Diabetes mellitus complicating systemic lupus erythematosus: analysis of the UCL lupus cohort and review of the literature

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Systemic lupus erythematosus (SLE) often coexists with other diseases. Diabetes mellitus (DM) is an example and patients with overlap SLE-DM can present with clinical features common to both disorders. In this review, we describe the patients with overlap SLE-DM, focusing on the clinical features common to both diseases that these patients can present, and on the challenges of managing such complications. A detailed review of the patients’ notes (n = 485) was performed. At every outpatient appointment the patients’ urine was tested for glucose, protein and blood. Patients with persistent glycosuria were investigated with fasting blood glucose and a glucose tolerance test to help make the diagnosis of DM. Particular note was made of those patients whose symptoms could be due to SLE, DM or both. Nine patients with DM were identified. Three had type 1 DM, four had type 2 DM and two were considered to have steroid-induced DM. Among these patients, three had renal involvement (two with WHO class IV lupus nephritis; two had peripheral neuropathy (one had a mixed sensory and motor neuropathy, one had a sensory peripheral neuropathy); two patients had retinopathy and cataracts and one had angina. The combination of SLE and DM is uncommon but the predisposition to renal, peripheral neuropathy and retinal disease means that great care must be taken when deciding which clinical feature is due to which disease, because active SLE requires additional immunosuppression whereas DM requires optimization of the metabolic control. Interestingly, although in theory patients with SLE and DM are in double-jeopardy of developing atherosclerosis, to date, only one of our overlap patients has developed angina. *Lupus* (2008) 17, 977–980.

Key words: diabetes; nephropathy; neuropathy; retinopathy; SLE

**Introduction**

Lupus patients often have accompanying diseases. Approximately 30% of patients with systemic lupus erythematosus (SLE) develop a second, third or fourth autoimmune condition. Diabetes mellitus (DM) is one such complicating disease, though few patients have been reported to have both DM and SLE. Indeed, the latest edition of the Dubois’ *Lupus Erythematosus* Textbook only mentions the connection in a Table. However, managing patients who have both conditions can be challenging: for example, is the patient with both diseases whose renal function is deteriorating suffering principally from lupus nephritis requiring more intensive immunosuppression or diabetic neuropathy in which case tighter control of the plasma insulin level would be more appropriate? Likewise is a peripheral neuropathy in a patient with both diseases more likely to be due to one disease than the other? Furthermore, are patients with both diseases in ‘double jeopardy’ of developing atherosclerosis? We have carefully reviewed the notes of patients with SLE attending our Lupus Clinic at University College Hospital London to identify patients with type 1 and type 2 DM. Their histories are detailed here. In the discussion, a review of the literature was presented and practical management issues were considered.

**Patients, materials and methods**

Between January 1978 and June 2007, 485 patients with SLE meeting the revised classification criteria of the American College of Rheumatology were
identified and followed up. Their detailed medical records patients were carefully reviewed. At every outpatient attendance, the patients’ urine was tested for glucose (as well as for protein or blood). Those patients meeting criteria for type 1 or type 2 DM were identified, according to the American Diabetes Association classification and diagnostic criteria. Whether they had developed clinical features whose cause might be difficult to ascertain and whose management was made more complicated as a consequence was noted.

Results

Nine out of 485 patients (1.9%) with SLE were also diagnosed with DM. Three patients had type 1 DM, two patients had steroid-induced DM and four had type 2 DM. The principal features of these nine patients are shown in Table 1.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>DOB</th>
<th>Age of diagnosis of SLE</th>
<th>Age of diagnosis of diabetes</th>
<th>Type of diabetes</th>
<th>SLE involvement</th>
<th>Problems that can be due to SLE or DM</th>
<th>Serology</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>F</td>
<td>19.01.43</td>
<td>58</td>
<td>−58</td>
<td>Type 2</td>
<td>(Autoimmune hypothyroidism) - Pleurisy - Leucopenia - Lymphopaenia</td>
<td>-Pleurisy -Leucopenia -Lymphopaenia</td>
<td>ANA/dsDNA/Coombs +ve; thyroglobulin</td>
</tr>
<tr>
<td>B</td>
<td>M</td>
<td>08.03.49</td>
<td>−46</td>
<td>−31</td>
<td>Type 1</td>
<td>(Hypothyroidism) - Arthritis - Pleurisy - Rash (photosensitive) - Leucopenia</td>
<td>-Arthritis -Pleurisy -Rash -Leucopenia</td>
<td>ANA/dsDNA/IgG ACA</td>
</tr>
<tr>
<td>C</td>
<td>F</td>
<td>23.05.60</td>
<td>−34</td>
<td>−18</td>
<td>Type 1</td>
<td>-Lymphopaenia - Arthritis - Anaemia - Mouth ulcers</td>
<td>-Retinopathy -Cataract -Renal insufficiency</td>
<td>ANA/dsDNA/Ro Sm, IgM ACA/ thyroglobulin</td>
</tr>
<tr>
<td>D</td>
<td>M</td>
<td>06.01.36</td>
<td>−63</td>
<td>−44</td>
<td>Type 2</td>
<td>-Pleurisy - Renal - Lymphopaenia</td>
<td>-Proteinuria +++; renal biopsy WHO IV in 1/2001 – some diabetic features also seen.</td>
<td>ANA/Ro/RNP</td>
</tr>
<tr>
<td>F</td>
<td>F</td>
<td>10.11.58</td>
<td>−41</td>
<td>−11</td>
<td>Type 1</td>
<td>-Alopecia - Arthritis - Skin rashes</td>
<td>-Mixed sensory &amp; motor neuropathy</td>
<td>ANA</td>
</tr>
<tr>
<td>G</td>
<td>F</td>
<td>7.10.55</td>
<td>−43</td>
<td>−33</td>
<td>Type 2</td>
<td>-Rash (photosensitive) - Renal - Arthritis - Lymphopaenia - Mouth ulcers</td>
<td>-Renal disease; biopsy WHO IV; SLE no diabetic features; now heading for renal failure</td>
<td>ANA/dsDNA/ thyroglobulin</td>
</tr>
<tr>
<td>H</td>
<td>F</td>
<td>10.11.51</td>
<td>−51</td>
<td>−55</td>
<td>Type 2</td>
<td>-Panniculitis - Arthritis - Peripheral neuropathy - Rash</td>
<td></td>
<td>ANA</td>
</tr>
<tr>
<td>I</td>
<td>F</td>
<td>30.04.41</td>
<td>−42</td>
<td>−65</td>
<td>Steroid-induced DM</td>
<td>-Arthritis -Panniculitis -Peripheral neuropathy -Rash</td>
<td>-Peripheral neuropathy</td>
<td>ANA, Ro, RNP</td>
</tr>
</tbody>
</table>

*Patient did not have a biopsy because of concerns about low platelet count.

Discussion

In our cohort, overlap SLE-DM is uncommon (1.9%) and although we cannot exclude the possibility that some diabetic patients might have been missed,
which is unlikely. Our patients were tested for glycosuria at every outpatient attendance with a follow-up fasting glucose if it proved to be positive. Furthermore, approximately 150 of our lupus patients, without overt evidence of diabetes, have had kidney biopsies without any changes compatible with diabetic nephropathy being reported (much of these data are reported in). We were a little surprised that the prevalence of 1.9% was as low as it was and the possibility exists that SLE may in someway be protective of the development of diabetes. In our literature review, however, we could not find an accurate prevalence of DM in SLE patients.

Reviewing the literature, we noted that few SLE patients with DM have been described (usually focusing on the cardiovascular risk) and surprisingly, little appears to have been written about managing the overlap of SLE and DM. Renal disease occurs in around a third of patients with SLE but nephropathy is also a common complication of DM and is the single most common condition found in patients with end-stage renal disease in western countries. The pathophysiological mechanisms involved and the management of renal impairment are different in the two conditions. Lupus nephritis is autoimmune in nature. The glomerular injury is due to the local formation of immune complexes. Although proteinuria is a common feature for both SLE and DM, SLE activity (BILAG), strong serology (ANA, dsDNA antibodies, Sm antibodies), low complement and presence of urinary casts and fragmented RBCs are markers of SLE-renal pathology. In addition, tests for anti-C1q antibodies are becoming more available and are a useful marker for SLE nephritis.

The management of active disease includes corticosteroids and major immunosuppressive drugs. In diabetic nephropathy, the pathophysiological mechanisms involved are complex and hyperglycaemia plays a central role in the glomerular injury process. However, in both conditions persistent proteinuria may be the first evidence of renal injury. A renal biopsy is mandatory to help distinguish the aetiology of the lesions.

Prior to a renal biopsy, what diagnostic ‘clues’ should be ascertained in these patients? Risk factors for DM include poor glycaemic control, high blood pressure, positive family history, hyperglycaemia in pregnancy, duration of the diabetes, obesity and insulin resistance. The presence of retinopathy also seems to be a risk factor, although its absence does not exclude a DM. In our study, patient G had mild retinopathy and lupus nephritis on biopsy, with no diabetic features. Patient C (type 1 DM) has retinopathy and renal insufficiency. Although this patient refused to have a biopsy, the longstanding DM (29 years) strongly suggests that this is the cause of the renal impairment.

Reciprocally, the predictive factors for non-diabetic renal disease in SLE-DM patients with persistent proteinuria (pre-biopsy) include: short duration of DM; an absence of diabetic retinopathy and microscopic haematuria.

Peripheral neuropathy (PN) also complicates diabetes and SLE. PN is uncommon in patients with SLE. In a review of eight series it was present in 8% or fewer in six. In contrast, it is the most frequent complication of DM and its prevalence is higher in patients with longstanding disease. As with renal disease, the pathophysiological mechanisms involved are different in SLE and DM. The latter has a complex mechanism, and metabolic, vascular and genetic factors as well as protein glycosylation and neurotrophism are involved in the pathogenesis. The most common form of diabetic neuropathy (75%) is a distal sensori-motor neuropathy (stocking and glove). Asymmetrical neuropathies can also occur and are usually of abrupt onset resulting from ischaemic infarction of vasa nervosa.

In SLE, a mild sensory or sensorimotor neuropathy is more common with evidence of a distal axonopathy in the electrophysiologic studies. Vasculitis has been reported as the pathogenic mechanism in some cases. In our series only one patient (F- with longstanding DM and SLE for 8 years and patient I, longstanding SLE but just 2 years with DM) had a PN.

The management of PN in patients with diabetes includes tight control of serum glucose levels and treatment of the neuropathic pain includes analgesics, non-steroidal anti-inflammatory drugs, antidepressants and anticonvulsants. The treatment of autonomic neuropathy is symptomatic. Corticosteroids and cytotoxic drugs are the mainstay of treatment for patients with SLE who have a PN of vasculitic origin.

Serious retinal involvement is uncommon in SLE. In contrast, it is a frequent and troublesome DM complication and a major cause of blindness. It is a consequence of the microangiopathy affecting the retinal pre-capillary arterioles, capillaries and venules.

In SLE, the most common form of retinopathy is a microangiopathy with diffuse capillary non-perfusion and small arterial or arteriolar occlusions in the retina. Vasculitic injury of the retinal vessels has been implicated in the pathogenesis. Rarely, a severe vaso-occlusive retinopathy can occur, often associated with poor visual prognosis and neovascularization. Anti-phospholipid antibodies have been associated with this kind of thromboembolic retinopathy.
Treatment is aimed at preventing further thrombosis and complications arising from neovascularization.

In a cohort of 194 patients with SLE, retinal vascular abnormalities were found in 34.5% with retinal angiopathy being the most common (80.6%). These abnormalities were usually minor, but retinopathy was correlated with disease activity.16

In our cohort, retinopathy was found in two patients (C and G). Co-management with an ophthalmologist is essential if suspected. Patients with visual complaints must be screened both ophthalmologically and for the presence of anti-phospholipid antibodies. If diabetic control is poor glycaemic, blood pressure control must be improved. Aspirin or, on occasions, warfarin may be needed for patients with suspected retinal vasculo-occlusive disease.

SLE patients are at increased risk for cardiovascular and cerebrovascular events, even after adjustment for traditional risk factors.16 Premature coronary heart disease (CHD) is a major cause of morbidity and mortality in SLE patients, who have a five- to sixfold increase risk of CHD. This increased risk is especially pronounced in younger women.16 Although the classical cardiovascular risk factors seem to be more prevalent in SLE, they do not completely explain the excess risk. Chronic inflammation is now considered central to the pathogenesis of atherosclerosis and an important risk factor for vascular disease.17

Diabetes mellitus is well recognized as an important cardiovascular risk factor, and a major cause of accelerated atherosclerosis. 80% of the mortality in DM patients is due to major cardiovascular events.18

Thus, the DM-SLE patient is likely to be at significantly higher risk for cardiovascular events, although we do not know the exact contribution of each disease to the patients’ absolute risk. The fact is that these patients have two independent risk factors for cardiovascular disease. It would be interesting to study the incidence of cardiovascular events with a controlled trial of SLE alone and SLE with DM. One of our patients (D) has angina which is almost certainly related to his diabetes, which long antedates his SLE.

Finally, the question of the steroid use in patients with SLE-DM needs consideration. Steroids are important in SLE for controlling systemic inflammation, but disturb glucose metabolism that can worsen diabetes. It is challenging to treat a DM-SLE patient with steroids – it requires a more careful control of glycaemia than most diabetic patients. The early use of additional immunosuppression and lower than usual doses of steroids can be effective.

In summary, SLE-DM patients may well be at increased risk of developing renal impairment, neuropathy, retinopathy and cardiovascular events. Careful consideration of which of these conditions is likely to be the major culprit needs to be undertaken and the help of other colleagues, ophthalmologists, nephrologists and endocrinologists is likely be very helpful. This unfortunate combination of diseases clearly places patients in double jeopardy of developing several complications and calls for particular vigilance from their physicians.

References


17 Bruce, I. ‘Not only...but also’: factors that contribute to accelerated atherosclerosis and premature coronary heart disease in systemic lupus erythematosus. Rheumatology 2005; 44: 1492–1502.