Late Onset Systemic Lupus Erythematosus with Severe Hypercalcaemia

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ABSTRACT

We report a case of a 76-year old female presenting with symptomatic severe hypercalcaemia, and subsequently diagnosed with late onset SLE due to the presence of anaemia, leucopenia, antibodies of antinuclear (ANA), anti-dsDNA, and also kidney impairment. Serum levels of FGF23 and intact-parathyroid hormone (iPTH) were low in this patient. Serum calcium, FGF23 and iPTH levels responded to steroids, which occurred simultaneously with disease activity. On follow-up, the faster increase in FGF23 than in parathyroid hormone suggested that FGF23 might be involved in the pathogenesis of hypercalcaemia in SLE.

Keywords: Hypercalcaemia, late onset, systemic lupus erythematosus (SLE)

Lupus Eritematoso Sistémico de Inicio Tardío con Hipercalcemia Severa

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RESUMEN

Se reporta el caso de una mujer de 76 años de edad que se presentó con hipercalcemia sintomática severa, y a la que posteriormente le fuera diagnosticada LES de inicio tardío con presencia de anemia, leucopenia, anticuerpos antinucleares (ANA), anti-dsDNA, e insuficiencia del riñón. Los niveles séricos del factor de crecimiento fibroblástico 23 (FGF23) y la hormona paratiroidea intacta (iPTH) fueron bajos en este paciente. Los niveles de calcio séricos, FGF23 e iPTH respondieron a los esteroides, que ocurrieron simultáneamente con la actividad de la enfermedad. En el seguimiento, el hecho de que el factor FGF23 aumentara más rápidamente que la hormona paratiroidea, sugiere que el FGF23 podría estar involucrado en la patogénesis de la hipercalcemia en LES.

Palabras claves: Hipercalcemia, inicio tardío, lupus eritematoso sistémico (LES)

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INTRODUCTION

Hypercalcaemia is a relatively common clinical problem. The most common causes of hypercalcaemia, affecting 90% of all patients, are primary hyperparathyroidism (PHPT) and malignancy (1). Systemic lupus erythematosus (SLE) is a rare cause of hypercalcaemia. The association of hypercalcaemia with SLE is limited to case reports involving middle age or juvenile patients (2–8). Here we report a patient with late onset SLE and hypercalcaemia. This has never been reported.

CASE REPORT

The patient was a 76-year old female who was admitted to hospital in June 2009 with a history of several weeks of cough, weakness, headache, nausea, episodic attacks of vomiting of stomach contents, fatigability and lumbago with mild oedema of both lower extremities. The patient had no known chronic diseases like diabetes mellitus, hypertension or coronary heart disease. Her family had no similar or any genetic diseases. Physical examination revealed an afebrile, absentminded female with pallor but no malar flush. Temperature was 36.4 °C, respiratory rate 18/minute, and there was a regular pulse of 71 bpm. Blood pressure was 120/80 mmHg. No further focal neurological deficits were found. Apart from reduced breath sounds, lung and heart examination was normal and likewise the abdominal examination. Mild bilateral leg oedema was observed. A high resolution computed tomography (CT) scan of the head indicated multiple brain infarction and senile brain changes.

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Results of laboratory investigations revealed severe hypercalcaemia with total calcium 16.2 mg/dL. Alkaline phosphatase was normal, intact-parathyroid hormone (iPTH) was 6.4 pg/mL and parathyroid hormone–related protein (PTHrP) was negative; 1,25(OH)-vitamin D3 was 30.6 nmol/L; iFGF23 level was 7.2 pg/ml and 24-hour urinary calcium was 125 mg. The haemoglobin level was 81 g/L, leukocytes 3.1×10^{9} /L, platelets 84×10^{9} /L and reticulocytes 2.23%. Urine analysis showed proteinuria and 5 to 6 dysmorphic erythrocytes per high-power field. Twenty-four hour urinary protein was 0.43 grams. The creatinine clearance was 16.45 ml/min.

Immunological results are shown in Table 1. Anti-Sm, anti-U1RNP, anti-SSA, anti-SSB, anti-Scl-70, anti-JO-1, anti-

Table 1: Immunological results

Item		Value	Normal range	
ANA		1:3200	Negative	
dsDNA		1:32	Negative	
Ro		Positive	Negative	
IgG		18.6	0.7–4 g/L	
IgA		8.26	0.7–4 g/L	
Č3		0.67	0.9-1.8g/L	
Urinary	kappa chain	57.2	0–7.1 mg/L	
	lamda chain	38.6	0-3.9 mg/L	
Serum	kappa chain	5.01	1.7–3.7 g/L	
	lamda chain	3.03	0.9–2.1 g/L	

neutrophil cytoplasmic antibodies and rheumatic factor were negative. Anticardiolipin IgG antibody was positive. Thyroid function tests, angiotensin-converting enzyme and tumour markers were normal. Serology for hepatitis B, C and E viruses were all negative. Total-body CT scan did not disclose any neoplasm. A TC-MIBI scan showed no parathyroid pathology. Bone scintigraphy showed no pathological uptake in the skeleton. Bone marrow aspirate showed mild erythroid and myeloid hyperplasia. Femoral and lumbar bone mineral density were normal. The patient did not consent to renal biopsy. After confirming the diagnosis of SLE, the patient received five daily pulses of methylprednisolone (250 mg/day) and a dose of intravenous cyclophosphamide (300 mg/1.73 m²) followed by oral prednisolone 40 mg daily, which was tapered down to 10 mg daily over three months, in combination with cyclophosphamide 2 mg/kg per day after she was discharged from hospital. Serum calcium level decreased to 12.0 mg/dL in two weeks; however, renal function did not recover. Antinuclear antibody was persistently positive, anti-dsDNA and anti-Ro antibodies were negative and C3 levels returned to normal after one month. Serum calcium level has remained normal during six months of follow-up (Table 2). Under a maintenance therapy with prednisolone and cyclophosphamide, the patient remained asymptomatic. Upon last followup, nine months later, creatinine clearance was 15.5 ml/min.

Table 2: Biochemical parameters in relation to pre- and post-treatment

	Pre-	Post-		Normal
		One month	Six month	Range
Calcium	16.2	10.8	8.4	8.4-10.3
Phosphate	6.0	4.9	3.8	2.5-4.5
Parathyroid hormone	6.4	15.2	37.8	10-88
1,25 (OH)-vitamin D3	30.6	32.3	29.7	27.7-107
iFGF23	9.2	82.6	396.8	12-56
Ccr	16.45	19.6	18.2	



Figure: Results of serum protein electrophoresis.

DISCUSSION

The association of hypercalcaemia with SLE is very uncommon and limited to case reports. Until now, 10 similar cases of SLE-hypercalcaemia without primary hyperparathyroidism were reported (2–8). Serum levels of 1,25(OH)2-vitamin D3 and iPTH were low in all patients. The presence of anti-PTH receptor antibodies has also been suggested as a cause of SLEhypercalcaemia (5).

The index patient fulfilled the American College of Rheumatology (ACR) classification criteria for SLE. After excluding other common and uncommon causes of hypercalcaemia, we considered that hypercalcaemia was a feature of SLE. Hypercalcaemia lymphadenopathy syndrome was also not considered because of the absence of serositis and lymphadenopathy. The presence of hypercalcaemia, absence of PTHrP, low levels of PTH and iFGF23 in the present patient suggested that hypercalcaemia might be secondary to circulating peptides or autoantibodies. Serum calcium, iFGF23 and PTH levels responded to steroids, which occurred simultaneously with disease activity, and seem to demonstrate that autoantibodies played the pivotal role in the pathogenesis of SLE-hypercalcaemia.

FGF23 is a 32-kDa (251 amino acids) protein with an N-terminal region containing the FGF-homology domain and a unique 71 amino acid C-terminus. FGF23 and PTH are each markedly increased in advanced renal failure (9). Recently, the results of elegant experiments using an animal model of chronic kidney disease and anti-FGF23 antibodies favour FGF23 elevation as the upstream pathophysiological event that lowers 1,25(OH)2-vitamin D3 and thus increases PTH (9). In this patient, the faster increase in FGF23 than in PTH on follow-up suggested anti-FGF23 antibody might be involved in the pathogenesis of hypercalcaemia in SLE.

Unlike the patients previously reported, this patient was diagnosed as late onset SLE. In the group of late onset SLE patients, skin manifestations, photosensitivity, arthritis and nephritis were less frequent in comparison with the SLE patients in whom the disease began at a younger age (10). As ageing proceeds, the level of serum cytokines and acute phase reactants increases 2–4 times (11). In patients with late onset SLE, a higher prevalence of rheumatoid factors was observed, as well as of anti-Ro, and anti-La antibodies (12). The positive result of anti-Ro antibody in this patient was not mentioned in those previous reports. Whether anti-Ro antibody is associated with hypercalcaemia requires further research to clarify precise molecular mechanism.

CONCLUSION

The present case demonstrated a good response to corticosteroids, and the hypercalcaemia seemed to be related to the disease activity of SLE, while FGF23 might be involved in the pathogenesis of hypercalcaemia in SLE.

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