Biclonal gammopathy of undetermined significance in a patient with systemic lupus erythematosus and antiphospholipid syndrome

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SUMMARY

The case of a patient suffering from systemic lupus erythematosus with associated antiphospholipid antibody syndrome is described. In this patient, on protein electrophoresis, two monoclonal immunoglobulin G λ and k peaks were seen, defining a condition of biclonal gammopathy of undetermined significance (BGUS). This condition is extremely rare, especially in chronic inflammatory rheumatic diseases. The criteria of a BGUS are defined. We also underline how this condition can be the expression of a concomitant unrecognized cancer, a possible amyloidosis or an infectious process.

Key words: *Biclonal gammopathy; SLE; APS; neoplastic disease; amyloidosis, infection.*

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INTRODUCTION

The presence of a monoclonal component (MC) in the gamma region of serum protein electrophoresis may have various causes. It could be the expression of multiple myeloma (MM) or, less frequently, Waldenstrom macroglobulinemia or cryoglobulinemia. In some cases, this condition can appear in the course of solid or hematological cancers (leukemia, lymphoma) and can be considered a concomitant idiopathic paraproteinemia. When these conditions are not present, a monoclonal gammopathy is classified as of undetermined significance (MGUS). A MGUS is found in about 3-4% of the general population over the age of 50 (1) and can remain stable throughout life or evolve in 10% of cases within 5 years into a full-blown MM (2).

The evidence of a double monoclonal band with characters of undetermined significance in protein electrophoresis is a very rare occurrence, which has never been described in a patient with systemic lupus erythematosus (SLE) associated with antiphospholipid syndrome (APS).

CASE REPORT

A 64 year-old lady, with no family history of rheumatic diseases or neoplasms, was in good health until the age of 37, when she had a protracted episode of fever with arthralgia, myalgia and bilateral pleurisy. The blood chemistry analysis showed high levels of antinuclear antibodies (ANA 1:640 with IFI method on HEp-2 cells) and anti-native-DNA antibodies (n-DNA 1:20 with IFI method). A diagnosis of SLE was made and therapy with prednisone 10 mg/day, azathioprine 50 mg bid, and hydroxychloroquine 200 mg/day was started, which resolved the clinical picture.

One year after diagnosis, the patient had an episode of deep vein thrombosis in the lower limbs complicated by pulmonary embolism. Antiphospholipid antibodies were present, with positive lupus anticoagulant, IgG anti-cardiolipin antibodies 103.2 U/ml (nv<20 U/ml) by ELISA, IgG anti-beta 2 glycoprotein 1 antibodies 47 U/ml (nv<20 U/ml) by ELISA, which results were confirmed after 12 weeks. APS was diagnosed and dicumarol treatment started.

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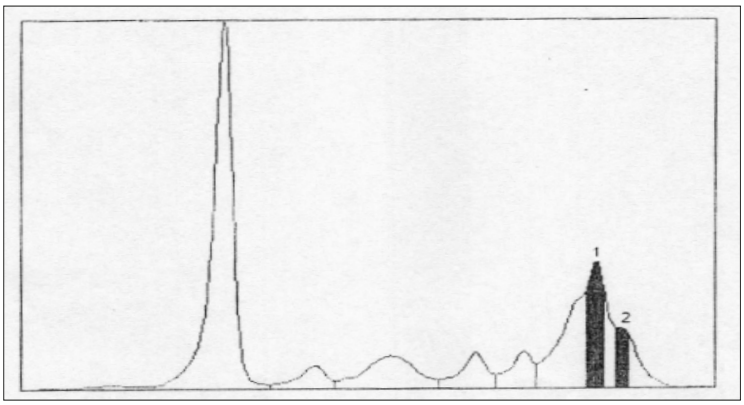

Figure 1 - Serum electrophoresis of the patient.

For many years, the patient followed the same therapy, with good disease control and a systemic lupus erythematosus disease activity index (SLEDAI) of 0. Various attempts to suspend the corticosteroid treatment, however, were unsuccessful, with occurrence of arthralgia, headache, asthenia and increased erythrocyte sedimentation rate.

In 2017, the patient began to suffer from exertional dyspnea and irritating cough, without any environmental or occupational exposure to inhalants. A high-resolution lung CT scan showed pulmonary interstitial disease with few and limited ground glass-type consolidation areas. Respiratory function tests and diffusing capacity of the lungs for carbon monoxide (DLCO) were normal and a trans thoracic B-mode echocardiography showed no pulmonary hypertension.

Blood chemistry analysis showed high erythrocyte sedimentation rate (ESR) with normal C-reactive protein (CRP) and progressing polyclonal hypergammaglobulinemia. ANA were positive (1:1280), while anti n-DNA was negative. Complement fractions, antibodies to extractable nuclear antigens (ENA), and anti-neutrophil cytoplasmic antibodies (ANCA) were negative. Furthermore, complete blood count and leukocyte formula, urine test, LDH and alkaline phosphatase were normal. For this reason, other laboratory tests such as lymphocyte populations were not carried out. The patient did not report any clinical symptoms suggesting another type of connective tissue disease; in particular she did not have xerophthalmia, xerostomia or Raynaud's syndrome.

In 2020, serum protein electrophoresis showed a double monoclonal band in the gamma area for the first time (Figure 1), in the context of hypergammaglobulinemia (34%). The serum immunoglobulins were: IgG 3150 mg/dL (nv 540-1822 mg/dL), while IgA and IgM levels were within the normal range. Serum immunofixation revealed monoclonal IgG λ and IgG k components. Urinary immunofixation was negative for light chains. The serum concentration of the free light chain k was 83.3 mg/L (VN 6.7-22.4), that of λ was 174 mg/L (VN 8.3-27.0). The λ component (peak 1 in the figure 1) was 0.8 g/dL and the k component (peak 2) was 0.3 g/dL.

The patient had no anemia, kidney failure or osteolytic skeletal lesions. A lung CT scan showed the already known interstitial lung disease. An abdominal-pelvic ultrasound was negative, as was echocardiography. Both gastroscopy and colonoscopy were negative.

DISCUSSION AND CONCLUSIONS

MGUS is characterized by a MC less than 3 g/dL, the absence of Bence-Jones proteinuria, and bone marrow plasmacytosis less than 10%. Furthermore, there is no anemia, kidney failure, osteolytic lesions nor hypercalcemia. In our patient, we did not consider it appropriate to perform a bone marrow aspiration and biopsy, as all the main criteria pointed to the diagnosis of MGUS.

In 3-6% of MGUS cases, a second monoclonal band appears, thus leading to a condition of BGUS, which is rare and does not progress towards MM, unlike MGUS (3). BGUS can be characterized by two different heavy chains with the same light chain, or by the same heavy chain with different light chains or by two different heavy chains with different light chains. In our patient, we observed the same heavy chain with different light chains.

Usually, a double MC appears in the course of lymphoproliferative diseases (leukemia,

lymphomas), while it is not a common occurrence in the course of autoimmune rheumatic diseases. A single case of Schnitzler syndrome was reported with BGUS IgM λ and k, but the occurrence of monoclonal IgM gammopathy is usual in this condition (4).
The association of SLE and MM is also a very rare occurrence and only a few cases are reported in the literature (5). An association between SLE, APS and BGUS has never been described to our knowledge, and may support some speculations on its pathogenesis. SLE is characterized by immunological hyperreactivity with the production of autoantibodies against various constituents of the organism. The polyclonal activation of B lymphocytes determines the formation of ANA and anti-DNA antibodies, which closely correlate with disease activity. The activation of B lymphocytes can lead to plasma cell dyscrasia, which can manifest as MGUS. In our case, there were two IgG monoclonal bands, highlighting a rare BGUS.
The appearance of BGUS in our patient may also have been induced by the immunosuppressive therapy, which can result in a dysregulation of the immune system, as seen after hematopoietic stem cell transplantation (6).
The appearance of a monoclonal component in the polyclonal hypergammaglobulinemia, normally present in the course of SLE, can have various explanations of clinical interest. In fact, it could be the expression of an unrecognized lymphoproliferative disease, including leukemia and lymphoma, or of a solid neoplasm (7). This is particularly true in a condition such as SLE, in which there is an increased risk of hematological, pancreatic and lung tumors (8). It could also be an expression of systemic light chain amyloidosis (AL), a rare but known association in SLE (9). In AL, there is a prevalence of light chains λ over the k ones, like in our patient, as opposed to what happens in healthy subjects. Finally, it could be the expression of an infectious overlap, in particular of tuberculosis (10).
However, all the diagnostic tests carried out in our patient for a concomitant cancer and an infectious form were negative. In addition, there were no symptoms and clinical signs of the multiorgan involvement typical of AL, and the related diagnostic investigations were negative.
In conclusion, the appearance of a BGUS in SLE and APS is a rare event, which was never described before. It could be considered as a potential indicator of infections, amyloidosis and hidden cancer, especially in SLE, a disease with a high neoplastic risk.

Conflict of interest
The authors declare no potential conflict of interest.

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