Title page

Renal thrombotic microangiopathies / thrombotic thrombocytopenic purpura in a patient with primary Sjögren's syndrome complicated with IgM monoclonal gammopathy of undetermined significance

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Running Head: TMA / TTP in a patient of pSS with MGUS

Key words: Thrombotic microangiopathies, Thrombotic thrombocytopenic purpura, Primary Sjögren's syndrome, Monoclonal gammopathy of undetermined significance, Acute renal failure

Abstract

Thrombotic microangiopathy (TMA) / thrombotic thrombocytopenic purpura (TTP) is a rare but potentially lethal condition requiring rapid recognition, diagnosis, and initiation of therapy. We experienced a case of a 61-year-old woman with primary Sjögren's syndrome (pSS) complicated with severe renal TMA / TTP following IgM monoclonal gammopathy of undetermined significance (MGUS). She was admitted to our hospital for further evaluation of hypergammaglobulinema, acute renal failure and severe thrombocytopenia. She had been diagnosed with pSS 13 years prior to admission. Histological examination of her kidney revealed fibrin thrombi in the glomeruli and arterioles, a finding that is consistent with TMA / TTP. The patient was subsequently treated with plasma exchange, which resulted in a successful outcome without any complications. This rare case suggests that it is important to make a therapeutic decision based on appropriate and prompt pathological diagnosis.

Introduction

Thrombotic microangiopathy (TMA) / thrombotic thrombocytopenic purpura (TTP) typically presents with varying degrees of the pentad of Coombs-negative hemolytic anemia, thrombocytopenia, acute renal failure, neurological disturbances, and fever [1]. Several potential causes have been identified in this setting; however, no absolute cause has yet been proven.

Monoclonal gammopathy of undetermined significance (MGUS) has been reported in association with several non-malignant disorders, including autoimmune disorders [2]. MGUS also occurs in patients with Sjögren’s syndrome (SS), being detected in 22 % of patients in whom immunoelectrophoresis was performed [3]. The present report describes a Japanese patient with TMA and IgM MGUS, which developed 13 years after the diagnosis of primary SS.

Case report

A 61-year-old Japanese female, who was diagnosed with primary SS 13 years earlier, complained of general fatigue and edematous eyelid. Laboratory blood examination showed thrombopenia, hypergammaglobulinema, and elevation of creatinine, while the urine test showed a protein concentration of 1 g/dl and numerous red blood cells (RBCs) in each microscopic field. She was admitted to our hospital for further evaluation.

On admission, physical examination revealed petechial purpura on the lower thigh. Laboratory investigations revealed the following: hemoglobin (Hb) 8.6 g/dL, white blood cell count $3.8 \times 10^3/\mu L$ (neutrophils 58%, lymphocytes 31%, monocytes 9%

and eosinophils 1%), platelet count (PLT) 58 × 10^3/μL, C reactive protein (CRP) 0.10 mg/dl (0.95 nmol/L), total protein 7.8 g/dL (78 g/L), albumin 2.7 g/dL (27 g/L), total bilirubin 0.6 mg/dL (10.3 μmol/L), lactate dehydrogenase (LDH) 471 IU/L, alkaline phosphatase 412 U/L, aspirate aminotransferase (AST) 40 IU/L, alanine aminotransferase (ALT) 33 IU/L, γGTP 19 IU/L, blood urea nitrogen (BUN) 51.0 mg/dL (18.2 mmol/L), creatinine 1.8 mg/dL (159.1 μmol/L) and haptoglobin 4.6 mg/dL (0.04 g/L). Peripheral blood smear showed burr and helmet cells.

Coagulation tests indicated the following: prothrombin time international normalized ratio (PTINR) 0.99 (normal 0.85-1.22), activated partial thromboplastin time (APTT) 26.9 sec (normal 25.2-34.4 sec), fibrinogen 328 mg/dL (3.28 mmol/L), D-dimer 8.3 μg/mL (normal < 1.0 μg/mL), protein C 126 % (normal 65-135 %), protein S 113 % (normal 70-130 %) and thrombomodulin 62.8 U/ml.

Immunological studies showed the following: antinuclear antibody 1:80, anti-dsDNA antibody 0.5 IU/mL, anti-Sm antibody 2.5 U/mL, anti-SS-A antibody 129 U/mL, anti-SS-B antibody 38 U/mL, IgG 3300 mg/dL (33000 g/L) and IgM 1140 mg/dL (11400 g/L). Anti Jo-1 antibody was negative. Immunofixation revealed a monoclonal protein, IgM.

Complement C3 was 63.7 mg/dl (normal 60-115 mg/dl), C4 was 45.1 mg/dl (normal 15-50 mg/dl) and CH50 was 28.5 U/ml (normal 25-50 U/ml). The following test results were all negative: direct and indirect Coombs test, cryoglobulin, proteinase-3 anti-neutrophil cytoplasmic autoantibodies (PR3-ANCAs), myeloperoxidase anti-neutrophil cytoplasmic autoantibodies (MPO-ANCAs), and anti-glomerular basement membrane (GBM) antibody.

The three tests for the detection of antiphospholipid antibodies (APA) Lupus anticoagulant (LA) activity, and anticardiolipin antibodies and anti-β 2-glycoprotein I antibody (both IgG and IgM) were all negative.

We showed the clinical course of the present patient (Fig. 1). Immunofixation revealed a monoclonal protein of IgM, however, the bone marrow smear did not show abnormalities toward multiple myeloma and Waldenstöm's macroglobulinemia; therefore, methylprednisolone pulse therapy (500 mg/day for 3 days) was introduced on hospital day 6. Oral 30 mg of prednisolone were also given daily in conjunction with low-molecular-weight heparin (2000 U/day). Renal dysfunction did not improve and renal biopsy on hospital day 12 showed fibrin thrombi in the glomeruli and arterioles, indicating TMA (Fig. 2). No immune deposits were shown by electron microscopy or by immunofluorescence microscopy. Further serum analysis revealed a reduced A Disintegrin And Metalloprotease with ThromboSpondin repeats-13 (ADAMTS13)

metalloproteinase level of 21.8% (normal 66-126%), but with the absence of anti-ADAMTS13 IgG autoantibodies. Based on these findings, the present case was diagnosed as TMA / TTP leading to acute renal failure through ischemia. We decided to initiate therapeutic plasma exchange (on hospital days 30, 32, 35) and strengthened anticoagulation therapy. After these treatments, the patient recovered from these manifestations, and the levels of Hb, PLT, LDH and creatinine were all normalized and the patient was discharged on hospital day 65.

Discussion

Renal involvement is often seen in patients with pSS. The most frequent renal complication in SS is tubulointerstitial nephritis. In addition, glomerular immune-complex deposits were initially suspected to associate with renal failure in the present case [4]. Unexpectedly, the results of renal biopsy revealed fibrin thrombi in the glomeruli and arterioles in the absence of immune deposits, which is characteristic of TMA / TTP. The involvement of larger vessels, such as arteries or veins, in the renal biopsy specimens suggested APS nephropathy [5]. However she did not meet the classification criteria for antiphospholipid syndrome (APS) [6, 7], since no APA was found in the serum.

Recent studies indicate that the severe deficiency of a VWF cleaving metalloproteinase, ADAMTS13, is the main cause of platelet thrombosis in TMA / TTP [8, 9]. In our case, low ADAMTS13 activity and the presence of schistocytosis may suggest ADAMTS 13-related TMA / TTP rather than APS in the present case. In addition, MGUS may additionally contribute to the development of TMA / TTP through hyperviscosity or excess antibody production against unknown targets.

A quick diagnosis of TMA / TTP, which is a potentially lethal condition, made it possible to treat the present case successfully. Thus, we would like to emphasize the importance of performing renal biopsy in patients with collagen disease who present acute renal dysfunction and thrombocytopenia simultaneously. The use of low molecular weight heparin was thought to be effective for treating thrombi in the kidney. Plasma exchanges in combination with corticosteroids also appeared to be effective in reducing immunoglobulin and autoantibodies, which may contribute to TMA / TTP.

In summary, we presented a rare case of pSS complicated with severe renal TMA / TTP following MGUS. Although the pathophysiological mechanism remains to be precisely determined, we could successfully treat the present case based on appropriate and prompt pathological diagnosis.

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Figure legends

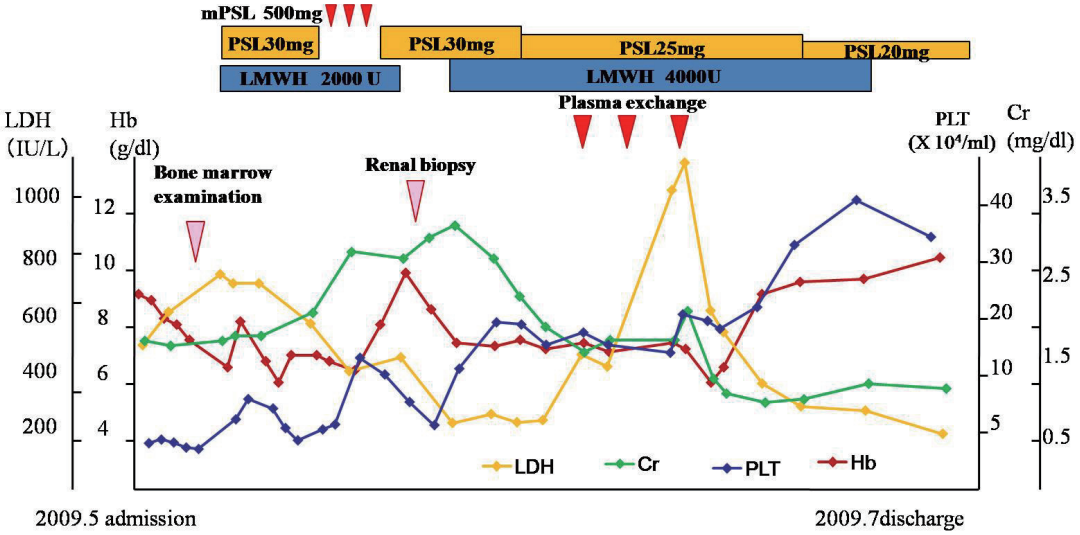

Figure 1. The clinical course of the present patient. The graphs display the hemoglobin, platelets, LDH and creatinine values, and the treatment interventions during the hospital course. (PSL: prednisolone LMWH: Low-molecular-weight heparin)

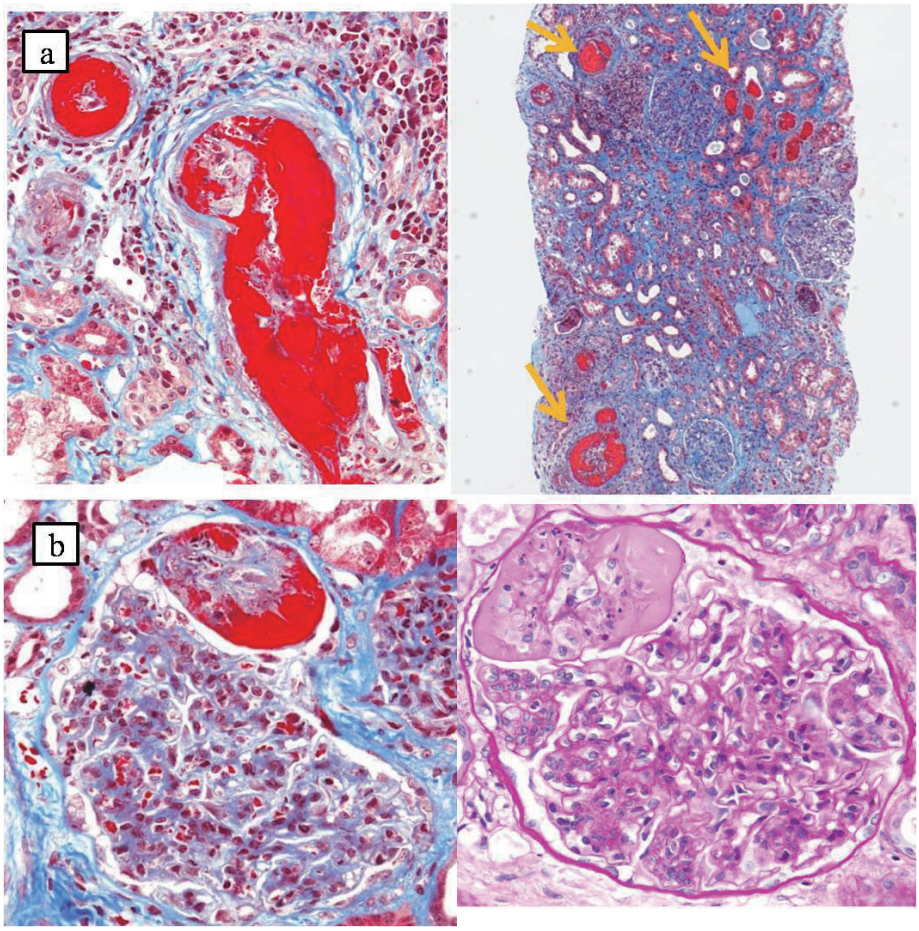

Figure 2. Histological examination of kidney. a. Renal biopsy specimen. Fibrin thrombi in arterioles were found (arrows). (Left: Masson trichrome stain, original magnification ×400; Right: Masson trichrome stain, original magnification ×40) b. Fibrin thrombi in the glomeruli, which are compatible with the histology of TMA / TTP, were evident. (Left: Masson trichrome stain, original magnification ×400; Right: hematoxylin and eosin staining, original magnification ×400)