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CASE REPORT

Blue Toe Syndrome Associated with Rapidly Progressive Glomerulonephritis: Ultimately Revealed Essential Mixed Cryoglobulinemia

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ABSTRACT

The blue toe syndrome is a rare presentation in a number of medical disorders. We report a 35-year-old woman who initially presented with blue toe syndrome and rapidly progressive glomerulonephritis. Essential mixed cryoglobulinemia with vasculitis and renal failure was documented by laboratory tests and renal biopsy. She was on maintenance hemodialysis as renal failure persisted after steroid and immunosuppressive agents therapy. Her gangrenous changes of bilateral toes were autoamputated symmetrically and uneventfully.

Key Words: Blue toe syndrome; Cryoglobulinemia; Rapidly progressive glomerulonephritis; Vasculitis.

INTRODUCTION

The term “blue toe syndrome” was introduced at first by Karmody et al. in 1976 to describe acute digital cyanosis secondary to microembolism from a proximal atheromatous source (1). It is characterized by the sudden development of one or more discrete blue or
purple areas on the foot or toes. Tissue necrosis, ranging from small superficial ulceration to gangrene, may develop. Classically, this syndrome occurs in the presence of normal peripheral pulse, but it may occur in patients with preexisting peripheral vascular disease. Several medical disorders including atheroembolism, cardiac embolism, hyperviscosity syndrome, hypercoagulability states, vasculitis, etc., can produce this picture (2,3). We report an unusual presentation of a women with mixed essential cryoglobulinemia which was characterized with blue toe syndrome and rapidly progressive glomerulonephritis.

**CASE REPORT**

A 35-year-old married women was admitted to the hospital because of progressive cyanosis over the lower feet and renal failure. The patient had been well until 6 weeks earlier, when she began to experience poor appetite, mild exertional dyspnea, progressive abdominal distention, and lower leg edema with decreased urine output. The patient was taken to another hospital, where acute renal failure due to systemic lupus erythematosus and vasculitis was impressed by laboratory data which showed blood urea nitrogen 118 mg/dL, creatinine 9.5 mg/dL, and antinuclear antibody 1:160 speckled type with low complement level. Hemodialysis and pulse therapy with methylprednisolone were instituted. Because cyanotic toes became deteriorated to gangrenous changes and renal function did not improve, she was transferred to our hospital.

The temperature was 36.2°C, the pulse was 110/min, and respirations were 22/min. The blood pressure was 130/90 mm Hg. On physical examination, consciousness of the patient was clear. The heart sounds were normal. No malar rash, discoid lesion, or oral ulcer was seen. The lung fields were clear. Abdominal examination revealed a normal-sized liver and spleen. The pulse examination showed normal amplitudes over bilateral carotid, radial, femoral, popliteal, and dorsalis pedis arteries. Gangrenous changes of all toes were detected (Fig. 1).

![Figure 1](image.png)  
**Figure 1.** Photograph of feet of patient, demonstrating symmetric gangrenous changes of all toes.
Her white blood cell count was 14,300/μL, with 91% segmented polymorphonuclear leukocytes, 8% lymphocytes, and 1% band form leukocytes. Her hemoglobin was 11.2 g/dL. The erythrocyte sedimentation rate was elevated at 75 mm/h. Her blood urea nitrogen was 68 mg/dL, creatinine 8.7 mg/dL, albumin 2.7 g/dL, globulin 3.3 g/dL, sodium 131 mEq/L, potassium 4.4 mEq/L, chloride 98 mEq/L, 24-h creatinine clearance 3.36 mL/min, and 24-h urine total protein was 4.29 g/day. Her blood viscosity was 1.67 times of water. Arterial blood gas showed pH 7.39, pCO₂ 29.7 mm Hg, HCO₃ 18.1 mmol/L. Immunologic studies revealed negative antinuclear antibody and anti-DNA antibody, C3 118 mg/dL, C4 28.3 mg/dL, IgG 1700 mg/dL, IgM 174 mg/dL, Ig A 673 mg/dL, and Ig E 1280 units/mL; cryoimmunoglobulins of IgG, IgM, and IgA were positive, anticardiolipin antibody IgG was 7.9 GPL units/mL, and IgM was negative. VDRL, hepatitis B surface antigen, hepatitis C antibody, IgM-anti-hepatitis A, rheumatoid factor and anti-neutrophil autoantibody were negative. Immunoelectrophoresis revealed no paraprotein. Renal sonography showed normal-sized kidneys with renal parenchymal disease. Peripheral vascular doppler showed normal duplex arterial study of bilateral lower limbs, and echocardiogram revealed normal heart size without both thrombosis or myxoma.

Histologic examination of renal biopsy revealed marked mesangial proliferation with lobular pattern, microthrombi over the glomeruli, and tubular lumen dilatation with large cast; interstitial had mild chronic inflammation and moderate fibrosis. Immunofluorescence microscopy showed diffuse 2+ IgM, 3+ C3, focal 2+ IgG, and IgA staining. All studies suggested membranoproliferative glomerulonephritis consistent with cryoglobulinemia. Skin biopsy revealed vasculitis. Bone marrow biopsy was normal. Essential mixed cryoimmunoglobulinemia with rapidly progressive glomerulonephritis and blue toe syndrome was diagnosed finally.

In spite of intensive immunosuppressive therapy including cyclophosphamide 100 mg/day and prednisolone 25 mg/day, her renal function did not recover and she is currently on maintenance hemodialysis. Her gangrenous changed toes were autoamputated after 6 months of therapy with aspirin and dipyridamole (Fig. 2).
DISCUSSION

The blue toe syndrome is characterized by the sudden development of acute focal ischemia which may result from embolism, thrombosis, mechanical obstruction, and inflammation, or from a combination of these mechanisms (2). Several medical disorders including cholesterol crystal embolism, infective endocarditis, cardiac myxoma, cryoglobulinemia, polycythemic rubra vera, leukemia, malignancy, antiphospholipid syndrome, essential thrombocythemia, disseminated intravascular coagulation, deep vein thrombosis, vasculitis, systemic lupus erythematosus, microscopic polyarteritis, etc., can produce blue toe syndrome (2,3). In this patient, essential mixed cryoglobulinemia with vasculitis was documented by laboratory tests and histopathologic findings of renal and skin biopsy. Her ultrasound examination of heart, aorta, and peripheral arteries showed normal studies without stenosis. Embolism from cardiovascular system was ruled out. Why could vasculitis cause blue toe syndrome? There are several factors including release of endothelial and platelet-derived growth factors that promote cellular proliferation, leading to obstruction of small vessels and damage to the endothelial surface; release of thromboxane from platelets; and systemic coagulation abnormalities leading to dominance of procoagulant activity and possibly superimposed thrombosis (4). Our patient had renal failure requiring hemodialysis, which might involve fluid shifting in short time, and this may have a contributory role for this clinical picture. In blue toe syndrome, unilateral lesions are usually associated with atherosclerotic plaques or aneurysm; cholesterol embolism is usually with bilateral and asymmetrical, and immunologically mediated disorders are more likely to be bilateral and symmetrical (2,5,6). This patient had a typical presentation of symmetrical and bilateral blue toes and essential mixed cryoglobulinemia may have contributed to it.

There are three types of cryoglobulinemia, proposed by Brouet et al. (7). In this patient, bone marrow showed no evidence of malignancy, and laboratory tests revealed negative antinuclear antibody and antineutrophil autoantibody; infectious diseases including hepatitis B, hepatitis C, and cytomegalovirus were all negative. Type 3 essential mixed cryoglobulinemia was diagnosed in our patient. The renal biopsies in cryoglobulinemia patients usually have membranoproliferative exudative glomerulonephritis associated with intraluminal thrombi. Immunofluorescence microscopy revealed granular capillary wall and mesangial deposits, and intraluminal masses of C3, IgM, and IgG that are immunologically similar to the circulating cryoglobulins (8). In this patient, the renal biopsy was consistent with the typical findings. In previous reports, pulse methylprednisolone therapy followed by long-term oral prednisolone and cytotoxic therapy has been shown to be efficacious in treating renal and systemic manifestations of cryoglobulinemia (9). However, salvage of renal function with immunosuppressive therapy failed and she entered into maintenance hemodialysis.

The natural history and optimal management of patients with blue toe syndrome vary according to the underlying disease. In patients with atheroembolism, early surgery to remove the embolic source is recommended (1-3). However, immunologically mediated patients should be treated with steroid and cytotoxic agents at first; then with combination aspirin and dipyridamole (2,8-10). In this patient, dry gangrenous changes without evidence of bacterial infections developed although we prescribed aspirin and dipyridamole with immunosuppressive agents. Fortunately, dry gangrene on all toes was autoamputated spontaneously without surgical intervention 6 months later. This suggests that dry gangrene without infections of toes should be closely followed, and that autoamputation is possible.

In summary, we have reported a very rare presentation of essential mixed cryoglobulin-
emia associated with vasculitis, blue toe syndrome, and rapidly progressive glomerulonephritis. The patient’s renal function was not improved after steroid pulse therapy and she entered into maintenance hemodialysis. Blue toes became gangrenous and autoamputated eventually.

REFERENCES