Crystalglobulinemia with Fulminant Course with Cylinder-like Bodies on Peripheral Blood Smear

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Abstract

A 63-year-old woman presented to our hospital with fever, purpura and pain in both legs and died 4 days after admission. Her blood smear and skin biopsy showed cylinder-like bodies (20×120 μm). She was diagnosed to have monoclonal gammopathy (IgG, lambda type). An autopsy revealed cylinder-like bodies in the vasculature of various organs. We noted a proliferation of atypical plasma cells in her bone marrow, suggesting pre-existing myeloma. Crystalglobulinemia is a rare manifestation of hypergammaglobulinemia that can cause multiple embolisms of the small vessels, and this resulted in the patient’s fulminant course. The identification of cylinder-like bodies in the peripheral blood may help in reaching a diagnosis in such cases.

Key words: crystalglobulinemia, cylinder-like bodies, multiple myeloma

(Intern Med 53: 1847-1851, 2014)
(DOI: 10.2169/internalmedicine.53.1775)

Introduction

The deposition of immunoglobulin-derived crystals has been reported in patients with multiple myeloma (1). The clinical manifestations of this condition differ depending on the organ in which crystal deposition occurs. Terms such as crystalglobulinemia (2-14), crystal-storing histiocytosis (15), crystal nephropathy (16), and crystalline keratopathy (17) have been used. The clinical manifestations of crystalglobulinemia resemble those in patients with vasculitis or sepsis; namely, purpura, neuropathy, and multiple organ failure. The pathogenesis is considered to be the embolization of small vessels due to the crystallized immunoglobulin. Crystalglobulinemia can manifest as mild clinical symptoms in the course of multiple myeloma; however, one report described a fulminant course (4). We herein describe a case in which the autopsy findings revealed fulminant crystalglobulinemia and multiple organ failure. The cylinder-like bodies found in patient’s peripheral blood smear were helpful in arriving at the diagnosis.

Case Report

A 63-year-old woman was admitted to a local hospital with a history of edema, pain, and purpura on her extremities that had persisted for several months; however, a diagnosis was elusive despite an extensive examination. She developed fever and severe pain, followed by paralysis and the loss of sensation in both lower legs for five days before she was transferred to our hospital.

On admission, the patient had hypertension (190/95 mmHg), tachycardia (98 bpm), and tachypnea (26/min). Purpura was found on her legs, hands, and part of her face. (Fig. 1). Her arms and legs felt cold to be touch; however, pulses in the peripheral arteries were palpable. A neurological examination showed spastic paralysis of both legs, loss of sensation under the area of thoracic vertebrate 12 (Th12), and incontinence. Her complete blood count results showed an increased white blood cell count (WBC 11,900/μL), anemia (9.3 g/dL), and thrombocytopenia (87,000/μL). The patient’s fibrin degradation product (FDP 120 μg/mL) was in-
Increased, and her prothrombin time international normalized ratio (PT-INR) was prolonged. Electrophoresis of her serum protein revealed an M-peak (Fig. 2A). Her serum IgG level increased to 3,773 mg/dL, and immunoelectrophoresis of her serum protein showed an IgG-lambda band (Fig. 2B). In addition, increased levels of serum enzymes (aspartate transaminase [AST] 109 IU/L, alanine transaminase [ALT] 60 IU/L, lactate dehydrogenase [LDH] 728 IU/L, creatine kinase [CK] 5,991 IU/L) suggested injury to multiple organs and rhabdomyolysis. The patient’s haptoglobin level was normal, suggesting that there was no massive hemolysis. The level of C-reactive protein was also increased (14.97 mg/dL). Three sets of blood cultures were all negative.

Cylinder-like bodies (approximately 20×120 μm) were observed in several fields of peripheral blood smears (Fig. 3) and on a Giemsa-stained bone marrow smear. A skin biopsy of the purpura revealed hexagonal eosinophilic bodies in the small vessels (Fig. 4); however, we were unable to clarify the composition of the cylinder-like bodies at that time.

The patient’s symptoms of tachypnea, tachycardia, and elevated WBC count met the criteria for the diagnosis systemic inflammatory response syndrome. We first considered systemic vasculitis, infection of the soft tissue, and/or sepsis. In addition, her elevated FDP and the presence of thrombocytopenia suggested that she also had disseminated intravascular coagulation (DIC). Although thrombotic thrombocytopenic purpura (TTP) was also considered, there was limited evidence of hemolysis. Although she was treated with antibiotics, heparin, corticosteroid, and other intensive supportive reagents, the symptoms of rhabdomyolysis, thrombocytopenia, and coagulation abnormality were exacerbated. She consequently developed renal failure and hyperkalemia and died on day four of admission.
An autopsy revealed cylinder-like bodies in the skin, muscle, and various organs, including the intestines and uterus, and these tested positive for anti-IgG-lambda by immunohistochemistry (Fig. 5A). We also observed proliferation of atypical plasma cells in thoracic vertebrae 11 (Th11) (Fig. 2C), and these cells were positive for IgG-lambda (data not shown), suggesting pre-existing multiple myeloma. Hemorrhages and necrotic lesions were found in multiple organs, including the stomach, colon, liver, spleen, and the iliopsoas muscle. We also noted fibrin thrombus in multiple organs, including the kidneys, which suggested DIC. Gram-positive cocci were seen in necrotic tissue in the stomach and colon; however, proliferation was limited.

Laser micro dissection technique was performed to obtain material from the cylinder-like bodies, and a Western blot assay revealed that they were positive for anti-IgG-lambda (Fig. 5B). Therefore, the cylinder-like bodies were considered to be the result of crystallization of the IgG-lambda paraprotein produced by the multiple myeloma, namely crystalglobulinemia. We considered the pathogenesis in the present case to be as follows: the cylinder-like bodies caused small-vessel embolization in association with DIC and resulted in the patient’s fulminant course with systemic rhabdomyolysis and multiple organ failure.

**Discussion**

It is well known that serum protein can be precipitated under certain conditions (18). Crystalized immune globulin in patients with hypergammaglobulinemia in various organs has been reported (Table). Among these, angiitis-like clinical manifestations in patients have been identified as crystalglobulinemia or cryocrystalglobulinemia (2-14). In addition, patients found to have only crystal phagocytosis, renal crystal lesions, or corneal lesions have been diagnosed with crystal-storing histiocytosis (15), crystal nephropathy (16), and crystalline keratopathy, respectively (17).

Systemic microangio-embolization of crystallized paraprotein derived from immunoglobulinemia is considered to be the pathogenesis of crystalglobulinemia. Its common symptoms, such as purpura, skin ulcer, neuropathy, and renal failure are difficult to distinguish from those of sepsis or systemic vasculitis; however, biopsies from patients with crystalglobulinemia do not show histological angiitis (4). Instead, crystallized paraprotein injures endothelial cells, causes local emboli, and disturbs blood supply to organs (5). In the present case, crystallized IgG-lambda positive cylinder-like bodies in the vessels were accompanied by necrosis and inflammation; however, there were no findings...
Crystalglobulinemia is a very rare clinical manifestation associated with diseases involving hypergammaglobulinemia and microangiopathy. Multiple myeloma is the most common underlying disease; however, other diseases, such as monoclonal gammopathy of undetermined significance, can also cause this condition (Table).

In the present case, we were unable to identify the cylinder-like bodies observed in peripheral blood smear, when the patient was alive. This raises the concern that crystalglobulinemia may have been overlooked in a significant number of cases to date. A careful examination of peripheral blood smears may be helpful in reaching an accurate diagnosis. In the future, it will be important to examine a greater number of crystalglobulinemia cases to clarify its pathogenesis and establish an effective treatment.

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

References