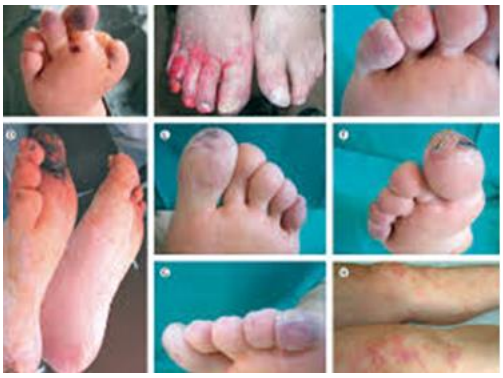

Figure 3. Blue toe/Purple toe syndrome.

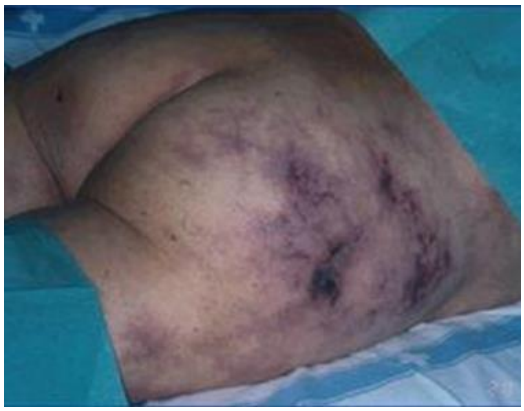

Figure 4. Cutaneous lesions secondary to cholesterol atheroembolism.

Diagnosis

AERD presents with:

- Acute/subacute/chronic renal failure.
- Mild to moderate degree of proteinuria, hematuria.
- Accelerated hypertension or new onset of hypertension.
- Eosinophilia, eosinophiluria,
- Hypocomplementemia

Subtypes

There are 3 forms of AERD:

1. Acute: develops a few days after the inciting event and is due to a massive embolization.
2. Subacute: or in a stepwise fashion, probably due to recurrent embolization or endothelial inflammation that results in further vessel occlusion. Most frequent type.
3. Chronic and slowly progressive: impairment of renal function and is often mistaken for nephrosclerosis and/or ischemic nephropathy.

Evaluation

The combination of:

- Risk factors.
- Inciting or triggering event.
- Acute/subacute renal failure.
- Signs of peripheral emboli.

In the presence of these, the diagnosis of AERD can be made without doing a kidney biopsy. Renal biopsy: required in some cases to exclude vasculitis, ATN, allergic interstitial nephritis, etc. And may provide a definite diagnosis. A skin biopsy may be a simple and minimally invasive way of making the diagnosis if there are skin lesions (digital infarcts, livedo reticularis). In the presence of muscle damage and if a specific muscle can be identified, muscle biopsy may be another minimally invasive way to establish the diagnosis.

Management

- No specific therapy for AERD.
- Mostly symptomatic and supportive.
- Dialysis may be appropriate if no evidence of continued embolic events.
- Anticoagulation should be discontinued.
- Performance of more invasive diagnostic/therapeutic vascular procedures should be avoided or delayed, if possible.
- Treatment with aspirin and statins.
- Smoking cessation.
- Blood pressure control.
- Glycemic control.
- Distal protection vascular devices are being used in interventional procedures to prevent embolic material from lodging in distal sites.

Prognosis

AERD is associated with poor renal and patient survival. The cause of death is usually a multi-organ failure, visceral ischemic disease, or cardiovascular disease rather than end-stage kidney failure. 30% of patients require dialysis, and some of them may end up on long-term dialysis [7,8].

Renal function may improve in approximately one-third of these patients after variable time if there are no more embolic events and tubular recovery ensues. Renal function may improve in approximately one-third of these patients after variable time if there are no more embolic events and tubular recovery ensues[9,10].

Pearls and other issues

- AERD is frequently an iatrogenic disease.
- May follow surgical procedures, angiography, angioplasty, or endovascular grafting, and may be related to anticoagulation or thrombolytic therapy.
- Presents with acute/subacute/chronic renal failure.
- Mild to moderate degree of proteinuria, hematuria, accelerated hypertension, or new onset of hypertension.

Case Presentation

In this case report, there is a patient who presented with symptoms of unstable angina in the cardiology department and was started on anticoagulation therapy. She was planned for coronary angiography but developed worsening renal functions for which she was transferred to Nephrology. On workup under nephrology for her renal functions, she was suspected to have AERD and was worked up accordingly after excluding all other suspected causes of worsening renal functions.
A 65-year-old female, with a history of type 2 diabetes was admitted under cardiology as a case of unstable angina with ECG showing ST segment changes. She was referred for Coronary angiography because of her symptoms and ECG changes. She was admitted to ICU under cardiology for evaluation and management. On her routine lab tests, she was detected to have deranged renal functions with sr. creat of 2.4. Her angiography was deferred and she was referred to nephrology for review.

On evaluation by nephrology, she was noted to have long-standing uncontrolled dm/t2. She was taking OHAs for her diabetes. Her lab reports from our hospital was showing proteinuria of 2+. On inquiry, she had been evaluated previously in medical centers and her blood investigations had been done. She was advised to get her previous lab reports to look for previous renal functions and establish the diagnosis of diabetic kidney disease. On evaluating her previous reports it was revealed that she had

renal dysfunctions 6 months back and her sr. creat was 2.3 and urine showed 1+ proteinuria.

Given the above finding, CAG was deferred by a cardiologist and she was managed medically with double anti-platelet therapy and heparin infusion. She developed hyperkalemia during the ICU stay and was referred to nephrology again. She was suspected to have type 4 RTA, as her ABG showed compensated metabolic acidosis. She was managed with potassium-binding resins and bicarbonate therapy. Her serum potassium normalized.

After 3 days of ICU stay, she was shifted to the ward, as she did not have any fresh changes in ECG. She started developing fever and a rise in sr. creatinine. She was empirically started on oral antibiotics after sending a urine culture and was transferred to Nephrology care for further management. Under nephrology, her CRP levels were sent and she was detected to have a high CRP of 200. Given the above findings and progressively increasing sr. creat to 3.1, she was suspected to have sepsis from some hidden source. So her blood cultures were sent and broad spectrum i/v antibiotics were started. Her serial sr. creatinine showed an upward trend and CRP did not decrease. Her plain CT scan abdomen was done to look for the source of the infection, but it was reported as normal except there was diffuse atherosclerosis of the abdominal aorta. Given this finding and previous history of receiving anti-coagulation in ICU under cardiology, diagnosis of Atheroembolic renal disease, as a cause of the rise in sr. creat was suspected. Her ESR and Sr. Compliments were sent, along with ANA and ANCA titers to rule out the rare possibility of autoimmune diseases. Her blood and urine cultures were sterile and her ESR was high, which supported our diagnosis of AERD. Although her complement levels were normal. She was continued on Antiplatelet therapy and the statin dose was maximized. As an inflammatory cause of acute deterioration of renal functions, she was also suspected to have? drug induced Acute interstitial nephritis. All drugs suspected to cause AIN was stopped and she was also empirically started on steroids.

Her renal functions started improving and sr. creatinine progressively decreased from 3.8 to 2.8 over the next 2 days-3 days along with a decrease in CRP levels from 200 to 25. Her Sugars went high on steroids and were controlled on SUs and sliding-scale insulin. Her steroids were gradually tapered with improving inflammatory markers and renal functions. She was discharged on a tapering dose of steroids, to follow up in OPD after 5 days. It was advised to the cardiology team that this patient is at a very high risk of developing dialysis-dependent renal failure if she undergoes Coronary angiography or any other invasive intravascular intervention. So she was managed medically for her CAD.

Discussion

Atheroembolic renal disease is caused by the occlusion of small arteries in the kidneys by cholesterol crystal emboli from ulcerated atherosclerotic plaques and is a part of systemic atheroembolism disease. The proximity of the kidneys to the abdominal aorta and high renal blood flow makes them the most frequent target organ [11,12].

AERD occurs in patients with significant atherosclerotic plaques, particularly in the aorta and large to medium-sized vessels. These plaques have a lipid-rich core and thin fibrous cap. Mechanical and hemodynamic stresses can rupture the fibrous cap and release the cholesterol-rich matrix, which enters circulation and lodges a distal site causing vascular occlusion [13]. The release of cholesterol plaques into the circulation can occur spontaneously or after intravascular trauma with angiographic catheters or after the use of anticoagulants and thrombolytic agents [14-16].

The exact incidence of AERD is not known. The clinical experience is limited to isolated case reports and clinic pathologic case discussions. Thurlbeck and Castleman reviewed their autopsy cases and reported an incidence of 4% in elderly subjects (age 65 years and older) who had minimal atherosclerosis. However, the incidence increased to 77% in older patients with severe atherosclerosis. Most of these later subjects had undergone surgical repair of an abdominal aortic aneurysm. In a biopsy study, Jones and Iannaccone reported an incidence of 1.1%. Of the 755 renal biopsies reviewed in this study (all age groups), only 8 (1.1%) had features of AERD. Greenberg et al. reviewed 500 renal biopsies and detected AERD in 24 cases (1.6%). Preston et al. reported an incidence of 4.25% in older patients (age 65 years and older) who underwent a renal biopsy. The low incidence of AERD diagnosed on renal biopsy most likely is due to a selection bias. The reported incidence of AERD varied in the literature because of the differences in study design and the different criteria used for making the diagnosis [17,18]. Clinical observations that are based on a short duration of follow-up after an invasive vascular procedure and the infrequency of the confirmatory renal biopsies can lead to an underestimation of the true incidence of AERD. However, during the past few years, the observed incidence of AERD in clinical practice seems to have increased. The possible reasons include increased clinical awareness, increased longevity of patients with atherosclerotic vascular disease, an increase in the number of invasive vascular procedures, and the routine use of thrombolytics and anticoagulants in clinical practice [19].

Prevention is critical for atheroembolic renal disease as there is no effective treatment available at present. It is useful to act in anticipation and initiate prophylaxis against further events of chemoembolization [20-23]. As it is a serious complication of many invasive vascular procedures, it is recommended that excess anticoagulation, surgical procedures, and angiography be limited as much as possible in cases with severe atherosclerosis [24]. Newer noninvasive diagnostic investigations, such as spiral CT angiography, duplex ultrasonography, and angiomagnetic resonance might reduce iatrogenic AERD [25].

Conclusion

AERD remains an unexplored "gold mine" for nephrology research. Apart from the clinicopathologic case discussions, single case reports, and a few retrospective studies, there are no prospective studies that evaluated the precise relationship between invasive vascular procedures or thrombolytic/anticoagulant therapy and atheroembolic renal disease. Whether there is any potential benefit of screening the thoracoabdominal aorta for the presence of atheromatous plaques (by use of noninvasive devices such as ultrasound or magnetic resonance imaging) before performing the invasive vascular procedure should be studied in a prospective manner.

The pathogenesis of renal failure in AERD may not be due entirely to occlusion of medium-sized arterioles with cholesterol emboli. Reactive inflammation surrounding the cholesterol crystals may play a significant role in causing the luminal occlusion and subsequent renal failure. Activation of complement (particularly C5) by cholesterol crystals in vitro and the clinical observation of low serum complement and peripheral eosinophilia strongly suggest a possible role for inflammation in the pathogenesis of AERD, and this area needs to be explored. Furthermore, the nature of inflammatory cells involved in pathogenesis of AERD remains to be defined. If inflammation surrounding the cholesterol emboli is indeed the cause of progressive renal failure, there could be a potential role for the use of steroids in this disease. Supporting this concept is the observation of Dahlberg et al. , who noted improvement in clinical symptoms in two patients with AERD after the use of high-dose corticosteroids.

Patients should be made aware of their disease and its implications on different systems of the body. Should it indicate the need for dialysis in a patient, a thorough awareness program with the help of an interprofessional team should be carried out in such cases.

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