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CASE REPORT

Successful treatment of a mycophenolate mofetil-refractory proliferative lupus nephritis with Belimumab in a 19-year-old woman

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We report the case of a 19-year-old woman with progressive proliferative lupus nephritis (LN) class III after induction and maintenance therapy with mycophenolate mofetil (MMF). Despite a satisfying clinical improvement proteinuria progressed under this medication. We treated the patient with additional belimumab after discussing other options. Following treatment with belimumab, proteinuria rapidly improved to almost normal levels and clinical remission lasted. Belimumab might hold promise for this indication. *Lupus* (2013) **22,** 1523–1525.

Key words: Proliferative lupus nephritis; belimumab; systemic lupus erythematosus; mycophenolate mofetil

Introduction

Renal involvement is common in systemic lupus erythematosus (SLE). It is estimated that up to 90% of patients with a diagnosis of SLE will have some form of renal involvement on biopsy. About 50% will develop a clinically significant nephritis.[1] The histological classification of lupus nephritis (LN) was updated in 2003. Class III is defined as focal LN involving less than 50% of all glomeruli.[2] It requires aggressive management with a steroid pulse and immunosuppressive induction therapy consisting of either mycophenolate mofetil (MMF) or cyclophosphamide (CYC) and maintenance therapy with MMF or azathioprine according to current guidelines.[3] In March 2011 the FDA approved the use of belimumab in combination with standard therapies to treat active autoantibody-positive SLE. The drug's efficacy has not been evaluated in patients with severe active LN so far. Belimumab is not recommended in this situation.[4]

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Case report

We report the case of a 19-year-old female patient who presented to the Emergency Department of our hospital in May 2011 with deteriorating general condition including malaise, fever, arthralgias, diffuse alopecia, retroauricular lymphadenopathy, aphthous oral ulcers, a butterfly rash and retrosternal pain which increased during inspiration. In 2006 she consulted a local rheumatologist because of facial erythema. Elevated ANA antibodies and later in 2007 also positive antibodies to double-stranded DNA had been detected without specific therapy due to the lack of systemic signs or symptoms.

On admission laboratory results revealed a mild pancytopenia, leukocytes $3.5 \times 10^3/\mu l$ (normal range (NR) 4.0–11.0 $10^6/\mu l$), erythrocytes $3.82 \times 10^6/\mu l$ (NR: 3.9–5.1 $\times 10^6/\mu l$), platelet count $149 \times 10^3/\mu l$ (NR: 150–350 $\times 10^6/\mu l$), LDH of 285 U/l (NR: 125–220 U/l), CRP 11.4 mg/l (NR: <5 mg/l), ESR of 84 mm (NR: <20 mm) and elevated transaminases AST 72 U/l (NR: <34 U/l), ALT 47 U/l (NR <31 U/l), GGT 58 U/l (NR: 9–36 U/l). ANA-immunofluorescence was >1:640 (NR: <1:80), anti-ds-DNA antibodies were >400 IU/ml (NR: <15 IU/ml). C3c 0.45 g/l (NR: 0.9–1.8 g/l) and C4 0.07 g/l (NR: 0.1–0.4 g/l) levels were decreased. Renal function was preserved with creatinin of

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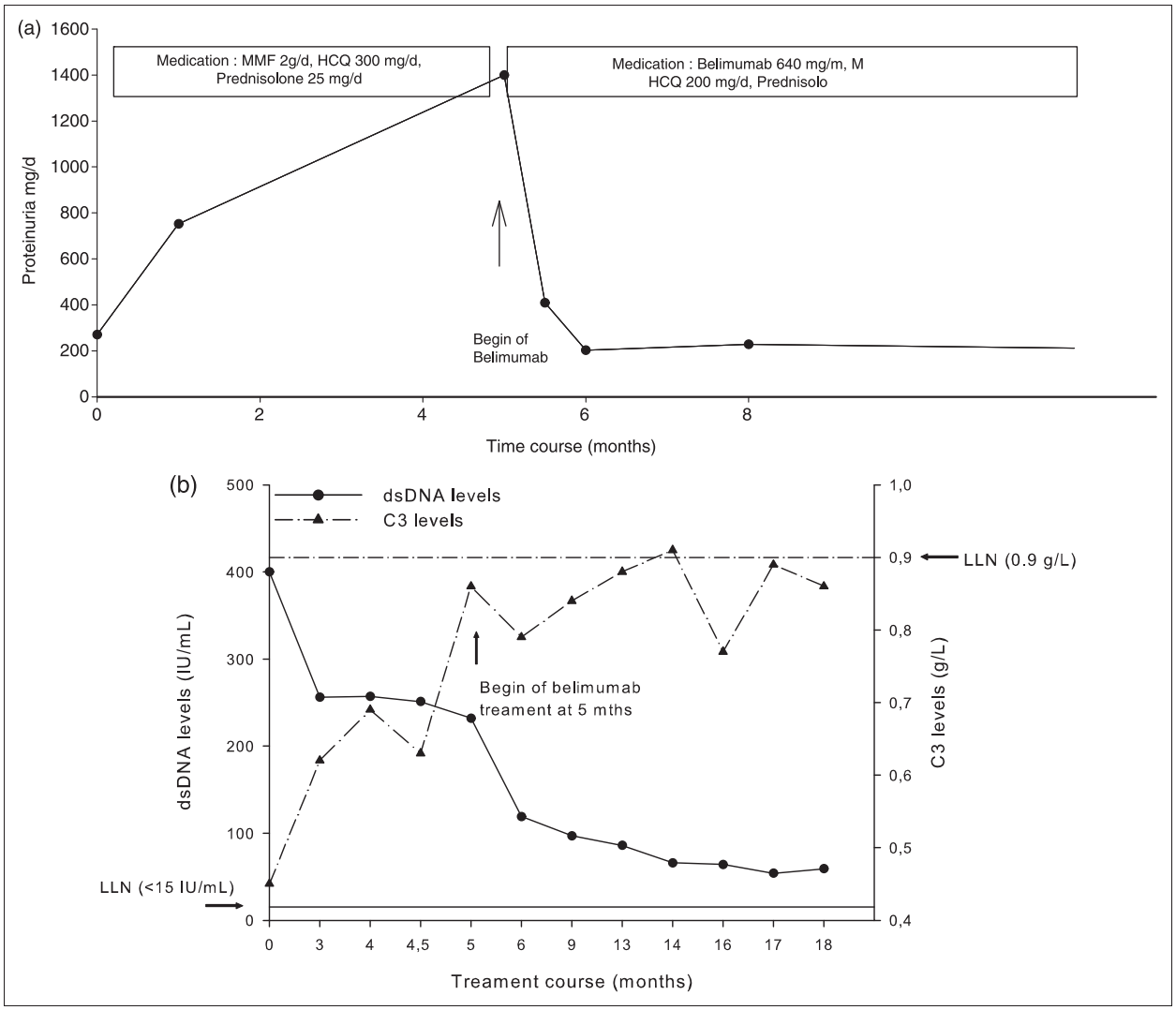

Figure 1 (a) Proteinuria over time. Addition of Belimumab 5 months after first diagnosis led to a significant and sustained reduction of proteinuria. (b) Anti-ds-DNA antibodies and C3c levels over time. Belimumab led to significant and sustained increase of complement levels and decrease of anti-ds-DNA antibodies.
HCQ: hydroxychloroquine, MMF: mycophenolate mofetil, LLN: lower limit of normal.

0.59 mg/dl (NR: 0.5–1.0 mg/dl), blood urea nitrogen of 8 mg/dl (NR: 7–19 mg/dl) resulting in an estimated glomerular filtration rate of 138 ml/min/1.73 m^2 using the 4-variable modification in renal diet measurement formula. Urinalysis revealed a low level proteinuria of 270 mg/d (NR: <150 mg/d) and microscopic hematuria. Albumin was within the normal range with 18.4 mg/l (NR: <20 mg/l). Urinary sediment showed 5–9 white blood cells/high power field (HPF) and 5–9 red blood cells/HPF. There were no schistocytes or casts. Transthoracic echocardiography showed a pericardial effusion of 5 mm which was not hemodynamically relevant.

After exclusion of malignant and infectious disorders, a diagnosis of SLE was made. The patient fulfilled 10 out of 11 of the ACR classification criteria.[5] We discussed a renal biopsy, but because of a prolonged bleeding time and missing consent of the patient, we did not perform it.

An immunosuppressive induction therapy with a prednisolone pulse (250 mg/d) and MMF (2 g/d) was inducted. Prednisolone was then tapered slowly to 20 mg/d.

Despite of a rapid clinical and laboratory improvement, there was an increasing proteinuria (Figure 1(a)). In September 2011 proteinuria reached 1.4 g/d with a microalbuminuria of 119 mg/l (NR: <20 mg/l) and urine-IgG of 13.3 g/l (NR 3.5 g/l). Sediment was nephritic with 10–20 schistocytes/HPF. CRP was <0.2 mg/l, C3c slightly reduced to 0.86 g/l, C4 0.11 g/l and anti-ds-DNA

antibodies were 232 IU/ml. Maintenance therapy then included prednisolone (25 mg/d), MMF (2 g/d) and hydroxychloroquine (HCQ) (300 mg/d). MMF dose then was increased to 3 g/d as remission induction.

In October 2011 a renal biopsy was performed and showed a LN class III (A/C) with focal segmental necrosis and sclerosis. The glomerular activity index reached 12 (range 0–24) and a tubulointerstitial chronicity index of 0.6 (range 0–6) showed no significant chronic damage. Different treatment options with this young patient were discussed. We decided to conduct a steroid pulse with a total of 2.5 g over 3 days. Belimumab was added on day 4 at standard dose (10 mg/kg = 520 mg).

Two weeks later proteinuria decreased to 409 mg/d and four weeks later to 202 mg/d (Figure 1(a)). Clinical remission could be reached with a maintenance therapy consisting of HCQ (200 mg/d), MMF (1 g/d), belimumab (640 mg per month) and prednisolone (5 mg/d). In September 2012 proteinuria declined to 75 mg/24 h without microalbuminuria, anti-ds-DNA antibodies were 64 IU/ml, C3c level was 0.77 g/l (Figure 1(b)).

Discussion

This case illustrates that proteinuria can progress even under a standard treatment with MMF, and that significant kidney damage, documented by renal biopsy, may also occur with low levels of proteinuria.[6] It is important to note that we cannot exclude the possibility that standard treatment options (methylprednisolone pulse, MMF) already might have been sufficient to control the renal activity. Mycophenolate mofetil dose had been increased about 4 weeks before belimumab; it is therefore possible that remission induction could already have been achieved with this drug and effects were just not observed by adding belimumab. Another viable therapeutic option would have been treatment with cyclophosphamide according to the Euro-Lupus protocol. However, after discussing different treatment options with the patient, she decided against CYC due to possible side effects.

Although not approved for use in severe LN, belimumab was used with success in this young female patient with a LN class III, thus avoiding potential side effects from CYC use. In phase 3 clinical trials leading to the approval of belimumab, the agent was generally well tolerated and showed positive effects on disease activity and led to possible reduction of glucocorticoid doses.[7,8] A recent analysis suggested that high disease activity, positivity for anti-ds-DNA, low complement levels or higher corticosteroid doses were associated with greater benefit than standard therapy.[9] However, the role of belimumab for the treatment of severe LN is unclear. We conclude that belimumab might be a treatment option for patients with severe LN (class III + IV) in combination with standard therapy (i.e. MMF) in the future, although further data are strongly necessary. Results of clinical trials for this indication, which are currently being performed, are eagerly awaited.

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Conflict of interest statement

PK declares that he received lecture fees from GlaxoSmithKline. All other authors declare no conflict of interest.

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