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Cholesterol crystal embolism: Diagnosis and treatment

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Cholesterol crystal embolization (CCE) is a dreaded complication of radiology, vascular surgery, and/or anticoagulation in patients with atherosclerosis and ulcerated aortic plaques. It also represents a cause of early graft failure and of poor results of renal artery surgery. Crystals lodge in small caliber renal arteries, where they induce early, transitory thrombosis followed by delayed, definitive obstruction by endarteritis, accompanied by evidence of inflammation and eosinophilia. Massive CCE leads to early oligoanuria. In subacute forms, renal insufficiency is often delayed by weeks or months following the triggering event. A third, chronic subset of CCE is easily mistaken for atherosclerotic renal ischemia and/or nephrosclerosis. The kidney is rarely the sole organ involved in acute/subacute forms, in which the central nervous system, the coronary arteries, the spinal cord, and the mesenteric and pancreatic blood supply compromise represent the main causes of death. Cutaneous, retinal, and muscle involvement allow diagnosis by inspection or scarcely invasive biopsies in about 80% of cases, whereas renal biopsy as the only diagnostic procedure is required in 20% of cases. Prevention is based on avoidance of endovascular radiology maneuvers, vascular surgery, and excess anticoagulation in atherosclerotic patients. Treatment of acute/subacute forms of renal insufficiency consisting of stopping anticoagulation and forbidding any new radiologic and/or vascular surgery procedure; treating hypertension with angiotensin 2 antagonists and vasodilators, strict volemic control by loop diuretics and ultrafiltration, along with parenteral nutrition and prednisone, has been credited with improved outcome. Iloprost may obtain favorable results. Statins definitely ameliorate the renal and patient's prognosis.

Kidney International (2006) **69,** 1308–1312. doi:10.1038/sj.ki.5000263; published online 1 March 2006

KEYWORDS: clinical nephrology; focal segmental glomerulosclerosis; chronic renal failure; arteries; acute renal failure; cholesterol crystal embolism

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Received 1 December 2005; revised 6 January 2006; accepted 10 January 2006; published online 1 March 2006

Considering the progress of invasive endovascular procedures, one can assume that the frequency of cholesterol crystal embolism (CCE) increases with passing time. In fact, although atheroembolism ranks among the dreaded complications of radiology and of vascular surgery, it is still underdiagnosed and its treatment is not clearly codified.

CCE should no longer be the 'Cinderella of nephrology'.[1] However, few papers deal with numbers of patients allowing statistical analysis on this common complication of atherosclerotic ischemic renal disease,[2] a masquerader which manifests with such disparate signs and symptoms that the diagnosis is far from being readily made. An extensive review by Scolari *et al.*[3] thoroughly analyzed the spectrum of CCE that spans the fortuitous discovery of a few crystals at autopsy to the life-threatening occurrence of multiorgan involvement including acute renal failure.

EPIDEMIOLOGY AND FREQUENCY

CCE is mostly a complication of widespread atherosclerosis in the white Caucasian. It is apparently rare in Blacks,[4] or underdiagnosed owing to the difficulty to assess livedo and purple discoloration on black skin. The frequency of CCE is variably appreciated, depending on systematic search on autopsy material as opposed to clinical diagnosis. Fine *et al.*[5] reviewed 221 histologically proven cases. Among 75 cases, clinical diagnosis of gastrointestinal and pancreatic involvement was made in 26.7%, of renal involvement in 22.7%, and of spleen, liver, and adrenal involvement in 1.33%. At autopsy, among 92 cases, the respective figures were 95.6, 83.7, and 100%. The frequency of localizations to viscera is roughly proportional to their blood flow. Considering that the renal blood flow represents 1/5th to 1/4th of the cardiac output, it comes as no surprise that CCE ranks among common etiologies of acute, subacute, and chronic renal disease in atherosclerosis.

BACKGROUND

The typical candidate for CCE is a male (male/female ratio 91/9% in Belenfant *et al.*[6]), in his 60s, smoker, lean, and suffering from various manifestations of atherosclerosis.[3,7] When sought by angiography or magnetic resonance imaging virtually all patients (97% in Belenfant *et al.*[6]) have plaques on their thoracic aorta. Strong correlations appear between CCE and certain localizations of the atherosclerotic process.

Belenfant *et al.*[6] found that 67% of their patients had an aortic abdominal aneurysm. Renal artery imaging following coronarography identifies the frequency of renal artery stenoses in patients with coronary disease, a frequency of ~30% when their renal function is diminished.[2] CCE is common in renal artery atherosclerotic disease. In 1988, we found that in 32 patients with atherosclerotic disease, 10 had evidence of CCE to the kidneys, including six in whom the diagnosis was made by histology.[8] The Cleveland Clinic Foundation Urology and Pathology team[9] evaluated the impact of CCE on morbidity and survival after surgical revascularization for atherosclerotic disease. CCE was found in the intraoperative biopsy specimen in 16/44 (36%) of the patients. The survival and the incidence of morbid events were significantly different at 6 years in patients with, as opposed to those without CCE. Interestingly, there were no distinguishing preoperative clinical or laboratory features in patients with and without atheroembolic renal disease.

TRIGGERING EVENTS

CCE is iatrogenic in a majority of cases: 79% in Scolari *et al.* [3] and 76% in Belenfant *et al.*[6] experience. The most common triggering events[7] consist of angioplasty or vascular surgery (50 and 15%, respectively in Scolari *et al.*,[3]) and long-term anticoagulant therapy (76% in Belenfant *et al.*[6]). Fibrinolytic therapy is another reported etiology.[3,10,11] The atherosclerotic patient may also suffer spontaneous detachment of a plaque, or low grade, clinically silent migration of crystals from the aortic wall. Cross[12] in a series of 372 necropsies estimated the incidence of 'spontaneous' cholesterol embolism to be 1.9%.

RENAL INVOLVEMENT

Renal complications of CCE cover three scenarios: acute, subacute, and chronic renal failure. Acute renal failure (ARF) occurring within ~7 days following the inciting event is observed in about one-third of the cases. It is often fulminant, following massive migration of crystals, and the kidney is seldom if ever the sole organ involved. This multiorgan involvement differentiates CCE from early ARF from iodinated contrast media toxicity,[7] or that complicating vascular surgery. Depending on the site of plaques, multiple vital organ damage has been described, including in a descending progression from the aortic arch to the abdominal aorta, the retina, the central nervous system, the coronary arteries, the spinal cord artery, the pancreas, the mesenteric blood supply, and the adrenal glands. A case of CCE to the lung with alveolar hemorrhage adds this condition to the list of pulmonary-renal syndromes.[13] Oligoanuria appears rapidly and is accompanied with severe hypertension or the abrupt aggravation of previous hypertension. Half of 129 patients reported by Lye *et al.*[14] were hypertensive, most of them severely. Flank pain and/or hematuria are uncommon. Conversely, abdominal pain and discomfort is frequent, due to mesenteric and pancreatic ischemia. Massive CCE usually involves lower limb muscles. Gastrointestinal and muscle ischemia explain wasting.

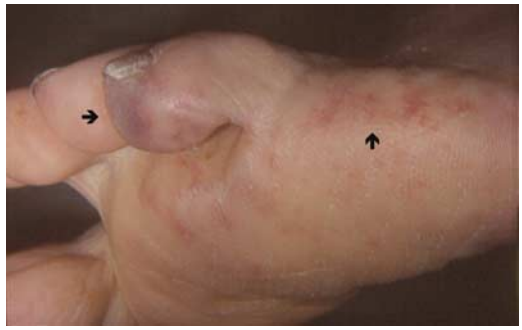

Figure 1 | Typical appearance of cutaneous lesions. This figure shows a purple toe (→) and an area of *livedo reticularis* (↑).

Cutaneous involvement is virtually constant, consisting of purple toes (Figure 1), lower limb *livedo reticularis*, which may extend to the lumbar area. Painful, localized, or complete necrosis of toes may require amputation.

The subacute subset is particular, and deceptive in that renal manifestations appear weeks or months after the inciting event. Frock *et al.*[15] in 17 patients with CCE observed that ARF occurred 5.3 ± 0.9 weeks after angiography. Renal function impairment often develops in a stepwise fashion over the following weeks. Each aggravation follows a triggering event eliciting another shower of crystals, such as repeat angiography, vascular surgery, and/or anticoagulation.[6]

In most cases of CCE proteinuria is nonsignificant. Some cases however may be accompanied by nephrotic proteinuria. Greenberg *et al.*[16] found 10 cases of focal segmental glomerulosclerosis in 24 patients with CCE, whose proteinuria reached nephrotic levels. Nevertheless, the relationship between CCE, focal segmental glomerulosclerosis, and nephrotic proteinuria is not perfectly established. Other glomerular lesions, such as diabetic glomerulopathy, cannot be excluded. Also, high-renin malignant hypertension may also induce significant proteinuria. In the same line, atherosclerotic renal artery stenosis, which is a common finding in patients with CCE, may be accompanied by focal segmental glomerulosclerosis and abundant proteinuria, without documented evidence of concomitant CCE.[17–19] These observations have fostered speculations on the relationship between renal ischemia and focal segmental glomerulosclerosis, including its collapsing variant.[20]

The chronic subset is frequent and underdiagnosed, understandably if one considers the patients' background. It manifests by a slowly progressive form of renal insufficiency with bouts of aggravation. In an atherosclerotic patient in his 60s, suffering from hypertension and renal insufficiency, and in whom stenotic renal artery plaques are common, low-grade CCE to the kidneys is usually ascribed to nephrosclerosis.[21]

PATHOPHYSIOLOGY

Figure 2 shows the source of atheroembolism. Cholesterol crystals are too small to close up the artery in which they

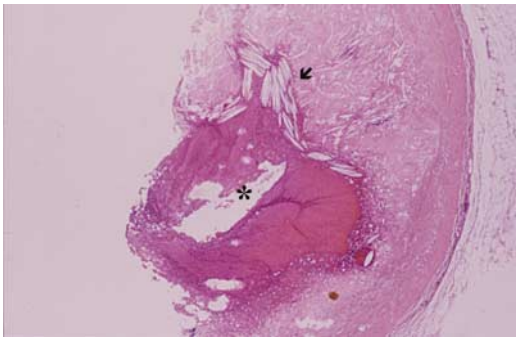

Figure 2 | Ulcerated aortic plaque. A clot (*) separates cholesterol crystals (↙) from the bloodstream. Clot dislodgement or lysis sets crystals free. Once showered into the bloodstream, they lodge in renal arteries with a diameter of 150–200 μm, mostly arcuate and interlobular arteries. Courtesy: Patrick Bruneval MD.

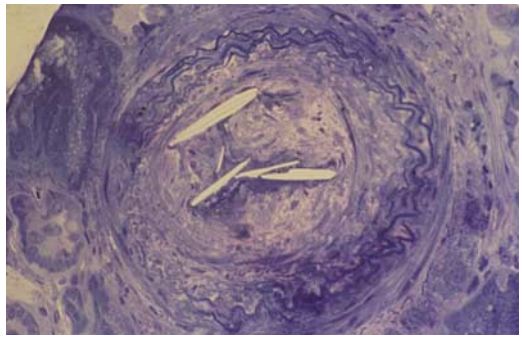

Figure 3 | Renal biopsy at a late stage. Cholesterol crystals appear as transparent clefts. This interlobular artery is obstructed by endarteritis and fibrosis. Toluidine blue, original magnification: $\times$ 400.

lodge, but induce an endothelial inflammatory reaction, which leads to complete obstruction within weeks or months. Crystals are seen in the lumen of arteries, where they appear as elongated, biconvex transparent clefts, dissolved by the tissue processing. Some small crystals may enter a glomerular afferent arteriole. Early ARF may follow massive crystal into the renal arterial tree. However, the onset of renal insufficiency is often delayed for weeks or months. This silent spell is explained by the endothelial reaction to crystals followed by obstruction. From this viewpoint, CCE induces a form of anti-neutrophil cytoplasmic antibody negative angiitis, accompanied by clinical and laboratory features of inflammation: rapid erythrocyte sedimentation rate high C reactive protein levels, high eosinophil blood counts, and much more rarely hypocomplementemia.[3,6,7,22] The pathophysiology of these last two findings is currently unclear.

Animal experiments have been based on the injection of cholesterol crystals into the renal artery followed by serial observations of the vascular lesions.[23] Shortly after lodging in the lumens crystals induce platelet aggregation and thrombosis. Thereafter the thrombus undergoes lysis. Subsequently, from 5 days to 1 month onwards, progressive fibrous endarteritis leads to complete arterial obstruction (Figure 3). The fate of cholesterol crystals is to persist indefinitely. These findings help understand the course of the human disease: massive CCE complicated with early ARF induces widespread thrombosis of the renal arterial tree with scattered multifocal infarction, whereas milder forms progress to delayed, obstructive inflammatory reaction to foreign bodies.

DIAGNOSIS

The diagnosis is readily made when fulminant CCE occurs within days after radiology maneuvers or vascular surgery, and is accompanied by purple toes and *livedo reticularis*. It is more difficult in the subacute subset, when renal insufficiency appears or worsens weeks later, especially when the clinician's mind is not prepared to consider the likeliness of atheroembolism. Yet, the diagnosis workup is rewarding when lower limbs are examined and funduscopy carried out, as cutaneous changes are almost constant and retinal crystals are found in up to 25% of cases.[3,6] The yield of nonrenal biopsies is high. Lower limb skin biopsies, calf or thigh muscle biopsies, bone marrow biopsies, and biopsies of the gastric and the colon mucosa altogether disclose crystals in about 80% of cases. It follows that renal biopsy may be avoided in a majority of patients. When the diagnostic workup is properly conducted, renal biopsy as the only means of making a diagnosis of CCE is necessary in about 20% of cases only. However, histology is useful for diagnosing CCE in the chronic, smoldering form of atheroembolism. Zucchelli and Zuccala[21] examined the kidneys of 136 patients diagnosed as 'hypertensive nephrosclerosis'. In total, 29.4% had in fact biopsy evidence of cholesterol embolization, with or without atherosclerotic renal artery stenoses, found in 26.5%. This illustrates the interest of renal histology in case of rise in serum creatinine levels unexplained by a recent factor, such as a change in antihypertensive therapy, a nephrotoxic or immunizing medication, and iodinated contrast media injection. The discovery of crystals is a strong incentive to forbid any form of anticoagulant treatment and to limit the indications of renal artery revascularization to cases where rescue from impending renal loss appears mandatory.[6]

DIFFERENTIAL DIAGNOSIS

Among many diagnostic challenges, renal artery atherosclerotic stenosis and hypertensive nephrosclerosis stand out as common deceptive conditions. Iodinated contrast media toxicity is another cause of confusion with the early, acute form of CCE induced renal insufficiency, especially in patients at risk, mostly diabetics with renal insufficiency. In the others, the time course of renal insufficiency is different from that of iodinated contrast media toxicity where the rise in serum creatinine appears early, plateaus between 5 and 10 days and is followed by a slow return to baseline.[7] Rapidly progressive glomerulonephritis is easily ruled out as the urinary findings in CCE are not nephritic. In subacute forms, skin involvement, fever, wasting, laboratory evidence of inflammation, and high eosinophil counts have often been

mistaken for vasculitis and published as 'pseudo-polyangiitis'. The availability of anti-neutrophil cytoplasmic antibodies makes this confusion unlikely. At any rate, the polymorph clinical and renal expression of CCE may justify renal histology in case of hesitance.

CCE IN RENAL ALLOGRAFTS

To date, 25 cases of CCE in renal transplants have been published,[11] too scarce a number to reflect the real incidence of this complication. The source of crystals can be ascribed to the donor at the time of procurement (12/25 cases), to recipient's atherosclerosis (8/25 cases), to invasive radiology (2 cases), or to anticoagulation/fibrinolytic treatment (2 cases). The time course to the graft compromise (when specified) is short (6–18 days) when emboli emanate from the donor's artery and apparently long, in the order of years when the recipient is atherosclerotic. In fact, CCE may be triggered up to 19 years after grafting by angioplasty, anticoagulation, or fibrinolytic therapy.

CCE occurring at the time of transplantation led to rapid graft loss in eight cases and recovery in five. In iatrogenic CCT, all kidneys but one recovered renal function. CCE due to the recipient's atherosclerosis had a rather better prognosis with recovery in 6/9 cases.

One may postulate that CCE is more common in renal transplantation than thought, and often misinterpreted as acute or chronic rejection, or resulting from calcineurin inhibitor toxicity. Outside the case of rapid graft failure followed by thorough pathologic examination of a surgically removed transplant, many cases fail to be diagnosed on the limited amount of tissue yielded by a thin needle renal biopsy.

TREATMENT

There is no curative treatment of CCE. Therapeutic modalities are symptomatic and preventive.

Until recently prognosis was considered disastrous. At the time of Fine *et al.*'s publication,[5] a majority of cases dealt with autopsy series. In fact, as in other forms of ARF, death from CCE is not the consequence of renal failure but of concomitant visceral ischemia. Patients with severe brain, coronary, spinal cord, mesenteric, and/or pancreatic necrosis are doomed to die, irrespective of the degree of renal failure.

Belenfant *et al.*[6] elaborated a treatment protocol based on: (i) stopping any form of anticoagulation and forbidding any new radiologic and/or vascular surgery procedure; (ii) treating hypertension drastically with angiotensin 2 antagonists and vasodilators, along with strict volemic control by loop diuretics and dialysis/ultrafiltration; (iii) implementing parenteral nutrition; and (iv) giving $\sim\frac{1}{3}$ mg/kg/day of prednisone to improve appetite and relieve abdominal discomfort. Peritoneal dialysis was deemed inappropriate, owing to gastrointestinal ischemia, risk of peritonitis and the loss of serum albumin pertaining to peritoneal dialysis. In-hospital mortality was 16%. Survival at 1 year was 87% and at 4 years 52%, which compared favorably with corresponding figures published earlier. However, some form of bias might have influenced these figures as Scolari *et al.*,[3] using a conservative regimen obtained roughly similar results.

Elinav *et al.*[24] treated four patients suffering from CCE complicated with painful cutaneous necrotic lesions and renal insufficiency with the prostacyclin analog, iloprost. The drug was administered continuously in gradually increasing dosage for 10–14 days followed by 8 h infusions thrice a week for 3 weeks and thereafter once a week. At 1 month, this regimen had clearly improved skin lesions, pain, and renal function. To the best of my knowledge, this is the only publication on the favorable effect of iloprost in CCE, a result that would deserve further clinical trials.

Prevention is based on weighing the pros and cons of anticoagulation, invasive radiology, and vascular surgery in patients with atherosclerosis. The medical, radiological, and surgical team must join their experience to make a decision between the hazards of treatment and the risk of CCE. Statins, which stabilize, and even obtain regression of atherosclerotic plaques,[25] offer hope that the incidence of CCE might diminish: a prospective study showed that they ameliorate the renal and patient outcome in CCE.[26]

ACKNOWLEDGMENTS

Figures 1 and 2 were reprinted from EMC Néphrologie, 18-046-A-10, Meyrier A. Athérosclérose et reins, 2003, with permission from Elsevier SAS, Paris, France

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