Letters to the Editor

Autoantibodies against U1RNP and monoclonal gammopathy of uncertain significance: an unusual association

Sirs,

A 74-year-old man was admitted to our hospital due to acute arthritis of the 1st metatarsophalangeal joint on the right. The pain started 24 hours prior to admission and was accompanied by local signs of inflammation as well as low grade fever up to 38.5ºC, loss of appetite and nausea. He denied any trauma to the area. He also denied recent sexual activity. Upon further questioning he denied arthralgias involving other joints, Raynaud's, or skin rash. He had a past medical history of duodenal ulcer. His only medication was ranitidine as needed. Physical examination verified the presence of arthritis of the 1st metatarsophalangeal joint on the right but was otherwise unremarkable. Blood examination showed Haematocrit: 35.1%, with normochromic and normocytic RBC indices, Creatinin: 1.5mg/dl, uric acid: 10.1 mg/dl. The rest of the chemistry profile was normal. Inflammatory markers were elevated (erythrocyte sedimentation rate; 124 mm/h, C-reactive protein; 64 mg/l). Immunology tests including rheumatoid factor, antiphospholipid (anti-cardiolipin and anti-b2GPI) and anti-neutrophil cytoplasmic antibodies (ANCA), complement (C3, C4), antibodies against double-stranded DNA (anti-dsDNA) and thyroid antigens were normal. Cryoglobulins were not present. On admission, ANA were positive at a titre of 1:160 with a fine speckled pattern. The staining pattern prompted further evaluation for the presence of antibodies against specific extractable nuclear antigens which revealed persistently positive anti U1RNP antibodies, whereas anti Ro/La and anti-Sm were negative. Serum immunoelectrophoresis revealed 3 monoclonal IgG spikes (chain λ) and urine immunoelectrophoresis revealed traces of free λ chain (Quantitation of the immunoglobulins in the serum revealed: IgG=1810 mg/dl, IgM=269 mg/dl, IgA=114 mg/dl). Paracentisis of the affected joint revealed urate crystals consistent with a diagnosis of uric arthritis. Synovial fluid and blood cultures were negative.

The presence of monoclonal gammopathy prompted work up for malignancy including computed tomography (CT) of the lung and abdomen which were negative. Bone marrow aspirate revealed mild dysplasia of the erythroid and myeloid series with a fraction of plasma cells of only 1%. Temporal artery biopsy was negative for vasculitis and minor salivary gland biopsy was negative for Sjogren's syndrome. The patient was initially treated with colchicine and NSAIDs, with clinical improvement and normalization of the inflammation markers, and was subsequently started on allopurinol. At six months follow-up the patient was completely well. However, he remained persistently positive to U1RNP antibody while repeated serum electrophoresis continued to demonstrate monoclonal gammopathy consisting of IgG λ chains.

We report a patient with MGUS and concurrent presence of U1RNP autoantibody in his serum. MGUS, or monoclonal gammopathy of undetermined significance, is a plasma cell disorder characterized by the abnormal presence of a monoclonal protein, *i.e.* the M component, in patients without evidence of multiple myeloma, macroglobulinemia or other paraproteinemia. The serum levels of M component are less than 3g/dl and the percentage of BM plasma cells is less than 10%. MGUS can be associated with a host of different conditions including infections, inflammatory diseases, transplants of inorganic material and malignancies (1, 6, 22). There is also some evidence pointing to possible genetic predisposition (20, 21). Although the disorder may remain stable it does progress to malignancy in up to 30% of cases (23).

MGUS and other paraproteinemias have been linked to autoimmune disease (9-12). MGUS in particular is present in 3–6% of patients with rheumatoid arthritis, SLE, Sjögren's syndrome and scleroderma (13). In some cases, autoantibodies are detected in the sera of paraproteinemic patients in the absence of overt autoimmune disease (14, 15). These include ANA (1), anti-histone (2), anti-cardiolipin (1), ANCA (3), rheumatoid factor (4, 5), anti-La/SSB, and anti-Ro/SSA (6-8). λ light chain paraproteins tend to be more frequently associated with anti-Ro/SSA and anti-La/SSB compared to k light chain paraproteins (8).

To date, the association of the antibody against U1 ribonucleoprotein and MGUS has been described only once (17). We consider it to be an important finding since the antigenic target is highly evolutionarily conserved and antibody response to it is not found in normal individuals but only in association with clinical pathology (18). The antibody against U1 RNP is directed against RNA-protein complexes which are abundant in the nuclei of eukaryotic organisms and form part of a pre-mRNA processing complex called spliceosome (24). It is a serological marker for mixed connective tissue disease (MCTD) although it can be found in up to 40% of SLE cases (19).

There is a paucity of data regarding the evolution and natural history of the asymptomatic presence of autoantibodies in patients with paraproteinemias in general and MGUS in particular. Occasionally the monoclonal proteins of such patients have been shown to possess antibody activity directed at autogenous or foreign antigens. Such autoantibodies include cold agglutinins, mixed cryoglobulins, and antineural components and they produce the clinical pictures of hemolytic anemia, mixed cryoglobulinemia, or peripheral neuropathy, respectively (16). About half of the autoantibodies detected in the presence of paraproteinemia are monoclonal which suggests either that the paraproteins themselves have antibody activity or that they activate usually silent autoreactive B cells (9).

It remains unclear whether the presence of antibodies against nuclear components puts the patient at higher risk for the development of overt autoimmune disease and whether these antibodies have prognostic significance for the paraproteinemia itself. In this context, the potential early therapeutic implications of antibody detection become very interesting. If indeed autoantibodies were a prodromal sign of overt autoimmunity it would be valuable to know whether plasmapheresis or immunosuppressive therapy would prevent clinical progression. Study of these autoantibodies will provide new insights into the pathogenesis of paraproteinemias as well as into the link that exists between these disorders and autoimmunity.

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