Published in final edited form as:

J Eur Acad Dermatol Venereol. 2016 October ; 30(10): 1799–1804. doi:10.1111/jdv.13760.

Epidemiology of Cutaneous Sarcoidosis, 1976–2013: A Population Based Study from Olmsted County, Minnesota

P. Ungprasert, MD^{1,*}, D.A. Wetter, MD², C.S. Crowson, MS^{1,3}, and E.L. Matteson, MD, MPH¹

¹Division of Rheumatology, Department of Internal Medicine, Mayo Clinic College of Medicine, Rochester, MN 55905, USA

²Department of Dermatology, Mayo Clinic College of Medicine, Rochester, MN 55905, USA

³Division of Biomedical Statistics and Informatics, Department of Health Sciences Research, Mayo Clinic College of Medicine, Rochester, MN 55905, USA

⁴Division of Epidemiology, Department of Health Sciences Research, Mayo Clinic College of Medicine, Rochester, MN 55905, USA

Abstract

Background—The epidemiology of cutaneous sarcoidosis is not well-characterized as only referral-based studies are available.

Objectives—To characterize the epidemiology of cutaneous sarcoidosis, with emphasis on annual incidence and clinical characteristics, from 1976 to 2013.

Methods—Inception cohorts of patients with incident isolated cutaneous sarcoidosis and incident systemic sarcoidosis with cutaneous involvement in 1976–2013 in Olmsted County, Minnesota, United States were identified based on comprehensive individual medical record review. Inclusion in the isolated cutaneous sarcoidosis cohort required physician diagnosis and skin biopsy showing non-necrotizing granuloma. Inclusion in the systemic sarcoidosis with cutaneous involvement cohort required presence of systemic sarcoidosis and cutaneous lesions. Presence of systemic sarcoidosis was determined by physician diagnosis supported by histopathology of non-necrotizing granuloma, characteristic radiologic features of intrathoracic sarcoidosis and exclusion of other granulomatous diseases. Cutaneous lesions were defined as either sarcoidosis-specific or non-specific.

*Corresponding author; P.U.: P.Ungprasert@gmail.com; Ungprasert.Patompong@mayo.edu, Division of Rheumatology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA. Tel 507-284-8450 Fax 507-284-0564.

Conflict of interest statement for all authors: We do not have any financial or non-financial potential conflicts of interest.

Author contribution:

Patompong Ungprasert: 1. Conception and design 2. Acquisition and interpretation of data 3. Drafting of the manuscript 4. Statistical analysis

David A. Wetter: 1. Conception and design 2. Acquisition and interpretation of data 3. Critical revision of the manuscript for important intellectual content 4. Supervision

Cynthia S. Crowson: 1. Conception and design 2. Analysis and interpretation of data 3. Critical revision of the manuscript for important intellectual content 4. Statistical analysis

Eric L. Matteson: 1. Conception and design 2. Acquisition and interpretation of data 3. Critical revision of the manuscript for important intellectual content 4. Statistical analysis 5. Supervision

Patompong Ungprasert and Cynthia S. Crowson had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Results—There were 62 cases with sarcoidosis-specific cutaneous lesions (36 cases of sarcoidosis-specific cutaneous lesions and 26 cases of isolated cutaneous sarcoidosis) which corresponded to an incidence of 1.9 per 100,000 population. The female to male ratio was 2.1:1. Plaques, papules and subcutaneous nodules were the most commonly observed cutaneous lesions. There was no significant difference in cutaneous presentation between those who had isolated skin disease and those who had skin disease in association with systemic sarcoidosis. Prognosis of cutaneous sarcoidosis was favorable as over 90% of patients had a good response to either glucocorticoids, hydroxychloroquine or tetracycline antibiotics. This study has a significant limitation that the studied population was predominantly Caucasian who generally have a lower prevalence of skin disease.

Conclusions—The incidence of sarcoidosis-specific cutaneous lesions was about 1.9 per 100,000 population with female predominance. The cutaneous presentations were similar among those with and without systemic sarcoidosis.

Keywords

Sarcoidosis; Epidemiology; Incidence

Introduction

Sarcoidosis is a chronic granulomatous disease characterized by the presence of non-necrotizing granuloma. The most common site of involvement is the lungs and hilar lymph nodes. However, sarcoidosis virtually can affect any organ and sometimes poses a great diagnostic challenge.^{1, 2}

Skin is one of the most common sites of extra-thoracic involvement of sarcoidosis. Cutaneous sarcoidosis is typically categorized into isolated cutaneous sarcoidosis and cutaneous manifestations associated with systemic sarcoidosis. The latter is also usually subdivided into specific and non-specific lesions based on the presence of non-necrotizing granuloma.^{3, 4}

The epidemiology of cutaneous sarcoidosis is not well-characterized as most of the previous studies were based on referral-based cohorts that do not provide incidence data and may not represent the true spectrum of the disease in the community.^{5–9} The objective of this study was to describe the epidemiology of cutaneous sarcoidosis in a geographically well-defined population of patients.

Methods

Data source and study population

Through the resources of the Rochester Epidemiology Project (REP), the population of Olmsted County, Minnesota, is well suited for investigation of the epidemiology of cutaneous sarcoidosis because of the availability of complete medical records for all residents seeking medical care for over six decades. This medical record linkage system allows access to the records from all local health care providers. This system allows a virtually complete ascertainment of all clinically recognized cases of cutaneous sarcoidosis

among the residents of Olmsted County, Minnesota.^{10, 11} Approval for this study was obtained from the Mayo Clinic and Olmsted Medical Center institutional review boards and the need for informed consent was waived.

Study design

Two cohorts containing Olmsted County, Minnesota residents diagnosed with sarcoidosis between January 1, 1976 and December 31, 2013 were identified. The first cohort included patients with isolated cutaneous sarcoidosis. The second cohort included patients with systemic sarcoidosis with cutaneous involvement. Potential cases were initially identified using diagnosis codes related to sarcoidosis and then underwent comprehensive individual medical record review. Cases with a diagnosis of sarcoidosis prior to residency in Olmsted County were excluded.

Inclusion in the isolated cutaneous sarcoidosis cohort required physician diagnosis and skin biopsy showing non-necrotizing granuloma without evidence of acid-fast bacilli or fungi. Patients in this cohort did not have any evidence of other organ involvement by sarcoidosis at diagnosis and during follow-up.

Inclusion in the systemic sarcoidosis with cutaneous involvement cohort required the presence of systemic sarcoidosis and cutaneous lesions which could be either sarcoidosis specific lesions or erythema nodosum (EN). Presence of systemic sarcoidosis was determined by physician diagnosis supported by histopathology of non-necrotizing granuloma without evidence of acid-fast bacilli or fungi; characteristic radiologic features of intrathoracic sarcoidosis; compatible clinical presentation; and exclusion of other granulomatous diseases. Patients in this group were further categorized as those with only EN and those with sarcoidosis specific lesions (with or without EN).

Statistical analysis

Descriptive statistics were used to summarize the data from each cohort which were then compared using chi-square and rank sum tests. Age- and sex-specific incidence rates were calculated by dividing the number of incident cases by population estimates for adults (age 18 years) based on decennial census counts, with linear interpolation to estimate population size for intercensal years. Overall incidence rates were age- and/or sex-adjusted to the 2010 white population of the United States. Trends in incidence rates were examined using Poisson regression with smoothing splines for age and calendar year. The annual incidence rates were graphically illustrated using a 3-year, centered, moving average to reduce random fluctuations over time.

Mortality rates were estimated using the Kaplan-Meier method and compared to expected mortality for persons of the same age, sex and calendar year estimated using Minnesota population life tables. The standardized mortality rate (SMR) was estimated as the ratio of the observed and expected number of deaths

Results

A total of 345 incident cases of systemic sarcoidosis were identified in 1976–2013 (mean age at incidence 45.6 years, female 50%, white 90%). Of these, 62 (18%) had cutaneous involvement including 36 with sarcoidosis-specific lesions (mean age 44.0 years, female 69%, white 71%); 26 had only EN (mean age 42.4 years, female 69%, white 96%). There were 26 incident cases of isolated cutaneous sarcoidosis (mean age 46.1 years; female 65%, white 92%). Age was similar across the groups, but the percentage of females was significantly higher in patients with cutaneous sarcoidosis compared with the systemic sarcoidosis patients without cutaneous involvement ($P<0.001$).

Among patients with systemic sarcoidosis with cutaneous involvement, skin lesions were often the initial presentation. A diagnosis of skin disease was present in 47% of patients in the sarcoidosis-specific lesions cohort and 38% of patients in the EN cohort prior to the diagnosis of systemic sarcoidosis.

The annual age- and sex-adjusted incidence of sarcoidosis-specific skin lesions in 1976–2013 was 1.9 per 100,000 population (1.1 per 100,000 population for systemic sarcoidosis with a sarcoidosis-specific cutaneous lesions and 0.8 per 100,000 population for isolated cutaneous sarcoidosis), and incidence of systemic sarcoidosis with EN was 0.8 per 100,000 population (Table 1 and Figure 1).

Plaques (35%) and papules (31%) were the most commonly observed cutaneous lesions in patients with isolated cutaneous sarcoidosis (Table 2). Lower extremities (38%), head/neck (35%) and upper extremities (31%) were the most commonly affected areas. Subcutaneous nodules (33%) were the most common type of lesions seen in patients with systemic sarcoidosis with sarcoidosis-specific cutaneous lesions (Table 2). The lesions usually affected the lower extremities (42%), head/neck (42%) and upper extremities (25%).

Skin biopsy revealed non-necrotizing lesions in all patients in the isolated cutaneous sarcoidosis group (by definition). Skin biopsy was also performed in the majority of patients in systemic sarcoidosis with sarcoidosis-specific cutaneous lesions (31/36 cases), and typical sarcoidal granuloma was found in about 90% of these. Only 3 patients in the EN group underwent skin biopsy and all 3 had septal panniculitis.

Oral glucocorticoid was the most frequently used medication to treat systemic sarcoidosis with sarcoidosis-specific cutaneous lesions (36%) (Table 2). In contrast, systemic glucocorticoids were infrequently used in isolated cutaneous sarcoidosis (8%); most were most commonly treated with topical glucocorticoids (38%; Table 2).

Response to treatments was favorable with complete response by 2 years after diagnosis in 84% of systemic sarcoidosis with sarcoidosis-specific cutaneous lesions, 96% of systemic sarcoidosis with EN and 96% of isolated cutaneous sarcoidosis. The median time from the first appearance of cutaneous lesions to resolution was 4.4, 1.6 and 4.4 months for the three cohorts, respectively (Figure 2).

Two patients died during a mean follow-up of 13.4 years (830 total person-years) in the two cohorts of isolated cutaneous sarcoidosis and systemic sarcoidosis with sarcoidosis-specific cutaneous lesions combined. The standardized mortality ratio was 0.23 (95% CI: 0.03–0.84).

Discussion

The reported prevalence of skin disease among patients with systemic sarcoidosis varies from 9% to 37%,^{5, 12–14} depending on the studied population. In the current study, approximately 10% of patients with systemic sarcoidosis had sarcoidosis-specific cutaneous lesions, which was lower than most studies. The fact that the population of Olmsted County is predominately Caucasian likely accounts for this lower prevalence as most previously published cohorts had higher frequencies of black patients.^{13, 14} However, as also described in other studies, in the current study there was a higher prevalence of sarcoidosis-specific cutaneous lesions among African-Americans compared with Caucasians (33% vs 8%). Furthermore, the cohorts of patients with sarcoidosis-specific cutaneous disease had a higher female to male ratio compared with patients with sarcoidosis without cutaneous lesions (2.1:1 vs 0.9:1), which might indicate a true difference of cutaneous manifestations or might reflect different patterns of health-care utilization between the two sexes.

Plaques, papules and subcutaneous nodules were the most common types of skin lesions observed in both the isolated cutaneous sarcoidosis cohort and in the systemic sarcoidosis with sarcoidosis-specific cutaneous lesions cohort. Classic sarcoidosis-specific lesions such as tattoo/scar sarcoidosis and lupus pernio were less commonly observed. Distribution of the skin lesions was similar in both cohorts.

Interestingly, the SMR of those with sarcoidosis-specific cutaneous lesions was lower than the general population. The reasons for this are unclear. It may be that these patients may have higher rates of healthcare visits and better health-related outcomes.

The major strengths of this study are that it is population-based with a long median duration of follow-up of over 10 years. This approach allows capture of the complete spectrum of the disease and minimizes referral bias. Diagnoses were verified by medical record and histopathology report review, which would minimize the likelihood of misclassification, a common concern in coding-based studies.

The major limitations are those inherent in retrospective studies. The population of Olmsted County is predominately of Northern European ancestry. The healthcare system in Olmsted County is relatively unified and there is a higher proportion of health-care workers and correspondingly higher education level in this population, which might affect disease detection and adherence/response to treatment.

Conclusion

The incidence of sarcoidosis-specific cutaneous lesions is about 1.9 per 100,000 population with female predominance. Cutaneous presentations were similar among those with and without systemic sarcoidosis.

Acknowledgments

We certify that the manuscript represents valid work and that neither this manuscript nor one with substantially similar content under their authorship has been published or is being considered for publication elsewhere.

Funding: This study was made possible using the resources of the Rochester Epidemiology Project, which is supported by the National Institute on Aging of the National Institutes of Health under Award Number R01 AG034676, and CTSA Grant Number UL1 TR000135 from the National Center for Advancing Translational Sciences (NCATS), a component of the National Institutes of Health (NIH). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

1. Thomas KW, Hunninghake GW. Sarcoidosis. *JAMA*. 2003; 289:3300–3303. [PubMed: 12824213]
2. Chen ES, Moller DR. Etiology of sarcoidosis. *Clin Chest Med*. 2008; 29:365–377. [PubMed: 18539232]
3. Wanat KA, Rosenbach M. A practical approach to cutaneous sarcoidosis. *Am J Clin Dermatol*. 2014; 15:283–297. [PubMed: 24820822]
4. Rosenbach M, Yeung H, Chu E, et al. Reliability and convergent validity of the cutaneous sarcoidosis activity and morphology instrument for assessing cutaneous sarcoidosis. *JAMA Dermatol*. 2013; 149:550–556. [PubMed: 23677081]
5. Yanardag H, Pamuk ON, Karayel T. Cutaneous involvement in sarcoidosis: analysis features in 170 patients. *Resp Med*. 2003; 97:978–982.
6. Chong WS, Tan HH, Tan SH. Cutaneous sarcoidosis in Asians: a report of 25 patients from Singapore. *Clin Dermatol*. 2005; 30:120–124.
7. Jacyk WK. Cutaneous sarcoidosis in black South Africans. *Int J Dermatol*. 1999; 38:841–845. [PubMed: 10583617]
8. Tong C, Zhang X, Dong J, He Y. Comparison of cutaneous sarcoidosis with systemic sarcoidosis: a retrospective analysis. *Int J Clin Exp Pathol*. 2014; 7:372–377. [PubMed: 24427359]
9. Henke CE, Henke G, Elveback LR, Beard CM, Ballard DJ, Kurland LT. The epidemiology of sarcoidosis in Rochester Minnesota: A population-based study of incidence and survival. *Am J Epidemiol*. 1986; 123:840–845. [PubMed: 3962966]
10. Rocca WA, Yawn BP, StSauver JL, Grossardt BR, Melton LJ III. History of the Rochester Epidemiology Project: Half a century of medical records linkage in a U.S. population. *Mayo Clin Proc*. 2012; 87:1202–1213. [PubMed: 23199802]
11. Melton LJ 3rd. History of the Rochester Epidemiology Project. *Mayo Clin Proc*. 1996; 71:266–274. [PubMed: 8594285]
12. Marchell RM, Judson MA. Cutaneous sarcoidosis. *Semin Resp Crit Care Med*. 2010; 31:442–451.
13. Baughman RP, Teirstein AS, Judson MA, et al. Case Control Etiologic Study of Sarcoidosis (ACCESS) research group. Clinical characteristics of patients in a case control study of sarcoidosis. *Am J Respir Crit Care Med*. 2001; 164(10 Pt 1):1885–1889. [PubMed: 11734441]
14. Benatar SR. Sarcoidosis in South Africa: a comparative study in whites, blacks and coloured. *S Afr Med J*. 1977; 52:602–606. [PubMed: 918803]

Figure 1.

Incidence rates of isolated cutaneous sarcoidosis (Panel A), systemic sarcoidosis with sarcoidosis-specific skin lesions (Panel B), and systemic sarcoidosis without specific skin lesion (i.e. with erythema nodosum only; Panel C) according to calendar time by sex (women shown with solid line and open circles; men shown with dashed line and squares).

Figure 2.

Cumulative incidence of resolution of Olmsted County, MN residents with incident cutaneous sarcoidosis in 1976–2013 by group (isolated cutaneous sarcoidosis [solid line] and systemic sarcoidosis with sarcoidosis-specific skin lesions [dashed line] and systemic sarcoidosis without specific skin lesion (i.e. with EN only) [dotted line]).

Table 1

Incidence rate of isolated cutaneous sarcoidosis, systemic sarcoidosis with sarcoidosis-specific cutaneous lesions and systemic sarcoidosis with erythema nodosum in 1976–2013 among adult (age 18 years) residents of Olmsted County, MN, by sex and age

Isolated cutaneous sarcoidosis						Systemic sarcoidosis with sarcoidosis-specific cutaneous lesions						Systemic sarcoidosis with erythema nodosum						
Age group	Females		Males		Total	Females		Males		Total	Females		Males		Total			
	N	Rate	N	Rate	N	N	Rate	N	Rate	N	N	Rate	N	Rate	N			
18–29	1	0.2	2	0.5	3	0.4	1	0.2	3	0.8	4	0.5	3	0.7	1	0.3	4	0.5
30–39	2	0.6	3	0.9	5	0.7	7	2.0	2	0.6	9	1.3	4	1.1	4	1.1	8	1.1
40–49	7	2.3	2	0.7	9	1.5	7	2.3	5	1.7	12	2.0	6	2.0	3	1.0	9	1.5
50–59	4	1.7	0	0.0	4	0.9	8	3.4	0	0.0	8	1.7	3	1.3	0	0.0	3	0.6
60–69	1	0.6	2	1.4	3	1.0	2	1.2	1	0.7	3	1.0	1	0.6	0	0.0	1	0.3
70–79	2	1.7	0	0.0	2	1.0	0	0.0	0	0.0	0	0.0	1	0.9	0	0.0	1	0.5
80+	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Total	17	1.1*** (0.6, 1.6)	9	0.6*** (0.2, 0.9)	26	0.8*** (0.5, 1.2)	25	1.6*** (0.9, 2.2)	11	0.7*** (0.3, 1.0)	36	1.1*** (0.7, 1.5)	18	1.1*** (0.6, 1.6)	8	0.5*** (0.1, 0.7)	26	0.8*** (0.5, 1.0)

* Rate per 100,000 population

** Age-adjusted to the US white 2010 population

*** Age- and sex-adjusted to the US white 2010 population

Table 2

Demographics, clinical characteristics and treatment of patients with cutaneous sarcoidosis

	Number (%) of patients		
	Isolated cutaneous sarcoidosis (N=26)	Systemic sarcoidosis with sarcoidosis-specific cutaneous lesions (N=36)	Systemic sarcoidosis with erythema nodosum (N=26)
Demographics			
Mean age at diagnosis + SD (years)	46.1 + 14.2	44.0 + 11.1	42.4 + 12.1
Female	17 (65)	25 (69)	18 (69)
<i>Race</i>			
Caucasian	24 (92)	24 (71)	22 (96)
African American	1 (4)	6 (18)	0 (0)
Asian	1 (4)	2 (6)	0 (0)
Other	0 (0)	2 (6)	1 (4)
Unknown	0	2	3
Clinical characteristics			
<i>Lesion morphology</i>			
Plaques	9 (35)	7 (19)	N.A.
Subcutaneous nodules	7 (27)	12 (33)	N.A.
Papules	8 (31)	11 (31)	N.A.
Lupus pernio	1 (4)	4 (11)	N.A.
Scar lesions	3 (12)	3 (8)	N.A.
Tattoo lesions	1 (4)	1 (3)	N.A.
Ulcers	0 (0)	3 (8)	N.A.
Erythema nodosum	0 (0)	4 (11)	26 (100)
<i>Distribution</i>			
Upper extremities	8 (31)	9 (25)	1 (4)
Lower extremities	10 (38)	15 (42)	24 (92)
Head/neck	9 (35)	15 (42)	0 (0)
Trunk	2 (8)	5 (14)	0 (0)
Hands	2 (8)	2 (6)	2 (8)
Feet	5 (19)	4 (11)	3 (12)
<i>Skin biopsy</i>			
Sarcoidal granuloma	26 (100)	28 (78)	0 (0)
Septal panniculitis	0 (0)	0 (0)	3 (12)
Other	0 (0)	3 (8)	0 (0)
Not performed	0 (0)	5 (14)	23 (88)
Treatment			
Oral glucocorticoid	2 (8)	13 (36)	7 (27)
Topical glucocorticoid	10 (38)	10 (28)	0 (0)
Intralesional glucocorticoid	0 (0)	6 (17)	0 (0)

	Number (%) of patients		
	Isolated cutaneous sarcoidosis (N=26)	Systemic sarcoidosis with sarcoidosis-specific cutaneous lesions (N=36)	Systemic sarcoidosis with erythema nodosum (N=26)
Topical calcineurin inhibitor	1 (4)	5 (14)	0 (0)
Oral NSAIDs	0 (0)	1 (3)	15 (58)
Methotrexate	0 (0)	2 (6)	0 (0)
Hydroxychloroquine	2 (8)	5 (14)	0 (0)
Minocycline	3 (12)	3 (8)	0 (0)
Doxycycline	0 (0)	2 (6)	0 (0)
SSKI	0 (0)	0 (0)	1 (4)
Observation	4 (15)	6 (17)	4 (15)
Median time to resolution (mo)	4.4	4.4	1.6

N.A. indicates not applicable; NSAIDs, non-steroidal anti-inflammatory drugs; mo, month; SD, standard deviation; SSKI, saturated solution of potassium iodide