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Ocular inflammation in the setting of concomitant systemic autoimmune conditions in an older male population

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Abstract

Purpose—This retrospective cross-sectional study was designed to investigate the frequency and types of inflammatory ocular manifestations of specific systemic autoimmune diseases in a South Florida Veterans Affairs Hospital population.

Methods—Demographic and medical diagnosis information was extracted from the Veterans Administration database for 1225 patients. These patients were seen in Miami and Broward Veterans Affairs hospitals between 4/18/2008 and 4/17/2013 and were diagnosed with at least one of the following: systemic lupus erythematosus, sarcoid, rheumatoid arthritis, polymyalgia rheumatica, Takayasu arteritis, giant cell arteritis, Kawasaki disease, polyarteritis nodosa, Buerger disease, Henoch-Schonlein purpura, Behcet syndrome, granulomatosis with polyangiitis, other polyarteritis nodosa associated vasculitides, or arteritis NOS.

Results—Of 1225 patients, 618 were seen in the VA eye clinic, and 25 were diagnosed with concomitant inflammatory ocular conditions. Uveitis was the most common, and included 8 cases of anterior, 1 anterior-intermediate, 1 intermediate, 2 panuveitis, and 3 unspecified. Other manifestations included 7 cases of keratitis and 2 each of scleritis, episcleritis and AION. The overall frequency of inflammatory ocular disease was 2%. The diseases associated with the highest frequency of ocular involvement were granulomatosis with polyangiitis (1/8), sarcoid (9/198), giant cell arteritis (2/68), and rheumatoid arthritis (11/576). Of these 25 patients, 9 were diagnosed with eye prior to systemic disease.

Conclusions—In this population, ocular manifestations were rarely the presenting feature of systemic disease, but autoimmune disorders are an important underlying cause of inflammatory eye disease that should be considered on first evaluation, even in this “non-traditional”, predominantly male, autoimmune disease population.

Keywords

autoimmune disease; eye manifestations; uveitis; keratitis; epidemiology

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Introduction

As a category, autoimmune disease is quite common. A 1997 study reported an overall prevalence of 3% within the United States.¹ A more recent estimate, using newer data from Denmark for a slightly different group of 29 diseases, put this number at 7.6–9.4%.² Ocular inflammation can be a feature of some, but not all of the diseases included in this estimate, and may be the presenting feature of disease.³ Many autoimmune diseases are well associated with specific types of inflammatory ocular manifestations. For example, keratoconjunctivitis sicca is the most frequent ocular complication in Sjogren's disease and rheumatoid arthritis,⁴ while acute anterior uveitis is the primary manifestation of ankylosing spondylitis.⁵ These ocular manifestations range widely in severity from causing mild discomfort to a complete loss of vision.⁴

Although it is well known that patients with autoimmune diseases can present with ocular pathology, the epidemiology of these manifestations has not been well characterized, particularly in more rare forms of disease. For example, the epidemiology of ocular inflammation has been extensively studied in diseases such as sarcoidosis and the HLA-B27 associated arthropathies, which are associated with high rates of anterior uveitis. Previous studies have reported that 25–40% of ankylosing spondylitis patients and 7.5–42% of patients with sarcoid present with anterior uveitis sometime during the course of their disease.^{3,5} However, anterior uveitis is also one of the primary manifestations in more rare conditions such as Behcet's disease, where the prevalence has not been well established.⁵ Even less well understood are the frequencies of rare ocular manifestations. For example, the specific manifestations of inflammatory keratitis associated with autoimmune disease have not been well characterized in any previous studies.

Awareness of the frequency and manifestations of autoimmune eye disease is important both to the ophthalmologist and rheumatologist, as ocular symptoms may be the first presentation of systemic disease. This study aims to assess the epidemiology of autoimmune eye disease in a south Florida veteran population to fill in knowledge gaps with regards to the frequency and manifestations of disease in this unique population.

Methods

Patient Population

This Miami Veterans Administration Institutional Review Board approved the retrospective review of charts for this study. The methods adhered to the tenets of the Declaration of Helsinki and were Health Insurance Portability and Accountability Act (HIPAA)-compliant. The study population included all patients who received care at the Miami Veterans Affairs Healthcare System (VA) and affiliated satellite eye clinics between the dates of 4/18/2008 and 4/17/2013. All patients had an International Classification of Disease, 9th edition (ICD-9CM) diagnosis of one or more autoimmune diseases (Table 1). Nearly all patients were former active-duty military personnel now residing in or near Miami, FL. However, this population does not include or represent all former military personnel.

Data Collection

All data was extracted from the Veterans Affairs administrative database by a VA-employed programmer and reported in spreadsheet format. The information obtained included demographic information (date of birth, gender, race, ethnicity) and medical diagnosis information (based on ICD-9CM codes). A chart review was then conducted in those patients who had an eye evaluation to assess for the presence of inflammatory ocular manifestations of their systemic disease. Ocular inflammatory diseases included in the analysis were anterior, anterior-intermediate, intermediate, posterior, pan, and unspecified uveitis (i.e. uveitis location not further specified in clinical chart), as well as keratitis, scleritis, episcleritis, and acute ischemic optic neuropathy (AION). Dry eye represents another important and common inflammatory manifestation of systemic disease. However, due to the variability in diagnosis of this condition, these patients were not included in our analysis unless they also carried one of the inflammatory diagnoses listed above. In cases where eye disease patients had multiple systemic diagnoses, the record was reviewed to determine which underlying disease was most likely associated with the ocular pathology.

Statistical Analysis

Descriptive statistics were used to summarize our patient population. The frequencies of ocular manifestations by specific autoimmune disease type were calculated in two ways. The first considered only patients seen in a VA affiliated eye clinic in the denominator. The second considered all patients with the specific autoimmune disease in the denominator, regardless of whether or not they had been seen in the eye clinic. The chi-squared test was used to compare categorical variables between groups while the Student's *t*-test was used to compare continuous variables. All statistical analyses were performed using SPSS Statistics version 22 (IBM, Armonk, New York).

Results

Patient demographics

Between 4/18/2008 and 4/17/2013, 107,088 unique patients were seen at the Miami and Broward VA hospitals. 1,225 of these patients (1.1%) were found to have at least 1 ICD-9CM diagnosis of autoimmune disease (Table 1). Within the same period, 23,689 of these patients (22% of all patients seen at the VA) were also seen in an affiliated eye clinic, 618 of whom had a diagnosis of autoimmune disease. Similar to the overall VA population, the majority of autoimmune disease patients were male and white (Table 2), and although women and non-whites were diagnosed with ocular complications at a higher frequency, there were no statistically significant differences between genders or racial groups.

Autoimmune conditions and their ophthalmic manifestations

The frequency of inflammatory ocular manifestations in all patients with qualifying autoimmune disease was 2% (25/1225 patients). When considering only the autoimmune disease patients also seen in the eye clinic, the frequency of concomitant inflammatory ocular disease is 4.1% (25/618 patients). Rheumatoid arthritis was the most common autoimmune condition, present in 41% of all autoimmune disease patients (n=576/1225),

followed by sarcoid ($n = 198$) and systemic lupus erythematosus (SLE) ($n = 179$) (Table 3). Per disease, the frequency of ophthalmic manifestations was highest in granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis, 1 out of 8 total GPA patients); After GPA, the frequency of inflammatory eye disease was highest in sarcoid (9/198 patients), GCA (2/68 patients), and rheumatoid arthritis (11/576 patients). Dates of diagnosis for both autoimmune disease and ocular disease were available for 21 of the 25 patients. Of these, ocular diagnosis preceded the systemic autoimmune disease in 9 cases (42.9%), making eye disease the presenting feature in 1.5% of the autoimmune disease patients evaluated in the eye clinic. This was seen in giant cell arteritis ($n = 2$, 100%), sarcoid ($n = 5$, 56%), arteritis NOS ($n = 1$, 33%) and rheumatoid arthritis ($n = 1$, 9%).

Regarding specific inflammatory ocular manifestations, anterior uveitis was the most common, constituting 36% of all inflammatory diagnoses ($n = 8$), followed by keratitis ($n = 7$, 28%). The ophthalmic findings in rheumatoid arthritis were most diverse, and included inflammation in the cornea, episclera, and sclera, as well as uveitis. On the other hand, sarcoid patients most frequently presented with intraocular disease (e.g. anterior uveitis). Table 4 depicts a grid considering ocular diagnoses as independent associations with each systemic diagnosis carried by the patient. Because 3 patients were diagnosed with multiple ocular inflammatory ocular conditions, the totals represented in the table overestimate the number of patients with each disease (28 cases of eye disease in 25 patients). These were all rheumatoid arthritis patients, and their ocular diagnoses were as follows: anterior uveitis and episcleritis, keratitis and unspecified uveitis, and anterior uveitis and keratitis. The counts of patients with each inflammatory ocular diagnosis is as follows (per 10,000 frequencies provided for the two most common diagnoses): 8 anterior uveitis (65 per 10,000 in the overall autoimmune disease population, 129 per 10,000 patients with autoimmune disease seen in the eye clinic), 1 anterior-intermediate uveitis, 1 intermediate uveitis, 2 panuveitis, 3 unspecified uveitis, 7 keratitis (60 per 10,000 overall or 110 per 10,000 in the eye clinic), 2 episcleritis, 2 scleritis, and 2 AION. Figure 1 depicts some of the varied clinical presentations of autoimmune keratitis in this population

Discussion

While some systemic autoimmune diseases are common, many are quite rare, which makes establishing the true epidemiology of ocular complications difficult. In this study, we evaluated a range of autoimmune diseases from the most common (RA), to the more rare, (i.e. GPA and PAN) to address gaps in the literature regarding the epidemiology of ocular disease in these conditions. We excluded the HLA-B27 associated arthropathies, the most common identifiable cause of acute anterior uveitis, as ocular manifestations of these conditions are common and have been relatively well characterized.⁶⁻⁸ We found that the overall frequency of inflammatory ocular complications in this population of autoimmune disease patients was 2%, most commonly anterior uveitis. This number must be taken in context of the specific diseases queried (i.e. which did not include HLA-B27 associated disease) and the ocular conditions evaluated (which included only inflammatory conditions and did not include dry eye). Also important to consider is our population, which was predominately composed of older white males. In comparison, a Romanian study of 375 patients seen in a rheumatology clinic found that 7% had ocular manifestations related to

their disorder, with anterior uveitis again being the most common.^{5,9} However, this population was comprised of mostly women, included HLA-B27 associated disease, and included keratoconjunctivitis sicca as an associated ocular outcome.

The autoimmune diseases found to be associated with the highest frequency of inflammatory ocular complications in the overall autoimmune disease population were GPA, sarcoid, and giant cell arteritis. Rheumatoid arthritis was the most prevalent autoimmune disease in this population, and as such, generated the most cases of inflammatory ocular disease, despite a relatively lower frequency of ocular involvement. These systemic diagnoses were responsible for the bulk of the associated ocular disease in this population, and are discussed below

GPA had the highest frequency of inflammatory ocular complications, manifesting as keratitis, an association that has been previously described in the literature.^{5,10,11} Past studies have established orbital or ocular involvement in GPA patients at 29–52%, which is slightly higher than our frequency estimate of 12–25%,^{5,12} and have also described uveitis, retinal vasculitis, scleritis, and episcleritis as ocular manifestations of the disease.¹³ Sarcoid had the second highest frequency of inflammatory ocular manifestations, all of which were forms of uveitis, primarily anterior. This also fits well with previous research, which has estimated that 25–60% of sarcoid patients will develop eye disease, of which uveitis is most common, constituting 30–70% of ocular involvement.^{3,8,14–16} Similar to other studies, we found that approximately 50% of sarcoid patients were diagnosed with eye disease prior to systemic disease.^{3,8,16} As in the United States overall, rheumatoid arthritis was the most prevalent autoimmune disease in our study.¹⁷ Likewise keeping with the general population, rheumatoid arthritis was found to be associated with diverse ocular manifestations, including uveitis, keratitis, scleritis, and episcleritis.^{9,18,19}

Keratitis was the second most common type of inflammatory ocular involvement in this population after anterior uveitis. As an entity associated with underlying systemic disease, its presentation is more heterogenous and less well described. Keratitis was most frequently seen in association with rheumatoid arthritis (57% of cases), in concordance with previous studies that have attributed 34–42% of non-infectious cases of peripheral ulcerative keratitis (PUK) to rheumatoid arthritis.^{10,20–22} Keratitis was also found as a complication of SLE, GPA, and unclassified arteritis, again in agreement with previous literature that reports keratitis, specifically PUK, in association with GPA and other ANCA associated vasculitides, PAN, relapsing polychondritis, Behcet's and SLE.^{10,20} Interstitial keratitis has been described less frequently, but has been associated with similar conditions (including rheumatoid arthritis, PAN, and GPA), as well as sarcoid. Cogan's syndrome has also been reported in association with rheumatoid arthritis.²³ The epidemiology of more central forms of keratitis in the setting of systemic disease has not been well established.

As with all studies, the current work has limitations that need to be considered. First, we used ICD-9 diagnoses to define the presence of autoimmune disease, which may have included patients who did not meet full criteria for a particular disease or excluded those without an appropriate code. Second, in patients with one of the qualifying systemic diagnoses, the presence of concurrent inflammatory eye disease was assumed to be related

to the underlying systemic diagnosis, an assumption validated to the extent possible by the review of the medical record. However, to more confidently state that these ocular diagnoses occurred at higher frequencies in the context of specific diseases would require perhaps a case-control approach, which was outside the scope of the current investigation. Third, the concept of “autoimmune disease” itself is somewhat problematic, thus the selection of a subset of systemic diseases to include in this study may not accurately capture all useful data. Specifically, the ICD-9 codes we chose to include were selected with the principal aim to study less common autoimmune diseases and those diseases known to be associated with more rare inflammatory ocular manifestations such as keratitis. As such, autoimmune conditions with well-established and prevalent associated eye disease, such as the HLA-B27 arthropathies, were not included. Fourth, results from our patient population, which consists of primarily older male US veterans seeking eye care services, may not be generalizable to other autoimmune disease populations, including female patients. Finally, only patients seen in a VA affiliated eye clinic were accounted for. Patients diagnosed and treated for eye disease exclusively in other venues were not included.

Despite these limitations, this study is important, as ocular manifestations of autoimmune disease may lead to significant morbidity. In addition, they may be the first sign of an underlying systemic illness. Thus, it is important to understand the epidemiology of ophthalmic involvement in systemic autoimmune disease in different populations. In this aging, predominately male population, we have established patterns of frequency and types of eye involvement similar to those in the existing literature, and further illuminated the specifics of the inflammatory ocular manifestations of the diseases studied.

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Figure 1.

Clinical manifestations of autoimmune keratitis A&B) Interstitial keratitis: 78 year old white male with history of psoriasis and RA presents with photosensitivity, ocular pain, and reduced visual acuity in the right eye (two views pictured). C&D) Interstitial keratitis: 54 year-old female with a history of lupus presents with long standing corneal scarring in both eyes, right and left eye pictured, respectively. E) Peripheral ulcerative keratitis: 46-year-old black female with history of RA presents with sectoral hyperemia of the left eye and thinning. F) Peripheral ulcerative keratitis: 61 year-old male presents with redness and pain;

on examination pannus is evident in both eyes (left > right). Based on this finding, subsequent testing revealed a diagnosis of ANCA associated vasculitis.

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Table 1

Included autoimmune diagnoses with corresponding ICD-9CM codes

Autoimmune Diagnosis	ICD-9CM codes
Systemic lupus erythematosus	710.0, 695.4, 729.30, 373.34
Sarcoid	135
Rheumatoid arthritis	714.0
Polymyalgia rheumatica	725
Takayasu arteritis	446.7
Giant cell arteritis	446.5
Kawasaki disease	446.1
Polyarteritis nodosa	446.0
Buerger disease	443.1
Arteritis NOS	447.6
Henoch-Schonlein purpura	287.0
Behcet syndrome	136.1 or 711.2x
Granulomatosis with polyangiitis	446.4
Other polyarteritis nodosa associated vasculitides	446.xx

Table 2

Study population demographics

	All AID patients	Seen in eye clinic	With ophthalmic manifestations
<i>N</i> (%)	1225 (100)	618 (50.4)	25 (2.0)
Average age (SD)	67.6 (14.5)	66.5 (13.3)	62.6 (14.5)
Gender			
% Male (n)	83.5 (1023)	49.9* (510)	1.7* (18)
% Female (n)	16.5 (202)	53.5* (108)	3.5* (7)
Race			
% White (n)	57.6 (706)	50.3* (355)	1.6* (11)
% Black (n)	26.9 (330)	63.6* (210)	3.6* (12)
% Unknown or other (n)	15.3 (188)	28.2* (53)	1.1* (2)

AID=autoimmune disease, *N*=total number in group, *n*=number in subgroup, SD=standard deviation

* Percentages calculated using corresponding "All AID patients" value as the denominator; no significant differences between the groups.

Table 3

Inflammatory ophthalmic diagnoses amongst autoimmune diseases

Autoimmune Diagnosis	N*	% Seen in eye clinic (n)	% Ophthalmic manifestation frequency (n)**	% Ocular Diagnosis Preceding Systemic Diagnosis (n)
Rheumatoid arthritis	576	43.4 (250)	1.9 – 4.4 (11)	9.1 (1)
Sarcoid	198	65.7 (130)	4.5 – 6.9 (9)	55.6 (5)
SLE	179	57.5 (103)	0.6 – 1.0 (1)	-
PMR	132	44.4 (59)	-	-
Other, PAN associated	98	65.3 (64)	-	-
Arteritis NOS	80	61.3 (49)	1.3 – 2.0 (1)	33 (1)
Giant cell arteritis	68	76.5 (52)	2.9 – 3.8 (2)	100.0 (2)
Henoch-Schonlein	15	40.0 (6)	-	-
Buerger syndrome	13	53.8 (7)	-	-
Behcet disease	10	50.0 (5)	-	-
GPA	8	50.0 (4)	12.5 – 25.0 (1)	-
Takayasu arteritis	5	60.0 (3)	-	-
Polyarteritis nodosa	2	50.0 (1)	-	-
Kawasaki disease	1	0.0 (0)	-	-

SLE = systemic lupus erythematosus, PMR = polymyalgia rheumatica, PAN = polyarteritis nodosa, NOS = not otherwise specified, GPA = granulomatosis with polyangiitis

* Counts represent cases of each diagnosis (some patients were diagnosed with multiple systemic autoimmune diseases)

** The low end of the prevalence range gives the prevalence of ophthalmic manifestations amongst all autoimmune disease patients while the high end gives the prevalence of ophthalmic manifestations amongst only the autoimmune disease patients seen in the eye clinic.

Table 4

Specific ophthalmic diagnoses associated with autoimmune conditions

	AU	AIU	IU	PU	UU	Keratitis	Scleritis	Episcleritis	AION	Total
SLE	-	-	-	-	-	1	-	-	-	1
Sarcoid	5	1	1	1	1	-	-	-	-	9
RA	3	-	-	1	2	4	2	2	-	14
GCA	-	-	-	-	-	-	-	-	2	2
GPA	-	-	-	-	-	1	-	-	-	1
Arteritis NOS	-	-	-	-	-	1	-	-	-	1
Total	8	1	1	2	3	7	2	2	2	28

AU = anterior uveitis, AIU = anterior-intermediate uveitis, IU = intermediate uveitis, PU = panuveitis, UU = unspecified uveitis, AION = anterior ischemic optic neuropathy, SLE = systemic lupus erythematosus, RA = rheumatoid arthritis, GCA = giant cell arteritis, GPA = granulomatosis with polyangiitis, NOS = not otherwise specified