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Osteoarticular tuberculosis in patients with systemic lupus erythematosus

B. HODKINSON[1], E. MUSENGE[2] and M. TIKLY[1]

From the [1]Division of Rheumatology, Department of Medicine, Chris Hani Baragwanath Hospital, University of the Witwatersrand, Johannesburg and [2]Epidemiology Centre, School of Public Health, University of the Witwatersrand, Johannesburg, South Africa

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Summary

Background: Systemic lupus erythematosus (SLE) patients are at increased risk of developing tuberculosis (TB), particularly extrapulmonary TB (ExP-TB).
Aim: The present study was undertaken to investigate whether SLE patients showed increased susceptibility to develop osteoarticular TB (OA-TB).
Design and Methods: We retrospectively reviewed and compared the frequency of ExP-TB, in particular OA-TB, in patients with SLE at a tertiary hospital in South Africa, to a non-SLE control TB group seen at the same hospital.
Results: TB was diagnosed 111 times in 97 (17%) of the 568 SLE patients. The relative frequency of ExP-TB in the SLE group (25.2%) was significantly lower than in the control group (38.5%) (OR = 1.9, $P = 0.006$). In contrast, OA-TB was diagnosed in the SLE group in nine (8.1%) patients (seven with peripheral arthritis and two with TB spine) compared to 54 (0.4%) in the overall control group (OR = 20.8, $P < 0.001$) and 13 (0.2%) in the subgroup of known HIV positive patients in the control group (OR = 44.4, $P < 0.001$). Within the SLE group, Black ethnicity ($P = 0.003$), lymphopaenia ($P = 0.001$), C3/C4 hypocomplementaemia ($P = 0.05$), corticosteroids [maximum dose ($P = 0.002$) and duration of treatment ($P = 0.02$)] and immunosuppressive agents ($P = 0.02$) were risk factors for TB. Duration of corticosteroid therapy was the only risk factor for OA-TB ($P = 0.04$).
Conclusion: While the relative frequency of ExP-TB was lower in the SLE group compared to the control group, our findings suggest that SLE patients are at particular risk of developing OA-TB. Further prospective studies are needed to better understand the mechanisms that predispose SLE patients to OA-TB.

Introduction

Systemic lupus erythematosus (SLE) is a multisystem immune-mediated disease of unknown aetiology. Patients with SLE are susceptible to common and opportunistic infections, and these contribute significantly to morbidity and mortality.[1] In many populations including our own, infection remains the leading cause of death in SLE.[2] This increased susceptibility is due to both inherent immune abnormalities and immunosuppressive therapy used to treat the disease.[3,4] Risk factors for infection include disease flares as well as the use of corticosteroids, by either oral or intravenous route, and cytotoxics, particularly pulse cyclophosphamide.[1,5,6]

Several studies have shown that SLE patients have a higher prevalence of tuberculosis (TB) than the general population.[7] Immunocompromized patients are increased risk of extrapulmonary disseminated

Address correspondence to: M. Tikly, Division of Rheumatology, Chris Hani Baragwanath Hospital, PO Bertsham, South Africa. email: tikly.mohammed01@gmail.com

TB (ExP-TB)[8] and studies in SLE patients have shown that ExP-TB is especially common, with the spectrum of organ involvement including pleura, meninges, skin, joints and kidney.[9,10] Predisposing factors for TB in SLE patients include high-SLE activity and in particular active lupus nephritis, corticosteroid treatment and the use of immunosuppressive drugs.[11–14] Recent studies highlight the high-relapse rate and high mortality associated with TB in SLE patients.[15,16]

There has been a universal increase in the incidence of TB in recent years, and TB is endemic in parts of the developing world such as sub-Saharan Africa, parts of Asia and central Europe. Tuberculosis is rife in South Africa, a public health problem that has been exacerbated over the last two to three decades by human immunodeficiency virus (HIV) infection.[17] These two conditions account for a large proportion of deaths in young-to-middle-aged adults in South Africa.[18,19]

Osteoarticular TB (OA-TB), a rare form of ExP-TB, accounts for 1–3% of all TB cases. Sites of involvement include the spine, long bones and less commonly, the peripheral joints, usually presenting as a chronic monoarthritis.[20,21] Diagnosing OA-TB is often challenging due to non-specific features and insidious onset, and diagnostic delay is frequent.[22] Recognized predisposing factors for OA-TB include advanced age, long-term corticosteroid treatment, ethnicity, low socioeconomic and previous TB.[23,24] The long-term outcome with a prolonged course of anti-TB therapy, with or without surgical intervention, is generally good but relapse is well described.[25]

The present study was undertaken to determine whether SLE patients were at increased risk of developing OA-TB by comparing its frequency in SLE patients to non-SLE patients with TB attending a tertiary hospital. The Human Ethics Committee of the Faculty of Health Sciences, University of the Witwatersrand, approved the study.

Patients and methods

Medical records of all SLE patients attending the Chris Hani Baragwanath Hospital (CHBH) Lupus Clinic between January 1989 and March 2006, were reviewed. The hospital is a tertiary referral centre servicing the urban predominantly Black population of Soweto, South Africa. All patients were 14 years and older at disease onset and fulfilled the 1997 updated American College of Rheumatology (ACR) criteria for SLE.[26] Disease duration was defined as onset of SLE symptoms to last visit or death, and the follow-up period was defined as the period from first presentation to our clinic to last visit or death. Clinical data were abstracted from the clinical records using ACR classification criteria definitions for nephritis, skin, central nervous system (CNS) involvement and arthritis. Laboratory data included antinuclear and antiphospholipid antibody results, lymphopaenia and C3/C4 hypocomplementaemia. Drug therapy was recorded, including maximum daily oral dose of prednisone (CS), use of intravenous corticosteroids CS (IVCS), duration of oral CS therapy and use of immunosuppressive drugs including cyclophosphamide, azathioprine, cyclosporine, methotrexate and mycophenalate mofetil.

The relative frequency of ExP-TB in the SLE group was compared to all TB cases (excluding SLE cases), 14 years and older, registered at the CHBH TB centre between the inception of the registry in January 2004 and March 2006, henceforth known as the control group. The CHBH TB centre is a central registry for all TB cases and captures, amongst other parameters, site of TB and HIV status.

The diagnosis of TB was based on direct microscopy of sputum and fluid using either the Ziehl-Nielsen or auramine staining methods or mycobacterial culture, histology or typical chest X-ray (CXR) findings in the setting of suggestive constitutional symptoms. Extrapulmonary TB was defined as *Mycobacterium tuberculosis* infection at a site outside of the lungs, including pleural involvement.

Risk factors for TB and disseminated TB within the SLE group were determined using a nested case control design, with each SLE patient with TB or disseminated TB matched for age (within 24 months) with two SLE patients without TB. Disseminated TB was defined as a miliary pattern on CXR, or involvement of bone marrow, lymph nodes, meninges, skin or osteoarticular system. To determine risk factors for OA-TB, each patient with OA-TB was matched with four SLE patients without TB infection.

Statistical methods

The chi-square test (with Yates' correction) or the two-tailed Fishers' exact test was used to compare frequencies between groups and subgroups within the SLE group. Multivariate analysis was done by stepwise conditional logistic regression. Variables showing a $P \leqslant 0.1$ in univariate analysis were included in the model. A $P < 0.05$ was considered significant.

Results

Of the 568 patients who fulfilled the ACR classification criteria for SLE, 513 (90%) were female, the

Table 1 Spectrum of osteoarticular TB in SLE patients at Chris Hani Baragwanath Hospital

Patient	Site (s)	Diagnosis	Concurrent TB	Diagnostic delay (months)
Patient 1	Knee	Fluid microscopy and culture	No	13
Patient 2	Wrist	Synovial histology	No	8
Patient 3	Knee	Fluid culture	No	Unknown
Patient 4	Wrist and knee	Fluid culture and histology	No	23
Patient 5	First MTP	Fluid culture	PTB	3
Patient 6	Wrist	Fluid culture and histology	No	15
Patient 7	Wrist	Synovial histology	No	12
Patient 8	Spine (L4/5)	MRI	Skin[a]	15
Patient 9	Spine (T12/l1)	MRI	No	3

[a]Erythema induratum; MTP: metatarsophalangeal joint; MRI: magnetic resonance imaging.

mean age was 34.9 (SD ± 12.5) years, mean duration of follow-up was 52.6 (SD ± 56.0) months and the vast majority of patients were Black (92.6%). None of the patients were on anti-TNF drugs. Only 13 patients received isoniazid (INH) prophylaxis.

Frequency and spectrum of TB infections in the SLE group

Tuberculosis was diagnosed 111 times in 97 patients representing 17% of the total SLE cohort and a prevalence of 4.4/100 patient-years of follow-up. Pulmonary TB (PTB) was seen in 69 patients and 28 (41%) of patients were diagnosed with TB within the first 2 years of diagnosis of SLE. The diagnosis of PTB was based on direct sputum microscopy in 69 (81%) of patients, and of the remaining patients, two (3%) had positive sputum cultures, two (3%) had transbronchial biopsies with suggestive histology and nine (13%) had constitutional symptoms and a CXR highly suggestive of TB. Extensive pulmonary disease affecting more than one lobe was noted in seven patients. Three patients had a miliary pattern on CXR.

Extrapulmonary TB was diagnosed in 28 patients, 17 (57%) of whom developed TB within the first 2 years of the diagnosis of SLE. Nine patients had pleural effusions, three patients had TB lymphadenitis, five patients had TB meningitis, one had evidence of bone marrow infiltration and two had biopsy-proven erythema induratum. Osteoarticular TB occurred in nine patients, whose clinical presentation and diagnosis are shown in Table 1. In two patients, active TB was evident simultaneously in more than one site, one with skin and spine involvement and one with pulmonary TB and OA-TB. None of the patients with pleural effusion had PTB.

Recurrent TB infection was diagnosed 14 times and of these 12 patients had recurrent PTB, and two patients developed extrapulmonary disease: TB meningitis occurring 3 years after PTB, and TB lymphadenitis occurring 5 years after PTB. Multidrug resistant (MDR) TB occurred in seven patients, six in patients with recurrent TB and one case of primary PTB. Thirteen patients died of TB and three of these had MDR TB. Of the deaths, 10 had PTB, 1 had a pleural effusion, 1 had TB meningitis and 1 had HIV and TB lymphadenitis. Of the total cohort of SLE patients, 18 were known to have HIV infection, but only three had co-infection with TB.

Spectrum of TB in control group

Tuberculosis was diagnosed 12 772 times in 12 658 control cases registered with the CHBH TB centre (114 patients had recurrent TB infection). Of these patients, 51% were known HIV positive, 17% were known HIV negative and in the remaining 32% of cases the HIV status was unknown. As shown in Table 2, the relative frequencies of ExP-TB overall and specifically bone marrow TB, was significantly higher in the overall control group (OR = 1.9 and 12.2, $P = 0.006$ and 0.002, respectively) and known HIV positive control subgroup (OR = 2.0 and 15.3, $P = 0.006$ and 0.0005, respectively), compared with the SLE group. By contrast, the relative frequency of OA-TB was significantly higher in the SLE group compared with both the overall control group and subgroup of known HIV positive patients in the control group (OR = 20.8 and 44.4, respectively, $P < 0.0001$ for both). In the control group, OA-TB was diagnosed in 24 (1.1%) of the known HIV negative patients compared with 13 (0.2%) of the known HIV positive patients (OR = 5.6, 95% CI = 2.9–11.1, $P < 0.001$). In the control group, the relative frequency of OA-TB remained higher in the known HIV negative subgroup compared with 30 (0.3%) cases in the combined known HIV positive

Table 2 Relative frequencies of extrapulmonary tuberculosis in SLE and control TB groups

	SLE (%) $n=111$	Controls (%) $n=12\,772$	OR (95% CI)	*P*-value	HIV positive controls (%) $n=6556$	OR (95% CI)	*P*-value
Overall ExP-TB	28 (25.2)	4912 (38.5)	1.9 (1.2–2.8)	0.006	2655 (40.5)	2.0 (1.3–3.1)	0.006
Osteoarticular TB	9 (8.1)	54 (0.4)	20.8 (10–43.2)	<0.0001	13 (0.2)	44.4 (18.6–106.3)	<0.0001
TB pleural effusion	9 (8.1)	1522 (11.9)	0.7 (0.3–1.3)	NS	724 (11.1)	0.7 (0.4–1.4)	NS
TB lymphadenitis	3 (8.2)	609 (4.8)	0.6 (0.2–1.8)	NS	345 (5.3)	0.5 (0.2–1.6)	NS
TB meningitis	5 (2.7)	889 (7)	0.6 (0.3–1.6)	NS	483 (7.4)	0.6 (0.2–1.5)	NS
Bone marrow TB	1 (0.9)	1277 (10)	12.2 (1.3–87.6)	0.002	801 (12.2)	15.3 (2.1–109.8)	0.0005
Other	1 (0.9)	865 (6.8)	8.0 (1.1–57.3)	0.03	286 (4.4)	0.2 (0.03–1.4)	NS

[a]Other: skin, pericardial, peritoneal or liver TB; ExP-TB: extrapulmonary tuberculosis.

Table 3 Univariate analysis of risk factors for tuberculosis in the SLE group

	Non-infected $n=194$[a]	TB $n=97$[a]	OR (95% CI)	*P*-value
Age in years, mean (SD)	34.5 (12.9)	33.7 (13.2)	1 (1.0–1.04)	NS
Disease duration in months, mean (SD)	51.0 (52.5)	56.7 (62.0)	1.0 (1.00–1.01)	NS
Female (%)	175 (90.2)	86 (88.7)	0.84 (0.4–1.9)	NS
Ethnicity: Black Race (%)	174 (89.6)	96 (99.0)	11.0 (1.5–83.5)	0.003
Lupus nephritis (%)	58/164 (35.4)	28/83 (33.7)	0.9 (0.5–1.7)	NS
Skin (%)	118/165 (71.5)	33/51 (64.7)	0.7 (0.4–1.5)	NS
Central nervous system (%)	19/165 (11.5)	13/51 (25.0)	2.6 (1.1–6.2)	0.02
Arthritis (%)	111/165 (67.2)	38/52 (73)	1.3 (0.6–2.9)	NS
Leucopenia (%)	44/117 (37.6)	27/52 (52.0)	1.8 (0.9–3.7)	NS
Lymphopaenia (%)	47/117 (40.2)	35/52 (67.3)	3.1 (1.5–6.5)	0.001
C3/C4 hypocomplentaemia (%)	97/161 (60.3)	39/52 (75.0)	2.0 (0.9–4.4)	0.05
Antinuclear antibody positive (%)	146/163 (89.6)	50/52 (96.2)	2.9 (0.7–26.8)	NS
Steroid use ever (%)	143/180 (79.4)	61/80 (76.3)	0.8 (0.4–1.7)	NS
Steroid use > 15 mg (%)	101/180 (56.0)	50/81 (62.0)	1.0 (0.5–2.0)	NS
Intravenous corticosteroids (%)	2 (0.1)	5 (0.1)	5.2 (1.0–27)	0.04
Maximum oral corticosteroid dose in milligrams, mean (SD)	31.5 (19.1)	41.7 (20.5)	1.0 (1.01–1.04)	0.002
Duration of oral corticosteroid in months, mean (SD)	11.6 (15.3)	23.3 (39.4)	1.0 (1.01–1.04)	0.02
Immunosuppressive use ever (%)	60/179 (33.5)	40/83 (48.2)	1.8 (1.0–3.2)	0.02
Azathioprine (%)	30/168 (17.9)	21/82 (25.3)	1.6 (0.8–3.1)	NS
Cyclophosphamide (%)	41/168 (24.4)	20/83 (24.1)	1.0 (0.5–1.9)	NS
Methotrexate (%)	18/153 (11.7)	9/80 (11.1)	1.0 (0.4–2.4)	NS
HIV positive (%)	5 (0.3)	3 (0.3)	1.2 (0.3–5.7)	NS

[a]Denominator indicated in cases of missing data.

and HIV unknown subgroups (OR = 3.9, 95%CI = 2.3–6.8, $P < 0.001$).

Predictive factors for TB infection in SLE group

Univariate analysis for TB infection in the SLE group showed that Black ethnicity (OR=11.0, $P = 0.003$), lymphopaenia (OR = 3.1, $P = 0.001$), C3/C4 hypocomplementaemia (OR = 2.0, $P = 0.05$) and CNS involvement (OR = 2.6, $P = 0.01$) were associated with an increased risk of TB (Table 3). Significant drug related risk factors were the maximum oral CS dose (OR = 1.0, $P = 0.002$), use of IVCS (OR = 5.2, $P = 0.03$), duration of oral CS therapy (OR = 1.0, $P = 0.02$) and use of immunosuppressive drugs (OR = 1.8, $P = 0.02$). Multivariate regression analysis showed lymphopaenia (OR = 4.2, 95%CI = 1.6–11.5, $P = 0.005$), the maximum oral CS dose (OR = 1.0, 95%CI = 1.0–1.1, $P = 0.05$) and duration of CS treatment (OR = 1.0, 95% CI = 1.0–1.1, $P = 0.05$) to be significant independent risk factors.

Table 4 Summary of studies of extrapulmonary and osteoarticular tuberculosis in systemic lupus erythematosus

Country Period	Singapore (13) 1963–79	Turkey (10) 1978–2001	Philippines (16) 1985–1995	Hong Kong (12) 1984–20	Hong Kong (14) 1987–2001	Taiwan (27) 1985–2004	Present study 1989–2006
Total no of TB events	16	20	57	57	91	21	111
No of ExP-TB events (% of TB infections)	3 (18.8)	9 (45.0)	29 (50.1)	38 (66.7)	36 (39.6)	11 (52.4)	28 (25.2)
No of OA-TB events (% of ExP-TB)	1 (33.3)	7 (77.8)	12 (41.4)	5 (13.2)	8 (22.2)	5 (45.5)	9 (32.1)

ExP-TB: extrapulmonary tuberculosis; OA-TB: osteoarticular tuberculosis.

In the case of disseminated TB, no significant risk factors were found except for a trend towards an association with lymphopaenia (OR = 3.2, 95% CI = 1.1–9.8, $P = 0.06$). The duration of CS therapy was the only significant risk factor for OA-TB (mean duration in months of 66.8 in OA-TB vs. 11.2 non-infected group, $P = 0.04$). All except one of the nine OA-TB cases in the SLE group had pre-existing inflammatory arthritis compared with 17 of 29 (58.6%) patients in the non-infected SLE control patients, but the difference in frequency was not statistically significant.

Discussion

SLE patients are at increased risk of TB infection, with an incidence up to 7-fold higher than expected in the general population.[7] In addition, recent studies suggest that the spectrum of TB seen in SLE also differs from that seen in the non-SLE population. Extensive pulmonary involvement appears to be more common. In our study, multilobar disease was noted in 10% of PTB patients, compared with 44–47% reported in previous studies.[13,15] A high-relapse rate and disseminated disease are also features of TB infection in SLE. We noted a recurrent infection rate of 14%, and in a Hong Kong study 24% of patients were diagnosed with recurrent disease.[14] The high proportion (25.2%) of patients with ExP-TB in the present study is consistent with other reports where involvement of one or more extrapulmonary organs was seen in 19–67% of all TB infections (Table 4).[12,27]

The frequency of TB in our SLE cohort is higher than that reported in TB endemic areas of Asia and probably a reflection of the high-background incidence of TB in South Africa, estimated to be 600/100 000.[28] Three previous studies of SLE in South Africa have shown a similarly high incidence of TB, ranging from 4% to 15%.[29–31]

Our findings suggest that SLE patients are especially predisposed to OA-TB, notwithstanding the limitations of a retrospective review, the small absolute number of OA-TB cases and the possibility that OA-TB is more likely to be recognized and diagnosed in a rheumatology setting. The SLE group had a lower overall relative frequency of ExP-TB compared with the control group, but the relative frequency of OA-TB was 20 times higher. It is noteworthy that although none of the published reports on TB in SLE have focused specifically on OA-TB, OA-TB has constituted between 22% and 78% of all ExP-TB in these studies (Table 4).

The risk factors and mechanisms that facilitate OA-TB are not clear. The association between pyogenic joint infection and inflamed joints is well described.[32] *Mycobacterium tuberculosis* may have a similar predilection for inflamed joints[33,34] and several reports describe patients developing OA-TB at the site of previous musculoskeletal injury.[35,36] It has been postulated that macrophages that engulf *M. tuberculosis* at the primary site of infection (most commonly the lung) and migrate via chemotaxis to the injury site. Inflammatory arthritis did not emerge as an independent risk factor for the development of OA-TB in our study, probably due to small numbers. Since prolonged or high dose CS use was associated with TB, we postulate that the combination of inflammatory arthritis and CS might explain why SLE patients, as opposed to patients with other inflammatory joint diseases like rheumatoid arthritis, are uniquely predisposed to OA-TB.

The substantial delay (mean = 11 months) in the diagnosis of OA-TB is similar to that reported in the general population for ExP-TB and particularly OA-TB.[37,38] This is partly related to difficulties in proving the diagnosis of OA-TB. Synovial fluid cultures take up to 6 weeks to provide a positive result, though the yield is generally high. In the present study, five of the seven patients with peripheral arthritis had positive synovial fluid cultures. Histology is useful in providing a diagnosis, but synovial biopsy is an invasive procedure and thus is not undertaken until other investigations prove unhelpful. In SLE patients, further factors are

likely to contribute to this delay. Non-specific symptoms of loss of weight, night sweats, fever and elevated ESR are common to both SLE and TB. Moreover, the infected joint is often assumed to be an inflamed joint attributable to active SLE.

Our study, like other studies, shows that CS therapy, particularly in high doses and for prolonged periods, and the use of immunosuppressive drugs are major predisposing factors for the development of TB in SLE patients.[10,12] We found no specific association of TB with SLE nephritis. The overwhelming majority of patients developing TB were Black, and this probably relates to poorer socioeconomic status of this group and inherent genetic factors.[39] The association of lymphopaenia with TB in our study is similar to findings in other studies, where lymphopaenia in SLE patients has been found to increase risk of all infections, and in particular TB.[40,41] Lymphocytes play a major role in immunity to TB through the formation of granulomas.[42] Apart from a reduction in lymphocyte numbers, defects in T-cell function and cytokine signalling have been demonstrated in SLE, and probably underlie the SLE patient's susceptibility to ExP-TB.[43]

Isoniazid prophylaxis was not given to the majority of our patients because of concerns of INH resistance. It is still unclear whether INH prophylaxis given to SLE patients on oral CS therapy is effective in preventing TB in regions where TB is endemic.[44] A Hong Kong study where INH was given to any SLE patient receiving oral prednisone at a dose of 15 mg daily or more or other immunosuppressive agents failed to show a decrease in TB recurrence rates.[14] Two studies have shown otherwise: TB occurrence decreased by 82% in an Indian study where all SLE patients received INH for 1 year without development of resistance or toxicity, and in a Mexican study TB occurrence decreased by 97% where INH was given to patients receiving CS at a dose of >15 mg a day for 3 months or more.[9,45]

Immune suppression from HIV infection predisposes to ExP-TB, the most common sites of infection being the pleura, lymph nodes, bone marrow and central nervous system.[46] This is borne out by the high proportion of HIV positive patients in our control group with ExP-TB, particularly bone marrow TB. Surprisingly, the relative frequency of OA-TB in the known HIV positive group was significantly lower compared to the known HIV negative group. Even when we took the approach of assuming patients with unknown HIV status were HIV positive, there was still an almost 4-fold difference in the relative frequency of OA-TB. One explanation might be that patients with advanced HIV disease succumb to disseminated TB or other opportunistic infections before OA-TB is diagnosed. In other studies, HIV has not been found to be a risk factor for OA-TB, either of the axial or peripheral skeleton.[38] Similarly, there is no clear-cut evidence to show that pyogenic joint or spinal infections are increased with HIV disease.[47–49]

The retrospective nature of this study limited us determining more precisely the role of inherent SLE features, such as leucopaenia/lymphopaenia, hypocomplementaemia, inflammatory arthritis and global disease activity at the time of diagnosis of TB in predisposing to TB. We were further unable to accurately quantify the cumulative doses of CS and other immunosuppressive drugs. In some cases, we were unable to obtain laboratory data from patient files. The period over which TB registry data were collected overlapped with SLE period of study for only some of the time and this might have impacted on the observed relative frequencies of ExP-TB in the two groups.

Notwithstanding these limitations, our findings not only confirm that SLE patients are at increased risk of developing ExP-TB but also strongly suggest that they are predisposed to OA-TB. These findings highlight the need for physicians caring for SLE patients to have a high index of suspicion of TB arthritis in cases of unexplained refractory inflammatory monoarthritis, especially in patients on long-term oral corticosteroids. Further prospective clinical and laboratory studies are needed to better understand the mechanisms that underlie this predisposition in SLE.

Supplementary Data

Supplementary Data are available at *QJMED* online.

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