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Risk of gastrointestinal events among patients with sarcoidosis: a population-based study 1976-2013

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Abstract. *Background:* An increased risk of gastrointestinal (GI) diseases has been observed in immune-mediated disease but the risk in patients with sarcoidosis is not known. *Objectives:* This study was undertaken to characterize the risk of GI diseases in patients with sarcoidosis. *Methods:* A population-based cohort of 345 incident cases of sarcoidosis among Olmsted County, Minnesota residents in 1976-2013 was identified. A cohort of 345 sex and age-matched comparators were also identified from the same underlying population. Medical records of both groups were reviewed for GI diseases. Cox models adjusted for age, sex and calendar year were used to compare the rate of development of GI diseases between the groups. In addition, Cox models were used to evaluate the association between use of immunosuppressive agents and the development of GI diseases among patients with sarcoidosis. *Results:* GI events occurred in 101 cases and 63 comparators, corresponding to an adjusted hazard ratio (HR) of 1.90 (95% confidence interval [CI] 1.38-2.61). Patients with sarcoidosis had an increased risk for both upper (HR 1.90; 95%CI 1.27-2.83) and lower GI events (HR 1.97; 95%CI 1.27-3.05) relative to comparators. By disease type, patients with sarcoidosis had a significantly elevated risk of upper GI ulcer, upper GI hemorrhage and diverticulitis. Regarding medication use, the only significant association was an increased risk of upper GI events among biologic agent users (HR 11.09; 95%CI 2.16-56.97). *Conclusion:* Patients with sarcoidosis have a higher risk of both upper and lower GI events compared with subjects without sarcoidosis. *(Sarcoidosis Vasc Diffuse Lung Dis 2018; 35: 239-244)*

Key words: sarcoidosis, epidemiology, gastrointestinal disease

Introduction

Gastrointestinal (GI) disease is a common comorbidity seen in patients with immune-mediated diseases. The incidence and prevalence of GI diseases is increased in a number of these diseases such as rheumatoid arthritis and psoriasis (1-3). Use of medications, particularly glucocorticoids and non-steroidal anti-inflammatory drugs (NSAIDs), is believed to be the major factor for the increased risk (4, 5).

Sarcoidosis is an immune-mediated disorder characterized by the presence of non-caseating granuloma. Incidence of sarcoidosis varies considerably across ethnic groups with the highest incidence seen in African-Americans (6, 7). Sarcoidosis can affect virtually any organ, with lungs and mediastinal/hilar lymph nodes being the most commonly affected sites. Commonly affected extra-thoracic organs include skin, eye, joint and liver (8, 9).

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Little is known about the risk of GI diseases in patients with sarcoidosis. To address this question, a previously identified cohort of residents of Olmsted County, Minnesota (MN) who were diagnosed with incident sarcoidosis between 1976 and 2013 (10) was studied to compare the incidence of GI events with a sex and age-matched cohort of comparators randomly selected from the same underlying population.

Methods

Participants and study design

This retrospective cohort study utilized the medical record-linkage system of the Rochester Epidemiology Project (REP) to identify potential cases of sarcoidosis from 1976 to 2013 using diagnosis codes related to sarcoid, sarcoidosis, and contextual non-caseating granuloma. The REP is a unique medical record-linkage system that provides comprehensive access to medical records from all local health care providers, including the Mayo Clinic, the Olmsted Medical Center and their affiliated hospitals, local nursing homes and the few private practitioners for all residents of Olmsted County, MN seeking medical care for over six decades. The history and use of REP for epidemiologic study has previously been described (11).

Medical records of these potential cases with the aforementioned diagnostic codes were individually reviewed to verify the diagnosis of sarcoidosis. Inclusion into this cohort required physician diagnosis supported by presence of non-caseating granuloma on biopsy, radiologic evidence of intrathoracic sarcoidosis, compatible clinical presentation and exclusion of other causes of granuloma such as tuberculosis and fungal infection. The only exception to the requirement of histopathology was stage I pulmonary sarcoidosis that required only symmetric bilateral hilar adenopathy on thoracic imaging study without any other known etiologies. Isolated extra-thoracic sarcoidosis of a specific organ without intra-thoracic sarcoidosis was also included (except for isolated skin disease) if there was no better explanation for the presence of granuloma. Prevalent cases (i.e., cases with diagnosis of sarcoidosis prior to residency in Olmsted County) were excluded. This approach allows comprehensive identification of essentially all clinically recognized cases of sarcoidosis in the community.

For each sarcoidosis patient, a sex and age (within 3 years)-matched comparator without sarcoidosis at the time of the patient's sarcoidosis diagnosis was randomly selected from the same underlying population. The index date of the comparator was the same date as the date of sarcoidosis diagnosis of the corresponding case. Medical records of cases and comparators were individually reviewed for GI events. The following upper GI events were ascertained: ulcer, bleeding, obstruction, perforation, esophagitis and esophageal varices. The following lower GI events were ascertained: ulcer, bleeding, obstruction, perforation, diverticulitis and various types of colitis (ischemic colitis, infectious colitis, drug-induced colitis, other colitis and ulcerative colitis/Crohn's disease). Functional GI disorders (functional dyspepsia, gastroesophageal reflux and irritable bowel syndrome), hemorrhoid, hemorrhoid bleeding, appendicitis and asymptomatic diverticular disease were not included in this analysis. Data on treatment with glucocorticoids, disease modifying anti-rheumatic drugs (DMARDs) and biologic agents among cases were also collected.

This study was approved by the Mayo Clinic and the Olmsted Medical Center Institutional Review Boards (Mayo Clinic IRB 14-008651, Olmsted Medical Center IRB 012-OMC-15).

Statistical analysis

Descriptive statistics (percentages, mean, etc.) were used to summarize the characteristics of cases and comparators. Comparisons between the cohorts were performed using Chi-square, Fisher's exact and rank sum tests. The cumulative incidence of the first GI event (overall and by type) adjusted for the competing risk of death was estimated (12). These methods are similar to the Kaplan-Meier method with censoring of patients who are still alive at last follow-up. However, patients who die before experiencing GI diseases are appropriately accounted for to avoid overestimation of the rate of occurrence of GI diseases, which can occur if such subjects are simply censored at death. For the estimation of the overall cumulative incidence of GI events, the date of occurrence was the earliest date of occurrence of any of the individual types of GI events.

Cox proportional hazards models were used to compare the rate of development of GI diseases between patients with sarcoidosis and non-sarcoidosis comparators. In addition, Cox proportional hazards models were used to evaluate the association between use of immunosuppressive agents as well as presence of extra-thoracic disease and the development of GI diseases among patients with sarcoidosis. Exposure to immunosuppressive agents was modeled using time-dependent covariates which changed from unexposed to exposed at the time of initiation of the first immunosuppressive agent. A p-value of less than 0.05 was considered statistically significant for all analyses. 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).

Results

A total of 345 incidental cases of sarcoidosis (mean age 45.6 years, 50% female, 90% Caucasian and 5% African-American) and 345 comparators (mean age 45.4 years, 50% female, 95% Caucasian and 1% African-American) were identified. Baseline characteristics of the cohorts are described in table 1. The median length of follow-up for cases and comparators were 13.6 years and 15.9 years, respectively.

At diagnosis/index date, the prevalence of GI diseases was not significantly different between cases and comparators (p=0.90). After diagnosis/index date, GI events occurred in 101 cases and 63 comparators, corresponding to the adjusted hazard ratio (HR) of 1.90 (95% confidence interval [CI], 1.38-2.61). Analysis by location revealed an increased risk of GI events in patients with sarcoidosis compared with subjects without sarcoidosis for both upper GI events (HR 1.90; 95% CI, 1.27-2.83) as well as lower GI events (HR 1.97; 95% CI, 1.27-3.05). Analysis by specific type of GI disease revealed a significantly elevated risk of upper GI ulcer, upper GI hemorrhage and diverticulitis. The number of GI events, cumulative incidence at 10 years and HR of overall and specific types of GI events are shown in table 2.

Less than half of all patients with sarcoidosis required use of systemic glucocorticoids, DMARDs and/or biologic agents at some point during follow-up (151 cases, 37% by 30 years after sarcoidosis diagnosis). Oral glucocorticoids were the most commonly prescribed drug (113 cases) followed by hydroxychloroquine (13 cases), methotrexate (11 cases), other DMARDs (5 cases), tumor-necrosis factor (TNF) inhibitor (5 cases) and other biologic agents (4 cases). No significant association between use of the medications and risk of GI events was observed except for a significantly increased risk of upper GI events among biologic agent users (HR 11.09; 95%

Table 1. Baseline characteristics of patients with sarcoidosis and comparators without sarcoidosis

	Cases (N=345)	Comparators (N=345)	P value
Mean age at diagnosis/index date in years (SD)	45.6 (13.6)	45.4 (13.7)	0.87
Female	50%	50%	1.0
Race			<0.001
Caucasian	90%	95%	
African-American	5%	1%	
Asian	2%	0%	
Native American	1%	0%	
Other	2%	4%	
Median length of follow-up in years (IQR)	13.6 (6.3, 24.1)	15.9 (6.9, 25.9)	
Smoking status at diagnosis/index date			<0.001
Never	60%	42%	
Ex-smoker	21%	22%	
Current smoke	19%	36%	
Mean body mass index in kg/m^2 (SD)	30.1 (7.5)	27.4 (5.6)	<0.001

SD, standard deviation; IQR, interquartile range

Table 2. Numbers of patients with a gastrointestinal disease, cumulative incidence at 10 years and hazard ratio of overall and specific types of infection comparing patients with sarcoidosis with subjects without sarcoidosis

Comorbidity	Prior to non-Sarcoidosis index/ Sarcoidosis incidence date, no.	p-value comparing prior events*	Number of events after incidence/ index in non-Sarcoidosis/ Sarcoidosis	Cumulative incidence at 10 years for non-sarcoidosis subjects (± SE)**	Cumulative incidence at 10 years for Sarcoidosis patients (± SE)**	Hazard ratio (95% CI)***	p-value
Any GI events	38/40	0.90	63/101	11.3 (7.3 , 15.2)	22.1 (16.8 , 27.1)	1.90 (1.38 , 2.61)	<0.001
Any upper GI events	27/25	0.88	38/68	7.1 (4.0 , 10.2)	13.0 (8.8 , 17.0)	1.90 (1.27 , 2.83)	0.002
Any Lower GI events	11/16	0.43	32/54	4.3 (1.9 , 6.7)	9.6 (6.0 , 13.0)	1.97 (1.27 , 3.05)	0.002
Upper GI diagnoses							
Upper ulcer	21/19	0.87	11/27	1.9 (0.2 , 3.6)	4.5 (2.0 , 6.8)	2.56 (1.27 , 5.17)	0.009
Upper bleed	6/14	0.11	14/29	0.9 (0.0 , 2.0)	4.4 (1.9 , 6.9)	2.36 (1.24 , 4.47)	0.009
Upper perforation	2/0	0.50	0/1	--	--	--	--
Upper obstruction	1/3	0.62	7/8	1.4 (0.0 , 2.7)	0.3 (0.0 , 0.9)	1.20 (0.43 , 3.32)	0.72
Esophagitis	7/4	0.55	18/27	3.6 (1.4 , 5.8)	5.4 (2.7 , 8.1)	1.58 (0.87 , 2.88)	0.13
Esophageal varices	0/3	0.25	1/6	0.0 (0.0 , 0.0)	0.7 (0.0 , 1.8)	6.51 (0.78 , 54.16)	0.083
Lower GI diagnoses							
Lower ulcer	2/1	1.0	2/7	0.6 (0.0 , 1.4)	1.4 (0.0 , 2.8)	3.51 (0.73 , 16.92)	0.12
Lower bleed	5/3	0.72	12/15	1.8 (0.2 , 3.3)	2.9 (1.0 , 4.8)	1.32 (0.62 , 2.82)	0.48
Lower perforation	0/0	--	2/1	--	--	--	--
Lower obstruction	0/2	0.50	1/2	--	--	--	--
Diverticulitis	3/2	1.0	9/18	0.4 (0.0 , 1.1)	2.3 (0.6 , 4.0)	2.29 (1.03 , 5.10)	0.043
Ischemic colitis	2/0	0.50	3/7	0.0 (0.0 , 0.0)	0.6 (0.0 , 1.5)	2.38 (0.61 , 9.26)	0.21
Infectious colitis (including c diff)	1/5	0.22	7/13	0.6 (0.0 , 1.5)	2.9 (0.9 , 4.9)	1.99 (0.79 , 5.00)	0.14
Drug-induced colitis	0/0	--	0/0	--	--	--	--
Other colitis	1/1	1.0	2/2	--	--	--	--
Inflammatory bowel disease	2/2	1.0	1/3	--	--	--	--

* Fisher's exact test
**Cumulative incidence is adjusted for the competing risk of death.
***adjusted for age, sex and calendar year of Sarcoidosis/index date
SE, standard error; CI, confidence interval; GI, gastrointestinal

CI, 2.16-56.97). HR and 95% CI of use of other medications and GI events are as follows: HR 1.42 (95% CI, 0.84-2.41) for glucocorticoids and upper GI events; HR 1.37 (95% CI, 0.78-2.39) for glucocorticoids and lower GI events; HR 1.36 (95% CI, 0.38-4.84) for DMARDs and upper GI events; HR 0.68 (95% CI, 0.14-3.29) for DMARDs and lower GI events; and HR 1.78 (95% CI, 0.20-15.74). Analysis by baseline characteristics of sarcoidosis demonstrated that presence of extra-thoracic sarcoidosis was predictive of upper GI events (HR 1.76; 95% CI, 1.09-2.85).

Discussion

The current study is the first study using a population-based cohort of patients with sarcoidosis to determine the risk of GI diseases. An increased risk of GI events compared with sex and age-matched subjects was demonstrated for both upper and lower GI events.

The increased risk of upper GI events seems to be primarily driven by the increased risk of upper GI ulcer and upper GI hemorrhage. One potential explanation for this observation is the use of non-steroidal anti-inflammatory drugs (NSAIDs), which are a commonly used medication for treatment of sarcoidosis, particularly for musculoskeletal symptoms (13). NSAIDs predispose patient to gastric and duodenal ulcer through inhibition of cyclooxygenase-1 (COX-1) enzyme, resulting in decreased production of prostaglandins which are vital for the integrity of the mucosa (14). The role of NSAIDs in the initiation and perpetuation of peptic ulcer has long been recognized by epidemiologic studies (15). Unfortunately, data on use of NSAIDs was not available in this cohort and, therefore, this hypothesis could not

be formally analyzed. Of the 3 groups of medications analyzed in this study, use of biologic agents was a significant predictor for upper GI events. Since most of biologic agents used in this cohort were TNF inhibitors and upper GI ulcer/hemorrhage is not a known adverse effect of their use (16), it is unlikely that the observed association was causal. It is more likely that use of TNF inhibitors are a marker of more severe disease. The presence of extra-thoracic disease was a significant predictor of upper GI events in this cohort.

The increased risk of lower GI events appears to be primarily driven by the increased risk of diverticulitis. Increased risk of infection is a well-known complication of glucocorticoids due to their immunosuppressive effect (17, 18) which may explain the increased incidence of diverticulitis in patients with sarcoidosis. Another possible explanation is related to physical inactivity and obesity which are known risk factors for diverticular disease (19, 20). Chronic fatigue is a well-established manifestation of sarcoidosis (21) and may predispose patients to less physical activity and, subsequently, obesity. In fact, the mean body mass index of patients with sarcoidosis in this cohort was significantly higher than comparators (table 1).

The major strength of this study is that it is a population-based study. The medical record-linkage database of the REP allows capture of nearly all the clinically recognized cases of sarcoidosis in the community, which minimizes the likelihood of referral bias, a common concern for studies using referral-based cohorts. The duration of follow-up was also long which allows captures of the events of interest that occurred long after the index date. The diagnosis of both sarcoidosis and GI diseases were verified by individual medical record review, which minimizes the likelihood of misclassification, a common concern for studies relying on diagnostic codes of administrative databases.

The current study has some limitations associated with the retrospective nature of the study. Clinical information were obtained and recorded at discretion of physicians who saw the patients without a specific protocol. Thus, some of the pertinent data might not be available. Generalizability of the results to other populations could be limited as the clinical manifestation and severity of sarcoidosis varies between ethnic groups (8, 23) and the vast majority of population of Olmsted County is of northern European ancestry. Moreover, there are a high proportion of workers in the healthcare industry who may have a different pattern of healthcare utilization from the general population.

Conclusion

Patients with sarcoidosis have a higher risk of both upper and lower GI events compared with subjects without sarcoidosis.

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Authors' contributions:
All authors had access to the data and a role in writing the manuscript.

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