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Review

Does inflammatory bowel disease coexist with systemic lupus erythematosus?

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ABSTRACT

Background: The data regarding the association between inflammatory bowel disease (IBD) and systemic lupus erythematosus (SLE) is mostly composed of case reports and case series indicating an infrequent association.
Objectives: To investigate the association between IBD and SLE.
Methods: Patients with SLE were compared with age- and sex-matched controls regarding the prevalence of ulcerative colitis (UC) and Crohn's disease (CD) in a case–control study. Chi-square and *t*-tests were used for univariate analysis and a logistic regression model was used for multivariate analysis. The study was performed utilizing the medical database of Clalit Health Services.
Results: The study included 5018 patients with SLE and 25,090 age- and sex-matched controls. The prevalence of UC was significantly higher in patients with SLE than in controls in a univariate analysis (0.4% and 0.2%, respectively; $p < 0.017$). However, in a multivariate logistic regression model SLE was not associated with UC (OR 1.67, 95% CI 0.99–2.815, $p < 0.052$). The prevalence of CD was higher in patients with SLE than in controls in a univariate analysis (0.7% and 0.3%, respectively; $p < 0.001$). A multivariate logistic regression model confirmed this finding and corroborated that SLE was associated with comorbid CD (OR 2.23, 95% CI 1.46–3.4, $p < 0.001$).
Conclusions: Patients with SLE have a greater prevalence of CD than matched controls. The distinction of IBD from SLE gastrointestinal involvement can be challenging as clinical manifestations, laboratory tests, and radiographic findings may appear similar between the two diseases. Therefore, physicians treating patients with rather IBD or SLE should consider this potential association.

Contents

1. Introduction

Inflammatory bowel disease (IBD) is a chronic recurrent disease comprised of two major phenotypes, Crohn's disease (CD) and ulcerative colitis (UC) [1]. In fact neither CD nor UC is really 'autoimmune' since each of these diseases lacks an autoimmune serological signature,

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Table 1
Descriptive characteristics of the study population (n = 30,108.)

Characteristic	Patients with SLE (n = 5018)	Controls (n = 25,090)
Age, years		
Mean ± SD	50.2 ± 17.4	50.2 ± 17.4
Male sex, n (%)	905 (21.5%)	4525 (18.04%)
SES (n = 27,366), n (%)		
Low	1995 (39.8%)	9382 (42%)
Intermediate	1926 (38.4%)	8533 (38.2%)
High	1094 (21.8%)	4436 (19.9%)
UC, n (%)	20 (0.4%)	52 (0.2%)
CD, n (%)	33 (0.7%)	65 (0.3%)

SES, socioeconomic status; UC, ulcerative colitis; CD, Crohn's disease.

yet they have kept in the autoimmune terminology because of tradition and coexistences with several examples of autoimmunity [2]. Systemic lupus erythematosus (SLE) is a chronic multisystem inflammatory disease, known as a prototype for experimental animal and human autoimmune disease [3,4].

Autoimmune diseases tend to be viewed as distinct entities. However, the 'common threads' hypothesis, proposed by Noel Rose, suggests a broader perspective which may reveal shared mechanisms and therapies for autoimmune diseases [5]. The 'common threads' hypothesis has led to an extensive research for clustering, coexistences and overlaps of autoimmune diseases, among affected individuals and their family members.

So far, the data regarding the association between IBD and SLE is mostly composed of case reports and case series which indicate an infrequent association [6]. The aim of the current study was to search for a possible coexistence between IBD and SLE in a community-based approach, utilizing the large medical database of Clalit Health Services (CHS).

2. Materials and methods

For the current study, data mining techniques utilizing the CHS database were used. CHS is the largest healthcare provider organization in Israel, serving a population of 3,800,000 enrollees. CHS has a comprehensive computerized database with continuous real-time input from pharmaceutical, medical and administrative computerized operating systems. We have previously used the CHS database to study disease associations in psoriasis and described the methodology used [7–9]. Patients were defined as having SLE when there was at least one documented diagnosis of SLE in the medical records registered by a physician in the community or when SLE was listed in the diagnoses of discharge letters from a hospital. The control group was randomly selected from the list of CHS members, excluding patients with SLE, and frequency-matched to cases regarding sex and age. Data available from the CHS database included age, sex, socioeconomic status, and diagnoses of chronic diseases, including UC and CD. These diagnoses were extracted from the CHS chronic diseases registry, based on data from hospital and primary care physicians' reports and validated by primary physicians. The validity of diagnoses in the registry was previously found to be high [8–10].

The study was approved by the institutional review board of Soroka University Medical Center.

The distribution of sociodemographic and clinical factors was compared between patients with and without IBD using Chi-square test for sex and socioeconomic status and *t*-test for age. The proportions of UC and CD were compared between the study groups in the entire study sample as well as in age, sex and socioeconomic status subgroups. Crude and Mantel–Haenszel odds ratios (ORs) as well as 95% confidence intervals (CIs) are presented. Homogeneity of ORs across strata was tested using Breslow–Day and Tarone's tests. A logistic regression model was used to estimate the association between SLE and either UC and CD in a multivariate analysis. Statistical analysis was performed using SPSS software, version 18 (SPSS, Chicago, IL, U.S.A.).

3. Results

The study included 5018 patients with SLE and 25,090 age- and sex-frequency-matched controls. Characteristics of case and control patients are described in Table 1. In Tables 2a & 2b we describe ORs for UC and CD, respectively, in patients with SLE and controls in the entire study sample, and stratified by age, sex and socioeconomic status. The prevalence of UC was significantly higher in patients with SLE than in controls in a univariate analysis (0.4% and 0.2%, respectively; $p < 0.017$) (Table 2a). However, in a multivariate logistic regression model SLE was found not to be independently associated with UC (OR 1.67, 95% CI 0.99–2.815, $p < 0.052$) (Table 3a). The proportion of CD was higher in patients with SLE than in controls in a univariate analysis (0.7% and 0.3%, respectively; $p < 0.001$) (Table 2b). Also in a multivariate logistic regression model SLE was associated with CD (OR 2.23, 95% CI 1.46–3.4, $p < 0.001$) (Table 3b). The association between SLE and CD was prominent in all age groups and in both sexes (Table 2b). The prevalence of both CD and UC was significantly higher in patients with high socioeconomic status than in patients with intermediate socioeconomic status (Tables 3a & 3b).

4. Discussion

In the current study an association between SLE and CD was observed, with a multivariate OR of 2.23 (95% CI 1.46–3.4). The proportion of CD among patients with SLE was higher than the prevalence in controls (0.7% and 0.3%, respectively; $p < 0.001$). On the contrary, no significant association was found between SLE and UC in a multivariate analysis.

It is well acknowledged that SLE tends to either coexist or overlap with several other autoimmune diseases including rheumatoid arthritis (RA), systemic sclerosis–scleroderma (SSc), polymyositis, varieties of

Table 2a
SLE and UC: stratified analysis (n = 30,108).

Subgroup	n	UC in SLE (n = 5018)	UC in control (n = 25,090)	OR (95% CI)
All	30,108	20 (0.4%)	52 (0.21%)	1.927 (1.149–3.23)
Age (years)				
0–19	912	0 (0%)	0 (0%)	–
20–39	8166	2 (0.1%)	14 (0.2%)	0.714 (0.162–3.145)
40–59	11,604	7 (0.4%)	23 (0.2%)	1.524 (0.653–3.556)
60–110	9426	11 (0.7%)	15 (0.2%)	3.685 (1.69–8.039)
Gender				
Male	5430	2 (0.2%)	7 (0.2%)	1.43 (0.296–6.892)
Female	24,678	18 (0.4%)	45 (0.2%)	2.004 (1.159–3.466)
SES (n = 27,366), n (%)				
Low	11,377	5 (0.3%)	13 (0.1%)	1.811 (0.645–5.085)
Intermediate	10,459	8 (0.4%)	19 (0.2%)	1.869 (0.817–4.276)
High	5530	7 (0.6%)	19 (0.4%)	1.497 (0.628–3.57)