Thrombotic Thrombocytopenic Purpura and Myoglobinuric Acute Renal Failure following Radiation Therapy in a Patient with Polymyositis and Cervical Cancer

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A 73-year-old woman was admitted to receive radiation treatment for uterine cervical cancer, however a complex series of events ensued, leading to death. She developed an acute exacerbation of polymyositis complicated by thrombotic thrombocytopenic purpura, rhabdomyolysis and acute renal failure. Radiation therapy may have produced an immune disturbance leading to the acute exacerbation of polymyositis. Auto-immune-mediated endothelial damage might have triggered a series of events leading to thrombotic thrombocytopenic purpura. Rhabdomyolysis seemed to be the main cause of acute renal failure.

Key words: rhabdomyolysis, myoglobinuria, acute tubular necrosis, microangiopathic hemolytic anemia

Introduction

Polymyositis, a collagen disease, is characterized by a non-purulent form of myositis. The main clinical feature is symmetrical weakness of proximal muscle groups with elevated muscle enzymes, especially creatine phosphokinase (1). Although its etiology is not known, an autoimmune mechanism is believed to be involved (2). Many autoantibodies specific to polymyositis, such as anti Jo-1 (3) antibody and anti polymyositis 1 antibodies, are detected in the sera from patients with polymyositis.

Thrombotic thrombocytopenic purpura (TTP), a microangiopathy, is characterized clinically by fever, neurological manifestations, hemolytic anemia, thrombocytopenic purpura and evidence of renal disease (4). Renal involvement as manifested by proteinuria, hematuria, pyuria, casts, and/or azotemia has been noted in over one half of the cases. Recently TTP has been reported in association with autoimmune disorders and autoimmune etiology has been hypothesized (5, 6).

Myoglobinuric acute renal failure is seldom reported in patients with polymyositis, although myoglobin is detected both in urine and sera (7). We describe a patient with polymyositis who developed, thrombocytopenic thrombocytopenic purpura (TTP), acute renal failure, and rhabdomyolysis after a flare-up of polymyositis following radiation therapy given for uterine cervical cancer.

Case Report

This 73-year-old woman was admitted to the Gynecology Department of our university hospital on May 21, 1991 for radiation treatment of cancer of the uterine cervix. She had no family history of muscular diseases. Raynaud’s phenomenon had been noted three years earlier by a local physician. Pulmonary fibrosis was also diagnosed at that time (Fig. 1). Radiation treatment was interrupted because of the development of fever, watery diarrhea and malaise. Following its resumption, the patient developed progressive muscle weakness, fever and diarrhea (Fig. 2). Proximal muscle weakness was so severe that the patient could not lift her legs. The administration of antibiotics was ineffective. Acute polymyositis was suspected. The administration of prednisolone 40 mg/day led to a decrease in fever and return of muscle strength. However, the findings of urine color of red wine, chest discomfort, muscle weakness and finally, oliguria and somnolence, led her to transfer to the Third Department of the Internal Medicine and to the ICU on...
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She was then unconscious, with minimal response to deep pain. Her heart rate was 110/min; BP, 120/70 mmHg; respiratory rate, 30/min, and temperature, 35.2°C. Jaundice was noted. No heart murmurs were heard over the heart and Verclo rales were heard over the lower lung fields. Purpura was noted on the extremities and there was pretibial edema.

Laboratory data at that time (Table 1) revealed elevation of muscle specific enzymes, elevation of myoglobin in serum and urine, deterioration of renal function, platelet consumption, and the elevation of fibrinogen degradation products (FDP) in

![Fig. 1. Chest X-ray before admission showing lung fibrosis.](image)

![Fig. 2. Clinical course of the present case. BP: blood pressure, m-PSL: methylprednisolone, PSL: prednisolone, HD: hemodialysis, PE: plasma exchange.](image)

| Table 1. Biochemical Findings on Admission to ICU |
| Blood urea nitrogen (BUN) | Creatinine | Uric acid | Antinuclear factor cyto (+) |
| 43.2 mg/dl | 4.2 mg/dl | 15.1 mg/dl | Extractable nuclear antigen (+) |
| Aspartate aminotransferase (AST) | Alanine aminotransferase (ALT) | Alkaline phosphatase | SS-A (-) |
| 121 IU/l | 61 IU/l | 230 IU/l | SS-B (-) |
| Thymol turbidity test | Zinc sulphate turbidity test | Choline esterase | Unknown (+) |
| 14.9 MU | 23.5 KU | 57 IU/l | Anti-DNA Ab 3.6 U/ml |
| Aspartate aminotransferase (ALT) | Lactic dehydrogenase (LDH) | Leucine aminopeptidase | CH50 41.7 U/ml |
| 109 IU/l | 5,520 IU/l | 154 IU/l | C3 66.7 mg/dl |
| γ-glutamyltranspeptidase | Total protein | Albumin | C4 17.4 mg/dl |
| 306 mg/dl | 7.06 g/dl | 2.86 g/dl | Arterial blood gas analysis (O2 3 l/min) pH 7.415 |
| Na | Creatine phosphokinase (CPK) | 932 IU/l | PO2 37.0 mmHg |
| 134 mEq/l | 147.5 IU/l | 58.2 IU/l | PO2 108.0 mmHg |
| K | Aldolase (ALD) | 2.1 mg/dl | HCO3 23.5 mEq/l |
| 99 mEq/l | | Myoglobin(S) | Prothrombin time 97% |
| Ca | Myoglobin(U) | 773.5 ng/ml | Activated partial thromboplastin time 21.5 sec |
| 8.4 mg/dl | 33,460 ng/ml | Fibrinogen degradation products 198 mg/dl |
| P | Hemoglobin | 10.4 g/dl | Haptoglobin < 10 mg/dl |
| 2.1 mg/dl | 10.4 g/dl | 2.6×10⁶/mm³ |
serum. Tests for antinuclear antibody were positive and showed a cytoplasmic pattern. A test for antibody to extractable muscular antigen was positive but the latter could not be identified.

We diagnosed an exacerbation of polymyositis and acute renal failure with TTP and myoglobinuric rhabdomyolysis. The administration of methylprednisolone pulse therapy together with hemodialysis and plasma exchange therapies were initiated (Fig. 2). Despite intensive treatment, the patient remained comatose. The congestive heart failure grew worse and she developed respiratory failure. The patient died on July 3, the 44th hospital day.

Autopsy revealed residual squamous cell carcinoma of the cervix uteri. Superficial cortical vessels of the brain contained small fibrin thrombi (Fig. 3), and multiple infarcts were present. Multiple hyaline thrombi were found in the arteries of the myocardium and pancreas. We noted a marked degeneration of the muscle fibers and a slight infiltration of lymphocytes and plasma cells around the blood vessels (Fig. 4). The kidney showed focal areas of cortical necrosis, with degenerative and necrotic changes in the tubular epithelium, being more marked in the distal tubules and collecting duct than in the proximal tubules. Pigmented casts positively stained with anti-myoglobin antibody were seen in the lumina of some distal tubules and collecting duct (Fig. 5). The glomeruli showed no obvious proliferation or changes including the mesangium. The presence of eosinophilic fibrin thrombi in the glomerular capillary lumen indicated the presence of disseminated intravascular coagulation (Fig. 6). No hyaline thrombi were observed in the renal arteries.

Discussion

In this patient polymyositis was diagnosed clinically from the earlier findings of Raynaud’s phenomenon and pulmonary
fibrosis together with the presence of acute symmetrical proximal muscular weakness, fever, and the elevated serum levels of muscle enzymes and of certain autoantibodies. Prednisolone was effective for her clinical symptoms such as muscle weakness and fever. Furthermore she had no family history of muscular diseases and she was complicated with uterine cervical cancer. Results of histological examination of specimens of muscle obtained at autopsy were compatible with a diagnosis of rhabdomyolysis, but were not typical of polymyositis, although some infiltration by mononuclear cells was observed. These changes seemed to have been influenced by the high doses of steroids administered.

TTP was diagnosed from the presence of thrombocytopenia, microangiopathic hemolytic anemia and central neurological dysfunction and confirmed by the autopsy findings of microvascular thrombi in the brain, myocardium and pancreas. In the present patient, the TTP, which has been associated with a variety of causes and an unknown pathogenesis, seemed to be secondary to polymyositis rather than to the cervical cancer. TTP was detected during an exacerbation of polymyositis when uterine cervical cancer was almost controlled by radiation therapy. TTP rarely accompanies polymyositis/dermatomyositis; only 9 such cases reported in the literature (5, 6, 8–10). None of these cases was associated with rhabdomyolysis. Thus, this appears to be the first report of a patient with polymyositis associated with both TTP and rhabdomyolysis.

Rhabdomyolysis is implicated as the cause of approximately 5% to 25% of cases of acute renal failure (11). Traumatic and non-traumatic causes of rhabdomyolysis have been described (12, 13), with myopathy being one of the main non-traumatic forms. Alcoholic myopathy is a common cause of rhabdomyolysis and acute renal failure (14). Rhabdomyolysis is rarely associated with polymyositis and dermatomyositis (15–17). The literature contains few such cases, especially in Japan (18).

Although polymyositis myoglobinemia and myoglobinuria has been reported in many patients (4, 19), few develop acute renal failure. This indicates another important risk factor for renal failure. Ward pointed out that dehydration was predictive of acute renal failure in rhabdomyolysis (20). Fever and diarrhea in the present patient may have caused dehydration leading to acute renal failure in addition to the contributory role of TTP.

While TTP and rhabdomyolysis can each produce acute renal failure, the latter seemed to be the major cause in the present case, in that the autopsy revealed findings characteristic of acute myoglobinuric renal failure rather than those of TTP. Most striking was the acute tubular necrosis with myoglobinuric casts.

Judging from the patient’s clinical course, radiation therapy seemed to have caused not only the radiation enterocolitis, but also, the flare up of polymyositis. As mentioned, autoimmune mechanisms underlie the development of polymyositis. Radiation may have damaged the tissue, accelerating the release and denaturization of autoantigens. The production of autoantibodies may have been accelerated causing an aggravation of cellular immune phenomena.

The formation of platelet thrombi in TTP is thought to result from damage to the endothelium of small vessels. Patients with active rheumatoid disease are predisposed to form immune complexes, whose deposition may damage the endothelium (6). Noda et al demonstrated immune complexes and increased levels of von Willebrand’s factor antigen in a patient with dermatomyositis associated with TTP (5). Although no immunohistochemical study was performed in the present case, immune complex formation may have triggered the sequence of events culminating in TTP.

References