Performing Anticoagulation: A Puzzling Case of Cholesterol Embolization Syndrome

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ABSTRACT: The avoidance of any form of anticoagulation is advised in cases of cholesterol embolization syndrome (CES). We herein describe a case of CES in a man with a history of unprovoked pulmonary embolism for which warfarinization was performed. Despite anecdotal reports of successful anticoagulation in CES patients with certain indications, irreversible renal failure, which was sufficiently severe to require chronic hemodialysis, eventually developed in our patient. Our results emphasize the pitfalls of this procedure, which imply its limited feasibility and safety. Several therapeutic concerns associated with this case are also discussed.

Keywords: Cholesterol crystal embolization, pulmonary embolism, warfarin, end-stage kidney disease, hemodialysis

Introduction

Cholesterol embolization syndrome (CES) is a multisystem ischemic damage characterized by the occlusion of small vessels with cholesterol crystals that originate from ruptured atherosclerotic plaques lining the walls of major arteries.1 Plaque rupture may be spontaneous, iatrogenic after arterial manipulations, and/or related to thrombolytic therapy and anticoagulation.1–3 Although any organ may be affected, the brain, kidneys, gastrointestinal tract, skin, and skeletal muscles of the lower extremities are the most frequently involved.2 No specific treatment has been established for CES, and therapeutic modalities for this disease are still symptomatic and preventive.1–3 The avoidance of any form of anticoagulation is an alternative therapeutic option1–3; however, this strategy may not necessarily be appropriate for some subsets of CES patients with separate indications, such as mechanical prosthetic valves, atrial fibrillation, and deep vein thrombosis.1,2,4 In the current report, we describe our experience with one such case of CES in a man who had a history of unprovoked pulmonary embolism (PE), which obliged us to pursue anticoagulation with warfarin during the observation period. Several therapeutic concerns that emerged in this case are also discussed.

Case Report

A 76-year-old man was admitted in June 2014 due to progressive deterioration of renal function, loss of appetite, and asthenia. Nine months prior to his admission (September 2013), he was diagnosed with effort angina and infrarenal abdominal aortic aneurysm. At the beginning of October 2013, he was found to have unprovoked PE for which he had received oral warfarin, delivering a prothrombin time-international normalized ratio (PT-INR) of 1.7 to 2.1 (reference range: 0.9-1.2) with a favorable clinical course. He had no history of renal disease, and steady serum creatinine (sCr) levels ranging between 0.96 and 1.12 mg/dL (reference range: 0.63-1.03 mg/dL) were noted until mid-December 2013. His sCr level was 1.89 mg/dL in mid-March 2014 and increased to 7.33 mg/dL in early June 2014. Therefore, he was referred and admitted to our hospital for further examination. His medical history included a diagnosis of acute myocardial infarction at 58 years of age. He had been a smoker for more than 40 years but denied the use of any drugs.

At the time of admission, the patient was alert and had a blood pressure of 176/94 mm Hg. His physical examination revealed livedo reticularis on the soles of his toes and a blue-purple discoloration of all toes bilaterally (Figure 1A), whereas his feet were warm to the touch and the peripheral pulse remained intact. Laboratory examinations revealed the following: blood urea nitrogen (BUN), 64 mg/dL (reference range: 8-20 mg/dL); sCr, 7.23 mg/dL; white blood cell count, 9800/µL (reference range: 3900-9800/µL); eosinophils, 1092/µL (reference range: 0-400/µL); platelet count, 166 × 10³/µL (reference range: 130-369 × 10³/µL); erythrocyte sedimentation rate (ESR), 59 mm/h.

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(reference range: 0-10 mm/h); serum albumin, 3.5 g/dL (reference range: 6.9-8.4 g/dL); low-density lipoprotein (LDL) cholesterol, 129 mg/dL (reference range: <139 mg/dL); fibrinogen, 410 mg/dL (reference range: 129-271 mg/dL); fibrin/fibrinogen degradation products, 13.5 µg/mL (reference range: 0-5 µg/mL); D-dimer, 5900 µg/L (reference range: 0-1500 µg/L); PT-INR, 1.76; C3, 104 mg/dL (reference range: 86-160 mg/dL); C4, 45 mg/dL (reference range: 17-45 mg/dL); and C-reactive protein, 0.49 mg/dL (reference range: 0-0.14 mg/dL). Tests for anti-neutrophil cytoplasmic antibodies, anti-glomerular basement membrane antibodies, hepatitis B virus surface antigen (HBsAg), anti-HBsAg antibodies, and antibodies to the hepatitis C virus were all negative. His urine was trace positive for protein, 2+ for occult blood, and contained 0.09 g of protein in a 24-hour specimen, whereas his creatinine clearance was 3.9 mL/min. The urinary excretion of β2-microglobulin and N-acetyl-beta-d-glucosaminidase was 22 856 µg/L (reference range: <200 µg/L) and 5.4 U/g·Cr (reference range: 0.9-2.4 U/g·Cr), respectively. A computed tomographic scan revealed a calcified thoracic aorta without a dimensional disorder and an infrarenal aortic aneurysm with a maximum diameter of approximately 4.4 cm. Diagnostic noncontrast-enhanced T2-weighted half-fourier-acquired single-shot turbo spin echo (HASTE) magnetic resonance imaging subsequently revealed hypointense areas and bright signals, which were suggestive of an atheromatous plaque consisting of lipids and fibrous tissues, respectively, in the abdominal aorta (Figure 1B). Oral warfarin was discontinued on admission, and the patient was subjected to empirical treatment with pravastatin at a dose of 10 mg/day combined with limaprost alfadex at a dose of 30 µg/day. A 5-mm-deep punch biopsy was performed on clinical day 7 within the territory of livedo reticularis on the lateral aspect of the left first toe. Typical biconvex needle-shaped empty spaces, suggestive of cholesterol clefts, were observed within the lumen of the arteriole in the subcutis (Figure 1C). A diagnosis of CES was made based on pathological and imaging findings as well as clinical manifestations.

Due to the elevated D-dimer level of 10 600 µg/L confirmed on clinical day 8, the decision was made to resume anticoagulation therapy despite our failure to detect deep venous thrombotic lesions using ultrasonography. The patient was treated with intravenous heparin and then switched to warfarin 2.5 mg/day on clinical day 30. Oral prednisolone (PSL) at a dose of 20 mg/day was also initiated on clinical day 22, resulting in the amelioration of eosinophilia and cutaneous manifestations within a few days and the subsequent stabilization of sCr levels at approximately 4.3 mg/dL. His elevated blood pressure was also controlled at approximately 120-130/70-80 mm Hg with irbesartan (100 mg/day) and amlodipine besilate (5 mg/day). However, sCr levels started to increase when PSL was tapered to 5 mg/day. The patient developed general fatigue, appetite loss, decline in urine output, and progressive swelling in both legs without any calf pain at the end of September 2014, with an elevated sCr level of 8.07 mg/dL, and was readmitted for further examinations. Similar to his initial admission, a laboratory analysis at this point revealed mild hypoaalbuminemia (3.6 g/dL), whereas echocardiography and chest radiograph findings did not support the concurrent presence of heart failure. The relationship between deteriorated cutaneous manifestations and recurrent eosinophilia of 1365/µL resulted in the diagnosis of relapsed CES.

Figure 1. Physical, magnetic resonance imaging (MRI), and pathological findings. Bluish reticulated patches were noted on the soles and tips of the toes (A), whereas T2-weighted HASTE diagnostic MRI (B) at a slightly more cephalic position from the renal arteries revealed an atherosclerotic plaque consisting of lipids (arrow) and fibrous (arrowhead) tissues in the abdominal aorta. Abnormal fluid-filled lesions (*), which may be ascribed to bilateral simple renal cysts, were also noted. Light microscopy of cutaneous biopsy sections revealed characteristic cholesterol clefts occluding the lumen of the arteriole (C, hematoxylin-eosin stain; the scale bar is indicated).
The patient received hemodialysis (HD). After the resumption of an increased dose of PSL (15 mg/day) and the addition of a transient session of LDL apheresis (LDL-A) to the therapeutic regimen, his cutaneous manifestations improved and eosinophilia disappeared; however, severely deteriorated renal function did not recover, and he was finally started on a periodic HD program with favorable volume control (Figure 2).

**Discussion**

The clinical presentation of CES often consists of various signs specific to end-organ damage and systemic inflammatory responses. Patients with CES are more likely to be older men with a high prevalence of traditional cardiovascular risk factors and cardiovascular diseases and may present with a wide spectrum of clinical symptoms, including fever, weight loss, fatigue, anorexia, and myalgia with an elevated leukocyte count, rapid ESR, elevated C-reactive protein levels, high eosinophil blood counts, and, much more rarely, hypocomplementemia. The diagnostic hallmark of this disease is the histological confirmation of intravascular cholesterol crystals in biopsy specimens, whereas any organ system may be regarded as a candidate target for the procedure in theory. Although skin and muscle biopsies have a high diagnostic yield because of their favorable accessibility, it is important to note that tissues affected by CES are at risk of poor wound healing. Consequently, the clinical features of our patient are not surprising; however, the significance of our results needs to be evaluated carefully in terms of renal outcome after the resumption of anticoagulation.

Although a causal link between anticoagulation and CES has yet to be proven or denied, anticoagulation may lead to plaque hemorrhaging, plaque rupture, and subsequent cholesterol crystal embolization. Thus, therapeutic options for CES ordinarily include a withdrawal from or the avoidance of any form of anticoagulation unless there is a separate indication, such as mechanical prosthetic valves, atrial fibrillation, and deep vein thrombosis. In the present case, we did not identify any associated triggers nor did we identify risk factors for PE, including recent major surgery, prolonged immobilization, and obesity. Previous anecdotal case reports demonstrating the successful use of warfarin and/or heparin for specific indications in patients with CES as well as the unprovoked nature of the disease, which may require indefinite long-term anticoagulation, and elevations in D-dimer levels after the suspension of anticoagulation prompted us to resume warfarinization to prevent the recurrence of PE in the present case. The dose of warfarin was controlled according to the recommended target PT-INR for venous thromboembolism based on the Japanese therapeutic guidance.

Our failure to perform a renal histological analysis may preclude us from precisely evaluating the impact of CES on renal function.
pathology in the present patient. A number of conditions including small-vessel vasculitis and acute interstitial nephritis may simulate renal CES.20,21 However, the results of serological tests, as well as longitudinal data regarding urinary parameters, were unremarkable for these specific types of renal damage. The presence of a triad characterized by precipitating events such as anticoagulation, subacute renal failure, and pathologically confirmed peripheral cholesterol embolization prompted us to diagnose our patient with atheroembolic renal disease, as practiced in ordinary clinical settings.3,6 Fluctuations in estimated glomerular filtration rate may occasionally be observed during the given period of time before the commencement of renal replacement therapy, particularly in patients with cardiovascular disease22; thus, the transient improvement in renal function in our patient may mirror, at least in part, the natural course of end-stage kidney disease. Nevertheless, the tapering of PSL may be expected to attenuate corticosteroid-dependent lipid scavenging,23 thereby precipitating irreversible end-stage kidney disease through the exacerbation of latent inflammatory tissue injury due to warfarinization-mediated cholesterol embolism. We consider our results to emphasize the pitfalls of continuing or resuming anticoagulation even in CES patients who have separate indications, implying the limited feasibility and safety of this procedure.

The clinical course of the present patient did not allow us to precisely evaluate the therapeutic significance of statins and LDL-A, which have been attempted anecdotally as a therapeutic option for CES with limited success.1,2,24 Otherwise, our case may have emphasized the necessity of an extensive evaluation of the potential benefits of corticosteroids among patients with CES. Although the maintenance dose, duration, and tapering schedule of oral PSL in the present patient may not necessarily be adequate in terms of the overall renal outcome, the immediate decrease observed in sCr levels after the commencement of the treatment implies the therapeutic benefit of immunomodulation with steroids. The discrepancy between the results obtained for sCr and BUN levels after the resumption of the increased dose, as well as the initial dosing of oral PSL, was not unexpected because BUN levels are often elevated by excessive tissue catabolism resulting from the administration of corticosteroids.25,26

Rapid improvements in deteriorated renal function caused by CES have been demonstrated in patients treated with various therapeutic regimens using corticosteroids,3,27–29 implying that a number of these decisions are potentially empirical. We need to focus on previous findings showing that the tapering of corticosteroids coincides with the recurrence of CES, as in the present patient. In some subsets of CES patients, it may be necessary to either increase the dose or resume agents with careful monitoring for signs of exacerbation.28,30–33 There are currently no clear recommendations regarding how to administer corticosteroids to CES patients. No reliable indicators that may allow us to assess the optimal timing for the tapering of such agents have been reported. It also remains unclear which CES patients will benefit the most from corticosteroid treatments. Further encounters with similar cases to our patient will contribute to elucidating the therapeutic significance, as well as optimal duration and dosing of corticosteroids for this disease, thereby leading to the development of appropriate strategies for the treatment of CES patients.

**Author Contributions**

YIgarashi and TA drafted the manuscript. TK, YIwazu, TMiki, NOT, TI, TS, and TMasuda helped with the acquisition of clinical data. ST, SM, and DN provided a detailed review of the contents and structure of the manuscript, resulting in significant changes to the original document. All the authors have read and approved the final manuscript.

**Disclosures and Ethics**

As a requirement for publication, the authors have provided the publisher with signed confirmation of compliance with legal and ethical obligations, including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality, and (where applicable) the protection of human and animal research subjects. The authors have also confirmed that this manuscript is unique and not under consideration for publication or published in any other publications and that they have permission from the rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest.

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