

Immunologic Markers as Potential Predictors of Systemic Autoimmune Disease in Patients with Idiopathic Scleritis

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INTRODUCTION

Scleritis is a painful inflammatory condition that ranges from a benign, self-limited process to a fulminant course resulting in scleral necrosis. Thirty to forty percent of scleritis cases are associated with systemic autoimmune conditions including rheumatoid arthritis (RA), Wegener's granulomatosis (WG), systemic lupus erythematosus (SLE), and the seronegative spondyloarthropathies.^{1,2} Infectious causes including syphilis, aspergillus, and varicella zoster¹ are found in 5-10% of patients.³ The remaining 50% of cases are classified as idiopathic.

Despite its strong association with systemic disease, there remains no current published consensus on what should be included in an initial diagnostic work-up for scleritis patients presenting without known systemic disease. The role of serological markers such as rheumatoid factor (RF), anti-nuclear antibody (ANA), and anti-neutrophilic cytoplasmic antibody (ANCA) to determine risk of developing RA, SLE, or WG, in idiopathic scleritis patients has not been extensively studied. Some suggest that scleritis patients without evidence of systemic disease do not need to have serological testing.^{2,4} However, to date, there has been only one study providing an approximation of the frequency of serologic markers in scleritis patients,⁵ resulting in a lack of consensus as to whether obtaining serological testing in all idiopathic scleritis patients is clinically useful. For example, previous case series are divided as to how clinically useful ANCA screening is as a predictor of later development of WG in idiopathic scleritis patients, with some investigators claiming both high sensitivity and specificity,⁶ and others reporting only high specificity.⁴ Furthermore, although rheumatoid arthritis is

the most common rheumatic disease associated with scleritis, the role of RF screening in patients with idiopathic scleritis is even less well studied.

This study investigates the clinical value of ANCA and RF screening, and estimates a frequency for these serologic markers in patients with idiopathic scleritis.

METHODS

We obtained approval from the Institutional Review Board at the University of Illinois to review medical records of scleritis patients seen at the Uveitis Clinic with a waiver of informed consent and authorization. Consecutive cases of scleritis seen at the University of Illinois Uveitis Clinic between August 1995 and August 2006 were identified through a computerized database. Information collected included gender, race, age at presentation, age at ocular symptom onset, laterality of disease, type of scleritis, ocular complications (uveitis, exudative retinal detachment, and keratitis), and follow-up time. Patients were classified as having idiopathic scleritis, or scleritis secondary to known systemic autoimmune, infectious, or post-surgical etiology (e.g. RA, WG, SLE, any of the spondyloarthropathies, syphilis, varicella zoster, and herpes simplex).

Initial evaluation of the scleritis patient included a complete medical history and review of systems obtained by the examining physician, and supplemented by a questionnaire filled out by the patient. The questionnaire emphasized a rheumatologic and infectious disease review of systems, including questions about joint symptoms (pain, swelling, warmth, or stiffness), as well as location of joint involvement.

The diagnosis of scleritis was based on the characteristic clinical picture of inflammation, edema, and injection of the sclera. Scleritis was classified as diffuse anterior, nodular anterior, necrotizing, posterior, or scleromalacia perforans.⁷ Infectious etiologies such as herpes zoster and herpes simplex were diagnosed based on characteristic clinical presentation, or in the case of syphilis, based on serological

assays and an appropriate response to treatment. Rheumatologic diagnoses were based on patient history, lab tests, and/or a rheumatologist's evaluation.

Serological tests routinely ordered on scleritis patients included fluorescent treponemal antibody absorption (FTA-ABS), RF, ANA, and ANCA. A positive RF titer was recorded if titers were greater than 14 Units/mL, whereas a positive ANCA was greater than 1:16, a positive ANA was recorded if the titer was greater than 1:40. Ancillary testing including urine analysis, serum chemistries, chest x-ray, erythrocyte sedimentation rate, HLA-B27, lysozyme, Lyme titers, and angiotensin converting enzyme was obtained in the appropriate clinical context. If undiagnosed rheumatologic disease was suspected clinically or based upon laboratory test results the patient was referred for rheumatologic evaluation.

Statistical analysis

Statistical software used in the analysis of data included SPSS (v.14.0 for windows), SAS (v.9.1), and XLSTAT. Risk factors for having an associated systemic or infectious etiology at presentation were determined by making categorical comparisons between patients with an autoimmune condition (or infectious etiology) at presentation to those without (patients with idiopathic scleritis) using the Fisher's exact test, taking into account that some expected frequencies had 5 or fewer numbers. Risk factors for the development of systemic disease (RA and WG) among idiopathic scleritis patients after initial presentation were also analyzed with Fisher's exact test, and odds ratios (OR), likelihood ratios, sensitivity, specificity, negative and positive predictive values were determined. Continuous variables such as age, age of symptom onset, follow-up

time, and laboratory values were compared using the student's t test or analysis of variance methods. A p value of <0.05 was considered statistically significant. Bayes' theorem (stated below)^{8,9} was used to determine the post-test probability for a given diagnosis (RA or WG) given the prevalence of these diagnoses in the scleritis population.

Post-test probability for a positive test result = pre-test probability x sensitivity / [(pre-test probability x sensitivity) + ((1-pre-test probability) x (1-specificity))]

Post-test probability for a negative test result = ((1-pre-test probability) x specificity) / [((1-pre-test probability) x specificity) + (pre-test probability x (1-sensitivity))]

RESULTS

Characteristics of all patients with scleritis

128 patients with scleritis were seen at the University of Illinois Uveitis Clinic between 1995 and 2006. Of the 119 patients for whom we were able to find medical records, the mean age was 49.4 years-old, with a range of 9 to 92 years-old. The average age of scleritis symptom onset was 47.6 years-old (range 9-92). Eighty-two (68.9%) patients were female, and the mean follow-up time was 8 months (range 0-72 months). Fifty-four (45.4%) patients were White, 37 (31.1%) Black, 19 (16.0%) Hispanic, and 9 (7.8%) were of other races, which included Asian. Thirty-eight patients (32%) had bilateral scleritis. The most common type of scleritis was diffuse anterior scleritis (46.2%), followed by nodular anterior scleritis (30.3%), necrotizing scleritis (10.9%), posterior scleritis (13.4%), and scleromalacia perforans, which was rare, occurring in 2 (1.7%) patients (Table 1). On review of systems, 80 (67.2%) of 119 scleritis patients reported one or more joint symptoms (pain, stiffness, warmth, or swelling) in one or more joints. Ocular complications including uveitis, exudative retinal detachment, and keratitis, occurred in 22 (18.5%) patients (Table 1).

On initial presentation, 28 (23.5%) patients reported a previously diagnosed condition that was felt to be associated with their scleritis, including infectious etiologies (5, 4.2%) and systemic autoimmune conditions (22, 18.5%), resulting in 91 (76.5%) with idiopathic scleritis (Table 2). One patient (0.84%) developed scleritis as a result of cataract surgery and phacoanaphylaxis, and was also excluded from the idiopathic subgroup. Infectious etiologies on initial presentation included herpes simplex (2 patients), varicella zoster (1 patient), syphilis (1 patient), and pseudomonas (1 patient)

(Table 2). Of the 25 patients presenting with previously diagnosed systemic autoimmune disease, the most common condition reported was rheumatoid arthritis, occurring in 11 (9.2%) of all scleritis patients, followed by WG (2.5%), SLE (1.7%), relapsing polychondritis (1.7%), and inflammatory bowel disease (3.4%). Other systemic diseases less commonly associated with scleritis were also seen and included 1 patient with polyarteritis nodosa, 2 patients with Sjogren's syndrome, and 2 patients with sarcoidosis. Risk factors for presenting with a previously diagnosed autoimmune condition (compared to patients with idiopathic scleritis) included Hispanic origin (OR 3.4, 95% 1.2-9.9, $p=0.045$) and having necrotizing scleritis (OR 6.5, 95% CI 1.9-22.5, $p=0.007$) (Table 3). However, patients with scleritis who presented initially with a systemic autoimmune condition were less likely to develop ocular complications (0 out of 22, or 0%) than were patients with idiopathic scleritis (22 out of 91, or 23.9%), p value 0.006. There was no statistically significant difference in the presence of joint symptoms between patients who initially presented with systemic autoimmune disease and those patients with idiopathic scleritis (Table 3).

Characteristics of patients with idiopathic scleritis

Patients with idiopathic scleritis were more likely to have nodular anterior scleritis ($p=0.045$) and were more likely to develop ocular complications ($p=0.006$) (Table 3) than patients who reported a systemic autoimmune condition on initial presentation. Mean follow-up time was 7.97 months (range 0-72). Twenty-five of 91 (27.5%) patients with idiopathic scleritis developed systemic autoimmune conditions at subsequent follow-up, the most common of which was RA (11 patients, 12.1%), followed by WG (5

patients, 5.5%), relapsing polychondritis (1 patient, 1.1%), inflammatory bowel disease (1 patient, 1.1%), and seronegative spondyloarthropathies (2 patients, 2.2%) (Table 4). Other autoimmune conditions that developed on follow-up included Behcet Disease (1 patient), multiple sclerosis (1 patient), myasthenia gravis (1 patient), IgA nephropathy (1 patient), and Hashimoto's disease (1 patient). The prevalence of serologic markers in patients with idiopathic scleritis is shown in Table 4. RF was positive in 19 (27.1%) idiopathic scleritis patients for whom test results were available, ANA was positive in 14 (18.2%), and ANCA was positive in 7 (10%) patients with idiopathic scleritis. It is important to note that although the standard of care at our clinic was to routinely order the serologic tests shown on all patients with scleritis, regardless of other clinical symptoms, not all patients complied and results could not always be obtained from the primary physician.

Idiopathic scleritis and rheumatoid factor

Seventy of the 91 (76.9%) patients with idiopathic scleritis had RF results that were available to us. Of these 70 patients, 19 were RF positive (27.1%) and 51 were RF negative (72.9%). The number of patients in each category that developed RA at follow-up is shown in Table 5. Ten of 19 (52.6%) patients who were RF positive developed RA with a mean follow-up time of 10.6 months (range 0-72), resulting in a rate of 5.0 cases of RA diagnosed per patient-month of follow up (Tables 5 and 6), whereas only 1 of 51 (2%) RF negative patients developed RA with a mean follow-up time of 7.7 months (range 0-60), a rate of 0.3 cases of RA per patient-month of follow up. This represents a 16-fold difference in the rate of RA diagnosis when patients with

idiopathic scleritis had a positive versus negative RF (Table 6). The odds ratio of developing RA in RF positive patients was 55.6 (95% CI 7.8-369.8, $p=0.00001$) compared with RF negative patients (Table 5). The sensitivity and specificity of using RF results to predict the development of RA in patients with idiopathic scleritis was 90.9% and 84.7%, respectively. The positive and negative predictive values for this test were 52.6% and 98.0%, respectively (Table 9). Among patients with idiopathic scleritis, the cumulative incidence of developing RA at follow-up was substantially larger in patients who had a positive RF (Table 6). The data (Table 6) show that 8 out of the 10 RF positive patients who developed RA were diagnosed within 12 months of their initial visit, whereas the one case that occurred in the RF negative group occurred by 24 months.

Because many patients reported non-specific joint symptoms, we separately analyzed patients with idiopathic scleritis with and without one or more joint symptoms (Table 5). Of the 28 patients with idiopathic scleritis who reported no joint symptoms on presentation, 7 were found to be RF positive, five of whom developed RA (83.3%) with a mean follow-up of 17.3 months (range 0-72), representing a rate of 4.8 per patient-month of follow up. Twenty-one of the patients without joint symptoms were RF negative, 1 of whom (16.7%) developed RA with a mean follow-up of 13.0 months (range 0-60), representing a rate of 1.3 per patient-month of follow up. In other words, in patients without joint symptoms, there was a 3.4-fold increase in the rate of development of RA if RF was positive compared to if RF was negative, with an odds ratio of 50.0 (95% CI 4.6-498.8, $p=0.001$). The sensitivity and specificity of using RF in these patients was 83.3% and 90.9%, respectively, whereas the positive and negative

predictive values were 71.4% and 95.2%, respectively (Table 9). In patients with idiopathic scleritis who presented with 1 or more joint symptoms, all patients who went on to develop RA were RF positive. Therefore, both the sensitivity and negative predictive value for using RF to predict the development of RA in patients with idiopathic scleritis was improved (to the detriment of positive predictive value) in patients who reported one or more joint symptoms (Table 5). Likelihood ratios are also given in table 9. However, it is important to note that the only statistically significant risk factor for the development of RA in idiopathic scleritis patients was RF positivity (Table 5). The presence or absence of joint symptoms at time of presentation was not a statistically significant risk factor for the subsequent development of RA, nor was the type of scleritis ($p=0.292-1.00$), the presence of complications ($p=0.273$), or ANCA positivity ($p=1.00$).

Idiopathic scleritis and ANCA

Of the 91 patients with idiopathic scleritis, 70 patients (76.9%) had ANCA test results available. Of these 70, 7 had a positive ANCA, and 63 had a negative ANCA. One patient tested positive for both ANCA and RF, and went on to develop clinical RA (included in the previous section). Of the seven who were ANCA positive, 3 (42.9%) developed WG with a mean follow-up of 12.3 months (range 0-36) yielding a rate of 3.5 cases per patient-month of follow up, compared to only 2 of 63 (3.2%) ANCA negative patients who developed WG (mean follow-up 8.4 months, range 0-72), a rate of 0.4 cases of WG per patient-month of follow up (an 8.8 fold difference). This comparison yielded a statistically significant odds ratio for developing WG in patients who are ANCA

positive versus ANCA negative (OR 22.9, 95% CI 3.4-154.2, $p=0.006$) (Tables 7 and 8). The sensitivity and specificity for ANCA to predict the development of WG in patients with idiopathic scleritis was 60% and 93.8%, respectively, whereas the positive and negative predictive values were 42.9% and 96.8%, respectively (Table 9). Among patients with idiopathic scleritis, the cumulative incidence of developing WG at follow-up was substantially larger in patients who had a positive ANCA than with a negative ANCA (Table 8). Among the 28 patients who reported no joint symptoms, the odds ratio of developing WG in ANCA positive patients was 5.8 (95% CI 0.6-73.1, $p=0.298$). Likelihood ratios are also given table 9. As in RA, among patients who reported one or more joint symptoms, all patients who subsequently developed WG were ANCA positive. Therefore, both the sensitivity and negative predictive value for using ANCA to predict the development of WG was improved in patients who reported one or more joint symptoms. Among the 10 patients who reported sinopulmonary, renal, or dermatologic symptoms known to be related to WG, 3 were ANCA positive, and 7 were ANCA negative. Two out of three ANCA positive patients (66.7%) later developed WG, while none of the 7 ANCA negative patients developed WG ($p=0.067$).

The only statistically significant risk factor for the development of WG was ANCA positivity. The presence ($p=0.361$) or absence ($p=0.642$) of joint symptoms did not significantly increase the risk of developing WG. The presence of 1 or more extra-articular symptoms related to WG (including renal and sinopulmonary symptoms) yielded an odds ratio for the development of WG of 4.8 (95% CI 0.8-28.4), although this was not statistically significant ($p=0.146$). RF positivity also had no statistically

significant effect on the risk of developing WG ($p=0.318$), nor did type of scleritis ($p=0.202-1.00$) or ocular complications ($p=0.589$).

Bayesian analysis

Bayes' theorem has been employed in the literature to validate (or invalidate) the utility of laboratory tests given a disease prevalence in a certain population. Although the prevalence of RA is 1% in the general population,¹⁰ it is much more prevalent (at 15-21%) in the scleritis population.^{4,5} Our study shows a 15.7% prevalence (pre-test probability) of RA in patients with idiopathic scleritis for whom we had RF results (11 out of 70). Concordantly, the sensitivity of RF was much higher in scleritis patients (91%) than in the general population (28%).¹¹ By applying Bayes' theorem, we have determined the post-test probability of developing RA to be 52.6% in a patient with a positive RF result. In other words, the number of patients with initially idiopathic scleritis who will develop RA increased to 53 out of 100 if they had a positive RF. For a patient with a negative RF test, the post-test probability of RA decreases from 15.7% to <2.0%.

Whereas the prevalence of Wegener's granulomatosis is 3.0 per 100,000 people in the general population in the U.S.,¹² its prevalence is enriched in patients with scleritis to a rate of 7.1%. Using the enriched prevalence and our calculated sensitivity and specificity of ANCA for the development of WG in patients with scleritis (60% and 93.8%, respectively), the post-test probability was 42.9% for a positive ANCA. In other words, 43 out of 100 patients with initially idiopathic scleritis who have a positive ANCA

will develop WG. The post-test probability for a negative ANCA was 3.2%, representing a decreased probability from 7.1%.

DISCUSSION

The results of our study suggest that testing patients with idiopathic scleritis for RF and ANCA is clinically useful in identifying subgroups of patients who are at risk for the development of RA and WG. Despite the fact that rheumatoid arthritis is known to be the most common disease association in scleritis,^{4,5,13-15} the clinical utility of RF testing in scleritis patients has not been extensively studied previously. This study is one of the few of its kind that estimates the frequency of RF positivity in patients with idiopathic scleritis and attempts to determine its relationship to the development of RA. While most studies published to date have not been able to give the frequency of RF positivity among scleritis patients who present initially with idiopathic disease,⁴ a series by Watson and colleagues did report a frequency of 21.6%,⁵ which is slightly higher than the frequency that we report (15.7% of patients with initially idiopathic scleritis for whom we had RF results). Ours is the first study to provide follow-up data on whether or not the presence of RF in these patients increased the likelihood of later developing RA. Our series demonstrates that patients with idiopathic scleritis who tested positive for RF were at much greater risk for the development of RA at follow-up, even in the absence of joint symptoms. In fact, joint symptoms at initial presentation of scleritis were not a risk factor for the subsequent development of RA, suggesting that one should not use patients' reports of non-specific joint symptoms in determining who should be tested for RF.

We found that patients with idiopathic scleritis who tested positive for RF were at much greater risk of developing RA at follow-up, even in the absence of joint symptoms. According to the American College of Rheumatology (ACR) criteria for the diagnosis of

RA, a patient cannot be diagnosed with RA without joint symptoms/involvement, even with a positive RF.¹⁶ This study demonstrates that even in patients without joint symptoms at initial presentation, i.e. patients who could not have RA by ACR criteria at baseline, RF positivity increased risk of later developing RA. The utility of these findings becomes apparent as one realizes that the early diagnosis and treatment of rheumatoid arthritis has been shown to improve the outcome of rheumatoid arthritis.¹⁷ Therefore, a strong argument can be made that idiopathic scleritis patients should be tested for RF, and that those who are RF positive should be educated as to the signs and symptoms of RA, be advised that they may develop RA and consideration should be given to referral to a rheumatologist.

In contrast to RF, ANCA has been well-studied in the context of scleritis.¹⁸⁻²⁰ However, only one other study looked specifically at the clinical utility of ANCA testing in predicting idiopathic scleritis patients who were at risk for the development of WG.⁶ Although both their study and ours had few study numbers for WG, our series confirms the fact that ANCA testing has high specificity for the development of WG in patients who present initially with idiopathic scleritis. Our study is novel in that we also found that neither sinopulmonary, renal, and dermatologic symptoms, nor non-specific articular symptoms at initial presentation were found to be risk factors for the development of WG in patients with idiopathic scleritis on initial exam. However, the presence of these symptoms at initial exam increased the sensitivity of the assay. Our study supports the literature in that we have characterized a group of patients who developed WG with scleritis as their initial complaint.¹⁹ Three of five idiopathic scleritis

patients who developed WG presented initially with scleritis and no extra-ocular symptoms.

To further validate the use of RF and ANCA in patients with scleritis, Bayesian analysis was performed. Since patients with scleritis have an enriched prevalence of RA and WG and because the sensitivity and specificity of the above tests are greater than in the general population, the post-test probabilities of developing disease were substantially larger than their pre-test probabilities. In fact, even if one were to apply the lower sensitivities and specificities of these tests found in the literature for the general population,^{11,21} Bayes' theorem would show a great enough post-test probability in the scleritis population to warrant testing.

Inherent to all retrospective studies such as ours are biases and weaknesses that require a certain level of skepticism when interpreting results. The first is that the Uveitis Service at the University of Illinois is a subspecialty referral clinic for which the inherent bias is towards patients with more difficult to treat cases. Also, ours is not a population-based study but a single-practice-based study, which limits its ability to be generalized to the public, or even to community clinics. Additionally, there were many confounding factors specific to our study. For instance, we assumed that all rheumatologists utilized ACR criteria to diagnose RA, rather than using more subtle clinical judgements, adding inter-expert variability that is not accounted for in our study. Finally, it is important to realize that there are two ways to interpret the data regarding the cumulative incidence of RA (or WG) over time. A positive RF either led to an earlier referral and thus rheumatologic work-up, or it could be said that it represented a risk factor for the later development of symptoms qualifying patients for the diagnosis of RA

(according to ACR criteria) at an earlier time point than RF negative patients with scleritis. Either way, patients with a positive RF were not only more likely to be diagnosed with RA, but they were diagnosed at an earlier time point than RF negative patients, which is precisely the benefit of utilizing this test in the scleritis population. Despite these caveats, we believe that the results are robust enough to support our conclusions.

In conclusion, scleritis can be the initial manifestation of both RA and WG.²² Because early diagnosis and intervention may have significant effects on the prognosis and course of these systemic conditions, it is important to delineate which patients with scleritis are at risk for their development. Although it is well-understood that using serological markers indiscriminately in the general population, or even in patients who complain of non-specific joint symptoms, can lead to confounding diagnostic dilemmas, our study shows that RF and ANCA are clinically useful tests in the context of idiopathic scleritis.

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TABLES

Table 1. Demographics and disease characteristics of all patients with scleritis

	Number (%)
	N=119
Gender	
Female	82 (68.9%)
Male	37 (31.1%)
Race	
White	54 (45.4%)
Black	37 (31.1%)
Hispanic	19 (16.0%)
Other	9 (7.8%)
Age	
Mean Age at initial visit (years)	49.4
Range (years)	9-92
Mean Age at symptom onset (years)	47.6
Range (years)	9-92
Location and type of scleritis	
Bilateral Scleritis	38 (32.0%)
Diffuse Anterior*	55 (46.2%)
Nodular Anterior *	36 (30.3%)
Necrotizing	13 (10.9%)
Posterior Scleritis*	16 (13.4%)
Scleromalacia Perforans	2 (1.7%)
Presence of 1 more joint symptoms	80 (67.2%)
Ocular complications (any)	22 (18.5%)
Uveitis	14 (11.8%)
Exudative retinal detachment	4 (3.4%)
Interstitial Keratitis	2 (1.7%)
Sclerosing Keratitis	2 (1.7%)
Mean follow-up time (months)	8
Range (months)	0-72
* Note that some patients had more than one type of scleritis	

Table 2. Associated systemic disease at initial presentation in patients with scleritis

	Number (%)
	N=119
Infectious (any)	5 (4.2%)
Syphilis	1 (0.84%)
Herpes Simplex	2 (1.7%)
Varicella Zoster	1 (0.84%)
Pseudomonas	1 (0.84%)
Systemic autoimmune condition (any)	22 (18.5%)
RA*	11 (9.2%)
WG	3 (2.5%)
SLE	2 (1.7%)
RP	2 (1.7%)
IBD	4 (3.4%)
Other	5 (4.2%)
Post-surgical	1 (0.84%)
Idiopathic	91 (76.5%)
* 2 RA patients had concurrent Sjogren's ("other" category), 1 also had sarcoid (other), and 1 also had ulcerative colitis; "Other" includes Sjogren's, sarcoidosis, and polyarteritis nodosa	
RA=rheumatoid arthritis; IBD=inflammatory bowel disease; WG=Wegener's granulomatosis; SLE=systemic lupus erythematosus; RP=relapsing polychondritis	

Table 3. Risk factors for an autoimmune condition at initial presentation in patients with scleritis

	OR	95% CI	p value
Gender			
Female	1.0	Reference	N/A
Male	1.7	0.7-4.5	0.307
Race			
White	1.0	Reference	N/A
Black	0.8	0.2-1.7	0.446
Hispanic	3.4	1.2-9.9	0.045
Other	N/A	N/A	0.202
Location and type of scleritis			
Bilateral	2.4	0.9-6.0	0.082
Diffuse Anterior	0.9	0.4-2.3	1.000
Nodular Anterior	0.3	0.1-0.95	0.045
Necrotizing	6.5	1.9-22.5	0.007
Posterior Scleritis	1.5	0.5-4.9	0.511
Scleromalacia Perforans	4.3	0.4-42.7	0.353
Presence of joint symptoms	1.4	0.6-3.7	0.485
Ocular complications (any)	N/A	N/A	0.006
Uveitis	N/A	N/A	0.068
Exudative retinal detachment	N/A	N/A	0.585
Interstitial Keratitis	N/A	N/A	1.00
Sclerosing Keratitis	N/A	N/A	1.00
OR=odds ratio; CI=confidence interval			

Table 4. Patients with idiopathic scleritis at follow-up: systemic disease and serologic markers

	Number (%)
	N=91
Autoimmune condition on follow-up	25 (27.5%)
RA	11 (12.1%)
WG	5 (5.5%)
SLE	0 (0%)
RP	1 (1.1%)
IBD	1 (1.1%)
Other seronegative spondyloarthopathy	2 (2.2%)
Other *	5 (5.5%)
Frequency of serologic markers patients with idiopathic scleritis	
	Denominator=number of patients with test results available
Anti-nuclear antibody	14/77 (18.2%)
Rheumatoid factor	19/70 (27.1%)
Anti-neutrophilic cytoplasmic antibody	7/70 (10%)
*Includes Behcet disease, multiple sclerosis, myasthenia gravis, IgA nephropathy, and Hashimoto's disease	

Table 5. Rheumatoid factor increases the odds of developing rheumatoid arthritis in patients with idiopathic scleritis

Number tested for RF n=70					
	RF+	RF-			
Total	19	51			
Number that develop RA (%)	10 (52.6%)	1 (2.0%)			
Mean follow-up time in months (range)	10.6 (0-72)	7.7 (0-60)			
Odds Ratio (95% CI) of developing RA	55.6 (7.8-369.8)				
p value	0.00001				
Number tested without joint symptoms n=28	RF+	RF-			
Total	7	21			
Number that develop RA (%)	5 (71.4%)	1 (4.8%)			
Mean follow-up time in months (range)	17.3 (0-72)	13.0 (0-60)			
Odds Ratio (95% CI) of developing RA	50.0 (4.6-498.8)				
p value	0.001				
Number tested with 1 or more joint symptoms n=34	RF+	RF-			
Total	10	24			
Number that develop RA (%)	4 (40%)	0 (0%)			
Mean follow-up time in months (range)	7.65 (0-36)	3.63 (0-36)			
Odds Ratio (95% CI) of developing RA	N/A				
p value	0.005				
Risk Factors for developing RA					
	+ RA n=11	- RA n=59	OR	95% CI	p value
RF+	10 (90.9%)	9 (15.3%)	55.6	7.8-369.8	0.00001
ANCA+	1 (9.1%)	5 (8.5%)	1.1	0.2-8.0	1
1 or more joint symptoms	4 (36.4%)	30 (50.8%)	0.6	0.2-2.0	0.515
No joint symptoms	6 (54.5%)	22 (37.3%)	2.0	0.6-7.0	0.328
RF=rheumatoid factor; ANCA=anti-neutrophilic cytoplasmic antibody					

Table 6. Cumulative incidence of rheumatoid arthritis development on follow-up in patients with idiopathic scleritis at initial presentation

Cumulative incidence of RA			
Months (post initial visit)	RF+	RF-	p value
2	5 (26.3%)	0 (0%)	0.001
6	6 (31.6%)	0 (0%)	0.0001
12	8 (42.1%)	0 (0%)	0.00001
24	10 (52.6%)	1 (2.0%)	0.00001
36	10 (52.6%)	1 (2.0%)	0.00001
72	10 (52.6%)	1 (2.0%)	0.00001
Total number tested	19	51	
Rate of RA development/average patient-month of follow-up	5	0.3	Fold difference 16.7

Table 7. ANCA increases the odds of developing Wegener's granulomatosis in patients with idiopathic scleritis

Number tested for ANCA n=70		ANCA+	ANCA-			
Total		7	63			
Number that develop WG (%)		3 (42.9%)	2 (3.2%)			
Mean follow-up in months (range)		12.3 (0-36)	8.4 (0-72)			
Odds Ratio (95% CI) of developing WG		22.9 (3.4-154.2)				
p value		0.006				
Number tested with sinopulmonary, renal, or dermatologic symptoms n=10		ANCA+	ANCA-			
Total		3	7			
Number that develop WG (%)		2 (66.7%)	0 (0%)			
Mean follow-up in months (range)		8.5 (0.5-24)	0.9 (0-2)			
Odds ratio (95% CI) of developing WG		N/A				
p value		0.067				
Number tested without joint symptoms n=28		ANCA+	ANCA-			
Total		3	25			
Number that develop WG (%)		1 (33.3%)	2 (8%)			
Mean follow-up in months (range)		20.2 (0.5-36)	12.3 (0-72)			
Odds Ratio (95% CI) of developing WG		5.8 (0.5-73.1)				
p value		0.298				
Number tested with 1 or more joint symptoms n=33		ANCA+	ANCA-			
Total		3	30			
Number that develop WG (%)		2 (66.7%)	0 (0%)			
Mean follow-up in months (range)		6.38 (0-24)	5.8 (0-60)			
Odds Ratio (95% CI) of developing WG		N/A				
p value		0.006				
Risk factors for the development of WG						
	+ WG n=5	- WG n=65	OR	95% CI	p value	
ANCA+	3 (60%)	4 (6.2%)	22.9	3.4-154.2	0.006	
RF+	0	18 (27.7%)	0	0.000-2.148	0.318	
1 or more joint symptoms	1 (20%)	32 (49.2%)	0.3	0.04-1.8	0.361	
No joint symptoms	3 (60%)	26 (40%)	2.3	0.4-12.0	0.642	
Extra-articular symptoms relating to WG (renal, sinopulmonary, dermatologic)	2 (40%)	8 (12.3%)	4.8	0.8-28.4	0.146	

Table 8. Cumulative incidence of Wegener's granulomatosis development on follow-up in patients with idiopathic scleritis at initial presentation

Cumulative incidence of WG			
Months (post initial visit)	ANCA+	ANCA -	p value
2	2 (28.6%)	0 (0%)	0.009
6	2 (28.6%)	2 (3.2%)	0.047
12	2 (28.6%)	2 (3.2%)	0.047
24	3 (42.9%)	2 (3.2%)	0.006
36	3 (42.9%)	2 (3.2%)	0.006
72	3 (42.9%)	2 (3.2%)	0.006
Total number tested	7	63	
Rate of WG development/average patient-month of follow-up	3.5	0.4	Fold difference 8.8

Table 9. Sensitivity and specificity of RF and ANCA in patients with idiopathic scleritis

	LR+	LR-	Sensitivity	Specificity	PPV	NPV
RF (all)	6.0	0.11	90.9%	84.7%	52.6%	98.0%
RF (no joints)	9.2	0.18	83.3%	90.9%	71.4%	95.2%
RF (1+ joints)	5.0	0	100%	80.0%	40.0%	100%
ANCA (all)	9.8	0.43	60.0%	93.8%	42.9%	96.8%
ANCA (+ extra-articular)	8.0	0	100%	87.5%	66.7%	100%
ANCA (no joints)	4.2	0.72	33.3%	92.0%	33.3%	92.0%
ANCA (1+ joints)	31.0	0	100%	96.8%	66.7%	100%

LR+= likelihood ratio for a positive test; LR-=likelihood ratio for a negative test; PPV=positive predictive value; NPV=negative predictive value