Concise report

Cancer risk in cutaneous lupus erythematosus: a population-based cohort study

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Abstract

Objective. Immune dysregulation associated with chronic autoimmune diseases, such as SLE, has been associated with increased cancer risk. It is unclear whether isolated cutaneous lupus erythematosus (CLE) modifies cancer risk. We estimated the cumulative incidence of cancer in a population-based CLE cohort and compared the risk with a matched non-CLE cohort.

Methods. All incident cases of CLE in Olmsted County, MN, USA between 1965 and 2005 were identified and followed to December 2013. Estimates for the cumulative incidence of any cancer and skin cancer in patients with CLE were derived and compared with an age-, sex- and calendar-year-matched non-CLE cohort using Cox models.

Results. There were a total of 155 patients with CLE [age at diagnosis, 48 (S.D. 16) years; 65% females; BMI, 26.3 (S.D. 7.1) kg/m^2; 40% smokers, 9% with diabetes]. During a median follow-up of 14.6 years, we observed 35 cases of incident cancer (including 10 cases of skin cancer). The cumulative 1-, 5- and 10-year incidence of any cancer after diagnosis of CLE was 1.4, 7.5 and 11.6%, respectively. Compared with matched non-CLE controls, the overall risk of malignancies was not increased in patients with CLE (smoking-adjusted hazard ratio = 1.29; 95% CI: 0.78, 2.13; P = 0.31). There was also no significant increase in risk of any skin cancer in patients with CLE (hazard ratio = 2.51; 95% CI: 0.91, 6.96; P = 0.16).

Conclusion. CLE is not associated with an increased risk of any cancers, including skin cancers, compared with the general population. However, the number of events was small, limiting the power of the study.

Key words: inflammation, cutaneous lupus, cancer, melanoma, incidence

CLINICAL SCIENCE

Rheumatology key messages

- Cutaneous lupus erythematosus is not associated with an increase in cancer risk in a population-based cohort.
- Routine cancer screening practices should suffice for patients with cutaneous lupus erythematosus, without the need for targeted surveillance.

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Introduction

Epidemiological studies have shown that chronic inflammatory diseases, such as RA and SLE, are associated with increased risk of haematological, cutaneous and solid-organ malignancies [1, 2]. Even limited autoimmune dermatological conditions, such as psoriasis, are associated with increased risk of both cutaneous and systemic solid-organ malignancies [3]. The increased risk of malignancies in these patients may be attributed to systemic immune dysregulation leading to impairment of tumour surveillance [4] or, alternatively, to immunosuppressive therapy used to treat these autoimmune conditions, which may modify cancer risk [5, 6].

Cutaneous lupus erythematosus (CLE), defined as isolated cutaneous lupus lesions occurring in the absence of significant evidence of SLE, has a 2- to 3-fold higher prevalence than SLE, with a peak incidence in the seventh decade of life [7]. There are limited data on whether CLE affects cancer risk. As the pathogenesis of CLE is similar to SLE, with complex gene–environment interactions, autoimmunity and immune-mediated cutaneous damage, it is conceivable that patients with CLE may be at increased risk for cancer [8]. At the same time, the limited extent of organ involvement with absence of systemic damage suggests that chronic systemic inflammation may be absent in patients with CLE [9].

A Swedish nationwide registry-based study of 3663 patients with CLE followed for 4 years reported a significant increase in the risk of all cancers, buccal cancer, respiratory cancer, lymphoma and non-melanoma skin cancer (NMSC), compared with non-CLE controls [10]. However, the analysis was based on an administrative database, which was not validated for CLE diagnosis, and there was potential misclassification with SLE. Additionally, the database did not capture data on significant confounders, such as smoking.

We undertook this population-based cohort study of patients with CLE in Olmsted County, MN, USA to estimate the cumulative incidence of all cancers, and specifically skin cancers, in patients with CLE and to assess the relative risk of cancers in patients with CLE, compared with age-, sex- and calendar year-matched subjects without CLE.

Methods

This study was approved by the Mayo Clinic and Olmsted Medical Centre Institutional Review Boards. According to institutional policies, all patients had active authorization for use of their medical records for research.

Setting

Olmsted County, situated in Southeastern Minnesota, has a population of 144 260 inhabitants as of the 2010 US Census. Eighty-three per cent of the population is non-Hispanic white, and a substantial proportion is of North European ancestry. The majority of people reside in Rochester, which is the urban centre of an otherwise rural county. The residents of Olmsted County are socio-economically comparable to the US white population, although a higher proportion are employed in health-care services (25% in Olmsted County *vs* 8% nationwide) and have a higher level of education (30% completed college in Olmsted County *vs* 21% nationwide) [11, 12].

Medical care within Olmsted County, MN is practically self-contained within the region and is provided by Mayo Clinic, Olmsted Medical Centre and their affiliated hospitals, and the Rochester Family Medicine Clinic [13]. These health-care providers are connected through a unique medical records-linkage system [the Rochester Epidemiology Project (REP)], which allows for the conduct of true population-based research studies. Each year, >80% of the Olmsted County population is examined by one of the providers participating in the REP, and during any given 3-year period, >90% of local residents are examined at one of the REP providers.

The linkage of information essentially enumerates the Olmsted County population; in fact, REP population estimates are consistently higher than those reported by the US Census [14]. The central diagnostic index of REP comprises all diagnoses generated from outpatient evaluations, hospitalizations, emergency room evaluations, nursing home visits, surgical procedures, autopsy reports and death certificates. It is therefore possible to identify all cases of a disease for which patients sought medical attention over a particular period of time.

CLE case definition

Cases with isolated cutaneous lupus were identified using International Classification of Diseases-9 (ICD-9) codes. We used the REP linkage system to identify all medical records for residents of Olmsted County who had an established diagnosis of any of the subtypes of CLE from 1 January 1965 to 31 December 2005, including classic discoid lupus erythematosus, lupus panniculitis, bullous lupus erythematosus and subcutaneous lupus erythematosus confirmed by dermatological evaluation and histopathological analysis. Data were collected regarding patient demographics, serology, biochemical markers of inflammation (ESR, CRP) and treatment (details of serological tests are given in the supplementary Data, available at *Rheumatology* Online). We excluded non-residents of Olmsted County and patients with CLE who also had SLE at the time of diagnosis. Cases of drug-induced CLE were also excluded.

Using the definition of Sontheimer [15], subacute CLE lesions were described as a photosensitive, non-scarring, non-atrophy-producing, annular, erythematous, papulosquamous or psoriasiform rash. Patients were subclassified as having annular or psoriasiform subacute CLE. Classic discoid lupus erythematosus was defined according to the classification criteria of Gilliam and Sontheimer [15] as the presence of discoid lesions without subacute CLE or SLE. Patients were subclassified as having localized or generalized discoid CLE. Lupus panniculitis was defined as circumscribed subcutaneous nodules. Diagnosis of all forms of CLE was determined by clinical, serological, histopathological and immunopathological findings. The date of diagnosis was determined as the date of fulfilment of criteria for subtype definition.

Control subjects without CLE were identified from the same Olmsted County population and were matched, 1:1, with cases on age (birth year ±3 years), sex and index date of diagnosis of CLE.

Cancer diagnosis

Using the medical records linkage system, all cancers, including haematological malignancies, solid-organ cancers, melanoma and NMSC, in patients with CLE were identified, including those occurring before and after CLE diagnosis, and diagnosed at outpatient clinic visits

TABLE 1 Baseline characteristics of patients with cutaneous lupus erythematosus and subjects without cutaneous lupus erythematosus

Characteristic	Patients with CLE (n = 155)	Subjects without CLE (n = 155)	P-values
Demographics			
Age, mean (S.D.), years	48 (16)	48 (16)	0.96
Sex, female, n (%)	100 (65)	100 (65)	1.00
Follow-up, median (interquartile range), years	14.6 (8.1–23.6)	15.8 (8.7–24.3)	–
Race, white (%)[a]	117 (88.0)	136 (98.6)	0.03
History of malignancy prior to index date			
Any cancer, n (%)	11/155 (7.1)	14/155 (9.0)	0.53
Any cancer, n (%)[b]	3/155 (1.9)	5/155 (3.2)	0.57
Co-morbidities			
Smoking, current, n (%)[c]	61 (39.6)	32/155 (20.6)	0.001
BMI, mean (S.D.), kg/m^2[d]	26.3 (7.1)	26.5 (5.1)	0.18
Cardiovascular disease, n (%)	17/155 (11.0)	11/155 (7.1)	0.23
Hypertension, n (%)[e]	85/155 (54.8)	72/155 (46.8)	0.16
Diabetes mellitus, n (%)[f]	24 (15.7)	18 (12.2)	0.38
Hyperlipidaemia, n (%)[g]	62/155 (40.0)	72 (47.1)	0.22
Family history of early CAD, n (%)[d]	6 (4.1)	6 (3.9)	0.95

[a]Data available for only 133 patients with CLE and 138 subjects without CLE. [b]All skin cancers prior to index date were non-melanoma skin cancers; there were no cases of melanoma. [c]Data available for only 154 patients with CLE. [d]Data available for 147 patients with CLE and 144 non-CLE controls. [e]Data available for only 154 subjects without CLE. [f]Data available for only 153 patients with CLE and 148 subjects without CLE. [g]Data available for only 153 patients with CLE. [h]Data available for only 147 patients with CLE and 152 subjects without CLE. CAD: coronary artery disease; CLE: cutaneous lupus erythematosus.

or hospitalizations. Subsequently, all medical records were manually reviewed to verify the diagnoses.

Statistical analysis

Descriptive statistics (percentages, mean, etc.) were used to summarize the characteristics of each cohort, and comparisons between cohorts were performed using χ^2 and rank sum tests. The cumulative incidences of all cancers and skin cancers (including melanoma and NMSC), adjusted for the competing risk of death, were estimated [16]. Patients with cancer prior to CLE incidence/index date were removed from these analyses because they were not at risk of developing their first cancer of that type. Cox proportional hazard models were used to examine the association between CLE/non-CLE and the development of cancer adjusting for age, sex, smoking and calendar year of CLE incidence/index date. Further adjustments were not performed because of limited statistical power. To assess the effect of the extent of cutaneous involvement (as a possible reflection of inflammatory burden) on cancer risk, we compared the risk of cancer in patients with generalized CLE with those of localized discoid CLE.

Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria). Values of P < 0.05 were considered statistically significant.

Results

The study population consisted of 155 patients with CLE and 155 age-, sex- and calendar year-matched individuals without CLE (Table 1). The mean age at CLE diagnosis/index date was 48 (S.D. 16) years, and 65% were females. Of the 155 CLE patients, 88% were Caucasian. The CLE cohort included 128 patients with discoid CLE (73%; 91 with localized and 37 generalized), 23 with subacute CLE (15%; 6 annular and 17 psoriasiform), 3 with lupus panniculitis (2%) and 1 with bullous CLE (1%). Overall, 46 patients (30%) were treated with HCQ, and 6 patients (4%) were treated with prednisone (classified as users if they used medication for at least 3 months). The median (interquartile range) ESR and CRP at CLE diagnosis were 10 (4–20) mm at 1 h (n = 131) and 2.9 (1.5–3.7) mg/l (n = 21), respectively. Autoantibody data were present for a subset of patients, as follows: ANA positive, 70/146 (47.9%); dsDNA positive, 6/105 (5.7%); anti-Smith antibody positive, 1/79 (1.3%); anti-SSA/Ro positive, 32/80 (40.0%); anti-SSB/La positive, 10/79 (12.7%); and anti-RNP positive, 6/78 (7.7%). Total complement levels were abnormal in 7/82 (8.5%). At the time of last follow-up, 3/6 patients positive for anti-dsDNA progressed to SLE, whereas one patient positive for anti-Smith antibody did not progress to SLE.

Eleven patients with CLE (including 3 patients with skin cancer) and 14 patients without CLE (including 5 patients with skin cancer) had a history of malignancy prior to CLE diagnosis/index date. Patients with CLE were more likely to be current smokers compared with the non-CLE cohort (39.6 vs 20.6%, P = 0.001).

After excluding patients with cancer prior to CLE diagnosis, 35 patients with CLE developed new cancer over a median 14.6 years (interquartile range, 8.1–23.6 years) of follow-up. These included 11 patients with skin cancer
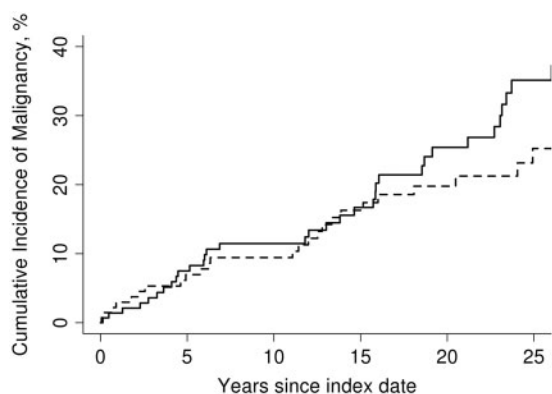
Continuous lines represent patients with CLE and dashed lines represent matched non-CLE controls. CLE: cutaneous lupus erythematosus.

(9 patients with NMSC and 2 patients with melanoma), 3 cases of haematological malignancies and 21 cases of solid-organ cancers (including 3 gastrointestinal cancers). The cumulative 10-year incidence of any cancer after diagnosis of CLE was 11.5% (Fig. 1). The risk of any cancer was not significantly different compared with the non-CLE cohort [adjusted hazard ratio (HR) = 1.29; 95% CI: 0.78, 2.13]. After excluding NMSC, the risk of any cancer was also not significantly different in patients with CLE compared with the non-CLE cohort (adjusted HR = 1.07; 95% CI: 0.61, 1.87). The cumulative 10-year incidence of any skin cancer after diagnosis of CLE was 4.3% (supplementary Fig. S1, available at *Rheumatology* Online). The risk of any skin cancer was not significantly different compared with the non-CLE cohort (adjusted HR = 2.51; 95% CI: 0.91, 6.96). Separate analysis of risk of melanoma was not feasible because of the small number of events.

In order to assess whether the extent of cutaneous involvement (as a marker of inflammatory burden) was associated with cancer risk in patients with CLE, we compared the risk of any cancer in patients with generalized *vs* localized discoid CLE. There was no significant difference in the risk of cancer in patients with generalized discoid CLE compared with localized discoid CLE (adjusted HR = 1.52; 95% CI: 0.72, 3.19).

Discussion

Chronic inflammatory diseases, such as SLE, are associated with increased risk of cancer, perhaps related to systemic immune dysregulation leading to impairment of tumour surveillance or, alternatively, to immunosuppressive therapy used to treat these conditions. CLE is a skin-limited autoimmune condition, and its treatment usually does not involve as much immunosuppressive therapy as is required for SLE. In our population-based inception cohort of 155 patients with CLE followed over 15 years, we observed that patients with CLE are not at increased risk of cancers, including skin cancers, compared with age-, sex- and calendar year-matched individuals without CLE. However, it is important to acknowledge that the number of events was small, limiting the power of the study.

Our findings are in contrast to observations from a Swedish nationwide cohort study. In their study of 3663 patients with CLE, Grönhagen and colleagues [10] identified 183 cases of cancer over a median follow-up of 4.1 years, with a significant increase in the risk of all cancers compared with matched controls without CLE (HR = 1.8; 95% CI: 1.5, 2.2). The risk for buccal cancer, respiratory cancer, lymphoma and NMSC was increased in this cohort, without a significant increase in risk of melanoma, haematopoetic and other forms of cancer. However, their case definition (single ICD-10 code for CLE) was non-validated, with potential for misclassification; 35% of patients in their CLE cohort were diagnosed with SLE (received a diagnostic code) either before (23%) or after (12%) CLE diagnosis. When patients with SLE were excluded, an increased risk of cancer persisted. Additionally, about 24% of these 'incident' cancers were diagnosed within 1 year of CLE, suggestive of diagnostic suspicion bias around the time when CLE was diagnosed. This is particularly true of NMSCs, which are diagnosed on a thorough skin examination (to which patients with CLE may be subjected). The highest relative risk was observed with buccal and respiratory cancer, both of which are smoking related; however, they were unable to adjust for smoking in their analysis. We, and others, have observed that smoking is more prevalent in patients with CLE compared with controls [17].

Our study has several strengths, which support the validity of our findings. Ours is a well-characterized population-based inception cohort of patients with CLE from a defined geographical area with a stable population, over an extended period of time. Our medical records linkage system allowed confirmation of CLE as well as cancer diagnosis through chart review, rather than relying solely on administrative diagnostic codes, minimizing the risk of misclassification. We carefully excluded patients with concomitant diagnosis of SLE. Finally, by comparing cancer risk in patients with generalized *vs* localized discoid CLE (the most common form of CLE in our cohort), we were able to estimate whether the extent of cutaneous involvement, as a possible surrogate for degree of inflammation, may influence cancer risk.

Limitations of the study include the small sample size; hence, the limited power for some detailed comparative analyses. The population of Olmsted County is predominantly Caucasian (90.3% at US 2000 census), which may limit the generalizability of the findings to other ethnicities. With increasing racial diversity in Olmsted County, it will be crucial to examine future trends. Owing to the retrospective nature of this study, we were unable to assess CLE disease activity and therapy comprehensively.

In conclusion, our findings suggest that patients with CLE are not at increased risk of cancers, including skin cancers, compared with matched controls. However, the number of events was small, limiting power of the study. Routine cancer screening practices, as in the general population, may suffice for patients with CLE, without the need for targeted surveillance.

Acknowledgements

Supplementary data

Supplementary data are available at *Rheumatology* Online.

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