

Hyperferritinemia in a woman with systemic lupus erythematosus, severe nephritis and an iron-rich intraspinal schwannoma mimicking lupus myelopathy

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ABSTRACT

We describe a lupus flare in a 59-year-old woman who presented with pancytopenia, nephritis, severe renal dysfunction and marked hyperferritinemia. The course of the disease was further complicated by an iron-laden, intraspinal ancient schwannoma that compressed the cervical cord mimicking a lupus-related myelopathy and was removed surgically. Treatment with mycophenolate mofetil (MMF) and prednisone induced a gradual decline in levels of serum ferritin with a concomitant improvement in renal function and reduction of proteinuria. Serum ferritin may be a useful marker of the response to treatment with MMF in renal lupus.

Case report

In September 2006, a 59-year-old woman was admitted with an exacerbation of systemic lupus erythematosus (SLE). Her blood pressure was 128/80 mm Hg, pulse rate 67/min, temperature 37.7°C and respiratory rate 20/min. A maculo-papular rash was seen on both upper arms. 2 painless palatal ulcers were noted. Pitting edema was present on both lower limbs. There were no abnormalities detected in the cardiovascular, respiratory, musculoskeletal and nervous systems.

CBC revealed leucopenia $2.7 \times 10^9/L$ ($4.0-11 \times 10^9/L$), lymphopenia $0.38 \times 10^9/L$ ($1.2-3.3 \times 10^9/L$), normochromic, normocytic anemia 9.72 g/dL (11.5-16.5 g/dL) and thrombocytopenia $24 \times 10^9/L$ ($150-400 \times 10^9/L$). ESR was 95 mm/hr (<25 mm/hr) and CRP 6 mg/L (0-10 mg/L). Renal function was severely impaired: serum creatinine was 370 $\mu\text{mol/L}$ (58-96 $\mu\text{mol/L}$) and estimated creatinine clearance (MDRD study equation) was 9.5 mL/min/1.73m² (90-120 mL/min/1.73m²). Work-up for anemia showed low serum iron 6 $\mu\text{mol/L}$ (9-30.4 $\mu\text{mol/L}$) and transferrin levels 1.9 g/L (2.0-3.6 g/L) with normal iron saturation 27% (15-50%), but marked hyperferritinemia 1432 $\mu\text{g/L}$ (6-81 $\mu\text{g/L}$). There was no hemolysis and Coombs' test was negative, all findings consistent with anemia of chronic disease. The concomitant presence of reactive hemophagocytosis as an alternative explanation for the abnormal

hematologic findings and for the increased levels of serum ferritin could not be ruled out as a bone marrow biopsy or other invasive procedures were not performed under conditions of severe illness and high risk of bleeding (1). Urinalysis revealed hematuria and proteinuria, with nephritic sediment. The urinary protein/creatinine ratio was 5.6 mg/mg (<0.2 mg/mg). C3 level was 0.27 g/L (0.9-1.8 g/L), with normal C4 0.11 g/L (0.1-0.4 g/L). Strong ANA reactivity with a homogeneous immunofluorescence pattern was found on HEp-2 cells. Anti-dsDNA antibody levels were markedly elevated >300 IU/mL (<30 IU/mL). Antibody tests for cardiolipins, SS-A, SS-B, Sm and RNP were negative.

Methylprednisolone 1 g was given daily IV for 3 days followed by prednisone 1mg/kg PO daily and tapered over the following 6 months to 7.5 mg daily. Treatment with MMF 750 mg BID was started and increased to 1g BID. The patient received also fosinopril 10 mg/day and atorvastatin 10 mg/day as total cholesterol level was 5.8 mmol/L (3.1-5.6 mmol/L). A 3-months course of erythropoietin had no effect on hemoglobin levels.

Mid-November 2006, the patient fell without losing consciousness and experienced transient numbness in the left arm associated with dizziness and palpitations. She was found to have hyperreflexia in all 4 limbs without sensory deficit. The plantar response was flexor. There was no nystagmus or cerebellar signs. Romberg's test was negative. An acute, lupus-related myelopathy of the spinal cord was suspected, but MRI demonstrated a mass of 2 cm in diameter at the level of C1/C2 (Fig. 1). During this phase, serum ferritin levels rose further to 1693 $\mu\text{g/L}$, but rapidly declined thereafter to 995 $\mu\text{g/L}$ preoperatively. On 27 December 2006, the patient underwent hemilaminectomy of C1 and C2 with removal of a tumor which was a vascularized, ancient schwannoma containing large numbers of siderophages (Fig. 2). The patient's neurological symptoms improved promptly after surgery. The immediate postoperative level of serum ferritin was 798 $\mu\text{g/L}$, which does not favour

Competing interests: none declared.

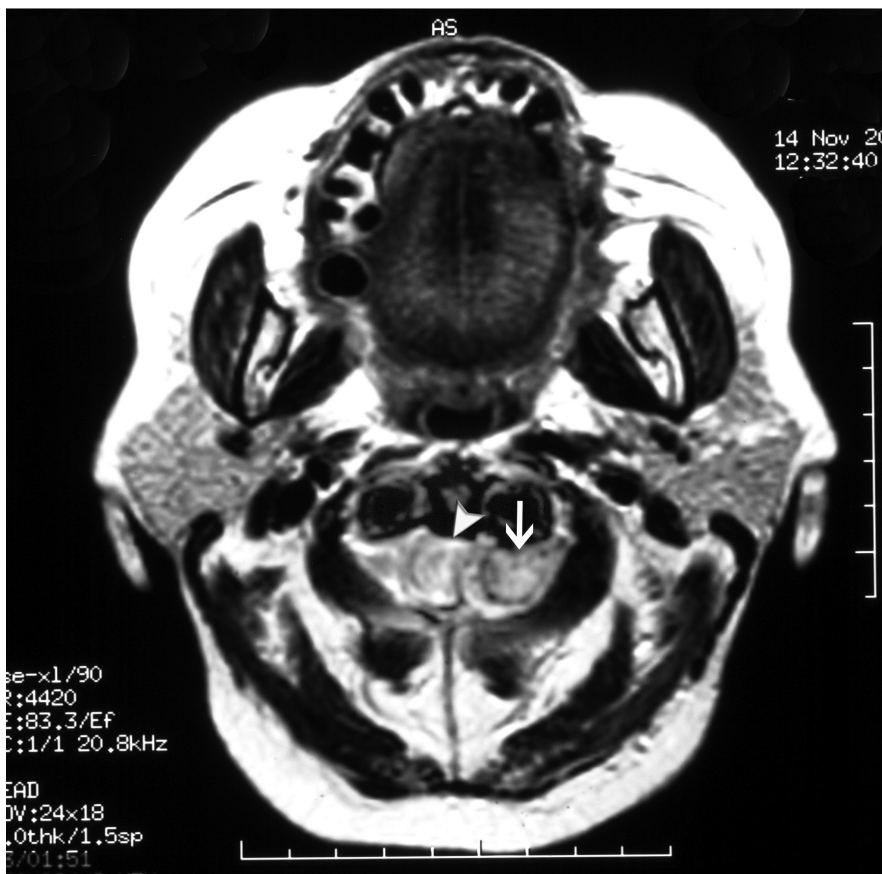


Fig. 1. T1-weighted axial scan which demonstrates the schwannoma of mixed signal intensity (arrow) within the spinal canal at the level of C1/C2 compressing and displacing the spinal cord (arrowhead) to the right side.

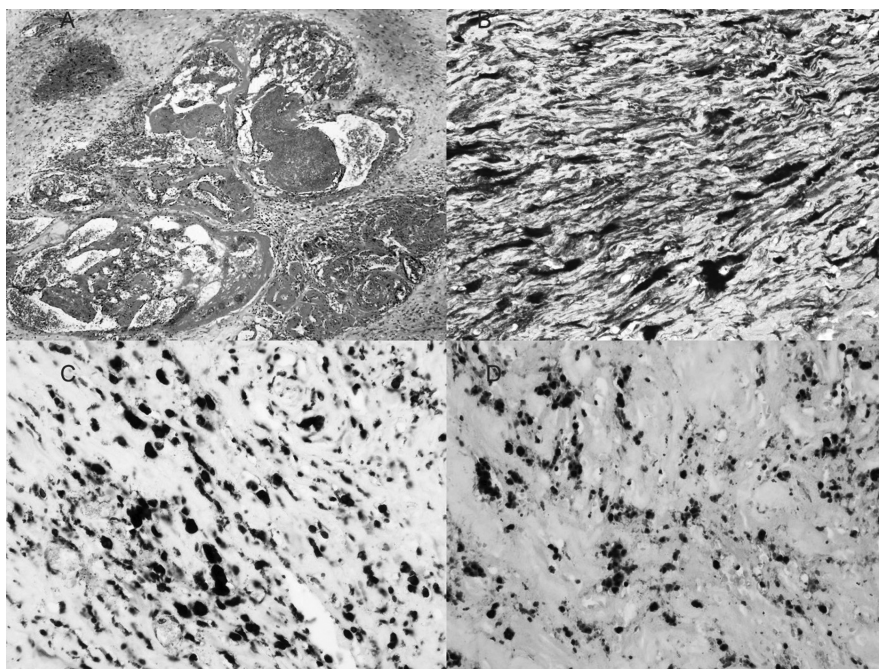


Fig. 2. Photomicrographs show an ancient schwannoma with proliferation of abnormal blood vessels, some with intraluminal thrombi and hyalinized walls (A). S-100 was positive in all tumor cells (B). Numerous CD68+ macrophages were present (C). Perl's Prussian blue stain demonstrated prominent deposits of hemosiderin within the macrophages (D).

the schwannoma as the major source of ferritin. Over the following months, changes in serum ferritin concentrations, urinary protein/creatinine ratio and creatinine clearance were temporally similar, although those in creatinine clearance were directionally opposite. Serum levels of C3 normalized promptly (Fig. 3).

In October 2007, treatment consisted of prednisone 7.5 mg/day, MMF 750 mg BID, hydroxychloroquine 200 mg /day, fosinopril 10mg/day, atorvastatin 10 mg /day, alfacalcidol 0.5 µg/day and calcium carbonate 1.2 g/day. ESR was 34 mm/hr and CRP 5 mg/L. CBC was normal. Levels of serum ferritin though still abnormal declined to 312 µg/L. ANA were negative, the titer of anti-dsDNA antibodies was 13 IU/mL and levels of C3 as well as C4 were normal. The estimated creatinine clearance increased to 38.4 mL/min/1.73m² and the urinary protein/creatinine ratio fell to 0.8 mg/mg. As outcome measures, a decrease in total SLEDAI score from 17 to 8 confirmed the clinical impression of remission and with regard to renal disease the ACR response criteria of improvement/partial response were fulfilled (2).

Discussion

Hyperferritinemia in SLE was described in previous reports which showed that increases in the levels of serum ferritin correlate with flares and dsDNA antibody titers, but not with CRP levels, in approximately 50% of patients (3-5). Another report confirmed in part these findings, suggesting that the heterogeneity of systemic autoimmunity in different ethnic backgrounds is reflected by the variable phenomenon of hyperferritinemia (6). Because a description of the temporal changes in concentrations of serum ferritin in response to MMF has not been published we here present such information from a carefully studied patient who demonstrates the efficacy of MMF in lupus nephritis with severe organ dysfunction (7).

Type I interferons, IL-10 and other cytokines could account for the elevated serum ferritin levels (8-10). Since *in vitro* mycophenolate reduces the production of IL-10, IL-12 and IFN-γ

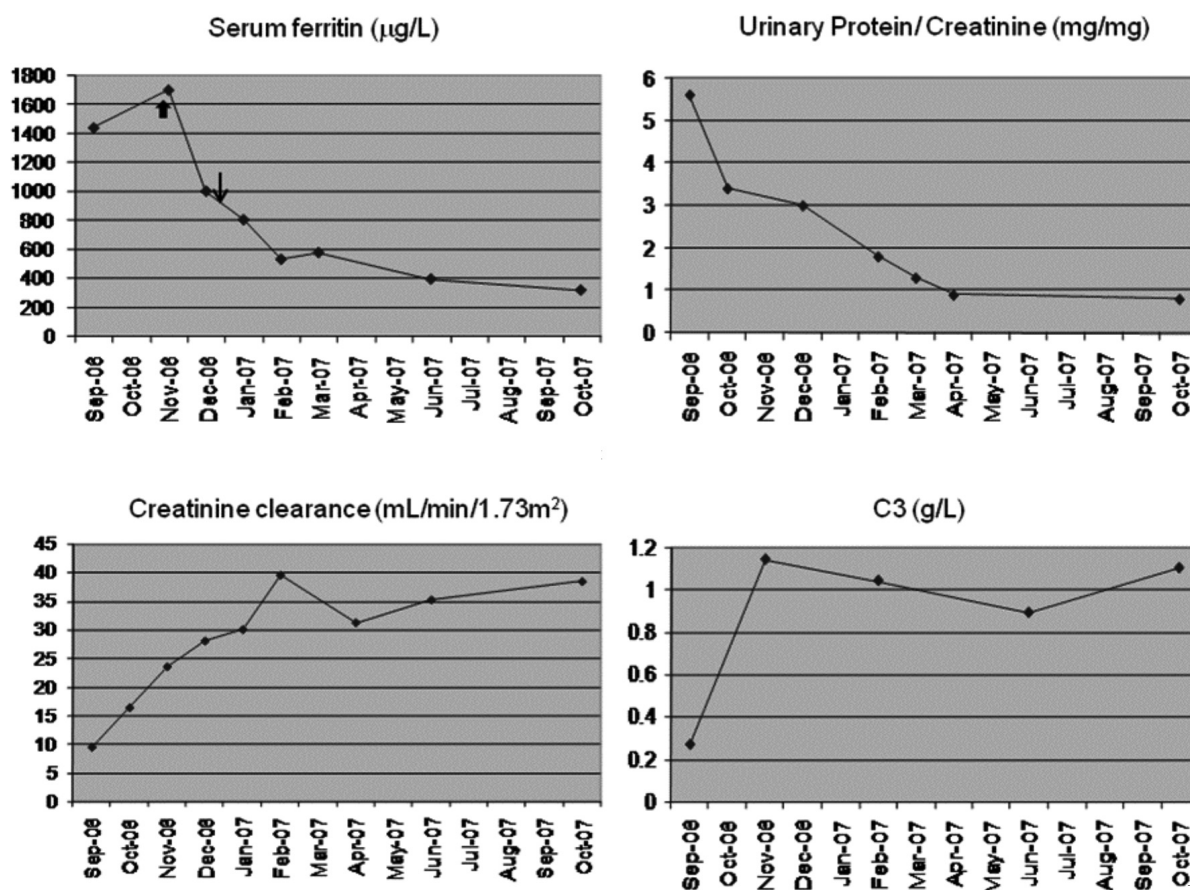


Fig. 3. Changes over time in levels of serum ferritin (6–81 µg/L), urinary protein/creatinine ratio (0.0–0.2 mg/mg), estimated creatinine clearance (90–120 mL/min/1.73m²) and levels of C3 (0.9–1.8 g/L). Reference ranges are in parentheses. Treatment with mycophenolate mofetil and prednisone was initiated at presentation in September 2006. The manifestations of spinal cord compression appeared mid November 2006 (bold arrow, upper left panel) and tumour excision was performed late December 2006 (thinner arrow, upper left panel).

released from PBMC obtained from lupus patients, the observed decrease in levels of serum ferritin in our patient could be explained by the inhibitory action of MMF on the synthesis of ferritin-inducing cytokines (11).

Hyperferritinemia was reported in renal diseases with glomerular involvement other than lupus nephritis (12). As ferritin and other iron-regulatory proteins are produced within the kidney we cannot exclude the possibility that in lupus nephritis ferritin is secreted from a glomerular or tubulo-interstitial source (13, 14). We can also assume that to a certain extent intratumoral synthesis of ferritin took place based on 2 observations: first, large numbers of CD68+ macrophages were packed with hemosiderin, which is a product of lysosomal degradation of the H subunit of ferritin. Second, the initial further increase in levels of serum ferritin coincided with the clinical manifestations of spinal

cord compression by the schwannoma. Release of intracellular iron and subsequent synthesis of ferritin could have been a consequence of uptake of hemoglobin via the hemoglobin scavenger receptor (CD163) pathway and subsequent degradation by heme oxygenase following intratumoral microhemorrhages from the numerous vessels. This hypothesis is based on comparable histologic findings in vestibular schwannomas (15). We are not aware of any association of SLE and nerve sheath tumors, but can assume that intratumoral hemorrhages were facilitated in the presence of thrombocytopenia at the onset of the flare. In contrast, lymphomas of the central nervous system were described in conjunction with SLE and its treatment modalities (16).

In summary, we demonstrate that both hyperferritinemia and severe renal dysfunction caused by lupus nephritis responded to a regimen consisting of a

combination of MMF and prednisone. The decline in levels of serum ferritin coincided in time with an improving glomerular filtration rate and a fall in the urinary protein/creatinine ratio. Although the sites of origin of serum ferritin were not defined, possibilities include cells of the immune system, the kidney and to some extent siderophages within a schwannoma.

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