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【 EDITORIAL 】

Angiogenic Dreaded Killer: Cholesterol Crystal Embolization

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We humans are very afraid of unknown and invisible enemies because we cannot fight against them. Cholesterol crystal embolization (CCE) - in some situations - can creep up insidiously and become a fatal disease. CCE was firstly reported in 1862 by Panum (1). Although a definite diagnosis of CCE can be made based on histopathological findings or the probable diagnosis can be done by predefined criteria (2), some atypical cases of CCE are encountered in clinical practice, as reported by Sato et al. (3). Their case first developed sudden small intestinal perforation followed by a second similar perforation and acute pancreatitis. Because the pancreatitis was caused by ischemia due to CCE, acute necrotic collection and walled-off necrosis could easily develop as well, as described in a previous report on ischemic pancreatitis (4). As Sato et al. stated, the treatment of pancreatic pseudoaneurysm with CCE-induced pancreatitis is very difficult, because minimally invasive interventional radiology is an exacerbating factor of CCE. If possible, surgery should also be considered for pseudoaneurysm with CCE. In addition, according to the recommended treatments, they treated the patient with HMG-CoA reductase inhibitor, prostaglandin E1, and steroids, but were unable to save him. CCE is an intractable condition with a poor prognosis, as they indicated. One reason for the difficulty in the early diagnosis of CCE is because the symptoms and imaging findings are non-specific and there are no biomarkers. As blood tests usually reflect non-specific end-organ damage (the kidney is most frequently affected, with an incidence rate of 30%), the early detection of CCE is difficult. Meanwhile, some reports have indicated that transient eosinophilia occurred in 22-73% of patients, which might be a clue to the diagnosis (2). There is currently no treatment that can effectively dissolve cholesterol crystal, although evolocumab was newly demonstrated to have an effect on CCE (anti-proprotein convertase subtilisin/kexin type 9 antibody: reducer of the LDL-cholesterol level) and it has also been shown to reduce inflammatory cytokines and promote the regression of atherosclerotic plaque (5). Thus, we have to take countermeasures for the early detection and prevention of CCE. First, we should know about CCE itself and risk factors for CCE, such as atherosclerosis, hypertension, smoking, chronic renal dysfunction, and iatrogenic factors, such as vascular surgery, angiographic study, and anticoagulant therapy; CCE is iatrogenic in a majority of cases (76-79%) (2, 6). Second, physicians should pay close attention to trivial signs, such as purple toes, lower limb livedo reticularis, or Hollenhorst's plaques, as retinal CCE is seen on funduscopy in patients with the abovementioned risk factors. Third, medical doctors should also enlighten people on the possibility of atherosclerosis leading to ischemic diseases, including CCE, and should avoid unnecessary vascular intervention or studies, which are major triggers.

For a differential diagnosis of CCE with gastrointestinal lesions, we also have to consider the possibility of non-occlusive mesenteric ischemia (NOMI), which is a life-threatening disease associated with mortality rate of 50%, while the mortality rate of CCE can reach 65%. The risk factors for NOMI include heart failure, diabetes mellitus, dehydration, renal or hepatic disease, the use of diuretics or mesenteric vasoconstrictive drugs, cardiac surgery and systemic atherosclerotic disease, which partially overlap with the risk factors for CCE (7, 8). In NOMI, CT image findings, such as pneumatosis intestinalis and vascular narrowing and several biomarkers, including intestinal fatty acid binding protein (I-FABP), a marker of enterocyte necrosis and smooth muscle protein 22 (SM22), a marker of muscle damage have been reported as effective detection tools (9, 10). Although there are no reports in the relevant literature on the I-FABP and SM22 levels in CCE, the investigation of these markers in CCE may be meaningful for

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the early detection of CCE in patients with gastrointestinal lesions.

At any rate, if we know the enemy and know ourselves, we need not fear the result of a hundred battles.

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