Crystalglobulinemia manifesting as chronic arthralgia and acute limb ischemia
A clinical case report
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Abstract
Rationale: Crystalglobulinemia is a rare disease caused by monoclonal immunoglobulins, characterized by irreversible crystallization on refrigeration. It causes systemic symptoms including purpura, arthralgia, and vessel occlusive conditions to be exacerbated by exposure to cold. We report a patient with crystalglobulinemia associated with monoclonal gammopathy of undetermined significance (MGUS) manifesting as chronic arthralgia and recurrent acute arterial occlusion.

Presenting concerns: A 61-year-old man, who had been diagnosed with MGUS and who had arthralgia of unknown origin, presented with recurrent acute limb ischemia after surgical thromboembolectomy. Refrigeration of his serum formed precipitates that looked like needle-shaped crystals. These crystals did not dissolve with warming, which is not a characteristic of cryoglobulins. Skin biopsy results showed crystal-like eosinophilic bodies in small vessels and we diagnosed crystalglobulinemia.

Intervention and outcomes: Although he underwent above-knee amputation, he was treated with a bortezomib and dexamethasone-based chemotherapeutic regimen, following lenalidomide maintenance therapy. Finally, he achieved complete remission and serum crystalglobulins diminished.

Lessons: Monoclonal gammopathy, previously diagnosed as MGUS, can cause systemic symptoms and thrombotic conditions by producing pathologic immunoglobulins, such as crystalglobulins. In such situations, MGUS, even when it has not progressed to multiple myeloma, can be a target of aggressive chemotherapy. Crystalglobulinemia should be considered for patients with monoclonal gammopathy manifesting as systemic and thrombotic symptoms exacerbated by cooling.

Abbreviations: IgG = immunoglobulin G, MGUS = monoclonal gammopathy of undetermined significance, M-protein = monoclonal protein.

Keywords: arthralgia, cryoglobulin, crystalglobulin, embolism, monoclonal gammopathy of undetermined significance, paraprotein, thrombosis

1. Introduction
Monoclonal gammopathy of undetermined significance (MGUS) is a premalignant condition without end-organ damage; treatment is not recommended unless there is progression to multiple myeloma.[1] However, paraproteins due to monoclonal gammopathy, including MGUS, can be pathogenic when the monoclonal protein (M-protein) has autoantibody activity or altered conformation leading to improper aggregation.[2] M-protein-related disease caused by pathological immunoglobulins and light chains, such as cryoglobulinemia, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome, AL amyloidosis, and light-chain deposition disease, can have diverse symptoms such as pyrexia, arthralgia, skin rash, peripheral neuropathy, thrombosis, and renal involvement, which mimic systemic rheumatic diseases.[3] Although M-protein-related diseases can cause fulminant end-organ damage,[4,5] indications for aggressive treatment of MGUS causing M-protein-related disease have not been known. We report a case of crystalglobulinemia, which is a rare form of M-protein-related disease, characterized by irreversible cryoprecipitation, and it is caused by monoclonal gammopathy that was previously diagnosed as MGUS. In this case, crystalglobulinemia manifested as chronic arthralgia and acute limb ischemia, and the patient was treated with a chemotherapeutic regimen for multiple myeloma.

2. Case report
A 61-year-old man presented to our unit in February 2014 with right femoral pain, pallor, paraesthesia, and poikilothermia. Five years previously, he had fever, arthralgia, and pain in the
extremities that worsened with cold exposure. At another hospital, immunoglobulin G (IgG) MGUS was diagnosed and confirmed by bone marrow aspiration. However, because of negative cryoglobulin test results, his symptoms did not appear to be related to IgG MGUS. Treatment with prednisolone, methotrexate, and infliximab for presumed autoimmune disease manifesting as polyarthritis did not result in appreciable clinical improvement.

On examination, he had widespread, nonpalpable, painful purpura covering his extremities, and his right leg was particularly cool and pale (Fig. 1). Ultrasonography revealed absence of Doppler signals on the right superficial femoral artery and acute arterial occlusion was diagnosed. Extensive thrombosis within the lower leg vein was also recognized. Although surgical thromboembolectomy was performed, reocclusion occurred 3 times at the same site. This recurrent thrombotic arterial obstruction was thought to be caused by extensive venous thromboembolism, which was not unresponsive to thrombolytic treatment. Therefore, we reevaluated his underlying disease.

Blood test results showed increased IgG (3262 mg/dL; reference range, 870–1700 mg/dL), normal immunoglobulin A (134 mg/dL), decreased immunoglobulin M (28 mg/dL; reference range, 33–190 mg/dL), and skewed free light-chain κ/λ ratio (152; reference range, 0.26–1.65). Serum immunoelectrophoresis detected IgG κ M-protein. Osteolytic lesions, anemia, renal insufficiency, and hypercalcemia were absent. Other blood test results revealed that serum complement components, total hemolytic complement level, antinuclear antibodies, antineutrophil cytoplasmic antibodies, lupus anticoagulants, protein S and C activity, antithrombin III activity, and hepatitis B and C serology were normal. Serum cryoglobulin and plasma cryofibrinogen results were negative again in routine study, but refrigeration of the serum and plasma samples at 4°C for up to 72 hours led to the formation of microscopic needle-shaped precipitates. Warming the samples to 37°C did not redissolve the cryoprecipitates. Skin biopsy of the purpura revealed crystal-like eosinophilic bodies in small vessels (Fig. 2). Immunofluorescence showed crystal-like bodies stained with anti-IgG antiserum and anti-κ light-chain antiserum (Fig. 3). There was no evidence of vasculitis. We diagnosed cryoglobulinemia caused by underlying plasma cell dyscrasia (previously diagnosed as MGUS).

In March, the patient presented with exacerbation of pain, pallor, and sensory loss below the right knee. The limb appeared marble white, and no pulse was palpable over the right popliteal artery. Acute limb ischemia developed rapidly and caused gangrene, leading to oliguria, creatine kinase elevation, hyperkalemia, and myoglobinuria with acute renal failure. He was admitted to the intensive care unit for the treatment of sepsis due to Staphylococcus aureus bacteremia, which originated from the necrotizing soft tissue of the ischemic limb. Critical care included sepsis management and continuous renal replacement therapy. The patient’s condition improved substantially, but his right lower extremity was not viable. An above-knee amputation was necessary; therefore, he was transferred to a high-volume center for orthopedic surgery. Bone marrow aspiration performed postoperatively revealed 17.5% plasma cells, which led to the final diagnosis of multiple myeloma. He was treated with 4 cycles of a bortezomib and dexamethasone-based chemotherapeutic regimen. Although the patient’s M-protein level decreased, his systemic symptoms exacerbated by cold exposure persisted. He was administered lenalidomide to diminish M-protein and achieved complete remission. During subsequent follow-up, he remained in hematologic stringent complete remission with lenalidomide. Monoclonal gammopathy and systemic symptoms resolved.

Figure 1. Widespread nonpalpable purpura covering the extremities.
3. Discussion

The case presented here showed that crystalglobulins, caused by monoclonal gammapathy, previously thought to be MGUS, cause chronic arthralgia and extensive venous thromboembolism, which is insensitive to thrombolytic agents, following acute arterial occlusion. Therefore, crystalglobulinemia can mimic systemic rheumatic disease, vasculitic syndrome, and thrombotic conditions. In addition, when end-organ damage is caused by pathogenic M-proteins, the underlying monoclonal gammapathy, despite being categorized as MGUS because of the limitations of the current diagnostic system, can be a therapeutic objective.

Crystalglobulinemia is a rare condition resulting from monoclonal gammapathy associated with multiple myeloma, MGUS, and other plasma cell disorders. Precise data regarding disease prevalence are still unknown. Crystalglobulins, characterized by irreversible crystallization on cooling, are deposited in blood vessel walls and lead to vascular endothelial injury, thrombosis, and vessel occlusion, thereby causing ischemic damage to various organs. Crystalglobulinemia manifests as recurrent purpura, skin ulceration, arthralgia, and thrombotic conditions such as renal arterial occlusion and limb ischemia, which are exacerbated by cold exposure.[3,6-8] Symptoms of crystalglobulinemia are similar to those of cryoglobulinemia. However, unlike cryoglobulins, crystalglobulins are not dissolved by rewarming. The pathogenesis of irreversible cryoprecipitation in cryoglobulinemia involves aggregation of the M-proteins as insoluble extracellular crystals.[9] This phenomenon is reportedly associated with structural characteristics such as abnormal N-glycosylation on the IgG κ chain, which is not observed in immunoglobulins from multiple myeloma patients without crystalglobulinemia. Nonfucosylated oligosaccharides on the κ chain of crystalglobulins, which lead to protein misfolding and insolubility of immunoglobulin, have been suggested.[9,10] In cases of crystalglobulinemia, despite negative findings of cryoglobulins and cryofibrinogens according to routine laboratory studies, cryoprecipitates can be observed grossly in blood collection tubes or microscopically in blood smears. Microscopic detection of irreversible cryoprecipitation and the presence of intravascular crystalized bodies in affected tissues in pathological specimens are critical for the diagnosis of crystalglobulinemia. In our case, at the time of admission, MGUS may have already progressed to multiple myeloma. However, based on the Unitarian theory known as Ockham’s razor, the early presentation of arthralgia exacerbated by cold exposure, which had persisted for several years, was thought to be caused by crystalglobulins from MGUS.

Patients with MGUS generally require only watchful waiting because clinical trials of early therapeutic interventions with standard chemotherapy have yielded negative results. Therefore, there is no standard treatment indication or chemotherapy for MGUS with M-protein-related disease in which M-proteins have autoantibody activity or altered conformation with aggregating improperly.[1,2] Aggressive treatment for symptomatic monoclonal gammapathy due to pathogenic paraproteinemia, even without progression to multiple myeloma, would be required because M-protein-related diseases can cause irreversible organ damage because of a delay in treatment. Chemotherapy for plasma cell dyscrasia and plasmapheresis to remove pathogenic immunoglobulins are presumed to be beneficial for symptomatic relief.[1,2,3,5] Therapeutic strategies should be established to prevent fulminant end-organ damage caused by pathogenic M-proteins, including crystalglobulins.

Crystalglobulinemia and AL amyloidosis have similar characteristics in paraproteins forming irreversible and insoluble structures, and they have similar clinical symptoms caused by aggregated paraproteins. In AL amyloidosis, one of the M-protein-related diseases, fibrilization of paraproteins has been observed.[11,12] An abnormal monoclonal light chain characterized by protein misfolding, aggregation, and deposition in tissues causes multisystem involvement, such as macroglossia, purpura, nephrotic syndrome, hepatosplenomegaly, restrictive cardiomyopathy, and peripheral neuropathy.[13] Like crystalglobulinemia, N-glycosylation of amyloidogenic κ light chains has also been reported.[14,15] However, the treatment strategy for AL amyloidosis is clearer than that for crystalglobulinemia. AL amyloidosis with organ dysfunction should be treated with high-dose melphalan followed by autologous hematopoietic cell transplantation or chemotherapeutic agents for multiple myeloma, depending on the patient’s transplant eligibility. The chemotherapeutic regimen includes melphalan and dexamethasone, a bortezomib-based regimen, or immunomodulatory derivatives, such as a lenalidomide-based regimen.[13]
As evidenced from this case, crystalglobulinemia can mimic rheumatic and thrombotic diseases; therefore, monoclonal gammopathy, although diagnosed as MGUS by definition, may be symptomatic because of the effects of pathogenic paraproteins. These diseases are often overlooked until symptoms become severe. Therefore, early recognition and appropriate treatment can prevent end-organ damage and improve prognosis. Various physicians (eg, rheumatologists, nephrologists, neurologists, and dermatologists) should remember that systemic symptoms of unknown cause for patients with MGUS may require further testing and differential diagnosis for M-protein-related diseases, including crystalglobulinemia. It is critical to detect the presence of crystalglobulins so that the chemotherapeutic regimen targeting the responsible clone plasma cells may improve the symptoms. In this case, we did not directly isolate M-proteins with crystalglobulin activity. However, the clinical course and treatment efficacy highly indicated crystalglobulinemia due to monoclonal gammopathy. Further reports are required to establish clinical practice for crystalglobulinemia and to formulate a treatment strategy for monoclonal gammopathy with pathological M-protein that has not progressed to multiple myeloma.

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