Cholesterol embolization syndrome: A report of two cases

Kolesterol embolizasyonu sendromu: İki olgu sunumu

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Summary—Cholesterol embolization syndrome (CES) is a multisystemic disease with immunological features, and a rare but an important cause of acute kidney injury (AKI) following invasive angiography. It frequently occurs in the elderly male population with extensive atherosclerosis. CES should be considered in the differential diagnosis of AKI following angiography, as prognosis and treatment are completely different from contrast-induced nephropathy. Two cases of CES that developed after invasive angiography are described in the present report. In the first case, renal biopsy was performed, and CES was diagnosed by presence of characteristic renal lesions. The second patient had blue toe syndrome and persistent renal dysfunction.

CASE REPORT

Case 1—A 72-year-old male was admitted with intermittent claudication in lower extremities. Peripheral contrast angiography was performed, which demonstrated severe stenosis of the right common iliac artery, and balloon dilatation was performed. Antiagregant treatment with acetylsalicylic acid and clopidogrel was initiated. After a week, serum creatinine had increased to 3.2 mg/dl from base level of 0.9 mg/dl. The patient was hospitalized with prediagnosis of contrast-induced nephropathy. On physical examination, body temperature was 36.4°C, blood pressure was 130/80 mmHg, and heart rate was 96/min. Heart sounds were normal without murmur or thrill. Peripheral pulses of upper and lower extremities were equally bilaterally palpable. Laboratory data were as follows: serum urea: 16 mg/dl; creatinine: 7.4 mg/dl; calcium: 9.5 mg/dl; lactate dehydrogenase: 227 IU/L; C-reactive protein: 1.7 mg/dl; triglyceride: 198 mg/dl; low-density lipoprotein (LDL): 86 mg/dl; white blood cell...
count: 11900/µL; eosinophils: 20/µL; hemoglobin: 12.4 g/dL; platelet count: 348000/µL; and erythrocyte sedimentation rate (ESR): 82 mm/h. Serum C3 and C4 levels were within normal range. In urinalysis, hematuria and pyuria were not present, and 250 mg/day proteinuria was detected. In urinary system and renal arterial Doppler ultrasonography (USG), no significant pathology could be detected. Fundoscopic examination showed early-phase hypertensive retinopathy, and no other pathology was found. Because renal dysfunction persisted with serum creatinine levels of 5.6 mg/dl, renal biopsy was performed 1 week after withdrawal of antiplatelet therapy. In renal biopsy, characteristic empty clefts were observed within the obliterated arteriolar lumen with surrounding multinucleated giant cells and lymphocytic infiltration (Figure 1). These findings were considered to be compatible with diagnosis of CES. At follow-up, dyspnea and chest pain manifested. With electrocardiographic findings and increased serum troponin levels, diagnosis of non-ST elevation myocardial infarction was established, and appropriate treatment was begun. Because of severe dyspnea, the patient was orotracheally intubated and transferred to the intensive care unit. In thorax computed tomography, bilateral severe interstitial infiltrations were observed. Due to the worsening of renal functions, continuous renal replacement therapy was performed. With prediagnosis of acute interstitial pneumonia, piperacillin-tazobactam, clarithromycin, trimethoprim sulfamethoxazole, and methylprednisolone 60 mg/day were started. For further investigation of pulmonary disease, bronchoscopy was planned. However, the patient died of respiratory failure.

Case 2—A 73-year-old male was admitted with new-onset pain and cyanosis in his feet. Toes and distal fingers were particularly affected. The patient had undergone coronary angiography and stent implantation to coronary arteries approximately 3 months prior, after which clopidogrel, acetylsalicylic acid, and statin treatments were begun. Smoking, 50 pack-years, was present in personal medical history. Upon physical examination, cyanotic lesions were present on the toes and distal parts of the fingers (Figure 2). Both dorsalis pedis and tibialis posterior arterial pulses were present on palpation. Lower extremity arterial Doppler USG was normal. Due to these characteristic findings, blue toe syndrome, a type of CES, was diagnosed. In biochemical analysis, total leuko-

![Figure 1. Renal biopsy showing slit-like spaces (arrows) with surrounding multinucleated giant cells (arrow heads) and lymphocytic infiltration in arterioles compatible with diagnosis of CES (H&Ex40).](image-url)
cyte: 5580/µL; eosinophil: 1350/µL (reference range: 0–700/µL); hemoglobin: 10 g/dL; platelets: 330,000/µL; ESR: 89 mm/h; creatinine: 4.5 mg/dl; lactate dehydrogenase: 241 IU/L; CRP: 3.9 mg/L; total cholesterol: 142 mg/dl; LDL: 92 mg/dl were detected. Rheumatologic markers were all negative, including ANA, RF, and ANCA. Serum complement levels (C3, C4) were within normal range. Urinalysis and retinal examination were normal. Because chronic findings, including bilateral grade 2 renal parenchymal disease, were found on urinary USG, renal biopsy was not performed. With antihypertensive, antihyperlipidemic, and antiaggregant treatments, and supportive care, cyanotic lesions regressed significantly, though serum creatinine levels remained high.

**DISCUSSION**

CES is a rare but an important cause of AKI following angiography. Risk factors for CES include age, male gender, hypertension, smoking, diabetes mellitus, and atherosclerotic vascular disease. Advanced atherosclerosis is the most important independent risk factor for the development of CES.[1,2] The present patients had all risk factors except diabetes mellitus. CES may, rarely, occur spontaneously, but often follows invasive cardiovascular procedures such as cardiac catheterization, coronary or peripheral angiography, cardiovascular surgery, cardiopulmonary resuscitation, and anticoagulant and thrombolytic treatments. [2,4] Atherosclerotic plaques contain fibrin, platelets, necrotic cell debris, and cholesterol crystals. [2,5] Hemodynamic changes, inflammation, and hemorrhage, caused by spontaneous or invasive procedures, may induce plaque erosion and rupture.[5] Dislodgment of cholesterol crystals to circulation following rupture of atherosclerotic plaque causes embolization of peripheral arterioles with diameters of 100–200 µm. Following arteriolar obstruction by the emboli, multinuclear cell and eosinophil infiltration, and secretion of vasoconstrictive mediators occur, leading to further ischemia and exacerbation of organ damage.[1,6–8]

Organs most commonly involved in CES are the kidneys, liver, spleen, pancreas, gastrointestinal tract, and adrenal glands. Mortality is as high as 81% in cases of multiple organ involvement. Primary extra-renal presentation is cutaneous involvement. Gastrointestinal involvement usually presents with ischemia and bleeding.[1–3] Cholesterol embolization to lungs is rare, but occurs when cholesterol crystal passes through systemic circulation into the venous system and pulmonary capillaries.[9] Alveolar hemorrhage may also present as a manifestation of CES.

Few cases of CES with pulmonary involvement have been reported, all of which were associated with high mortality.[10–12] In the first present patient, CES as the cause of pulmonary disease could not be proven, as bronchoscopy could not be performed due to poor general status. However, it is possible that underlying pathology of the pulmonary disease was CES.

In physical examination of CES, skin findings including livedo reticularis, gangrene, cyanosis, skin ulcer, purpura, and petechia are the most common features. As the embolism affects the arterioles with relatively small diameters, peripheral pulses are frequently palpable. Distal gangrenes with palpable pulses are considered to be strongly suggestive of blue toe syndrome, a subtype of CES.[1–3,6,8,13] Oliguria, edema, and dyspnea may also be caused by AKI.[9,14] Paleness, orthostatic hypotension, and abdominal tenderness may also be detected as physical findings of gastrointestinal bleeding, pancreatitis, and acalculous cholecystitis due to CES.[3,15,16] Paraplegia, confusion, and delirium are findings of neurologic involvement of CES. Hollenhorst plaque is the pathognomonic sign of CES in ophthalmologic examination.[13]

Laboratory findings of CES may reveal anemia, leukocytosis, eosinophilia, thrombocytopenia, increased ESR, hypocomplementemia, and azotemia. ANA and RF may be positive due to antigenic stimulation of cholesterol crystals.[1,2,6] Urinalysis typically shows hematuria, pyuria, and non-nephrotic proteinuria.[17] The first patient described had increased C-reactive protein levels and high ESR. However, eosinophilia was not present, as it was in the second
patient. Serum complement levels were normal in both patients.

The gold standard for the diagnosis of atheroembolic renal disease is renal biopsy revealing cholesterol crystals obstructing the arterioles. Characteristic pathologic finding in renal biopsy is empty clefts within the obliterated lumen of the arterioles. As this is usually distributed in a patchy manner, clefts may not be present in all renal biopsies.[2] Presence of CES was proven in renal biopsy in Case 1. However, due to the invasive nature of the biopsy, most cases of CES are diagnosed on clinical grounds, as was the case with the second patient. Renal involvement of CES has poor prognosis, compared to that of contrast nephropathy. In an observational study, 354 patients were enrolled with CES confirmed by either renal biopsy or presence of Hollenhorst plaques on ophthalmologic examination. The renal disease of more than 30% of these patients had progressed to an end-stage disease by the end of a 2-year follow-up.[4]

No proven standard treatment for CES currently exists. Efficacy of corticosteroid therapy remains controversial. Cholesterol embolization molecules were shown to activate inflammatory cytokines, and complement system and eosinophilic reaction. Exact pathophysiological reasons for this reaction are not well-known, but may be considered a kind of foreign body reaction to these molecules. Increased inflammation and eosinophilia may explain the efficacy of corticosteroid treatment reported in several cases.[18,19] Nevertheless, increased mortality with corticosteroid therapy has also been reported.[4]

Another point of discussion in the management of CES is the safety and efficacy of anticoagulant and antiplatelet treatments. Supportive care for end-organ damage is recommended in addition to secondary prophylaxis to prevent further episodes of cholesterol embolization. While use of antiplatelet agents has not been proven to prevent recurrence of cholesterol embolism, it should be considered a part of treatment, due to effects of preventing adverse cardiovascular events.[22] Cases of CES provoked by thrombolytic and anticoagulant treatments have been reported several times.[23,24] Atheroembolic plugs of CES are not composed simply of thrombus, but rather contain atheroembolic debris and inflammatory cells. Therefore, anticoagulation treatment may not be efficient. Anticoagulation is not recommended unless another indication such as mechanical valve or atrial fibrillation is present.[2,6]

As CES is predisposed by atherosclerosis, risk factors for atherosclerosis such as hypertension, smoking, and hyperlipidemia should be managed. Although statin treatment is generally used to stabilize atherosclerotic plaque, no randomized trial proving its benefits has been published.[2] LDL apheresis has been reported to improve brain and skin damage related to CES.[22] Iloprost as a vasodilator treatment was found to be beneficial for treatment of CES.[7] In spite of recent improvements in supportive care and targeted therapies, high rates of morbidity and mortality remain.[1,2]

In conclusion, CES is a multisystemic disease with immunological features mimicking various diseases. High clinical suspicion is required for timely diagnosis, as the disease may have poor prognosis in terms of irreversible end-organ damage. The clinician should keep CES in mind as an etiological factor of AKI following invasive cardiovascular interventions.

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REFERENCES

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