CASE REPORT

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An unusual case of systemic lupus erythematous, lupus nephritis, and transient monoclonal gammopathy

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Abstract A 23-year-old female patient suffering from active systemic lupus erythematosus (SLE) was treated with azathioprine (2 mg/kg per day) and prednisone. Lupus nephritis class III with increasing proteinuria developed 28 months after disease onset. Treatment was switched to monthly pulse cyclophosphamide administered intravenously for 6 months (total dose 6.3 g), followed by oral azathioprine and low-dose prednisone to maintain partial remission. Eight months later, the patient developed an acute exacerbation of SLE with fever, proteinuria of 9.1 g/day, pancytopenia, and cerebral involvement with cephalgias and a grand mal seizure. She responded well to high-dose corticosteroids (500 mg prednisolone pulses over 3 days, i.v.) and was switched from azathioprine to methotrexate (12.5–15 mg per week). Under this treatment, lupus activity gradually decreased and the patient felt well again. Five years after the initial diagnosis of SLE, a rapidly increasing immunoglobulin G-kappa type (IgG-κ) monoclonal gammopathy developed, reaching a maximal serum paraprotein concentration of 73.5 g/l. Bone marrow biopsy revealed 15% of moderately abnormal, highly differentiated plasma cells arranged in small clusters and expressing IgG-κ. No bony lesions were detectable on skeletal radiographs. Pulses of dexamethasone (40 mg) were administered and led to a transient decrease of paraproteinemia to a minimum of 31.9 g/l, followed by an increase to 62 g/l. At that point, high-dose chemotherapy supported by autologous stem cell transplantation was considered. Due to an intermittent pneumococcal sepsis, methotrexate was discontinued and dexamethasone was replaced by 5–10 mg prednol. At this point, totally unexpectedly, the paraprotein decreased spontaneously without any further cytostatic treatment and was no longer detectable 1 year later. Concomitantly, plasma cell counts in bone marrow biopsies fell to below 5%. As SLE remained inactive, the patient became pregnant and gave birth to a healthy child. During late pregnancy, SLE activity flared up with rising proteinuria and blood pressure. Therefore, after delivery, cyclophosphamide (100 mg/day, orally) was readministered for 4 months, resulting in an improvement of kidney function with stable proteinuria of 1–2 g/l to date. Paraproteins are no longer detectable. In conclusion, this case report documents the rare event of transient paraproteinemia in a patient with SLE. A self-limiting regulatory defect in the control of a terminally differentiated B-cell clone may be the origin of this phenomenon.

Key words SLE · Monoclonal gammopathy · Lupus nephritis

Introduction

Systemic lupus erythematous (SLE) is a systemic autoimmune disease characterized by high-titer antinuclear autoantibodies (ANA), hypocomplementemia, and immune complex-mediated organ damage eventually leading to terminal renal failure, cerebral lupus, polynuclear arthritis, polymorphic erythema, and autoimmune cytopenias [1]. Women of childbearing age are ten times more often affected than men. The disease appears to be polygenically determined by genes encoding...
early complement components, complement regulatory proteins, certain major histocompatibility complex (MHC) haplotypes, cytokines, apoptosis regulating proteins, and several other genes currently under investigation [2]. The B-cell compartment of SLE patients is hyper-reactive, expressing an increased frequency of autoreactive B cells. Hypergammaglobulinemia, low total serum complement, increased levels of C3d, and circulating immune complexes are typical serologic features [3]. Monoclonal gammapathies have occasionally been reported in association with SLE [4–11]. The prevalence of 2.2–3.3% [4, 5] is higher than in the general population, where M components are found in 0.9% with a clear increase in the elderly [12]. SLE-associated paraproteins may exhibit anti-Ro/SSA [13], anti-DNA, rheumatoid factor, or antinuclear factor activity, but usually their specificity remains unknown.

The underlying pathogenesis and clinical significance of the association between monoclonal immunoglobulins and SLE are unclear. Mechanisms leading to polyclonal B-cell activation may also lead to defective negative regulation of single B-cell clones, thereby giving rise to monoclonal gammapathies of unknown significance (MGUS), multiple myeloma, or non-Hodgkin’s lymphoma (NHL). Thus, a single B-cell clone may expand in an uncontrolled fashion as a result of a regulatory defect or a neoplastic transformation.

We report an unusual case of a 23-year-old female SLE patient with lupus nephritis and subsequent development of an impressive, but transient monoclonal gammapathy. The gammapathy first appeared 5 years after the onset of SLE during methotrexate maintenance therapy and disappeared completely within 1 year after discontinuation of methotrexate.

Case report

After a 2-year history of Raynaud’s phenomenon, a 23-year-old female patient presented with fatigue, butterfly rash, photosensitivity, and migrating polyarthralgia of the meta-carpalphalangeal, elbow, shoulder and knee joints. Laboratory examinations revealed an erythrocyte sedimentation rate (ESR) of 30 mm/h, mild anemia, microhематуria, and proteinuria of 0.61 g/day. Immunologic examinations showed positive ANAs (titer 1:6400) with a fine speckled pattern on HEP-2 cells. Antibodies to U1snRNPs (4+), Sm (3+), and dsDNA (3+) were detectable. Total hemolytic complement (CH50) was diminished to 10 units/ml (normal range 20–50 units/ml). C3 and C4 serum concentrations had also decreased to 0.16 and 0.06 g/l, respectively, while C3d was elevated to 21.9 mg/l (normal < 10 mg/l). Low-titer phospholipid IgG antibodies were detected at a concentration of 32 units/ml (reference value < 12 units/ml). Lupus anticoagulant activity was negative.

Physical examination was unremarkable except for the butterfly rash and polyarthralgia. The lymph nodes, spleen, and liver were not enlarged on palpation. Abdominal sonography demonstrated discrete splenomegaly (of 5.4 cm hilar diameter). Echocardiography revealed a small pericardial effusion. Magnetic resonance imaging (MRI) of the brain, performed because of recurrent migraine attacks, showed discrete hyperintensities in both medullary layers consistent with discrete vascular edema. The diagnosis of clinically and serologically active SLE was made according to the revised American Rheumatism Association criteria for the classification of SLE (six of the 11 criteria were met) [14]. A combined prednisone (initial dose 1 mg/kg body weight) and azathioprine (150 mg/day) treatment was administered and led to an improvement of fatigue and arthralgia.

As SLE remained inactive and because our patient wanted to become pregnant, azathioprine was stopped after 1.5 years of treatment. Kidney function was normal at that time, but high ANA titers persisted.

An acute exacerbation occurred 1 year later with arthralgia. Raynaud’s phenomenon, butterfly rash, weight loss, and fever. Serum creatinine was 1.4 mg/dl, proteinuria 0.61 g/day, and complement analysis showed a CH50 of 16 units/ml and elevated C3d levels of 14.9 mg/l, indicating increased intravascular complement turnover. A concomitant urinary tract infection caused by Klebsiella pneumoniae was treated with cefuroxime.

Renal biopsy revealed mild glomerular mesangial hypercellularity, segmental necrotic lesions, and focal capsular adhesions. Immunofluorescence microscopy revealed discrete complement (C3) and faint granular immunoglobulin (IgG, IgM, and IgA) deposits exclusively in the mesangial regions. According to the World Health Organization (WHO) classification, this morphologic pattern is consistent with class III lupus nephritis (Fig. 1). Immunosuppressive therapy with 100 mg/day azathioprine in addition to corticosteroids was readministered.

Because proteinuria increased to 5.6 g/day within the following 6 months and lupus was clinically and serologically active, a 6-month regimen of intravenously administered bolus cyclophosphamide (initial dose 1.5 g) was started. Due to leukopenia of 900/μl after the first bolus, the dose was reduced to 1.2 g/month and finally to 0.8 g/month, resulting in a total cyclophosphamide dose of 6.3 g. Despite this treatment, lupus remained active with arthritis, butterfly rash, elevated complement turnover (CH50 15 units/ml, C3d 34 mg/l), proteinuria of 4.4 g/day, creatinine 1.2 mg/dl, and recurrent episodes of fever. Thus, azathioprine was readministered. Because of persisting leukopenia and anemia, the dosage was adjusted to 50 mg/day. Eight months later, an acute exacerbation of SLE with fever up to 40 °C, anemia, thrombocytopenia, proteinuria up to 9.1 g/day, arthralgia, and myalgia prompted the readmission of our patient. Shortly after admission, she developed a generalized seizure (grand mal). Computed tomography (CT) showed widened subarachnoid spaces as a possible sign of the start of cerebral atrophy; MRI of the brain was normal. Neurologic evaluation revealed generalized muscle weakness and electromyography showed a myopathic pattern consistent with corticoid myopathy. Bone marrow biopsy, which was performed to clarify anemia and thrombocytopenia, showed a hypoplastic marrow with a moderate increase of perivascular cytologically normal plasma cells (Fig. 2). Arterial hypertension

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Fig. 1 Light microscopic appearance of a glomerulus illustrating an increase in mesangial cellularity and a small zone of adhesion to Bowman’s capsule. (H&E, bar = 30 μm)