EDITORIAL COMMENT

Cholesterol Emboli After Invasive Cardiac Procedures*

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“Atheromatous emboli” is a general description for embolization of any atheromatous material. The term “atheroemboli” is used to refer to the dislodgement of vascular plaque material that contains cholesterol crystals plus red blood cells and fibrin. These can occlude major systemic vessels and result in organ infarction. “Cholesterol emboli” consist primarily of release of cholesterol crystals from ulcerated vascular plaques; the particles are usually smaller in size and are more widely spread than atheroemboli. The cholesterol embolization syndrome (CES) was first noted in an autopsy series by Flory in 1945. This original observation found vascular occlusions in nine of 267 patients with advanced aortic atherosclerosis (1). Skin involvement from CES results in a variety of manifestations, often referred to as blue-toe syndrome, purple-toe syndrome, or trash foot.

Obstruction of cutaneous vessels results in the mottled purple pattern of livedo reticularis. Ulcers, cyanosis, purpura, and gangrene may result from diffuse extremity vascular obstruction. Renal, neurologic, and cutaneous manifestations tend to dominate the clinical picture after vascular interventions such as cardiac catheterization. Nearly every organ system has shown histologic involvement in autopsy studies (2). These include visual changes from retinal emboli (3), transient ischemic attacks and stroke (4,5), gastric (6) and small-bowel bleeding (7), and renal transplant organ failure (8). Major risk factors for this syndrome include advanced age (with most patients over 60 years of age), repeat vascular procedures, female gender, and peripheral vascular disease. The presence of identifiable aortic atherosclerosis by noninvasive means appears to increase the risk (9). Minor predictors for CES include the rate of anticoagulation administration, the use of thrombolytics, elevated baseline creatinine levels, low platelet counts, longer periods of anticoagulation, and use of larger catheters (10).

The pathogenesis of CES is thought to rely on the disruption of vascular plaque with the release of subendothelial cholesterol crystals into the bloodstream. The initial event may be spontaneous (i.e., due to plaque rupture) (11), medication-induced (i.e., after using thrombolytics or anti-coagulation) (12), or, most often, following vascular endothelial trauma (either surgical or percutaneous injury) (13,14). In addition to the vascular obstruction from the cholesterol crystals, an inflammatory process is incited, leading to lymphocytic and mononuclear cell infiltration, ultimately with fibrosis. The diagnosis of CES relies on clinical findings in a patient with recent intravascular instrumentation or evidence of significant vascular disease. Whereas dermatologic or neurologic impairment may be seen early, renal involvement is characterized by progressive worsening of function over a two- to four-week period beyond the index event. Biopsy specimens are diagnostic and reveal “ghost” crystals lodged within vascular spaces (15). Unfortunately, although specific, biopsies may suffer from a lack of sensitivity depending on the organ studied and the degree of embolization.

The incidence of CES varies based on population characteristics and diagnostic criteria. Large retrospective studies of patients undergoing intravascular procedures have reported a 0.6% to 0.9% incidence (10,16). Autopsy studies performed on patients after resection of abdominal aortic aneurysms show evidence of cholesterol emboli in as many as 77% (17). In a prospective study of CES, Saklayen et al. (18) evaluated 267 patients undergoing coronary angiography and found that no patients had dermatologic findings but five patients showed creatinine elevations >0.5 mg/dl, and three >1.0 mg/dl, at three weeks. They concluded the incidence of CES was <2%.

In the current study by Fukumoto et al. (19), in this issue of the Journal, the authors report the occurrence of CES in 1.4% of 1,786 patients undergoing left heart catheterization. This figure seems consistent with the prior prospective study (18) but is several-fold higher than the retrospective studies. There are several possible reasons for the discrepancy. “Definite CES,” as defined by the authors, accounted for only 12 of the 25 cases (0.75% incidence). Although the dermatologic changes noted are found in CES, they are not specific and may be noted with arterial thrombosis/embolization, hypercoagulable states, and severe peripheral vascular disease. The additional 13 cases of “possible CES” involved predominantly renal abnormalities. Because an elevated serum creatinine after cardiac catheterization has a broad differential diagnosis, other factors may have played at least a contributing role, especially related to the use of contrast media (20). As opposed to the progressive nature of renal failure due to cholesterol emboli, ischemic or direct nephrotic damage from contrast media administration results in an acute elevation in serum creatinine, usually peaking at 48 h, with a subsequent return to baseline. Long-term renal dysfunction due to contrast media is well described, but it is unusual and more likely to occur after the use of large volumes of contrast and in diabetic patients who have an elevation in their baseline creatinine (21). The pattern of an early creatinine elevation with a subsequent progressive decline to baseline values adds to the ability to

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discern contrast-related changes in renal function from cholesterol embolic changes. Factors that predispose patients to contrast media nephropathy include the type and amount of contrast dye, the baseline creatinine, the presence of diabetes mellitus, the use of hydration before the procedures, underlying congestive heart failure, and/or the performance of subsequent invasive procedures (20).

Additional, though unlikely, causes of renal dysfunction not fully excluded in this report include systemic illness such as vasculitis or endocarditis, direct nephrotoxins such as anti-inflammatory medications, allergic interstitial nephritis due to periprocedural antibiotics, and possible progressive ischemic nephropathy related to renal artery stenosis. Eosinophilia, while noted in 80% of cases of CES, may also be seen in systemic vasculitis, acute interstitial nephritis, and contrast-related hypersensitivity renal failure (18). Biopsy data, not available in this study, would have been compelling and significantly strengthened their arguments that the renal dysfunction they observed was due to cholesterol emboli.

Even if one accepts the limitations inherent in the diagnosis of CES-induced renal failure, the authors do point out a potentially important relationship between C-reactive protein (CRP) and CES. A 4.6-fold increase in risk of CES was noted in their patients with an elevated CRP. This observation is quite consistent with recent data suggesting CRP as a marker of the “inflamed, unstable” plaque (22,23). Additional observations supporting this relationship include the ability of statins to decrease CRP and atherosclerotic events. Anecdotally, simvastatin has been reported to improve renal dysfunction caused by CES (24). The unfortunate paradox is that an elevated CRP may be a marker for those patients with the greatest need for intervention as well as those at the greatest risk from the procedure.

Vascular interventional procedures are increasing in number, especially in the population that is elderly. Although possibly overestimating the incidence of clinical CES, the authors have importantly provided added awareness of this syndrome. Despite our best efforts, treatment of CES remains supportive. Besides statins, iloprost (25), pentoxifylline (26), and steroids (27) have all been tried with limited success. As current medical practice continues to discourage the continuity of care by stressing rapid discharge and minimizing follow-up, a higher index of suspicion on the part of those involved in the care of cardiac catheterization patients may be necessary to diagnose this elusive syndrome.

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REFERENCES