Atheroembolic Renal Disease

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Atheroembolic renal disease (AERD), also called atheroembolism (1), cholesterol embolism (2,3), cholesterol atheroembolic renal disease (4), or cholesterol crystal embolization (5), often is an underdiagnosed clinical illness. The kidney is usually involved because of proximity of the renal arteries to abdominal aorta, wherein the erosion of atheromatous plaque is most likely to occur. Cholesterol embolism also can occur in other visceral organs, as well as in the upper and lower extremities. Because the renal arteries have their origin from abdominal aorta and an enormous amount of blood flows through the kidney, it becomes a prime target in cholesterol crystal embolization.

Definition of AERD

AERD can be defined as renal failure secondary to the occlusion of renal arteries, arterioles, and glomerular capillaries with atheromatous plaques that are dislodged from the aorta and other major arteries. 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. Like the native kidneys, a transplanted kidney also can be affected with cholesterol embolism (6–8), and it should be considered in the differential diagnosis of worsening renal allograft function. Furthermore, AERD should be distinguished from other embolic disorders, such as atrial fibrillation, left atrial myxoma, and bacterial endocarditis.

Incidence of AERD

The exact incidence of AERD is not known. The clinical experience is limited to isolated case reports and clinicopathologic case discussion (9,10). There have been no prospective studies that focused on this problem in a systematic manner. From a historical perspective, Panum (11) first described this entity in 1862. Subsequently, Flory (12) published a series of autopsy cases of atheroembolism in 1945. Thurlbeck and Castlemann (13) reviewed their autopsy cases and reported an incidence of 4% in elderly subjects (age 65 yr 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 (14) 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. (15) reviewed 500 renal biopsies and detected AERD in 24 cases (1.6%). Preston et al. (16) reported an incidence of 4.25% in older patients (age 65 yr and older) who underwent a renal biopsy. The low incidence of AERD diagnosed on renal biopsy most likely is due to a selection bias. AERD was diagnosed as the primary cause of renal failure in 1.9% of our patients accepted for chronic dialysis between 1985 and 1990 and 2.7% between 1991 and 1995. It is conceivable that there may have been other patients who had chronic renal failure secondary to AERD and who were not in need of dialysis and were not included.

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. For example, retrospective data derived from autopsy or biopsy studies may exaggerate the frequency by including many subclinical cases. 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 (1) increased clinical awareness, (2) increased longevity of patients with atherosclerotic vascular disease, (3) an increase in the number of invasive vascular procedures, and (4) the routine use of thrombolytics and anticoagulants in clinical practice.

Diagnosis of AERD

There are many inherent difficulties in diagnosing AERD. It therefore has been labeled as the great masquerader (2). The specific diagnosis can be made only by demonstrating the cholesterol crystals within the renal vessels and glomeruli in kidney biopsy or autopsy specimens. However, in older patients with atherosclerotic vascular disease (who are the prime subjects for AERD), there is a general reluctance on the part of physicians to perform renal biopsies. Possible reasons for this reluctance include (1) advanced age of the patient and (2) smaller kidney size, from a coexisting renovascular disease.
AERD typically is observed after an invasive vascular procedure or after thrombolytic/anticoagulant therapy, but it also can develop spontaneously. The disease can present as sudden onset of acute renal failure or have a smoldering course with declining renal function over a period of several months. The renal failure in this setting often is attributed to other conditions such as (1) radio-contrast nephropathy, (2) acute tubular necrosis, (3) drug-induced interstitial nephritis, and (4) intravascular volume depletion. Presence of cholesterol emboli in other tissues will, of course, strengthen the diagnosis. In some individuals, cholesterol emboli maybe found in the skin and muscle biopsy specimens but not in the kidney. This scenario is more likely to occur when atheromatous plaques are dislodged from distal aorta, below the origin of renal arteries. The predisposing factors for the development of AERD are shown in Table 1.

Blakenship et al. (17) described cholesterol embolism in 12% of patients who underwent coronary angiography and bypass surgery after an acute myocardial infarction. They found no difference in the incidence among patients treated conservatively or those given thrombolics. The diagnosis was based on the examination of two muscle biopsy specimens and a skin biopsy specimen, which were taken at the time of harvesting the saphenous vein for bypass surgery. Because the patients were not systematically assessed for symptoms of AERD after the bypass surgery, it is conceivable that some of them could have developed AERD at a later stage and thus were not included in the 12% incidence reported earlier. Furthermore, the diagnostic sensitivity of the muscle or skin biopsy specimen can vary, depending on the site of the biopsy. Maurizi et al. (18) reported that the sensitivity of a skin biopsy specimen was 41%, compared with 100% for a muscle biopsy. One should consider the limitations of these studies, such as the variability of sample size and the small number of specimens examined. Because cholesterol embolism affects multiple organs and the disease progresses slowly over a period of several weeks to months, it also can mimic systemic vasculitis.

### Renal Histopathology

The classic lesion in AERD is the occlusion of arcuate and interlobular arteries and the glomerular capillaries with cholesterol emboli. The cholesterol crystal emboli generally are recognized by the characteristic biconvex, needle-shaped clefts appearing as “ghosts” (Figure 1). The crystals normally are dissolved during routine histologic preparation. However, when specimens are snap-frozen with liquid nitrogen and the frozen specimen is examined under polarized light, one can demonstrate the birefringent character of the cholesterol crystals (19). Although atherosclerosis contributes to blockage of the renal artery and its major branches, the atheroemboli typically occlude the medium-sized arterioles (150 to 200 μm in diameter) and glomerular capillaries. The involvement usually is patchy (1,14).

### Evolution of Histologic Lesion in AERD

In the initial stages of atheromatous occlusion, varying degrees of polymorphonuclear and eosinophilic infiltration occurs around the occluded vessel. Subsequently, other mononuclear cells accumulate in the infiltrate, because the crystals attract inflammatory cells to the site of injury. Frequently, multinucleated giant cells also are seen within this perivascular inflammatory cell infiltrate (20). Over a period of time, the affected blood vessels are occluded further from intimal hyperplasia and perivascular fibrosis. Although some affected vessels may recanalize, one can still find cholesterol crystals within the vascular lumen. Because of the ongoing ischemic injury, glomerular sclerosis, tubular atrophy, and interstitial fibrosis are frequent findings in the later stages of this disease (21). The dislodged atheromatous debris may be showered into the circulation at different time intervals. Consequently, the kidney biopsy specimens may reveal different stages of histologic evolution in individual patients. Because of the limited sample size and the patchy nature of this disease, a renal biopsy may not always show the classic pathologic lesions in patients who have AERD.

### Table 1. Predisposing factors for atheroembolic renal disease

<table>
<thead>
<tr>
<th>Atherosclerosis</th>
<th>Systemic hypertension</th>
<th>Cigarette smoking</th>
<th>Hypercholesterolemia</th>
<th>Diabetes mellitus</th>
<th>Age ≥55 yr</th>
<th>White race</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma to atheromatous plaque</td>
<td>Invasive vascular procedure involving the aorta proximal to origin of renal arteries</td>
<td>Thrombolytic therapy</td>
<td>Blunt trauma</td>
<td></td>
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<tr>
<td>Prevention of healing of the eroded plaque</td>
<td>Anticoagulant therapy</td>
<td>Thrombolytics</td>
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*Figure 1. Location of cholesterol crystals in the glomerular capillaries and renal arterioles in an elderly patient with atheroembolic renal disease.*
Atheromatous occlusion of the medium-sized arteries and arterioles can lead to ischemic injury and tissue infarction. Morphologic features of focal segmental necrotizing glomerulonephritis and crescentic glomerulonephritis also were noted in the renal biopsy specimens of patients with AERD (22). wrinkling of glomerular capillary basement membrane is not an uncommon finding. Because of the high prevalence of hypertension in these elderly patients, arteriolar nephrosclerosis often is observed (23). Previous studies also showed a statistical correlation between AERD and focal segmental and global glomerulosclerosis (15,23). Whether the focal sclerosis is from aging process, chronic ischemic injury, or glomerular hyperfiltration is not known and remains a matter of speculation. Vidt et al. (24) from Cleveland Clinic noted concurrent renal artery stenosis in 19 of 24 patients (77%) with AERD.

Role of Complement

Hammerschmidt et al. (21) showed that the material extracted from the human atheromatous plaques can trigger complement pathway in vitro. They also observed in vivo complement activation in a patient with AERD. Cosio et al. (20) noted hypocomplementemia in three patients with AERD. Subsequently, they measured serum complement levels in six additional patients and found that two thirds had decreased levels of serum complement (C3 and C4) in the absence of any other known cause of the hypocomplementemia. Others have confirmed these observations. The subacute and smoldering clinical course, characteristic renal histology, and evolving patchy inflammation around the occluded vessels suggest the possibility that vascular inflammation plays a role in the pathogenesis of AERD.

Previous studies showed that cholesterol embolism can occur in other tissues, including the skin, subcutaneous tissue, skeletal muscle, prostate, pancreas, liver, spinal cord, and gastrointestinal tract (1,5,25–27). Erosion of the atheromatous plaques from ascending aorta may cause embolic occlusions of intracerebral vessels and retinal circulation (28).

Experimental Models of AERD

Very few experimental studies have dealt with AERD (29–31). The animals used were either rats or rabbits. The experiments consisted of injection of the plaque suspension (after it is ground and filtered to keep the particle size below 200 μm) into the animal’s left carotid artery or the aorta. The model has provided a unique opportunity to study the evolution of renal lesions, by serial examination of the tissue specimens. These experiments have confirmed further the complement activation and hypocomplementemia, which has been noted often in patients with AERD (20,21).

One day after the injection of the plaque suspension, fragments of atheroma were identified in the lumen of renal vessels. Focal fibrin deposits were detected later in the glomeruli and in medium-sized arterioles. Patchy cortical infarction was common, perhaps the result of ischemic injury. Three days after the injection, the fibrin deposition was less prominent, but there was intense perivascular mononuclear and eosinophilic infiltration. Six days after the infusion, intimal proliferation and luminal occlusion were observed frequently (20,21).

Clinical and Laboratory Features

Because atherosclerosis seems to be a prerequisite for the development of AERD, it is not surprising that the disease is seen more commonly in patients older than 65 yr. They also have other risk factors for vascular occlusion, such as cigarette smoking, hypertension, and diabetes mellitus. In a series of 221 patients with cholesterol embolism reported by Fine et al. (5), only 12 were younger than 51 yr. Also, there seems to be a preferential involvement among white individuals (32). It is unclear whether the lower incidence in black individuals is due to less frequent performance of the invasive vascular procedures, greater difficulty in recognizing the cutaneous manifestations on a darker skin, or some unique properties of the atheromatous plaque with a lesser propensity for erosion. The disease is more prevalent in men (5,15,23,33).

Because of the involvement of multiple organs, the clinical manifestations of AERD are extremely variable (Table 2).

Table 2. Atheroembolic renal disease: clinical and laboratory features

<table>
<thead>
<tr>
<th>General</th>
<th>Renal</th>
<th>Cutaneous</th>
<th>Abdominal</th>
<th>Nervous system</th>
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<tbody>
<tr>
<td>myalgia</td>
<td>acute renal failure or acute on</td>
<td>digital mottling</td>
<td>anorexia</td>
<td>amaurosis fugax</td>
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<td>fever</td>
<td>chronic renal failure</td>
<td>and nail pulp</td>
<td>nausea-vomiting</td>
<td>headache</td>
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<td>weight loss</td>
<td>hematuria</td>
<td>infarcts</td>
<td>nonspecific</td>
<td>cerebrovascular</td>
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<td></td>
<td>worsening of hypertension</td>
<td>livedo reticular</td>
<td>abdominal pain</td>
<td>accidents of sudden</td>
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<td></td>
<td>proteinuria, occasionally in</td>
<td>purple toes</td>
<td>gastrointestinal</td>
<td>onset</td>
</tr>
<tr>
<td></td>
<td>the nephrotic range</td>
<td>gangrene of</td>
<td>hemorrhage</td>
<td>paraparesis</td>
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<tr>
<td></td>
<td>renal infarction</td>
<td>toes</td>
<td>bowel infarction</td>
<td>altered mental</td>
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<td></td>
<td>perforation</td>
<td>status</td>
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<td></td>
<td></td>
<td></td>
<td>acute pancreatitis</td>
<td>mononeuropathy</td>
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<td></td>
<td>abnormal liver</td>
<td>Eyes</td>
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<td></td>
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<td>enzymes</td>
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General

- myalgia
- fever
- weight loss

Renal

- acute renal failure or acute on chronic renal failure
- hematuria
- worsening of hypertension
- proteinuria, occasionally in the nephrotic range
- renal infarction

Cutaneous

- digital mottling and nail pulp infarcts
- livedo reticularis
- purple toes
- gangrene of toes

Abdominal

- anorexia
- nausea-vomiting
- nonspecific abdominal pain
- gastrointestinal hemorrhage
- bowel infarction and perforation
- acute pancreatitis
- abnormal liver enzymes

Nervous system

- amaurosis fugax
- headache
- cerebrovascular accidents of sudden onset
- paraparesis
- altered mental status
- mononeuropathy

Eyes

- retinal emboli
disease generally presents as an acute or subacute renal failure in elderly patients who have a history of renal insufficiency. Approximately 80% of these patients have serum creatinine levels of 2.0 mg/dl or more at the time of the initial presentation, and nearly 40% have far advanced renal failure, needing dialysis. There frequently is a worsening of systemic hypertension (9,33,34). The BP often is difficult to control; it can even be malignant on occasions because of excessive activation of the renin-angiotensin system.

Cholesterol embolization at other sites may lead to cutaneous, musculoskeletal, gastrointestinal, neurologic, and ophthalmic manifestations (25–28,35–37). The classic cutaneous lesions of AERD are livedo reticularis (purplish rash over the lower extremities and abdominal wall), small nail bed infarcts, and purple toes (35). The patients also may develop symptoms such as abdominal pain; nausea and/or vomiting; occult or frank blood loss; acute pancreatitis; and visceral perforation from cholesterol embolization in the gastrointestinal tract, liver, pancreas, and spleen (26,37). The musculoskeletal features include muscle pain, arthralgias, and, on occasion, rhabdomyolysis (36). Mental confusion, focal neurologic deficits, and amaurosis fugax are the common central nervous system findings (25). Funduscopic examination may show occlusion of retinal arteries leading to pallor from retinal infarction (Hollenhorst sign), which may be helpful as an additional diagnostic feature in this disease.

Constitutional symptoms of fever, malaise, and weight loss often are present in these patients, which may add to the diagnostic confusion. The hypocomplementemia, elevated sedimentation rate, and increased level of C-reactive protein and the peripheral blood eosinophilia are pseudo vasculitic presentations, and AERD should be distinguished from the true vasculitis on the basis of other clinical findings and renal histology. Subclinical involvement of the adrenal glands, testes, prostate, thyroid gland, and avascular necrosis of the head of the femur also were noted in autopsy studies of patients with atheroembolism (19,27).

The urinalysis may show bland urine, microscopic hematuria, or even red cell casts. The proteinuria can be minimal or high in the nephrotic range. Fine et al. (5) described proteinuria (1+ or more by dipstick) in 53% of patients with AERD. Nephrotic-range proteinuria, which once was considered a rare finding, is now being reported more frequently (38,39). It was suggested that the proteinuria and urinary sediment abnormalities are more likely to occur in patients who have glomerular embolization than the more typical vascular occlusion. Eosinophilia also was noted in 8 of 24 patients (33%) who had biopsy-proven AERD (40). Like in renal vasculitis, AERD patients frequently have an elevated erythrocyte sedimentation rate (5). However, in contrast to vasculitis, the platelet count usually is low (3). Both peripheral eosinophilia and eosinophiluria also were observed in this disease, but the findings are not consistent (40,41). Kasinath et al. (41) described eosinophilia in 80% of patients with AERD. We also observed it in 60% of our patients (42). Hypocomplementemia is common, but, like eosinophilia, it is not a consistent finding and lacks specificity.

The diagnosis of AERD requires that the physician be suspicious. If a patient presents with worsening renal failure, particularly after undergoing an invasive vascular procedure or thrombolytic therapy, one must look for evidence of cholesterol embolism in the kidney and other sites, including lower extremities, abdomen, and eyes. The diagnosis has to be confirmed by demonstrating cholesterol crystals in the biopsy specimens. Other diseases that should be considered in the differential diagnosis are (1) radio-contrast nephropathy, (2) ischemic acute renal failure, (3) systemic vasculitis, (4) thrombotic thrombocytopenia purpura, and (5) bacterial endocarditis (Table 3). In contrast nephropathy, the renal failure occurs within 48 to 72 h after the dye infusion and generally resolves within 4 to 7 d. Ischemic acute renal failure is diagnosed by its immediate onset, its association with hypotension, and the lack of systemic manifestations such as skin rash, eosinophilia, and hypocomplementemia. Because of the multisystem involvement, cholesterol embolism can mimic other systemic diseases such as vasculitis, bacterial endocarditis, polymyositis, and thrombotic thrombocytopenic purpura. These disorders have to be excluded through use of appropriate diagnostic studies.

Renal biopsy seems to be a reliable diagnostic test in patients with AERD. However, the procedure has some limitations. The typical lesion, i.e., blockage of small arteries, arterioles, and the glomerular capillaries, usually is focal. In a patient with AERD who died from acute renal failure, of the 12 renal cortical specimens studied at autopsy, only 9 (75%) showed the typical cholesterol emboli. The diagnostic sensitivity of a single renal biopsy is 75%. However, with two biopsies on the same patient, the sensitivity improves to 94%. In a patient who presents with worsening renal failure, in the absence of kidney biopsy, demonstration of cholesterol emboli in other tissues would support the diagnosis. Even in patients who have end-stage renal failure and are undergoing chronic dialysis, cholesterol embolization may occur after an invasive vascular procedure (42). AERD remains underdiagnosed because one of the clues to the clinical diagnosis—worsening of renal failure—often is absent. In elderly dialysis patients, the cutaneous manifestations of AERD, i.e., livido reticularis in the lower extremities, often are mistaken for ischemic skin lesions resulting from peripheral vascular disease.

### Relationship to Invasive Vascular Procedures and Thrombolytic/Anticoagulant Agents

AERD has a variable but temporal relationship to the performance of invasive vascular procedures and pharmacologic treatment with thrombolytic/anticoagulant agents. The clinical symptoms may develop immediately after the vascular procedure or several days later.

<table>
<thead>
<tr>
<th>Table 3. Atheroembolic renal disease: differential diagnosis</th>
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<tbody>
<tr>
<td>Radio contrast nephropathy</td>
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<tr>
<td>Acute tubular necrosis from ischemic injury</td>
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<tr>
<td>Systemic or renal vasculitis</td>
</tr>
<tr>
<td>Thrombotic microangiopathy</td>
</tr>
<tr>
<td>Bacterial endocarditis with embolic occlusion of renal vessels</td>
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</table>
ure or can evolve slowly over a period of weeks or months. Lack of awareness of this disease among nonrenal physicians, the variable clinical presentation, and the infrequency of obtaining biopsy specimens often lead to an underestimation of the true incidence of AERD as a complication of the invasive vascular procedures.

In a prospective study of 183 elderly patients who underwent cardiac catheterization, Rich and Crecelius (43) noted acute renal failure in 19 patients (10.5%) within 48 h after angiography. Surprising, AERD was not even considered in the differential diagnosis of acute renal failure. Thirty to 85% of patients with AERD have a history of antecedent invasive vascular procedure such as aortography or coronary angiography. At our own institution, 85% of patients who presented with AERD had had an invasive vascular procedure (abdominal aortography or carotid or coronary angiography) during the previous 3 mo (42).

Ramirez et al. (44) noted cholesterol emboli at autopsy in 30% of patients who died within 6 mo after undergoing aortography and 25.5% of patients who died within 6 mo after undergoing coronary angiography. In contrast, the incidence of cholesterol embolism was 4.3% in age-matched controls who had not undergone a previous invasive vascular procedure. The cholesterol emboli in the control group may have resulted from spontaneous erosion of atheromatous plaques or from previous anticoagulant or thrombolytic therapy. The authors did not indicate whether there were any cases of renal failure associated with atheroembolism in either the control or the reference group. The low incidence most likely is due to underdiagnosis, because renal function was not systematically monitored in patients after the angiography. Whether the approach used for aortogram or coronary angiogram has any impact on subsequent development of AERD remains only as a speculation. In a retrospective study of 1579 cases of coronary angiography, Johnson et al. (45) did not find any difference in peripheral vascular complications between the brachial and femoral approach. Only a single patient had cholesterol embolism after the femoral approach, which was the routine site used at their center.

AERD was found to occur more frequently after thrombolytic therapy than after the use of anticoagulants (6,46–51). Previous studies showed that 13 to 22% of patients with cholesterol embolism had previous anticoagulant therapy (either heparin or warfarin). This temporal relationship also was noted in several case reports (49–51). In a prospective study, Blankenship et al. (17) failed to find any increase in AERD after thrombolytic therapy, but the study had many limitations. Because the superficial clots stabilize the ruptured atherosclerotic plaque, dissolution of these by thrombolytic agents may cause showering into the systemic circulation and subsequent lodging in other organs.

Despite the widespread use of anticoagulants and thrombolytic agents, the incidence of AERD in the absence of a preceding invasive vascular procedure remains low, at 4.3%. One might conclude from these observations that AERD is not a common complication of these medications. However, “purple toes syndrome,” which was described as a complication of warfarin use by Fedar and Auerbach in 1961 (49), may very well be a manifestation of cholesterol embolization of small arterioles in the feet, and it may not always be associated with renal failure (48). AERD is known to occur spontaneously, but it is rare. Spontaneous cholesterol embolization may occur after a blunt trauma (10). In patients who experienced spontaneous atheroembolism, severe occlusive aorto-iliac disease or an aortic aneurysm with intramural thrombus was the frequent finding. Cholesterol embolism also can be a recurrent process. Of the 70 patients with AERD who were receiving chronic dialysis, we noted recurrent, spontaneous cholesterol embolization in 2 (42).

AERD Affecting the Renal Allograft

Twenty-one cases of biopsy-proven AERD were reported in the renal allografts (6–8). The time of the diagnosis ranged from immediately before transplantation to 15 yr posttransplantation (8). After reviewing 200 renal transplant biopsies performed at our center between 1990 and 1995, we found 2 other cases of cholesterol embolism. The source of cholesterol emboli in the transplanted kidneys could be (1) an unsuspected AERD in the donor kidney and (2) spontaneous dislodgment of an atheromatous plaque from the aorta of an elderly transplant recipient. AERD may remain as an incidental finding without any obvious clinical abnormalities such as hematuria, proteinuria, or decreased allograft function. The clinical course of these patients varied from complete recovery of renal function to permanent graft loss.

Therapy

There is no specific therapy directed against the existing vascular lesions. The interventions included (1) interposition of prosthetic bypass grafts, (2) angioplasty, and (3) extracorporeal arterial reconstruction (52). These surgical maneuvers may not be successful if the source of atheroembolism is in the suprarenal part of the aorta. With reference to medical management, there are a few case reports that documented recovery of renal function and disappearance of cyanotic features after the use of lipid lowering agents (53,54). However, no studies have analyzed the benefits of one form of therapy over the other in the management of patients with AERD.

Clinical Outcome

The prognosis in this disease is considered to be very poor. The reported mortality has varied from 64 to 81% (5). The high mortality most likely is due to a selection bias, because most of the published cases were diagnosed at autopsy. Over the past decade, a few case reports documenting the recovery of renal function in patients with AERD appeared in the literature (53).

To assess the course of AERD in the patients undergoing dialysis, we compared the rate of hospitalization and survival on dialysis of 40 patients with end-stage renal failure from AERD (mean age, 70.5 yr) and 1063 age-matched controls (mean age, 70.3 yr) who had other causes of end-stage renal failure. All patients included in the study were accepted for dialysis between 1986 and 1992. The diagnosis of AERD was made on the basis of the classic clinical presentation and the
demonstration of cholesterol crystals in tissue specimens. Our results showed that patients who were undergoing dialysis and who had a primary diagnosis of AERD had no significant increase in rate of hospitalization or mortality, compared with age-matched controls (42).

Future Research

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. (55), who noted improvement in clinical symptoms in two patients with AERD after the use of high-dose corticosteroids.

In patients who have AERD and are undergoing dialysis, it is not known whether the hemodialysis or peritoneal dialysis offers a better chance of survival and lower patient morbidity. Elderly patients who undergo hemodialysis frequently are treated with Coumadin for maintaining the patency of vascular access, and, in addition, they receive heparin during dialysis to prevent clotting in the extracorporeal circuit. Continued use of heparin and other anticoagulants in hemodialysis patients can potentially retard the healing of an eroded, atheromatous plaque and promote the dislodgment of cholesterol emboli into the renal and peripheral circulation. Hemodialysis-associated hypotension also is a common problem in elderly patients. Because the diseased kidney does not have the benefit of renal autoregulation, perhaps it is at higher risk for developing ischemic injury after each hypotensive episode. Whether peritoneal dialysis, which does not require the use of anticoagulants and usually is not associated with hemodynamic instability, would lead to better outcomes (patient survival and recovery of renal function) remains to be studied.

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