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【 EDITORIAL 】

Immunosuppression Therapy for Chronic Limb-threatening Ischemia in a Patient with Severe Polyarteritis Nodosa

Miona Arai, Tetsuya Ishikawa and Isao Taguchi

Key words: arteritis, Wound, Ischemia, and foot Infection (WIfI) stage, Global Limb Anatomic Staging System (GLASS) classification, infra-malleolar lesion

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Yagi et al. (1) reported a case of chronic limb-threatening ischemia (CLTI) that induced multiple gangrene lesions in the fingers of both hands and left foot digitals, owing to advanced-stage severe polyarteritis nodosa (PAN). They successfully treated the CLTI by partially reversing the gangrene (Fig. 2) with oral administration of prednisolone (PSL) 50 mg, first-line class 1, and evidence level B therapy with PAN. The reversed skin appearance was kept in remission by oral administration of azathioprine (AZA) 50 mg as second-line therapy (class 2b, evidence level B) (2, 3). They concluded that severe PAN should be considered as a differential diagnosis of CLTI with a biopsy so as not to delay the definitive diagnosis, and immunosuppressant agents would be effective for maintaining remission of CLTI.

As a clinical perspective of the present case report, it is important to consider several diseases of arteritis in the differential diagnosis of CLTI according to the Japanese Circulation Society (JCS) 2017 Guideline on Management of Vasculitis Syndrome (2). Arteritis relevant to CLTI was (a) PAN classified as medium-vessel vasculitis (MVV), (b) microscopic polyangiitis (MPA) in the category of small-vessel vasculitis (SVV) of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), and (c) Beçhet's disease (BD) in the category of variable-vessel vasculitis (VVV). The present case could not be distinguished by laboratory examinations, including the results of autoimmune antibody evaluations. In addition, the definitive clinical diagnosis of CLTI, including these categories of arteritis, could not be made on the basis of not only the skin appearances of gangrene (Fig. 1) but also the angiogram of the peripheral limb arteries (Fig. 2). The most important issue in defining PAN [ruling out cutaneous PAN (CPAN)] depends on the pathological assessment by a proximal skin biopsy, which involves the medium- and small-vessel arteries from the corium deep plexus. The pathological findings are essential for pharmacological treatment in conjunction with revascularization, as mentioned below.

The management of CLTI has been stated in the JCS/Japanese Society of Vascular Surgery (JSVS) 2022 Guideline on the Management of Peripheral Arterial Disease (4). As the first step in the management of CLTI, it is essential to define comprehensive limb staging, i.e. defining the Wound, Ischemia, and foot Infection (WIfI) stage. The local estimation of the present case based on the visual assessment in Fig. 1 and the results of laboratory examinations were W = 1, I = 0, and fI = 1. Therefore, the clinical stage of CLTI seems to be 1 or at most 2, defined as very low or low risk, respectively [not mentioned in the text (1)]. In addition, regarding the anatomical pattern of disease, the Global Limb Anatomic Staging System (GLASS) classification of infra-malleolar was defined as P 0 in the present case (Fig. 2). Therefore, the benefit of revascularization by either endovascular therapy (EVT) or bypass surgery is considered nil or very low.

According to the PLAN concept, the main treatment of gangrene is primarily care for the wounds around the gangrene in order to prevent infection of the limbs (4). In the present case, antiplatelet agents and prostaglandins to locally enhance the microvascular circulation resulted in an ineffective outcome. Therefore, the authors conducted immunological medical therapy for PAN. This treatment, which prevented systematic adverse effects, successfully reversed partial remission (Fig. 1). Therefore, as a clinical implication of the present case report, the optimal treatment of CLTI complicated in PAN, defined as a WIfI stage of (very) low risk without the need for revascularization, was immunological therapy as the primary treatment of PAN itself by administration of PSL and AZA.

Thus, the present (very) low-risk case of CLTI without the need for revascularization, primarily caused by MVV of

Department of Cardiology, Dokkyo Medical University Saitama Medical Center, Japan
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Correspondence to Dr. Tetsuya Ishikawa, tetsuya50ishikawa@gmail.com

PAN, implies several issues. First, it is necessary to perform a pathological assessment for the definitive diagnosis of arteritis among MVV, SVV, or VVV. In addition, it is important to discriminate non-atherosclerotic factors from atherosclerotic genesis in cases complicated by conventional atherosclerotic risk factors with accelerated atherosclerosis. Finally, the treatment of CLTI commonly needs to be based on the PLAN concept, which is based on the WIfI stage and GLASS classifications, regardless of the primary disease of CLTI. This strategy to first classify the risk stage using these two tools has been consistent with the most updated guidelines for lower extremity peripheral artery disease (LEAD) in the United States (5).

The recent guidelines of the United States (5) divide LEAD into four clinical subsets: 1) asymptomatic peripheral arterial disease (PAD), which may have functional impairment; 2) chronic symptomatic PAD, where claudication and other exertional leg symptoms are defined; 3) CLTI; and 4) acute limb ischemia (ALI) with acute clinical symptoms manifesting within two weeks. It is important to recognize the clinical subsets and the primary disease process, as these four subsets have been developed over time, with entities moving into and out of different subsets (5). CLTI is a severe clinical subset of PAD, because the estimated 1-year all-cause mortality rate is consistently as high as 25-35%. The guideline is mainly constructed by the atherosclerotic genesis of CLTI by separating arteritis including PAN in the differential diagnosis of non-atherosclerotic non-healing lower limb wounds (5). Thus, the present case report contributes to the differential diagnosis and treatment of low-risk CLTI, including CPAN (6), in daily practice, primarily in patients with severe PAN treated with immunosuppressants.

The authors state that they have no Conflict of Interest (COI).

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