CASE REPORT

Autoimmune myelofibrosis: a rare haematological involvement in systemic lupus erythematosus

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Accepted 18 December 2018

SUMMARY

Autoimmune myelofibrosis is a distinct clinicopathological entity that occurs with autoimmune disorders. We report the case of a 44-year-old woman admitted with pancytopenia and clinical features of systemic lupus erythematosus, Sjogren's syndrome and antiphospholipid antibodies syndrome. Bone marrow biopsy showed decreased global cells and an increase of reticulin fibres on argentic coloration, consistent with myelofibrosis. The JAK2 V617, Myeloproliferative leukemia (MPL) and calreticulin mutations were negative. The patient's condition improved after treatment with hydroxychloroquine, vitamin K antagonists and prednisone.

BACKGROUND

Haematological involvement in systemic lupus erythematosus (SLE) consists mostly of autoimmune peripheral cytopenia which is one of the diagnostic criteria for SLE.¹ Autoimmune myelofibrosis (AIMF) is an uncommon haematological disease characterised by cytopenia, bone marrow myelofibrosis and an autoimmune feature.² We report the case of a 44-year-old woman who was admitted with clinical presentation of SLE, Sjogren's syndrome and antiphospholipid antibodies syndrome. Persistent cytopenia led to the diagnosis of coexisting AIMF.

CASE PRESENTATION

A 44-year-old woman of sub-Saharan African origin presented to our department with fatigue, oral ulcerations, sicca syndrome and joint pains. She had a recent history of stroke and was treated with aspirin. She had an unremarkable family history. Physical examination revealed multiple conjunctival paleness, oral ulceration, non-scarring patchy alopecia (figure 1) and erythematosus malar rash. Joint examination demonstrated bilateral wrist synovitis with tenderness in all metacarpophalangeal joints and proximal interphalangeal joints. Neurological evaluation concluded to mild cognitive disturbance. The urine strips showed positive proteinuria and haematuria.

INVESTIGATIONS

Initial laboratory investigations were remarkable for a marked pancytopenia with a regenerative anaemia of 6.8 g/dL, mild leucopenia of 1800/mm³, lymphopenia of 480/mm³ and thrombocytopenia of 120 000/mm³. The 24-hour proteinuria was 0.8 g, and urinary sediment examination showed aseptic

leucocyturia and erythrocyte cylinder. Thyroid stimulating hormone (TSH) levels, serum electrophoresis, lactate dehydrogenase, plasma haptoglobin and liver function were normal. Haemostasis parameters showed prolonged spontaneous activated partial thromboplastin time. The peripheral blood smear did not show any features of haemolysis. HIV, hepatitis B virus and hepatitis C virus serology were negative. A CT scan of the thoracic and abdomen was unremarkable, showing no evidence of splenomegaly. A cardiac echography and standard radiography of swollen joints were normal. Head MRI showed occipital stroke but did not reveal central nervous system vasculitis or demyelinating lesions. Autoimmune assessment revealed positive antinuclear antibodies (ANAs) 1:1280 (speckled pattern), positive anti-double stranded DNA (anti-dsDNA, ELISA and Farr's test), anti-SSA (Ro52 and Ro60) and anti-Sm. C3, C4 fractions were consumed and type III cryoglobulinaemia was detected. Coombs test was positive. Anti-CCP antibodies were negative. IgG anticardiolipin, IgG anti- β 2GPI and lupus type circulating anticoagulant were detected and confirmed 12 weeks apart. The salivary gland biopsy showed lymphocytic sialadenitis (focus score equal to 1). Renal biopsy concluded to chronic inactive proliferative lupus nephritis. The marrow aspiration was normal. The bone marrow biopsy showed no evidence of lymphoma, solid tumour cells, or dysplasia, but decreased global cells. Argentic coloration showed an increase of reticulin fibres consistent with moderate medullar fibrosis, suggestive of myeloproliferative neoplasm (figures 2 and 3). The conventional medullary karyotype showed no abnormalities. The medullary lymphocytes' immunophenotype did not detect malignant lymphoproliferation. The JAK2 V617, MPL and calreticulin (CALR) mutations were negative. The presence of oral ulcers, non-scarring alopecia, synovitis, positive ANAs, anti-dsDNA, anti-Sm and antiphospholipids antibodies led to the diagnosis of SLE according to the revised 1997 American College of Rheumatology and the 2012 Systemic Lupus International Collaborating Clinic Classification Criteria, the diagnosis of SLE was retained.³ The presence of arterial thrombosis with IgG anticardiolipin, anti- β 2GPI and lupus anticoagulant detected and confirmed 12 weeks apart led to the diagnosis of antiphospholipid antibodies syndrome according to the international consensus statement on an update of the classification criteria for definite antiphospholipid syndrome.⁴ Sicca syndrome, lymphocytic sialadenitis on lip biopsy (focus score

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To cite: Belfeki N, Shankarasivam G, Declerck D, et al. *BMJ Case Rep* 2019;**12**:e227520. doi:10.1136/bcr-2018-227520

Figure 1 Non-scarring patchy alopecia in a patient with lupus.

equal to 1) and positive anti-SSA (Ro52 and Ro60) led to the diagnosis of Sjogren's syndrome according to American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjogren's syndrome criteria.⁵

DIFFERENTIAL DIAGNOSIS

In fact, myelofibrosis can be associated with different diseases such as chronic myeloproliferative malignancy, lymphoma, mast cell disease and metastatic carcinoma. Thus, JAK2 V617, MPL and CALR clonal markers, lymphocyte immunophenotype ruled out these conditions.

Marrow biopsy findings and positive antibodies led to the diagnosis of AIMF.

TREATMENT

The final diagnosis was AIMF in a patient with SLE,³ antiphospholipid antibodies syndrome⁴ and Sjogren's syndrome.⁵

Oral prednisone (1 mg/kg/day) and hydroxychloroquine (400 mg/day) were initiated. Aspirin was switched to vitamin K antagonists with a target international normalised ratio between 2 and 3.

OUTCOME AND FOLLOW-UP

After 2 months, the blood cell counts had returned to normal. The patient responded well, with complete resolution of her

Figure 2 Marrow biopsy showing reticulin medullar fibrosis.

Figure 3 Argentic coloration revealing an increase of reticulin fibres consistent with moderate medullar fibrosis.

joint pain and mucocutaneous involvement within the first month of treatment. Renal parameters remained normal. Pancytopenia gradually improved and completely normalised within 3 months. No immunosuppressive agent was added.

DISCUSSION

SLE is the prototypic multisystem autoimmune disorder with a broad spectrum of clinical presentations encompassing almost all organs and tissues. Haematological abnormalities are common and can be the presenting symptom or sign in SLE. Major clinical manifestations include anaemia, leucopenia and thrombocytopenia mainly due to destruction of peripheral blood cells by circulating antibodies or immune complex mediated attack or immunosuppressive therapy.⁶ More rarely, blood cell counts decrease in SLE due to bone marrow disease such as primary myelofibrosis, aplastic anaemia, bone marrow metastases, or AIMF.⁷ Pathogenesis of AIMF is unclear. The lupus autoimmune process is supposed to induce an increase of platelet derived growth factor, transforming growth factor β (TGF β) and epidermal growth factor that stimulates fibroblasts which overload collagen production and marrow fibrosis.⁸ This case illustrates a rare haematological feature in autoimmune condition. In fact, myelofibrosis has been long described in haematological malignancy and solid tumours. Cases series of myelofibrosis in SLE patients emerged in the beginning of the 1990s. Its management and global outcome were different from primary myelofibrosis. Since then, Paquette *et al* proposed the term of AIMF.⁹ In our case, the AIMF was simultaneously diagnosed with autoimmune disease. However, it seems not be the case in the previous report. Despite the fact that the prevalence of AIMF in SLE is unknown, we do believe that this condition is misdiagnosed because not well investigated with marrow biopsy. SLE is the archetype model of the autoimmune disease that involves protean system and this case illustrates that the bone marrow can represent one of the targets of the disease. All patients with SLE and AIMF were treated with steroids. Immunosuppressive therapy such as azathioprine, cyclosporine, mycophenolate mofetil and cyclophosphamide has been used with favourable outcome.⁶⁻⁸ In our case, mild proteinuria and haematuria were detected and is probably considered as sequelae of chronic and inactive lupus nephritis as found on the renal biopsy. C3, C4 fractions were consumed because of positive type III cryoglobulinaemia. The patient underwent

oral steroids and hydroxychloroquine which induced cell blood count (CBC) normalisation within 1-month of treatment. To our best knowledge, only 46 cases of AIMF in SLE patients have been previously reported in the English literature, and this is the first report of the occurrence of AIMF in mosaic autoimmune conditions associating SLE, Sjogren's syndrome and antiphospholipid antibodies syndrome.¹⁰ This case called to an increased awareness in unexplained cytopenia in SLE patients and early recognition of AIMF which is a rare but life-threatening condition with general favourable outcome if it can be managed at an early stage and benefits from appropriate treatment. We recommend performing autoimmune screening in JAK2 negative myelofibrosis, and in controversy, unexplained cytopenia in SLE patients with normal marrow smear have to undergo bone marrow biopsy to diagnose AIMF.

Learning points

- ▶ Autoimmune myelofibrosis (AIMF) is a rare but possible cause of cytopenia in lupus patients.
- ▶ Exhaustive haematological investigation is recommended in systemic lupus erythematosus (SLE) patients with unexplained and persistent cytopenia.
- ▶ Bone marrow biopsy, conventional karyotype and JAK2/calreticulin mutations are necessary to rule out neoplastic myelofibrosis AIMF is often associated with autoimmune disease. SLE seem to be the most common condition with 46 previous report in the literature. But other diseases are possible, for example, Sjogren's syndrome and antiphospholipid antibodies syndrome.

Contributors NB, GS, SD contribute to the elaboration of the clinical text and the management of the patient. DD performed an interpretation of the marrow biopsy.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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