Heart International / Vol. 2 no. 3-4, 2006 / pp. 155-160

Cholesterol crystal embolism (atheroembolism)

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ABSTRACT: Cholesterol crystal embolism, known as atheroembolic disease, is caused by showers of cholesterol crystals from an atherosclerotic plaque that occludes small arteries. Embolization can occur spontaneously or as an iatrogenic complication from an invasive vascular procedure (angiography or vascular surgery) and after anticoagulant therapy. The atheroembolism can give rise to different degrees of renal impairment. Some patients show a moderate loss of renal function, others severe renal failure requiring dialysis. Renal outcome can be variable: some patients deteriorate or remain on dialysis, some improve and some remain with chronic renal impairment. Clinically, three types of atheroembolic renal disease have been described: acute, subacute or chronic. More frequently a progressive loss of renal function occurs over weeks. Atheroembolization can involve the skin, gastrointestinal system and central nervous system. The diagnosis is difficult and controversial for the protean extrarenal manifestations. In the past, the diagnosis was often made post-mortem. In the last 10 yrs, awareness of atheroembolic renal disease has improved. The correct diagnosis requires the clinician to be alert. The typical patient is a white male aged >60 yrs with a history of hypertension, smoking and arterial disease. The presence of a classic triad (precipitating event, renal failure and peripheral cholesterol crystal embolization) suggests the diagnosis. This can be confirmed by a biopsy of the target organs. A specific treatment is lacking; however, it is an important diagnosis to make because an aggressive therapeutic approach can be associated with a more favorable clinical outcome. (Heart International 2006; 3-4: 155-60)

KEY WORDS: Cholesterol crystals, Renal atheroembolic disease, Atherosclerosis

INTRODUCTION

Cholesterol crystal embolism is a multisystemic disorder characterized by the occlusion of small arteries by cholesterol crystal emboli deriving from eroded atherosclerotic plaques of the aorta (1-7). The proximity of the kidneys to the abdominal aorta makes the kidney the most frequent target organ. In the past, cholesterol crystal embolization has been frequently overlooked as a cause of renal dysfunction. Usually, the diagnosis was made post-mortem (1-3). We discuss the pathogenesis, incidence and clinico-pathological findings of atheroembolic renal disease.

PATHOGENESIS

The formation of a complicated atherosclerosis lesion is a prerequisite for the development of cholesterol crystal emboli syndrome. Plaques with a large extracellular lipid-rich core and thin fibrous cap appear to be most vulnerable to rupture. Mechanical and hemodynamic stresses can rupture the fibrous cap, releasing the underlying extracellular cholesterol-rich matrix. Atheroembolization can occur spontaneously or after aortic wall trauma, including vascular surgery and angiographic procedures. Another etiologic factor is anticoagulation. Vascular surgery can disrupt plaques dur-

1826-1868/155-6$15.00/0

ing incisions, clamping or manipulation of the vessels. Radiological aortic instrumentation can act by inducing a mechanical trauma: catheter manipulations scrape the walls of the aorta, disrupting the atherosclerotic plaques. The third precipitating factor described is anticoagulant treatment, including both heparin and oral anticoagulants. These agents can prevent the formation of a protective thrombus overlying an ulcerated plaque or could initiate the disruption of a complex plaque by causing a hemorrhage into it. Thrombolytic therapy may lyze thrombi, including those covering atherosclerotic plaques (8-11). Once in the circulation, cholesterol crystal emboli lodge in small arteries, 150-200 mm in diameter; this is followed by an inflammatory reaction, intimal proliferation and intravascular fibrosis. The entire process results in the narrowing or obliteration of the lumen, causing ischemic changes (7).

Epidemiology

The syndrome of renal cholesterol crystal embolism usually affects elderly males with a history of diffuse atherosclerosis (1-3). The true incidence of atheroembolic renal disease is difficult to estimate. Retrospective autopsy (incidence 10-27%) or biopsy (incidence 1%) studies can exaggerate the frequency of the disease because they could detect subclinical cases. Conversely, the incidence of atheroembolic renal disease in clinical studies appears to be much less than that observed in autopsy and biopsy studies. However, in these studies, clinically significant atheroembolism has probably been underestimated due to short-term follow-up. Estimates of atheroembolic renal disease incidence after aortic catheterization is <0.2%, appearing to be much less than those observed in autopsy and biopsy studies (5, 8, 10-12). However, it remains difficult to quantify the magnitude of clinically significant angiography-associated atheroembolism because the majority of studies did not search the disease systematically, which can manifest weeks to months after the procedure.

Pathological characteristics

The histological features of renal cholesterol crystal embolization are highly characteristic (1-3). The hallmark of the condition is an occlusion of the lumen of the small arteries by atherosclerotic material. As the lipids are dissolved by the techniques used to prepare the tissue for histological examination, the cholesterol crystals may be identified by the presence of needle-shaped spaces, which appear empty in routine histological sections. Therefore, clefts are found that remain after cholesterol has dissolved during fixation. Renal histological examination shows characteristic, biconvex, needle-shaped clefts in vessels between 50-200 mm in diameter (arcuate and interlobular arteries). Rarely, the cholesterol crystals lodge in the afferent arteries and glomeruli. Numerous foci of patchy, irregular atrophy of the renal parenchyma and occasional areas of ischemic infarction can be seen. In the involved areas, glomeruli show various degrees of obsolescence or ischemic retraction of the tuft. Many tubules show atrophic changes from slight to severe; areas of acute tubular necrosis may also be present (1-3).

Clinical features

The clinical consequences of cholesterol crystal embolization vary considerably. Patients can be completely asymptomatic when the diagnosis is made coincidentally at renal biopsy, or they can present with a distinct clinical syndrome, ranging from a cyanotic toe to a multiorgan systemic disease that can mimic other systemic diseases (1-6, 8-11). The distribution of end-organ damage depends on the anatomic location of the original atherosclerotic plaques and the extent of organ involvement. For instance, cholesterol crystal embolization from carotid artery plaques leads to clinical involvement confined to the retinal and cerebral circulation. However, when the source of the atheroemboli is in the thoracic aorta or, more commonly, the abdominal aorta, the central nervous system, visceral organs, and extremities can be involved. Only the lower extremities are involved if the site is below the renal arteries. Moreover, individuals at risk of renal cholesterol crystal embolism commonly have other chronic illnesses causing renal failure, such as hypertension, renovascular disease and diabetes mellitus. Finally, patients at risk of atheroembolic renal disease usually have multiple risk factors for atherosclerosis and almost always have symptomatic atherosclerosis (1-6, 8-11).

Renal involvement

The kidney is the most frequent target organ for cholesterol crystal embolization. Although a small non-significant cholesterol crystal embolism can occur in the kidneys and be clinically silent, renal clinical manifestations are found at presentation or during the course of the clinical illness in approximately 50% of patients (1-3). In patients with the disease occurring after angiographic and vascular surgical procedures, the interval from the inciting event to the onset of renal symptoms can vary greatly. Some patients have immediate clinical features, but in others, the onset can be more insidious, with a delay of weeks or months between the precipitating event and clinical features (1-6, 8-11). Clinically, three types of atheroembolic renal disease have been described. In the first type, renal impairment can onset suddenly. This acute form of renal failure develops a few days after the inciting event and is considered to be due to a massive embolization. The second type of atheroembolic renal disease, the most frequently observed, is characterized by a subacute time course, probably explained by the foreign-body reaction or the cyclic occurrence of cholesterol crystal emboli showers. In this setting, renal impairment occurs in a stepwise fashion. A third clinical form has been observed which presents as chronic and stable renal impairment associated with the clinical presentation of nephroangiosclerosis and/or ischemic nephropathy (10, 12).

The renal outcome for patients with atheroembolic renal disease can be variable; some patients deteriorate or remain on dialysis, some improve, and some remain with chronic impairment. In both the acute and subacute scenarios, dialysis could be required in 28-61% of patients. In early reports, renal outcome was described as quite dismal, with progression over weeks to months to end-stage renal failure. However, more recent experiences suggest less inexorable deterioration, with a possibility for the spontaneous recovery of renal function in approximately one-third of patients, even after variable periods of dialytic support (8-10). Renal function recovery is probably caused by several factors, such as reversal of inflammation, resolution of acute tubular necrosis in ischemic areas and hypertrophy in surviving nephrons (10, 12).

Cutaneous manifestations

Among extrarenal findings, the most common is the skin. Cutaneous features most often found are purple toes and livedo reticularis. Typically, the purple/blue toe syndrome presents as the sudden appearance of a small, cool, cyanotic and painful area of the foot (usually a toe). The lesion is usually bilateral, and can progress to ulceration, digital infarcts and gangrene. In the majority of patients, the presence of digital cyanosis is characterized by well-preserved peripheral pulses (1-6). Livedo reticularis is also a frequent skin lesion. This consists of a blue-red mottling of the skin in a netlike pattern, most likely caused by the obstruction of small arteries, capillaries or venules in the deep dermis. It is often seen on the feet, legs, buttocks and lumbar region (1-3). Other dermatologic manifestations include nodules, which appear as the result of an inflammatory reaction surrounding cholesterol crystals, purpura and petechiae.

Gastrointestinal involvement

Atheroemboli to the gastrointestinal tract represent an important often unsuspected cause of abdominal manifestations. Involvement of the digestive system varies from 18.6-48% and can occur at any site along its length, producing many, often misleading, presentations (1-3, 12). Usually, the prognosis of patients with gastrointestinal disease is poor; the overall death rate is high. The most common mode of presentation of cholesterol crystal embolism to the bowel is hemorrhage and abdominal pain. Gastrointestinal bleeding most often results from superficial mucosal ulcerations, erosions or mucosal infarcts. Clinical presentation can range from occult blood loss and melena to bloody diarrhea, depending on the site and the extent of the lesions. Abdominal pain can be caused by non-infarctive ischemia, also inducing malabsorption and diarrhea, or by fibrous stricture with bowel obstruction caused by tissue-repair reactions after repeated showers of atheroemboli. Pancreatitis is a rare presentation, although the pancreas is a frequent emboli site. Necrotizing acalculous cholecystitis has been reported rarely. Intestinal symptoms, consisting mostly of nausea, abdominal pain, diarrhea and gastrointestinal bleeding, were present in 10-33% of patients in the largest patient series published (12).

Central nervous system manifestations

Cerebral cholesterol crystal embolism can be associated with various symptoms, such as transient ischemic attacks, cerebral infarction, amaurosis fugax, paralysis, confusional states and gradual deterioration in neurological function. In the largest case series, neurological manifestations occurred in 4-23% of patients with renal cholesterol emboli syndrome (2, 3, 8, 9). In clinical studies, a definite diagnosis of atheroemboli in the brain is difficult to make, and it ultimately depends on evidence of cholesterol crystal emboli to other organs. Finally, the retina is a frequent target organ, providing a unique opportunity to observe emboli. Although carotid artery disease may be more frequently the origin of retinal cholesterol crystal emboli, when central nervous system emboli accompany the more generalized form of the disorder, cholesterol crystal emboli arise from the proximal part of the aorta. The incidence of retinal cholesterol crystal emboli, responsible for retinal ischemic events, varies greatly, ranging from 6-25% in patients, and depends on the proportion of patients in whom the fundi were examined and the thoroughness of the examination (8, 9).

Other extrarenal manifestations

Showers of cholesterol crystals can occur in virtually any organ. Myositis and splenic infarcts are rare manifestations. Although uncommon, atheroemboli can involve the coronary arteries; the usual source is the aortic root or the proximal coronary artery. Recently, cholesterol crystal embolization to the lung has been described, suggesting that atheroembolic renal disease should be considered a new cause of pulmonary-renal syndrome. Non-specific findings, such as fever, weight loss, myalgias and headache, have been reported in a minority of patients and could suggest a systemic disease (1-3, 8-10).

Laboratory features

Laboratory features are non-specific. However, various laboratory tests help establish the cholesterol crystal embolism diagnosis. Atheroembolic renal disease is first characterized by elevations in serum creatinine (Cr) and blood urea nitrogen levels. Urinary investigation is generally non-diagnostic because it shows such non-specific alterations as mild proteinuria and microhematuria with hyaline and granular casts. Hematuria is found in 33-40% of patients; proteinuria in the non-nephrotic range can be detected in 50-60% of patients (2, 3, 8, 9). In our series, urinalysis showed mild-moderate proteinuria in the majority of patients (10, 12). Among the extrarenal laboratory features, eosinophilia appears to be the most common finding. An 80% incidence of eosinophilia was found when adequate white blood cell counts and differentials were reported. Subsequent reports found an incidence of eosinophilia varying from 14-71% (3, 8, 9, 10, 12). Laboratory markers of acute inflammation, such as erythrocyte sedimentation rate, serum C-reactive protein level and fibrin level, could be increased in a substantial proportion of cases (1-3). Hypercholesterolemia is a well-known risk factor for atherosclerosis of which crystal embolization can be considered a direct complication. However, the most important studies of atheroembolism usually have not reported serum cholesterol levels. Recently, hypercholesterolemia was considered a substantive risk factor for renal atheroembolization and it was found that 27% of patients had hypercholesterolemia (2, 3, 8-11).

Diagnosis

Diagnostically, cholesterol crystal embolism has challenged physicians for over a century. This is probably because atheroembolism is ubiquitous, with random and variable distributions in the body. Knowledge of the associated risk factors, recognition of its multiple clinical presentations, and its consideration after certain vascular invasive procedures could allow a pre-mortem diagnosis in a significant number of cases. The typical patient is a white male aged >60 yrs with a baseline history of hypertension, smoking and arterial disease (1-6, 8-11). The presence of a triad composed of a precipitating event, acute or subacute renal failure and peripheral cholesterol crystal embolization strongly suggests the diagnosis (9-11). The presence of other complications of atheroembolism, such as gastrointestinal bleeding and neurological involvement, should raise

the suspicion level. Among the laboratory features, helpful clues to the diagnosis include the presence of eosinophilia and an increase in acute inflammation markers. Histological confirmation has traditionally been considered essential to the pre-mortem diagnosis of atheroembolic renal disease (1-6). The confirmatory diagnosis involves a biopsy of the target organs. Renal biopsy should be considered the most definitive method of diagnosing atheroembolic renal disease (7). However, during the acute disease phase, many patients can be too sick to proceed with renal biopsy: in this setting, the use of an invasive procedure may not be justified. Moreover, because cholesterol crystal embolization is a patchy process, a focal lesion can elude the histological examination. Alternatively, the biopsy of characteristic cutaneous lesions could yield a positive diagnosis in several cases. Skin biopsy is a simple non-invasive procedure that can be easily performed. The histological confirmation of cutaneous atheroemboli was possible in 92% of patients (n=24) in whom a skin biopsy specimen was obtained. Skin lesions represent an easily accessible site. For this and for the frequency of the peripheral ischemic changes, skin biopsy specimens should be considered the best sample of choice for histological diagnosis (10, 12). Regarding the diagnosis, two final points deserve consideration. First, in the appropriate clinical setting, ophthalmoscopic examination showing retinal cholesterol crystal emboli could establish the diagnosis in a significant number of patients. Secondly, in contrast to the accepted teaching, in the presence of a specific set of clinical features (a triad including a precipitating event, subacute renal failure and peripheral cholesterol crystal embolization), the diagnosis of atheroembolic renal disease can be made without histological evaluation (9-11).

The differential diagnosis first includes contrast nephropathy, which immediately follows the radiographic study. There is an increase in Cr level a few days after the procedure; peak Cr level elevation occurs approximately 1 week after exposure and returns to baseline within 10-14 days (13). Conversely, atheroembolic renal damage frequently has a delayed onset (days to weeks) and a protracted course; the outcome is often poor, resulting in progressive renal failure requiring dialysis.

Management and outcome

To date, no effective treatment is available for this condition. Anticoagulants should be avoided because they can potentiate the problem. Disagreement exists concerning steroid treatment. Recently, statins have been found to be associated with better renal outcome. In the context of the emerging evidence of statin-induced plaque stabilization and regression (14, 15), the possible role of an aggressive lipid lowering therapy in the conservative treatment of cholesterol crystal embolization should be evaluated in a proper prospective study.

Medical treatment is mostly symptomatic, and supportive measures, including dialysis, are appropriate. Surgery is rarely indicated because the source of cholesterol crystal embolization is frequently uncertain. Moreover, patients are usually too weak for a major surgical intervention and the necessary aortic clamping during surgery would induce a major risk of recurrence. Prevention is very important; the main recommendation is to restrict the indications of angiography and surgical procedures as much as possible in severely atherosclerotic patients.

Patients with atheroemboli have a dismal outlook. Historically, the 1-yr mortality rate ranged from 64-87% (2, 3, 6, 8). However, in two recent studies, an aggressive supportive treatment was associated with a 1-yr survival rate of 79 (9) and 69% (16), respectively. This management was characterized by the avoidance of anticoagulation, good control of hypertension and heart failure, dialytic therapy and adequate nutrition; aortic manipulating procedures were usually postponed. Together, these data suggest that an aggressive therapeutic approach with patient-tailored supportive measures could be associated with a more favorable clinical outcome.

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