Introduction of catheterization techniques has greatly improved the diagnosis and treatment of cardiovascular disease; on the other hand, it is also the principle cause of a potentially catastrophic iatrogenic disease. Cholesterol embolization syndrome (atheroembolism, blue toe syndrome) is caused by distal showering of cholesterol crystals from ulcerated atheromatous plaques in the aortas in patients with diffuse atherosclerosis. This ailment can occur spontaneously, but is more often iatrogenic after catheterization or surgical procedures. In their review (1), for example, Scolari et al postulated that 79% of their 52 cases of cholesterol embolization syndrome were iatrogenic, while only 21% were spontaneous. This finding underscores the importance of following up patients closely after vascular procedures, so as not to overlook this potentially catastrophic complication.

Even before the widespread use of catheterization, arterial occlusions caused by emboli from eroded aortic plaques had already been observed by Flory among 267 autopsies (2). Moreover, he showed that intravenous injection of material containing cholesterol crystals obtained from an atheromatous human aorta produced similar lesions in the arteries of the lungs of rabbits. The prevalence of cholesterol embolization in the general population is not known, but the Dutch National Pathology Information System estimated frequencies of 6.2 per million among the general population of the Netherlands and 0.31% among autopsies (3). By contrast, the incidence of cerebral ischemic events after cardiac surgery typically ranges from 1 to 3 percent, with a greater risk among the elderly. This increased incidence reflects the fact that atheroemboli can be precipitated by surgical manipulation of the aorta during cardiac or vascular operations; catheter manipulation, in particular, is responsible for a large proportion of atheroemboli. The Cholesterol Embolism Study (CHEST) carried out by investigators in Fukuoka, Japan examined prospectively for the first time the incidence of cholesterol embolization among patients who underwent cardiac catheterization (4). A total of 1,786 consecutive patients who underwent left cardiac catheterization were prospectively evaluated to identify cholesterol embolization syndrome. The incidence in that patient population was 1.4%. What’s more, Keeley and Grines (5) showed that in over 50% of 1,000 percutaneous revascularization procedures evaluated, guided catheter placement was associated with the scraping off of debris from the aorta and suggested it is essential to pay meticulous attention to ensure that atheromatous debris exits the back of the catheter and is not injected into the vascular bed.

The clinical features of cholesterol embolization vary considerably. Patients may be asymptomatic, may present with skin lesions such as blue toe syndrome or may present with renal failure. Iatrogenic events are precipitated by a clear inciting factor (e.g., a vascular procedure), and the time to the onset of clinical disease after the inciting procedure can range from 1 day to several months (6). The clinical manifestations will depend on the organs affected. Common signs and symptoms on presentation include skin findings (51%), calf claudication (16%), GI bleeding (15%), weight loss (13%), fever (13%) and renal cholesterol emboli (11%) (7). Donohue et al (6) reported that, of the cutaneous findings, the most frequent were livedo reticularis (49%), gangrene (35%), cyanosis (28%), ulceration (17%), nodules (10%) and purpura (9%). Almost all involve the lower extremities, and most of the livedo reticularis and cyanosis cases and many of the gangrene cases are bilateral. Acute onset of pain with digital ischemia and small areas of cutaneous gangrene is often referred to as the “blue toe syndrome.”

Approximately 50% of atheroembolism cases show renal emboli at necropsy, and renal failure is one of the commonest (34%) findings on presentation (6). Gradual onset of skin manifestations accompanied by slow but progressive increases of blood urea nitrogen and creatinine following arterial catheterization suggests the diagnosis. The classical triad of this disease includes livedo reticularis, acute renal failure and eosinophilia (8). In their diagnostic criteria for cholesterol embolization syndrome following catheterization, the CHEST investigators (4) listed peripheral cutaneous involvement (e.g., livedo reticularis, blue toe syndrome and digital gangrene) as criterion 1 and acute renal insufficiency as criterion 2. If a patient presented with cutaneous signs, with or without renal impairment, they defined the diagnosis as “definite.” The diagnosis was defined as “possible,” if the patient had only renal dysfunction – i.e., serum creatinine
>1.3 mg/dl or a >50% increase in the creatinine level from baseline without skin lesions two weeks after catheterization. Application of these diagnostic criteria will help to ensure that cholesterol embolization syndrome is not overlooked following cardiac catheterization. It is noteworthy in that regard that the incidence of cholesterol embolization syndrome following catheterization found by the CHEST investigators (1.4%) is approximately 10 times greater than the previous reports (less than 0.2%, range 0.06% to 0.18%) (1).

Om et al (9) suggested that cholesterol embolization is underdiagnosed because it occurs after difficult procedures, and the symptoms may be atypical and therefore missed. They further suggested the only reliable means of establishing a diagnosis is biopsy, which is most often not performed. They also noted the importance of differentiating subacute bacterial endocarditis from cholesterol embolization syndrome. Indeed, a case of cholesterol emboli mimicking acute bacterial endocarditis has been reported (10). However, if the patient has valvular heart disease, as in the case reported in the last issue, differentiation from infective endocarditis will be extremely difficult (11).

Transesophageal echocardiography has greatly facilitated the diagnosis of cholesterol embolization syndrome. A few years after the introduction of this imaging technique, a group from the National Cardiovascular Center in Osaka, Japan described complicated lesions in the thoracic aortas of 62 patients with embolic stroke that were visualized using transesophageal echocardiography (12). Mild atherosclerosis will appear on transesophageal echocardiography as intimal thickening, irregularity and calcification, whereas in more severe cases, thick plaque with protruding atheromas that are sometimes mobile will be seen (see Fig. 1 in page 1061 in the last issue). Sato et al (13) reported a patient who manifested multiple emboli in the kidney, skin and upper gastrointestinal tract following coronary angiography. In that case, transesophageal echocardiography enabled visualization of the atherosclerotic debris in the thoracic aorta. To protect against cholesterol embolization, they recommended that patients with extensive atherosclerotic disease undergo transesophageal echocardiography before cardiac catheterization or other invasive procedures involving the aorta (13).

In addition, Duda et al (14) carried out an interesting study to determine whether the routine use of intraoperative surface aortic ultrasonography would reduce the stroke rate among patients undergoing coronary artery bypass graft surgery. They found that no strokes occurred among 195 patients who were evaluated using intraoperative surface aortic ultrasonography, whereas there were five strokes (3.0%) among the other 164 patients in whom the state of the ascending aorta was evaluated by inspection and palpation only.

The one-year mortality rate for cholesterol embolization syndrome remains as high as 23% to 87% (1), and there is still no specific therapy with which to effectively treat the syndrome (15). For that reason, we should apply diagnostic procedures such as transesophageal echocardiography to prevent occurrence, we should manipulate catheters so as not to scrape the aortic wall, and we should follow-up patients for weeks after intervention so as not to overlook this mostly iatrogenic disease.

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References