

Ultrasonographic features of an cryoglobulinemia vasculitis:Case report and Literature review

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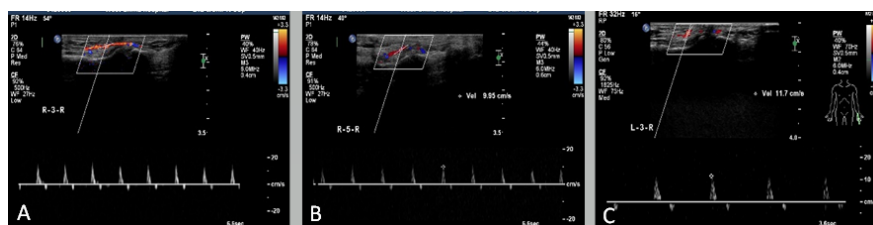
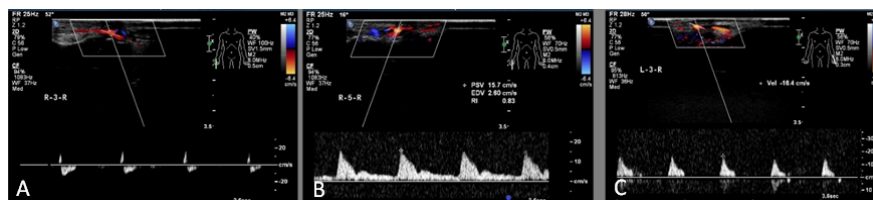
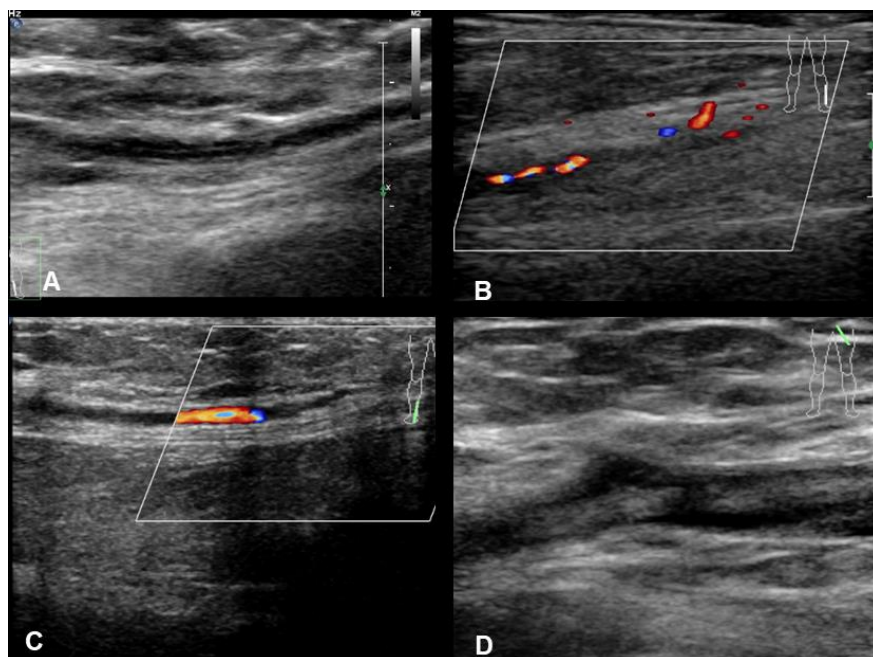
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Abstract

Cryoglobulinemia vasculitis (CV) is a rare, small vascular occlusive disease caused by cryoglobulin precipitation in the plasma. We report the case of a 61-year-old female suffering from pain in the toes of the left foot in autumn, who subsequently developed acute pain, during hospitalization.





ABSTRACT

Cryoglobulinemia vasculitis (CV) is a rare, small vascular occlusive disease caused by cryoglobulin precipitation in the plasma. We report the case of a 61-year-old female suffering from pain in the toes of the left foot in autumn, who subsequently developed acute pain in both hands with blackening of the distal fifth finger of the right hand, as well as the second and third toes of the left foot, during hospitalization. After treatment, the patient's condition improved, and she was discharged; laboratory blood tests confirmed a diagnosis of CV. In winter, the patient's condition worsened. Here, we report the ultrasonographic features of CV in this patient.

Abbreviations: CDFI = color Doppler flow imaging, RF = rheumatoid factor, CV = cryoglobulinemia vasculitis, HBV = hepatitis B virus, HCV = hepatitis C virus, Ig = immunoglobulin

Keywords: ultrasonography, type II cryoglobulinemia vasculitis(CV), hepatitis B virus (HBV), extremity gangrene

1. INTRODUCTION

In 1966, Meltzer et al.¹ defined the triad of purpura, arthralgia, and weakness associated with organic dysfunction, and elevated levels of rheumatoid factor (RF), as cryoglobulinemia. Cryoglobulinemia refers to an abnormal immunoglobulin (Ig) that exists in the blood; it is characterized by precipitation at low temperatures ($< 37^{\circ}\text{C}$) and dissolution after reheating.² Cryoglobulinemia is divided into three categories (I, II, and III) based on the composition of Ig. Type I is a monoclonal immunoglobulin associated with an underlying B-cell lymphoproliferative disease. Types II and III are commonly referred to as mixed cryoglobulinemia.³ Type II is a mixture of monoclonal IgM with RF activity and polyclonal IgG. Approximately 10% of patients with no identifiable cause have type III, which is characterized by polyclonal IgM and polyclonal IgG with RF activity. In general, cryoglobulins in mixed cryoglobulinemia result from a process of continuous immune-activated B-cell lymphocyte proliferation caused by chronic infection, autoimmune disease, or unknown cause. Susceptible diseases include lymphoproliferative diseases, autoimmune diseases, and hepatitis C virus (HCV) infections.⁴ HCV infection is the main cause of mixed cryoglobulinemia.

The term cryoglobulinemia vasculitis (CV), which may cause terminal organ damage from the inflammation in small-to medium-sized blood vessels, is often distinguished from cryoglobulinemia, which is asymptomatic.^{4,5} CV occurs in microvessels and triggers immune complex-mediated microvasculitis, leading to viscous syndrome and extremity necrosis induced by low temperature, and even multiple organ injuries. Therefore, it is particularly important to pay attention to the vascular conditions of patients. CV is considered a rare disease, with a prevalence of only 0-7% in healthy people.⁶ Due to the lack of definite diagnostic criteria, misdiagnosis is often made. Imaging manifestations of CV are rarely reported. Here, we report the ultrasonographic findings of major systemic vessels in a patient with idiopathic vasculitis.

2. CASE REPORT

In the autumn, a 61-year-old woman was admitted to our hospital because of pain in the second and third toes of her left foot. During hospitalization, she developed acute pain in both hands with

blackening of the distal fifth finger of her right hand as well as the second and third toes of her left foot (Figure 1); the area of foot pain and gangrene gradually increased. Cryoglobulins and RF were positive[normal, negative], IgA was 2380 mg/L [normal, 830–2900 mg/L], IgM was 3640 mg/L [normal, 700-2200 mg/L], IgG was 15.10g/L [normal, 8.00-15.50 g/L], Hepatitis B virus (HBV)-DNA 6.06 E+3 IU/mL [normal, <1.00E+02]; and γ -globulin, 21.4% [normal, 11.1-18.8%]; and other laboratory indicators were normal. Necrotic toe disease examination showed chronic suppurative inflammation with necrosis, dead bone formation, and calcium staining (-). PET-CT showed increased metabolism of the right shoulder and left ankle joint, mostly benign lesions, but no tumor bone metastasis was found on the rest of the body bone imaging.

The gray scale ultrasound of blood vessels in the extremities showed that the blood vessel walls of the distal right posterior tibial artery, the left anterior tibial artery, and the posterior tibial artery, especially the left posterior tibial artery, were thickened. Color Doppler flow imaging (CDFI) revealed no blood flow signal in the distal segment of the right posterior tibial artery, which indicated obstruction; blood flow signals of the left anterior tibial and posterior tibial arteries narrowed segmentally, and some segments had no blood flow signals, which implied segmental stenosis and occlusion of the left anterior tibial artery and posterior tibial artery. At the same time, gray-scale ultrasound revealed wall thickening of the deep vein of the left lower extremity and the great saphenous vein, and partial filling of isoechoic materials in the lumen. CDFI revealed filling defects of the deep vein of the left lower extremity and the great saphenous vein, which indicated chronic thrombosis with partial recanalization in these vessels (Figure 2). Finally, pulsed Doppler ultrasound showed a slow flow velocity and high resistance spectrum waveform in the proper artery spectra of the radial side of the third finger of the right hand and the radial side of the third finger of

the left hand; there was also a low-resistance spectrum waveform on the radial side of the fifth finger (Figure 3).

Three months later, in the early winter, the patient consulted her doctor again because of aggravation of this condition. Ultrasound examination revealed that there was no significant change in the vascular ultrasound of the lower limbs; the blood flow velocity of the proper arteries in the fingers of both hands was a little lower than that three months ago and completely changed into the spectrum of the high-resistance arteries (Figure 4).

The patient was finally diagnosed with type II CV. After prednisone plus cyclophosphamide and anti-HBV therapy, the serum cryoglobulin level was negative.

3. DISCUSSION

Cryoglobulin is an abnormal immunoglobulin present in the circulation, which is characterized by precipitation at 0-4°C and dissolution after rewarming to 37 °C. CV is a small vessel occlusive vascular disease caused by the precipitation of the cryoglobulin immune complex in plasma, which mainly affects small-to medium-sized vessels.⁷ It can cause disease by blocking microvessels or triggering immune complex-related microvascular inflammation, which can lead to viscous syndrome, acral necrosis, and organ damage. Therefore, it is particularly important to pay attention to the blood vessels of patients at an early stage.

At present, the exact pathogenesis of CV has not been clarified, but the co-pathogenic link of all hypotheses is through the cascade reaction of thrombotic occlusion of medium and small vessels, which leads to vascular spasm and venous stasis. In 2012, the International Chapel Hill Consensus Conference defined CV as a type of vasculitis of small vessels, in which cryoglobulin immune complex deposition mainly affects capillaries, venules and/or arterioles.² The predisposing diseases

of CV include hepatitis virus, autoimmune disease, malignant tumor and lymphoproliferative disease. Up to 50% of patients with primary CV may develop T or B lymphoma.^{8,9,10,11} Therefore, in understanding the etiology of CV, it is necessary to identify HBV-associated CV, hematological tumors, and immune factors. Cryoglobulinemia type II is often associated with HCV infection and less often with HBV infection.¹² There is increasing evidence of a possible causal relationship between viral pathogens and vasculitis^{13,14}

Cutaneous and systemic vasculitis are extrahepatic manifestations of hepatitis, and the patient was positive for HBV surface antigen and serum HBV-DNA, but HCV infection or malignancy was not detected. In contrast to idiopathic CV, HBV-associated CV rarely recurs, especially when viral replication stops and serum HBV antigen is converted to antibody after antiviral therapy.^{13,15,16} Beyond the initial discovery of HBV, the patient's disease continued to worsen despite multiple negative laboratory HBV reviews after discharge, so HBV-associated CV was ruled out. Skin manifestations are the earliest and most common pathological changes. Approximately 80% of cases first occur in the skin, with symptoms including Raynaud's phenomenon, purpura and reticular green spots, and severe, refractory ulcers and gangrene.¹⁷ CV is usually involved in tissues and organs such as the skin, blood vessels, kidneys, and peripheral nerves. When the qualitative test of serum cryoglobulin is positive, CV can be diagnosed.³ It is especially common in the extremities because these areas are more sensitive to cold, hence patients often experience episodes or exacerbations associated with cold. In this case, the patient was first admitted to hospital in autumn, and further aggravation occurred in winter after 3 months. CV should also be suspected in patients with painful skin ulcers on their limbs, especially in those who do not respond to standard treatment.¹⁸

Ultrasound is considered the preferred imaging method for the diagnosis and monitoring of small and medium vessels because of its real-time, reasonable price, and non-invasive ionizing radiation. Ultrasonography also played an important role in the diagnosis and management of this case. Ultrasonography is helpful in diagnosing medium -and small-sized vascular diseases, and locating blood vessels such as the tibiofibular artery and proper digital artery, but it does not have its limits. This case was similar to the thickening of the vascular wall in most cases of vasculitis, and the gray-scale ultrasound showed that the blood vessel walls of the distal right posterior tibial artery, left anterior tibial artery, and posterior tibial artery were thickened. Moreover, ultrasound imaging produced other findings: CDFI revealed obstruction in the distal segment of the right posterior tibial artery, as well as segmental stenosis and occlusion in the left anterior tibial artery and posterior tibial artery. Pulsed Doppler ultrasound showed a slow flow velocity and high resistance spectrum waveform in the proper artery spectra of the radial side of the third finger of the right hand and the radial side of the third finger of the left hand; there was also a low-resistance spectrum waveform on the radial side of the fifth finger. Three months later, ultrasonography follow-up revealed that the flow velocity of the proper digital artery had further decreased, and the resistance had further increased. Moreover, we also found chronic post-thrombotic changes in the deep vein and the great saphenous vein of the left lower limb with partial recanalization. This indicated that vasculitis involved both arteries and veins, leading to thrombosis. According to literature reports, thromboembolic events occur in 25% of patients with CV.¹⁹ Arteriovenous thrombosis occurs more frequently and helps diagnose the disease.

The ultrasonographic features of vasculitis are not characteristic and need to be differentiated from other forms of vasculitis, especially thromboangiitis obliterans (TAO). TAO is an

inflammatory occlusive disease that mainly involves the middle and small arteries of the limbs, and veins can also be involved.²⁰ It often occurs in young men, and lesions often show segmental changes. In the early stage, TAO can lead to vascular wall thickening, lumen stenosis, thrombosis, or even lumen occlusion. In the later stage, with vascular wall fibrosis, TAO can lead to vascular shrinkage, lumen occlusion, and establishment of collateral circulation. Therefore, the identification of these two pathologies mainly depends on the results of the laboratory examination.

In addition, CV should be differentiated from diabetic foot disease with arteriosclerosis obliterans.²¹ In the early stage of diabetic peripheral vascular disease, there may be no symptoms or only a cold feeling at the extremities; the course of the disease is long, and there is no obvious seasonal change. When the diabetic foot suffers from acral ischemia, lifting of the limb can trigger skin color changes, and foot ulcers generally occur in load-bearing areas, sometimes accompanied by elevated skin temperatures. Diabetic vasculopathy is dominated by smaller arteries below the knee. Ultrasonography reveals plaque and segmental occlusion of the arterial wall. Usually, there is no thickening of the blood vessel wall in diabetic lower extremity arterial disease and no simultaneous arterial and venous involvement.

In view of this case, any patient with Raynaud's phenomenon and acroangrene should be screened for cryoglobulin abnormalities, and vascular ultrasound must be performed as soon as possible. Early detection of such diseases should improve the prognosis and reduce the disability rate. Non-healing ulcers in healthy patients without evidence of macrovascular disease should also be suspected as primary CV, and early treatment can improve the prognosis.⁷ Vascular ultrasound is the preferred imaging method for diagnosis and follow-up of medium and small vascular diseases such as CV; it can provide early detection of vascular abnormalities

and help assess the progression and distribution of CV.

In conclusion, we report a rare case of CV with ultrasonographic features presenting as simultaneous involvement of the arteries and veins, vascular wall thickening, and lumen narrowing or occlusion to varying degrees; the patient's lesions worsened in the cold season, and combined with serum IgM and γ -globulin results, indicated a diagnosis of CV.

AUTHORS' CONTRIBUTIONS

Xing Wen and Xiaorong Wen contributed the central idea, analyzed all the data, contributed to the writing and revisions. Thanks to Dr Wenli Jing and Dr Yuan Luo for their help and suggestions on the later revision of the manuscript.

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