Thrombotic microangiopathy associated with monoclonal gammopathy

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Thrombotic microangiopathy (TMA) is a rare disease comprising of a diverse set of disorders linked by a common histologic finding of endothelial injury. Monoclonal immunoglobulins may act as a potential trigger in the pathogenesis of TMA. To determine the prevalence of monoclonal gammopathy and clinicopathological features of TMA associated with monoclonal immunoglobulin, we performed a retrospective study in adults (18 and older) with a clinical diagnosis of TMA. Of 146 patients with TMA, we detected monoclonal immunoglobulin in 20 patients (13.7%). Among patients 50 and older, the prevalence of monoclonal gammopathy was 21%, which is approximately five-fold higher than the 4.2% expected rate in this population. Fifteen patients had monoclonal gammopathy of undetermined significance, one had multiple myeloma, one with smoldering myeloma, two had POEMS syndrome, and one had T-cell lymphocytic leukemia. Renal biopsy was performed in 15 cases, of which six showed thrombi, 11 showed mesangiolysis, and all showed double contours along glomerular capillary walls. Acute tubular injury was present in 12 cases. Treatment options were varied and included therapeutic plasma exchange in 11 patients. Ten patients progressed to end-stage renal disease, of which two received kidney transplant. Thus, our study shows an unexpectedly high prevalence of monoclonal gammopathy in patients with TMA, suggesting a potential pathogenetic mechanism. This study underscores the importance of evaluating for a monoclonal gammopathy in patients with TMA as well as the potential for targeting the underlying hematologic disorder as an approach to treating TMA.

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Thrombotic microangiopathy (TMA) is a rare, potentially life-threatening condition comprising a diverse set of disorders including hemolytic uremic syndrome (HUS), complement-mediated TMA (also known as atypical HUS [aHUS]), thrombotic thrombocytopenic purpura (TTP), coagulation-mediated TMA, metabolic disorder-mediated TMA, and other associated conditions.[1] In the appropriate clinical setting, it is usually diagnosed by the presence of microangiopathic hemolytic anemia (characterized by the presence of schistocytes on a peripheral blood smear) and thrombocytopenia. The most common complications of TMA include acute kidney injury, neurologic abnormalities, and/or cardiac ischemia. The pathology of glomerular TMA is characterized by thrombi in glomerular capillaries, endothelial swelling, mesangiolysis, and subendothelial accumulation of fluffy and cellular material, often with a double-contour formation. The pathology of TMA involving arteries and arterioles often shows fibrin thrombi within vessels, intimal thickening with mucoid material, and myointimal proliferation, resulting in onion skinning and marked occlusion of the vascular lumen. Although thrombi are pathognomonic of TMA, they may not be present in all cases and the other features are then helpful in clinching the diagnosis.[2]

Monoclonal gammopathies consist of a heterogeneous group of disorders characterized by clonal proliferation of monoclonal Ig (M-protein) producing B-lymphocytes or plasma cells and is associated with a wide spectrum of malignant and benign conditions.[3–5] Thus, monoclonal gammopathy may be seen in the setting of malignant conditions such as multiple myeloma, Waldenström macroglobulinemia, and B-cell lymphoproliferative disorders. On the other hand, monoclonal gammopathy may be seen in the setting of nonmalignant conditions such as monoclonal gammopathy of undetermined significance. In patients with monoclonal gammopathies, symptoms may develop, not just due to malignant transformation, but also due to idiosyncratic properties of the secreted monoclonal Ig.

With respect to the kidney, monoclonal Ig can cause renal disease from either direct deposition of the monoclonal Ig in the kidney (e.g., proliferative glomerulonephritis, light chain proximal tubulopathy)[6–8] or by an indirect mechanism via dysregulation of the alternative pathway of complement (e.g., C3 glomerulopathy and aHUS).[9–12] Functional dysregulation of the alternative pathway of complement may occur by interference where the monoclonal Ig acts as autoantibody

to a complement-regulating protein, such as complement factor H.[13,14]

There are only case reports of TMA occurring in the setting monoclonal gammopathy.[15–21] To determine whether TMA is associated with monoclonal gammopathy, we studied 146 TMA patients over a 15-year period. We found a high prevalence of monoclonal Ig in these patients and present a detailed description of the clinical and laboratory findings, hematologic evaluation, kidney biopsy findings, treatment, and follow-up of TMA-associated with monoclonal gammopathy.

RESULTS

Clinical features

A total of 146 patients with TMA were tested for monoclonal gammopathy. Twenty patients (13.7%) had an M-protein and were included in the study (Tables 1 and 2). Among patients 50 years of age and older, the prevalence of monoclonal gammopathy was 21% ($N = 17$), which is ~5-fold greater than the expected rate in this population (4.2%). Among patients 60 years of age and older, the prevalence of monoclonal gammopathy was 24% ($N = 12$), which is also ~5-fold greater than the expected rate in this population (4.7%).[22,23]

Among the 20 patients with monoclonal gammopathy, 11 were assayed for ADAMTS13 (a disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13). Two patients (10%) were classified as having TTP (ADAMTS13 activity ≤10%) and 9 (45%) as atypical HUS. The remaining 9 patients (45%) could not be classified due to the lack of ADAMTS13 testing as a result of which TTP cannot be ruled out.[24] Patient 1 with TTP had a positive ADAMTS13 inhibitor level of 1.4 (normal <0.4). Patients 5, 6, 7, and 18 had low C3 levels, whereas patients 4, 6, 8, 10, and 18 had low C4 levels. Seven patients (patients 3, 9, 13, 15, 16, 17, and 19) had normal complement levels, and for the remaining 6 patients, laboratory values were not available. Patient 7 had a mild factor H deficiency (131 μg/ml; reference range: 160–412 μg/ml). Fifteen of 20 patients (75%) had kidney biopsies performed; the specimens were evaluated to confirm the diagnosis of TMA. The median age at diagnosis was 63 years (range, 22–80 years); 13 patients (65%) were male. The racial distribution was 19 white (95%) and 1 black (5%). At onset, the median hemoglobin level was 10.4 g/dl (range, 5.7–14.5 g/dl), the median platelet count was 128 × 10^9/l (range, 11–369 × 10^9/l), and median serum creatinine level was 2.9 mg/dl (range, 0.7–14 mg/dl). Six patients (patients 2, 4, 7, 11, 14, and 18) had evidence of schistocytes on the peripheral blood smear at onset, whereas 6 patients (patients 3, 5, 6, 9, 10, and 15) did not show schistocytosis. For the remaining 8 patients, a peripheral blood smear was not available. One patient had systemic lupus erythematosus but had a negative serology for lupus anticoagulant. Urinalysis performed in 14 patients showed hematuria in 9 patients (64%) at presentation; 5 patients (36%) did not have hematuria. The median proteinuria level at presentation was 2252.5 mg/24 h ($N = 16$; range, 146–14,000 mg/24 h). The clinical course of TMA was complicated by hemorrhagic stroke in 2 patients (patients 1 and 8) and deep venous thrombosis in 1 patient (patient 18). The median duration of follow-up was 35.6 months (range, 0.3–302.4 months). At final follow-up, the median hemoglobin level was 11.5 g/dl (range, 7.5–14.1 g/dl), the median platelet count was 229 × 10^9/l (range, 15–459 × 10^9/l), and median serum creatinine level was 1.5 mg/dl (range, 0.8–2.8 mg/dl; $N = 10$; end-stage renal disease [ESRD] developed in 10 patients, 2 of whom received kidney transplants), respectively. At final follow-up, the median proteinuria level was 282 mg/24 h (range, 135–1332 mg/24 h, $N = 10$).

Table 1 | Patient characteristics and laboratory evaluation of TMA with monoclonal gammopathy at diagnosis

Patient	Age (yr) at TMA diagnosis/sex	Type of TMA	Precipitating cause	Serum creatinine (mg/dl) at diagnosis	eGFR	Urinary protein (mg/24 h)
1	44/M	TTP	Idiopathic	6.0	10	NA
2	71/M	TTP	Idiopathic	1.2	>60	11,622
3	56/F	aHUS	Idiopathic	1.3	42	498
4	59/M	aHUS	Idiopathic	1.7	41	2000
5	64/M	aHUS	Idiopathic	14	3	3500
6	65/M	aHUS	Idiopathic	1.2	>60	14000
7	22/M	aHUS	Idiopathic	7.4	11	NA
8	61/M	aHUS	Infection	5.0	12	1406
9	69/F	aHUS	Idiopathic	6.5	6	2551
10	59/F	aHUS	Idiopathic	5.1	9	NA
11	80/M	aHUS	Idiopathic	8.4	6	172
12	56/M	Unclassified	Idiopathic	1.8	39	170
13	40/F	Unclassified	Idiopathic	2.0	28	3000
14	69/F	Unclassified	Idiopathic	0.7	>60	457
15	71/M	Unclassified	Idiopathic	4.8	12	2997
16	62/M	Unclassified	Infection	2.3	29	770
17	72/F	Unclassified	Idiopathic	2.1	23	5301
18	69/F	Unclassified	Infection	3.5	13	2505
19	70/M	Unclassified	Idiopathic	2.2	30	146
20	58/M	Unclassified	Cyclosporine	5.7	10	NA

aHUS, atypical hemolytic uremic syndrome (complement-mediated TMA); eGFR, estimated glomerular filtration rate; F, female; M, male; NA, data not available; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.