Ocular disease in patients with ANCA-positive vasculitis

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Abstract Anti-neutrophil cytoplasmic antibody (ANCA)-positive vasculitis—the term recently applied to Wegener's granulomatosis—is a rare multi-system inflammation characterized by necrotizing granulomas and vasculitis. We investigated the ocular manifestations of this disease in a group of patients drawn from five inflammatory eye disease clinics across the United States. Of 8,562 persons with ocular inflammation, 59 individuals were diagnosed with ANCA-positive vasculitis; 35 males and 21 females, aged 16 to 96 years, were included in this study. Ocular diagnoses were scleritis (75.0%), uveitis (17.9%), and other ocular inflammatory conditions (33.9%) including peripheral ulcerative keratitis and orbital pseudotumor. Mean duration of ocular disease was 4.6 years. Oral corticosteroids and other
systemic immunosuppressive agents were used by 85.7% and 78.5% of patients, respectively. Over time, patients with ANCA-positive vasculitis experienced 2.75-fold higher mortality than other patients with inflammatory eye disease.

**Keywords** ANCA-positive vasculitis · Wegener’s granulomatosis · Eye · Scleritis

**Introduction**

Anti-neutrophil cytoplasmic antibody (ANCA)-positive vasculitis—a term that is favored to designate the disease otherwise known as Wegener’s granulomatosis [1]—is a rare multi-system disease that is classically described as consisting of necrotizing granulomas and vasculitis of the respiratory tract, generalized small vessel vasculitis, and a focal necrotizing glomerulonephritis [2]. In addition to renal and respiratory tract involvement, patients may have cutaneous, rheumatologic, neurologic, and ocular inflammation. Cases in which renal manifestations are absent are considered to represent a “limited” form of the disease [2]. Although the pathogenesis of ANCA-positive vasculitis is incompletely understood, it is thought to be of complex mechanism involving aberrant humoral and cell-mediated immune responses [3]. More than 90% of patients with active disease test positively for the proteinase 3 anti-neutrophil cytoplasmic antibody (Pr3 ANCA). The precise role of ANCAs in the pathogenesis of the disease has not been defined, but they are believed to mediate the granulomatous inflammation and vascular destruction that are hallmarks of the disease [3].

The prevalence of ANCA-positive vasculitis in the United States is reported to be 3.0 cases per 100,000 population [4]. Various studies conducted in the United Kingdom have estimated the annual incidence to be 0.5 to 8.5 cases per million [2]. A large prospective study conducted by investigators at the National Institute of Allergy and Infectious Diseases (NIAID) did not demonstrate a gender predilection and suggested that the disease was more prevalent in whites than in other races [5]. Mortality and morbidity of ANCA-positive vasculitis are substantial. In the study performed at NIAID, the disease or complications arising from therapy led to death in 13% of 1,229 patient-years of follow-up [5]. In the same study, 86% of patients suffered irreversible disease-related morbidity, and 42% of patients experienced morbidity related to adverse effects of treatment.

Inflammatory eye disease is described in 50% to 60% of patients with ANCA-positive vasculitis, and for 8% to 16% of patients, it is an initial manifestation [6]. Case reports and studies from single centers describe a diverse range of ocular involvements, from eye wall inflammations, including conjunctivitis and scleritis, to orbital masses; the most commonly reported ophthalmic manifestations have been orbital disease and scleritis [5–16]. To provide a more complete description of the ocular disease in patients with ANCA-positive vasculitis, we investigated clinical aspects of the disease in a cohort of patients managed at five tertiary-referral inflammatory eye disease clinics located within the United States.

**Methods**

The Systemic Immunosuppressive Therapy for Eye Diseases (SITE) cohort is a group of individuals with non-infectious inflammatory eye disease who have been managed at five North American inflammatory eye disease subspecialty clinics between 1978 and 2007 [17].
cohort was assembled primarily to evaluate the risk of mortality associated with the use of systemic immunosuppressive drugs in this patient population [18]. Demographic, clinical, and treatment-related variables associated with each visit made by each patient to a study center have been collected retrospectively by standardized chart review. For four centers, all eligible patients were enrolled in the study. At the fifth center, approximately 40% of eligible patients were enrolled; sampling was random, with oversampling of patients most likely to be treated with systemic immunosuppression and patients presenting early in the observation period. Data collection followed the Declaration of Helsinki with approval from the institutional review boards of each institution.

The size and breadth of the SITE cohort provided an excellent opportunity for investigation of specific forms of inflammatory eye disease. In this study, the SITE database was mined to obtain data relating to all patients registered with the diagnosis of ANCA-positive vasculitis.

After identification of patients, demographic characteristics were collected, including gender, race, age at diagnosis, and duration of disease. The database was further scrutinized for disease-specific variables. In particular, the database was queried to calculate the proportion of patients with specific ocular diagnoses (i.e., anterior uveitis, intermediate uveitis, posterior uveitis and panuveitis, scleritis, and “other”), who also had a diagnosis of ANCA-positive vasculitis. The construction of the database allowed for documentation of more than one form of inflammatory eye disease when applicable. Subtypes and patterns of disease were collated for patients with scleritis. Scleritis was classified by subtype, as described by Watson and Hayreh, [19] and subtypes were defined according to laterality, distribution of the inflammation, and temporal course of the disease, as applicable.

Limited data relating to the management of patients with inflammatory eye disease according to systemic inflammatory diagnosis were reported in the original SITE cohort study [17]. In the present study, all relevant systemic medications administered during the study period and all surgical procedures were tabulated for patients with ANCA-positive vasculitis. Systemic medications included oral corticosteroids and other systemic immunosuppressive agents (i.e., methotrexate, azathioprine, mycophenolate mofetil, leflunomide, dapsone, cyclosporine, tacrolimus, sirolimus, cyclophosphamide, chlorambucil, and biologic agents). Surgical interventions were categorized as: cataract surgery, glaucoma surgery, and “other ocular surgery”.

Among the subset of patients seen on or before December 31, 2005, who were residents of the United States (i.e., maintaining an address within the United States), data on the risk of mortality through the end of 2005 were available. In the original SITE cohort study, ANCA-positive vasculitis was identified as a non-treatment factor that was associated with an increased risk of death in within cohort comparisons [17]. The risk of mortality for patients with ANCA-positive vasculitis was calculated with respect to patients free of that diagnosis using survival analysis. Cox multiple regression was performed to adjust for confounding by demographic and clinical characteristics, including age, sex, race, smoking status, primary site of ocular inflammation, Charlson Index score [20], and the presence of systemic immune-mediated diseases (i.e., reactive arthritis, psoriatic arthritis, ankylosing spondylitis, Behçet's disease, polyarteritis nodosa, giant cell arteritis, other forms of arteritis, systemic lupus erythematosus, scleroderma, Sjögren's syndrome, dermatomyositis, polymyositis, juvenile idiopathic arthritis, relapsing polychondritis, Cogan's syndrome, rheumatoid arthritis, Takayasu's arteritis, and pemphigus).

Results

Of the 8,562 persons registered in the SITE database as of June 11, 2008, 59 patients with ANCA-positive vasculitis were identified. Previous publications originating from centers that contributed to the database may have included data from some of these patients. Three subjects were excluded from the study due to discrepancies in dates recorded in the database. Of the 56 individuals with ANCA-positive vasculitis, 35 were male and 21 were female. The majority of individuals were white (49 patients, 87.5%). Mean age at diagnosis was 48 years (range, 16–96 years). The first recorded patient evaluation took place on March 31, 1986, and the last recorded patient evaluation took place on June 7, 2007. Mean duration of inflammatory eye disease, from diagnosis through last visit to a SITE study center, was 4.6 years (range, 0–26.3 years). Patient characteristics are presented in Table 1.

Among the 56 individuals with the diagnosis of ANCA-positive vasculitis, the distribution of ocular inflammatory diagnoses was significantly different from that for the remaining SITE population (p<0.001). There were 42 patients with scleritis (3.6% of 1,165 SITE cohort patients identified as having scleritis), ten patients with uveitis (0.13% of 7,239 SITE cohort patients identified as having uveitis), and 19 patients with “other” ocular inflammatory diagnoses (6.7% of 285 SITE cohort patients identified as having inflammatory eye diseases other than scleritis or uveitis). Non-necrotizing anterior scleritis was the most common subtype of scleritis and was present in 27 patients (64.3% of scleritis cases and 48.2% of all cases of ANCA-positive vasculitis); of these 27 patients, 74.1% of individuals had the diffuse form and 25.9% of individuals had the nodular form. Necrotizing scleritis was diagnosed in 12
patients (28.6% of scleritis cases and 21.4% of all cases of ANCA-positive vasculitis). Two patients suffered from concurrent anterior and posterior scleritis. Episcleritis was uncommon, affecting just three patients. The majority of cases of uveitis were classified as anterior (70% of uveitis and 19.6% of all cases of ANCA-positive vasculitis). Five patients suffered from both scleritis and uveitis. The diagnostic category, “other”, included peripheral ulcerative keratitis (n=9), orbital pseudotumor (n=6), and other conditions (n=4). Table 2 gives the ocular diagnoses for all patients. Laterality, distribution of inflammation, and temporal pattern of scleritis are presented in Table 3.

During the period of study, oral corticosteroid therapy was used by 48 patients (85.7%), and non-corticosteroid systemic immunosuppressive agents were used by 44 patients (78.6%). Thirty patients (53.6%) were treated with cyclophosphamide. A total of 15 cataract surgical procedures were performed on nine patients, and 17 patients had a total of 24 various other ocular surgeries, including dacryocystorhinostomy, and corneal or scleral patching. Medical and surgical interventions for the 56 patients with ANCA-positive vasculitis are listed in Tables 4 and 5.

The subset of the cohort seen by 2005 totaled 7,957 patients, including 56 with ANCA-positive vasculitis. Mortality occurred at a rate of 0.040/person-year (95% CI, 0.22–0.066) among patients with ANCA-positive vasculitis versus 0.014/person-year for the rest of the cohort (p<0.001; Fig. 1). The risk of mortality was 2.75-fold higher among patients with ANCA-positive vasculitis (95% CI, 1.49–5.06), after adjusting for the confounding factors listed in the Methods section. Figure 1 shows the Kaplan–Meier survival plot demonstrating probability of survival over time for patients with ANCA-positive vasculitis (n=56) versus patients with all other diagnoses (n=7,901).

### Table 1: Characteristics of patients with ANCA-positive vasculitis

| Patient-specific variable                                      | Number of patients (%) or mean ± SD (range) |
|---------------------------------------------------------------|--------------------------------------------|
| Gender                                                       |                                            |
| Male                                                         | 35 (62.5)                                  |
| Female                                                      | 21 (37.5)                                  |
| Race                                                        |                                            |
| White                                                       | 49 (87.5)                                  |
| Non-white                                                   | 7 (12.5)                                   |
| Age at diagnosis of inflammatory eye disease (years)        | 48.2±16.4 (16–96)                          |
| Age at presentation to SITE center (years)                  | 50.4±15.8 (17–97)                         |
| Duration of inflammatory eye disease at presentation to SITE center (months) | 26±54 (0–302)                             |
| Duration of follow-up at SITE center (months)               | 30±35 (0–129)                             |
| Duration of inflammatory eye disease (years)               | 4.6±5.7 (0–26.3)                          |

### Table 2: Ocular diagnoses in patients with ANCA-positive vasculitis

| Diagnosis (principal or other)                     | Number of patients, n=56 (%) | Number of eyes, n=90 (%) |
|---------------------------------------------------|------------------------------|--------------------------|
| Scleritis                                         | 42 (75.0)                    | 64 (71.1)                |
| Episcleritis                                      | 3 (5.4)                      | 5 (5.6)                  |
| Anterior Scleritis                                | 27 (48.2)                    | 43 (47.8)*               |
| Necrotizing Scleritis                             | 12 (21.4)                    | 16 (17.8)                |
| Posterior Scleritis                               | 2(3.6)                       | 3 (3.3)                  |
| Uveitis                                           | 10 (17.9)                    | 12 (13.3)                |
| Anterior                                          | 7 (12.5)                     | 8 (8.9)*                 |
| Intermediate                                      | 1 (1.8)                      | 1 (1.1)                  |
| Posterior or Panuveitis                           | 2 (3.6)                      | 3 (3.3)                  |
| Other Ocular Inflammatory Disease                 | 19 (33.9)                    | 27 (30.0)                |
| Dacroadenitis                                     | 0 (0)                        | 0 (0)                    |
| Orbital Myositis                                  | 0 (0)                        | 0 (0)                    |
| Orbital Pseudotumor                               | 6 (10.7)                     | 11 (12.2)                |
| Peripheral Ulcerative Keratitis                   | 9 (16.1)                     | 10 (11.1)                |
| Other                                             | 4 (7.1)                      | 6 (6.7)                  |
| Number of ocular diagnoses per patient or eye     |                              |                          |
| 1                                                | 44 (78.6)                    | 74 (82.2)                |
| 2                                                | 10 (17.9)                    | 14 (15.6)                |
| 3                                                | 2 (3.6)                      | 2 (3.6)                  |

*Information is not recorded for one patient*
ANCA-positive vasculitis is a multi-system inflammatory disease that may affect different ocular tissues and/or the orbit. Our study provides a comprehensive review of the clinical aspects of this condition, as documented for 56 patients at five tertiary-referral inflammatory clinics across the United States. Scleritis was the most common ocular

Discussion

ANCA-positive vasculitis is multi-system inflammatory disease that may affect different ocular tissues and/or the orbit. Our study provides a comprehensive review of the clinical aspects of this condition, as documented for 56 patients at five tertiary-referral inflammatory clinics across the United States. Scleritis was the most common ocular

Table 3 Characteristics of scleritis in patients with ANCA-positive vasculitis

| Subtype                  | Clinical features | Number of patients, n=56 (%) | Number of eyes, n=90 (%) |
|--------------------------|-------------------|------------------------------|--------------------------|
| Episcleritis             | Laterality        |                              |                          |
| (n=3 patients)           | Unilateral        | 1 (1.8)                      | 1 (1.1)                  |
| (n=5 eyes)               | Bilateral         | 2 (3.6)                      | 4 (4.4)                  |
| Distribution             | Diffuse           | 0 (0)                        | 0 (0)                    |
|                         | Nodular           | 1 (1.8)                      | 1 (1.1)                  |
|                         | Unknown           | 2 (3.6)                      | 4 (4.4)                  |
| Temporal pattern         | Single episode    | 0 (0)                        | 0 (0)                    |
|                         | Recurring         | 1 (1.8)                      | 1 (1.1)                  |
|                         | Chronic           | 1 (1.8)                      | 2 (2.2)                  |
|                         | Unknown           | 1 (1.8)                      | 2 (2.2)                  |
| Anterior scleritis       | Laterality        |                              |                          |
| (n=27 patients)          | Unilateral        | 10 (17.9)                    | 9 (10.0)                 |
| (n=43 eyes)              | Bilateral         | 17 (30.4)                    | 34 (37.8)                |
|                         | Unknown           | 0 (0)                        | 0 (0)                    |
| Distribution             | Diffuse           | 20 (35.7)                    | 32 (35.6)                |
|                         | Nodular           | 7 (12.5)                     | 11 (12.2)                |
| Temporal pattern         | Single episode    | 5 (8.9)                      | 6 (6.7)                  |
|                         | Recurring         | 11 (19.6)                    | 17 (18.9)                |
|                         | Chronic           | 11 (19.6)                    | 20 (22.2)                |
| Necrotizing scleritis    | Laterality        |                              |                          |
| (n=12 patients)          | Unilateral        | 8 (14.3)                     | 8 (8.9)                  |
| (n=16 eyes)              | Bilateral         | 4 (7.1)                      | 8 (8.9)                  |
|                         | Unknown           | 0 (0)                        | 0 (0)                    |
| Distribution             | Focal             | 6 (10.7)                     | 7 (7.8)                  |
|                         | Widespread        | 3 (5.4)                      | 4 (4.4)                  |
|                         | Unknown           | 3 (5.4)                      | 5 (5.6)                  |
| Temporal pattern         | Single episode    | 2 (3.6)                      | 2 (2.2)                  |
|                         | Recurring         | 3 (5.4)                      | 4 (4.4)                  |
|                         | Chronic           | 5 (8.9)                      | 7 (7.8)                  |
|                         | Unknown           | 2 (3.6)                      | 3 (3.3)                  |
| Posterior scleritis      | Laterality        |                              |                          |
| (n=2 patients)           | Unilateral        | 1 (1.8)                      | 1 (1.1)                  |
| (n=3 eyes)               | Bilateral         | 1 (1.8)                      | 2 (2.2)                  |
| Temporal pattern         | Single episode    | 0 (0)                        | 0 (0)                    |
|                         | Recurring         | 1 (1.8)                      | 1 (1.1)                  |
|                         | Chronic           | 1 (1.8)                      | 2 (2.2)                  |

*a Information is not recorded for one patient

b Both patients with posterior scleritis also had anterior scleritis
diagnosis in our patient cohort, accounting for 75% of the inflammatory eye disease. Non-necrotizing anterior scleritis was the most frequently observed subtype of scleritis, but necrotizing disease affected approximately one quarter of patients. Uveitis, peripheral ulcerative keratitis, and orbital inflammation were other manifestations. Notably, although an association between systemic and retinal vasculitis is commonly assumed, the majority of cases of uveitis were anterior in nature. Moreover, 50% of patients with uveitis also suffered from scleritis, suggesting that uveitis may have been secondary to the scleral inflammation. In many patients, ANCA-positive vasculitis required aggressive therapy. During the study, the majority of our patients were treated with systemic corticosteroids, and over three-quarters of the group were prescribed systemic immunosuppressive medications, including cyclophosphamide in 54% of cases. Patients with ANCA-positive vasculitis were at 2.75-fold increased risk of death in comparison to other patients with ocular inflammation.

Two single-center retrospective studies [10, 12] and one review of published cases [15] have documented the ocular and/or orbital involvement in patients with ANCA-positive vasculitis. All three reports describe a diversity of manifestations, including inflammations of the orbit and nasolacrimal system, conjunctiva, cornea, episclera, sclera, uvea, and retina. Some of these manifestations, such as conjunctivitis (12.5–25%) and nasolacrimal obstruction (up to 25%), were not specifically assessed for the SITE cohort of patients. With regard to the diagnoses that were recorded in the database, these three reports found orbital inflammation to be the most common manifestation (25–45%). Scleritis and episcleritis, the most common group of ocular diagnoses in our patients (75%), were also observed frequently (15–38%). One likely explanation for the different distribution of ocular diagnoses is that the cited reports included all patients presenting to the institution or all patients described in the literature of the day, respectively, whereas the clinical information in the SITE database was collected from tertiary-referral inflammatory eye disease clinics only. A fourth single-center study involved 47 patients who were managed at the Ocular Immunology Service of the Massachusetts Eye and Ear Infirmary (MEEI) [21], which is a tertiary-referral inflammatory eye disease clinic. Interestingly, in that series, 74% of patients with ANCA-positive vasculitis had scleritis, and in 67% of patients this was necrotizing. Some of those patients are included in this report. One notable conclusion from the MEEI-based study was that eye involvement may be the first clinical evidence of ANCA-positive vasculitis.

A comprehensive review of therapy for ANCA-positive vasculitis, published in 2006 by White and Lynch [22], provides recommendations for pharmacologic management. A regimen of daily corticosteroid combined with cyclophosphamide is the treatment of choice to induce remission in patients with severe, life-threatening disease.

| Medical therapies        | Number of patients (%) |
|--------------------------|------------------------|
| Oral corticosteroid      | 48 (85.7)              |
| Methotrexate             | 19 (33.9)              |
| Azathioprine             | 7 (12.5)               |
| Mycophenolate mofetil    | 5 (8.9)                |
| Leflunomide              | 1 (1.8)                |
| Dapsone                  | 1 (1.8)                |
| Cyclosporin              | 2 (3.6)                |
| Cyclophosphamide         | 30 (53.6)              |
| Chlorambucil             | 3 (5.4)                |
| Biologics                | 6 (10.7)               |

| Surgical interventions |
|------------------------|
| Cataract surgery       | 9 patients; 15 operations |
| Glaucoma surgery       | 0 patients; 0 operations |
| Other ocular surgery   | 17 patients; 24 operations |

(e.g., dacrocystorhinostomy, scleral or corneal patch grafting, ocular tissue biopsies)

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**Table 4 Medical interventions in patients with ANCA-positive vasculitis (n=56 patients)**

**Table 5 Surgical interventions in patients with ANCA-positive vasculitis (n=56 patients)**

**Fig. 1** Kaplan–Meier survival plot demonstrating probability of survival over time for 7,957 SITE cohort patients who were managed on or before December 2005, and who were residents of the United States. Patients with ANCA-positive vasculitis (n=56) are represented by the dashed line. Patients with all other diagnoses (n=7,901) are represented by the solid line.
effectiveness of cyclophosphamide 2 mg/kg body weight per day and prednisone 1 mg/kg body weight per day was tested by Hoffman et al. [5] in their prospective study conducted at NIAID. Of 133 patients treated with this therapy, 91% experienced improvement and 75% experienced complete resolution of disease. In patients with moderately severe disease, methotrexate or azathioprine may be used to maintain remission [22]. Metzler et al. [23] showed that leflunomide may be superior to methotrexate in the prevention of major relapses. Biologics such as tumor necrosis factor (TNF) antagonists and rituximab, an antibody directed against CD20, have been studied on a smaller scale [22]. Regardless of the chosen therapy, relapses are not uncommon, and complications of treatment can be severe. In one placebo-controlled trial of etanercept, in addition to systemic glucocorticoids plus cyclophosphamide or methotrexate for maintenance of remission, there was a striking difference in toxicity between the groups; solid malignancies developed in six of the 89 patients in the etanercept group but none of the 92 patients in the control group [24].

While trials focusing on the treatment of systemic manifestations of ANCA-positive vasculitis are often large, controlled, clinical studies, reports of therapy for patients with ocular and/or orbital manifestations are more limited in terms of numbers of patients and level of evidence. In 1997, Perry et al. [25] published a series of 13 patients with ANCA-positive vasculitis and orbital involvement. Systemic corticosteroids alone were used in ten patients, but only one of these patients experienced remission of disease. Eventually, the majority of the ten patients were treated with the combination of a systemic immunosuppressive medication or trimethoprim–sulfamethoxazole and corticosteroid. A retrospective series of 29 Australian and New Zealand patients with orbital and adnexal manifestations, published in 2001, included 83% of patients who received prednisone and 62% of patients who took cyclophosphamide [26]. Some subjects in this study were treated with trimethoprim–sulfamethoxazole (24%) or radiotherapy (17%). During the period of study, 86% of our population was treated with oral corticosteroids. Forty-four patients were treated with other systemic immunosuppressive agents; 19 individuals (34%) used methotrexate, and 30 individuals (54%) used cyclophosphamide. Six of the 56 patients received biologic agents. The use of biologic agents in our study alone probably reflects the fact that our clinical data were collected through 2007, i.e., including the period of time when biologic agents have become standard therapy for certain inflammatory diseases, whereas other studies were conducted prior to that time.

Our study has certain limitations that warrant discussion. Foremost are ascertainment bias and the retrospective nature of the data collection. In addition, the SITE database was constructed for the specific purpose of identifying incidence of malignancy in patients receiving systemic immunosuppressive medications for inflammatory eye disease. For this reason, some disease- and treatment-related data were limited in relation to the subject of our investigation. In particular, the clinical or laboratory criteria used to make the diagnosis of ANCA-positive vasculitis were not recorded in the database. Authors of smaller studies have specified their use of clinical features, ANCA positivity, and/or tissue biopsies demonstrating granulomatous inflammation with vasculitis and necrosis [11, 13, 21, 25, 26]. For our multi-centered review, we had to assume that the diagnosis was made appropriately by SITE clinicians, all of whom were academic uveitis specialists and expected to confirm a diagnosis of ANCA-positive vasculitis according to standard criteria, such as the 1990 American College of Rheumatology Criteria for Wegener's granulomatosis [27]. Finally, while some investigators have reported results of medical and surgical therapies by following clinical improvements and remission of different manifestations of ANCA-positive vasculitis [5, 11, 14, 25], our methods did not allow us to track the effectiveness of therapy in specific instances. The sampling procedure conducted at one institution is unlikely to impact our results because patients with ANCA-positive vasculitis are one subgroup that is likely to receive systemic immunosuppression.

Despite the discussed limitations, our description of the ocular manifestations of ANCA-positive vasculitis involves a relatively large group of patients who have been managed at multiple centers. In presenting data from five major tertiary-referral inflammatory eye disease clinics in the United States, our study provides a broad representation of ANCA-positive vasculitis. We observed that ANCA-positive vasculitis involved different ocular tissues and the orbit, but most commonly was manifested as scleritis. Patients with ocular complications of ANCA-positive vasculitis were at increased risk of mortality, despite the frequent systemic use of corticosteroid and immunosuppressive medications.

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