Orbital Granulomatosis With Polyangiitis (Wegener Granulomatosis)

Clinical and Pathologic Findings

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• The pathology of granulomatosis with polyangiitis (GPA), formerly Wegener granulomatosis, typically features a granulomatous and sometimes necrotizing vasculitis targeting the respiratory tract and kidneys. However, orbital involvement occurs in up to 60% of patients and is frequently the first or only clinical presentation in patients with systemic or limited forms of GPA. Orbital GPA can cause significant morbidity and potentially lead to complete loss of vision and permanent facial deformity. Fortunately, GPA is highly responsive to medical treatment with corticosteroids combined with cyclophosphamide or, more recently, rituximab. Therefore, it is imperative for this disease to be accurately diagnosed on orbital biopsy and distinguished from other histologically similar orbital lesions. Herein, we review the clinical and pathologic findings of orbital GPA, focusing on the differentiation of this disease from other inflammatory orbital lesions.

(*Arch Pathol Lab Med*. 2014;138:1110–1114; doi: 10.5858/arpa.2013-0006-RS)

Granulomatosis with polyangiitis (GPA), formerly known as Wegener granulomatosis,[1] is an autoimmune vasculitis that affects multiple organ systems and was first described in 1936 by Friedrich Wegener.[2] The 1990 American College of Rheumatology[3] criteria for diagnosis of GPA include (1) nasal or oral inflammation, (2) respiratory radiographic abnormalities consistent with respiratory tissue destruction (eg, nodules, infiltrates, and cavities), (3) microhematuria or red blood cell casts on urinary sediment analysis, and (4) granulomatous inflammation on biopsy for pathology. Based on this classification published in 1990, a diagnosis of GPA can be made with 88.2% sensitivity and 92.0% specificity when 2 out of the 4 criteria are met.[3] With the advent of serologic testing for antineutrophil cytoplasmic antibody (ANCA) levels, the combination of American College of Rheumatology criteria and serologic test results is essential for current GPA diagnosis.[4–6] The prevalence of GPA has been reported to be 3.0 cases per 100 000 in the United States.[7] A detailed epidemiologic study[8] from a prospective register of patients with systemic vasculitis between 1998 and 2012 in the United Kingdom reported an average annual GPA incidence of 11.3 cases per million and a prevalence of 145.9 cases per million. Granulomatosis with polyangiitis is significantly more common in persons of white race/ethnicity[7] and has been shown to have a slightly greater incidence among men in European populations.[9] It is rare in childhood and has a peak incidence in the fifth decade of life.[7] The etiology and pathogenic mechanisms that trigger the autoimmune inflammation in GPA are unknown. Similarly, the molecular mechanisms for the selective susceptibility of small-caliber and medium-caliber vessels in GPA are unclear. While GPA classically affects upper and lower respiratory tracts and kidneys, other organ systems can be targeted. The soft tissues of the orbit are one of the most frequent nonrespiratory, nonrenal systems affected, and orbital involvement has been reported in 45% to 60% of patients diagnosed as having GPA.[10,11] Furthermore, the orbit may be the only site targeted or can be the first presenting feature of GPA before progression to multisystem involvement.[6,11]

LABORATORY TESTS AND CLINICAL FINDINGS

Diagnosis of GPA requires laboratory and clinicopathologic correlation.[12] Laboratory tests have an essential role in current diagnosis of GPA. Serologic indicators of generalized inflammation, including erythrocyte sedimentation rate and C-reactive protein levels, are frequently elevated in GPA; conversely, C3 and C4 complement levels may be reduced.[5,13] However, erythrocyte sedimentation rate and C-reactive protein are acute-phase reactants, and increases may be seen in many systemic inflammatory conditions and are not specific for GPA.[5] Antineutrophil cytoplasmic antibody serologies for cytoplasmic ANCA reactive against proteinase 3, as well as perinuclear ANCA reactive against myeloperoxidase, are highly useful in GPA diagnosis when elevated.[5,11] In a meta-analysis,[14] pooled data showed that positive cytoplasmic ANCA serology was 91% sensitive and 99% specific in patients with active GPA. While the sensitivity was only 63% in patients with inactive disease, the specificity remained high at 99.5%. Based on these laboratory findings, indirect immunofluorescence and enzyme-linked immunosorbent assay testing of cytoplasmic

Accepted for publication July 15, 2013.

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The authors have no relevant financial interest in the products or companies described in this article.

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ANCA and perinuclear ANCA levels are recommended and widely used to diagnose GPA and to assist in the maintenance of patients with GPA.[4–6]

Clinical findings of ocular GPA arise from the inflammation of ocular structures, including the globe, orbital fat, orbital nerves, extraocular muscles, lacrimal glands, and optic nerve. Patients can present with ocular pain, erythema and edema of the eyelids, conjunctival injection, nasolacrimal duct obstruction, epiphora, limited extraocular muscle movements, afferent pupillary defect, proptosis, diplopia, and vision loss.[6,11,15] Vision loss can arise from compressive optic neuropathy due to adjacent inflammation or even direct penetration of the optic nerve itself by inflammatory cells.[11] Orbital pain can arise from inflammation, fibrosis leading to socket contracture, and bony erosion of orbital cavity. Computed tomography images of orbital GPA may show infiltration of the orbit by the granulomatous lesion with obliteration of the adjacent fat planes and sometimes bony destruction and sclerosis (Figure, A).[15] Magnetic resonance imaging of orbital inflammation can reveal hypointense lesions on T2-weighted studies with variable contrast enhancement.[15] Notably, all of these clinical and radiographic findings are nonspecific for GPA and may be seen with other orbital inflammatory processes. Therefore, biopsy of the orbital inflammatory process is performed to try to obtain definitive histopathologic diagnosis in cases of suspected orbital GPA.

PATHOLOGIC FINDINGS

Common histopathologic findings of GPA include granulomatous or nongranulomatous vasculitis, fat necrosis, granulomatous or nongranulomatous mixed acute and chronic inflammation, geographic fibrinoid degeneration, and microabscesses.[6,16–18] In a retrospective review of 11 orbital biopsies from patients with well-documented GPA at The University of British Columbia Orbit Clinic (Vancouver, Canada), mixed inflammation and perivascular lymphocytic infiltrates were observed in 10 biopsies, mixed acute and chronic infiltrates (neutrophils, lymphocytes, and eosinophils) in 11 biopsies, microabscesses in 2 biopsies, and giant cells in 5 biopsies.[19] In another retrospective review of 13 orbital biopsies from patients with GPA seen at the Mayo Clinic (Rochester, Minnesota), small vessel vasculitis was seen in 85% of cases, while tissue necrosis and granulomatous inflammation were seen in 62% of cases.[20] Multinucleated giant cells were present in only 31% of cases in this review.[20] Furthermore, the classic pathologic triad of GPA (vasculitis, tissue necrosis, and granulomatous inflammation) was present in only 54% of the orbital biopsies in this series.[20] By contrast, all 3 features of the triad have been found to be present in 91% of open lung biopsies from patients with GPA.[11] A third retrospective analysis with pooled data from multiple eye centers across the United States reported that all ophthalmic biopsies contained varying degrees of granulomatous inflammation with either giant cells or epithelioid histiocytes.[6] Many of the GPA specimens had obvious extravascular granulomas, some had inflammation surrounding (but not involving) vessels, and only one case had obvious granulomatous vasculitis.[6] Only 4 out of the total 13 cases showed necrotizing vasculitis with obliteration of the vessel lumen.[6]

The vasculitis associated with GPA begins as a mixed acute and chronic inflammatory infiltrate that can progress to granulomatous vasculitis (Figure, B through G) and eventual necrotizing vasculitis (Figure, H).[11,15] The pathology of GPA is centered on small to medium–sized vessels, helping to differentiate it from other vasculitides. Granulomas in GPA are typically composed of collections of epithelioid histiocytes. Multinucleated giant cells are variably present and nonspecific but can be helpful in raising the suspicion of GPA in a specimen without overt vasculitis or granulomatous inflammation.[6,16,17]

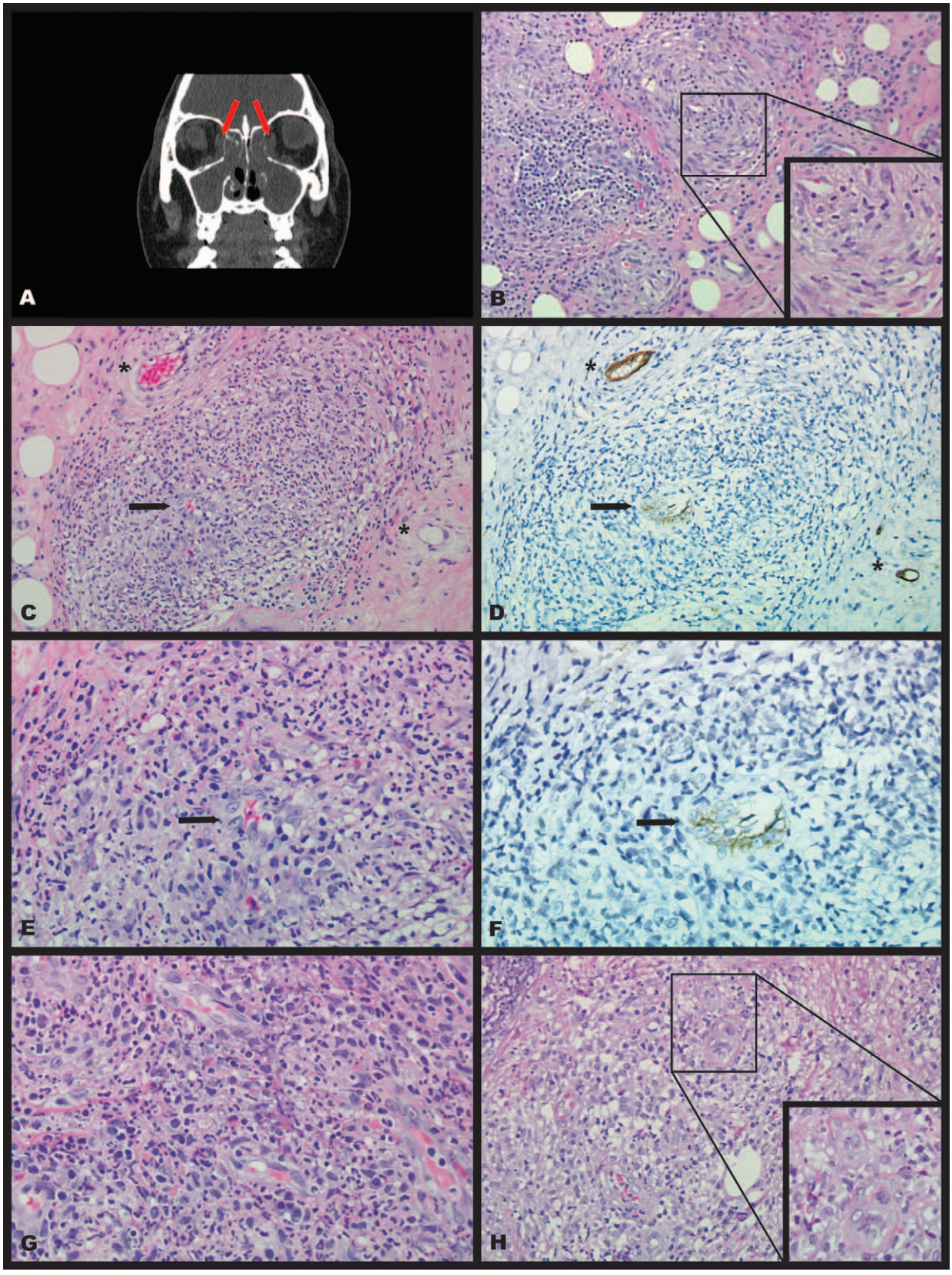
Ahmed and colleagues[6] have suggested secondary histopathologic features that should raise the pathologist's suspicion of a diagnosis of GPA. These include alteration of interstitial collagen and the presence of a rich polymorphous inflammatory infiltrate.[6] Alterations of collagen are manifested by mummification of collagen, granular degeneration, or frank necrosis, while the rich inflammatory infiltrate can consist of many plasma cells, lymphocytes, neutrophils, eosinophils, and epithelioid histiocytes.[6]

Although some cases may be strikingly obvious even at low power, spatial heterogeneity in biopsies from patients with GPA can render a diagnosis on small specimens from orbital biopsies particularly challenging. Therefore, correlation with ANCA serologies, upper and lower respiratory tract and kidney findings, and imaging is suggested whenever the possibility of GPA is raised. At our institution, when the pathology is consistent with clinical and laboratory data, we report our findings as "consistent with GPA" or "suspicious for GPA."

DIFFERENTIAL DIAGNOSIS OF ORBITAL LESIONS

As discussed above, the diagnosis of orbital GPA requires clinical and pathologic correlation in part because of highly variable histopathology. The differential diagnosis must consider infectious, neoplastic, and other inflammatory orbital diseases. Infectious etiologies need to be pursued foremost in the differential diagnosis for orbital biopsies with inflammation and necrosis.[21] Simple and inexpensive histochemical stains, complemented by cultures and molecular tests (eg, polymerase chain reaction), are essential in ruling out entities such as mycobacterial infections or invasive fungal sinusitis. Fungal infection is most commonly from *Aspergillus* or *Mucor* species, which can invade the orbit, especially in persons with diabetes and immunocompromised individuals.[21] Both primary and secondary neoplasms, ranging from benign to malignant, need to be ruled out when considering a diagnosis of GPA. In particular, orbital and ocular structures are common primary sites for extranodal marginal zone B-cell lymphoma[22] and, more rarely, other non-Hodgkin and Hodgkin lymphomas.[11,22]

Some common orbital inflammatory diseases to consider in a differential diagnosis include idiopathic sclerosing orbital inflammation, thyroid or Graves orbitopathy, sarcoidosis, and temporal arteritis. Churg-Strauss syndrome can be very similar to Wegener granulomatosis; however, it rarely involves the tissues of the orbit.[6] Polyarteritis nodosa and Kawasaki disease have also been rarely reported in orbital biopsies.[23] IgG4-related disease has been identified as a cause of a growing number of orbital inflammatory lesions.[24–26] One general histologic finding that may be helpful in suggesting a diagnosis of GPA over other orbital inflammatory diseases is the presence of many scattered eosinophils, particularly eosinophils admixed within formed granulomas.[6] Idiopathic sclerosing orbital inflammation, also known as orbital inflammatory pseudotumor, differs from GPA by swaths of sclerosis interrupted by a paucity of



Histopathology of orbital granulomatosis with polyangiitis (GPA). A, A noncontrast coronal computed tomography image of the paranasal sinuses demonstrates bilateral lobulated soft tissue within the nasal cavity extending through the medial orbital walls (red arrows) to bilateral retrobulbar extraconal orbital spaces in a patient with GPA. B, A micrograph of an orbital lesion biopsy depicts collections of epithelioid histiocytes (granulomas) surrounding small vessels (hematoxylin-eosin, original magnifications ×200 and ×400 [inset]). C and E, Shown are small vessels (black arrow) with necrotizing and granulomatous inflammatory infiltrate composed of epithelioid histiocytes, neutrophils, lymphocytes, scattered eosinophils, and karyorrhectic debris. Adjacent vessels with less inflammation are also shown in C (*) (hematoxylin-eosin, original magnifications

chronic inflammatory cells, typically CD3-positive T cells.[27] Thyroid or Graves orbitopathy can be distinguished clinically by endocrine manifestations, including abnormal serum thyroid hormone levels. The presence of granulomas consisting of collections of epithelioid histiocytes should raise the possibility of sarcoidosis, which can present with orbital involvement,[11] but necrosis and acute inflammation would be very rare in sarcoidosis. Noncaseating granulomas will predominate in sarcoid, and clinical correlation with radiologic pulmonary involvement and angiotensin-converting enzyme levels can be helpful.[11]

IgG4-related disease of the orbit may be distinguished on histology from GPA by increased IgG4-positive plasma cells, with reported IgG4 to IgG ratios ranging from 30% to 90% in IgG4-related disease.[24–26,28] Intriguingly, a recent retrospective analysis of 26 biopsies, including 7 orbital biopsies, performed at the Mayo Clinic from 1999 to 2011 of clinically and pathologically confirmed cases of GPA found that 8 of these 26 diagnosed GPA cases also showed IgG4 to IgG ratios greater than 40%.[29] Furthermore, these 8 cases with increased IgG4 to IgG ratios were composed exclusively of orbital ($n = 4$) or sinonasal ($n = 4$) biopsies.[29] These findings suggest that increased numbers of IgG4-positive plasma cells in an orbital biopsy alone are not sufficient to distinguish IgG4-related disease of the orbit from orbital GPA, and complementary clinicopathologic information is required. Additional histopathologic features of IgG4-related disease such as the presence of storiform fibrosis and dense lymphoplasmacytic infiltrates and relative paucity of necrosis and acute inflammation may be helpful in distinguishing IgG4-related disease of the eye from orbital GPA.[28]

PROGNOSIS AND TREATMENT

Before the advent of immunomodulatory therapies in the 1970s, GPA had a dismal prognosis, with a median survival time of 5 months and a greater than 80% mortality rate only 1 year following diagnosis.[11] Currently, medical management is favored with immunosuppressive agents.[15] The combination of intravenous glucocorticoids plus cytotoxic agents (cyclophosphamide, methotrexate, or azathioprine) has dramatically altered the prognosis of patients with GPA, with 95% survival at 5 years and 80% survival at 10 years.[23] Granulomatosis with polyangiitis is highly responsive to systemic corticosteroids and cytotoxins, commonly leading to induction and maintenance of remission.[10,15] Additional surgical management may be useful to decompress the orbit in cases of orbital GPA associated with severe pain, proptosis, or compressive optic neuropathy.[15]

Although immunosuppressive therapies are prolonging survival, they are not without serious adverse effects. More than 50% of the patients on this treatment regimen have been reported to acquire life-threatening opportunistic infections.[11] Rituximab anti-CD20 therapy has recently emerged as an attractive new therapy for GPA.[23] The Rituximab in ANCA-Associated Vasculitis multicenter study[30] of 197 patients with ANCA-associated disease found that rituximab was as effective as cyclophosphamide in treating the disease, with a superior adverse effect profile. Smaller clinical studies[31,32] have also found that rituximab is effective in treating orbital GPA. In addition, intravenous immunoglobulin has been used as medical treatment for GPA when first-line corticosteroids and cyclophosphamide regimens fail.[13,33] Purine and pyrimidine antimetabolites, including mycophenolate mofetil–leflunomide, antithymocyte globulin, and 15-deoxyspergualin, have also shown some promise as alternative treatments for GPA in small-scale investigations.[34] Anti–tumor necrosis factor α biological agents have shown mixed efficacy in treating GPA, with positive effects seen with infliximab but no significant positive findings with etanercept.[15,34,35]

CONCLUSION

In conclusion, GPA is a systemic necrotizing vasculitis targeting small to medium–sized vessels, typically involving the lungs and kidneys and commonly affecting the orbit and ocular structures. Orbital symptoms may be the first sign of GPA and necessitate biopsy for tissue pathology diagnosis to assist in differentiating GPA from other inflammatory diseases affecting the orbit. As with many of the vasculitides, clinicopathologic correlation of imaging, laboratory values, and tissue histology is optimal to most confidently diagnose GPA.

References

1. Falk RJ, Gross WL, Guillevin L, et al. Granulomatosis with polyangiitis (Wegener's): an alternative name for Wegener's granulomatosis. *Ann Rheum Dis*. 2011;70(4):704.
2. Fahey JL, Leonard E, Churg J, Godman G. Wegener's granulomatosis. *Am J Med*. 1954;17(2):168–179.
3. Leavitt RY, Fauci AS, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. *Arthritis Rheum*. 1990;33(8):1101–1107.
4. Savige J, Dimech W, Fritzler M, et al. Addendum to the International Consensus Statement on testing and reporting of antineutrophil cytoplasmic antibodies: quality control guidelines, comments, and recommendations for testing in other autoimmune diseases. *Am J Clin Pathol*. 2003;120(3):312–318.
5. Breda L, Nozzi M, De Sanctis S, Chiarelli F. Laboratory tests in the diagnosis and follow-up of pediatric rheumatic diseases: an update. *Semin Arthritis Rheum*. 2010;40(1):53–72.
6. Ahmed M, Niffenegger JH, Jakobiec FA, et al. Diagnosis of limited ophthalmic Wegener granulomatosis: distinctive pathologic features with ANCA test confirmation. *Int Ophthalmol*. 2008;28(1):35–46.
7. Cotch MF, Hoffman GS, Yerg DE, Kaufman GI, Targonski P, Kaslow RA. The epidemiology of Wegener's granulomatosis: estimates of the five-year period prevalence, annual mortality, and geographic disease distribution from population-based data sources. *Arthritis Rheum*. 1996;39(1):87–92.
8. Watts RA, Mooney J, Skinner J, Scott DG, Macgregor AJ. The contrasting epidemiology of granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis. *Rheumatology (Oxford)*. 2012;51(5):926–931.
9. Watts RA, Lane SE, Scott DG, et al. Epidemiology of vasculitis in Europe. *Ann Rheum Dis*. 2001;60(12):1156–1157.
10. Holle JU, Gross WL. Neurological involvement in Wegener's granulomatosis. *Curr Opin Rheumatol*. 2011;23(1):7–11.
11. Pakrou N, Selva D, Leibovitch I. Wegener's granulomatosis: ophthalmic manifestations and management. *Semin Arthritis Rheum*. 2006;35(5):284–292.
12. Takwoingi YM, Dempster JH. Wegener's granulomatosis: an analysis of 33 patients seen over a 10-year period. *Clin Otolaryngol Allied Sci*. 2003;28(3):187–194.
13. Wiwatwongwana D, Esdaile JM, White VA, Dolman PJ. Intravenous immunoglobulin (IVIG) for orbital Wegener's granulomatosis. *Can J Ophthalmol*. 2012;47(1):82–83.

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×200 [C] and ×400 [E]). D and F, Micrographs of CD34 immunostains highlight disrupted and reactive endothelium in a small, central vessel with vasculitis (black arrow). Multiple adjacent uninvolved vessels show confluent CD34 endothelial staining in D (*) (anti-CD34, original magnifications ×200 [D] and ×400 [F]). G, Many vessels are surrounded by a rich polymorphic inflammatory infiltrate (hematoxylin-eosin, original magnification ×400). H, This area shows chronic vasculitis with fibrinoid change in the vessels (hematoxylin-eosin, original magnifications ×200 and ×400 [inset]). A full workup, including histochemical stains and immunostains, reveal no fungal or bacterial microorganisms and no evidence of increased IgG4-positive plasma cells. Of note, the patient's serum cytoplasmic and perinuclear antineutrophil cytoplasmic antibody titers were both increased to 1:160.

14. Rao JK, Weinberger M, Oddone EZ, Allen NB, Landsman P, Feussner JR. The role of antineutrophil cytoplasmic antibody (c-ANCA) testing in the diagnosis of Wegener granulomatosis: a literature review and meta-analysis. *Ann Intern Med*. 1995;123(12):925–932.
15. Santiago YM, Fay A. Wegener's granulomatosis of the orbit: a review of clinical features and updates in diagnosis and treatment. *Semin Ophthalmol*. 2011;26(4–5):349–355.
16. Del Buono EA, Flint A. Diagnostic usefulness of nasal biopsy in Wegener's granulomatosis. *Hum Pathol*. 1991;22(2):107–110.
17. Narula N, Gupta S, Narula J. The primary vasculitides: a clinicopathologic correlation. *Am J Clin Pathol*. 2005;124(suppl):S84–S95.
18. Fienberg R. The protracted superficial phenomenon in pathergic (Wegener's) granulomatosis. *Hum Pathol*. 1981;12(5):458–467.
19. Perry SR, Rootman J, White VA. The clinical and pathologic constellation of Wegener granulomatosis of the orbit. *Ophthalmology*. 1997;104(4):683–694.
20. Kalina PH, Lie JT, Campbell RJ, Garrity JA. Diagnostic value and limitations of orbital biopsy in Wegener's granulomatosis. *Ophthalmology*. 1992;99(1):120–124.
21. Montone KT. Infectious diseases of the head and neck: a review. *Am J Clin Pathol*. 2007;128(1):35–67.
22. Ferry JA, Fung CY, Zukerberg L, et al. Lymphoma of the ocular adnexa: a study of 353 cases. *Am J Surg Pathol*. 2007;31(2):170–184.
23. Perumal B, Black EH, Levin F, Servat JJ. Non-infectious orbital vasculitides. *Eye (Lond)*. 2012;26(5):630–639.
24. Mehta M, Jakobiec F, Fay A. Idiopathic fibroinflammatory disease of the face, eyelids, and periorbital membrane with immunoglobulin G4-positive plasma cells. *Arch Pathol Lab Med*. 2009;133(8):1251–1255.
25. Kubota T, Moritani S, Katayama M, Terasaki H. Ocular adnexal IgG4-related lymphoplasmacytic infiltrative disorder. *Arch Ophthalmol*. 2010;128(5):577–584.
26. Zen Y, Nakanuma Y. IgG4-related disease: a cross-sectional study of 114 cases. *Am J Surg Pathol*. 2010;34(12):1812–1819.
27. Pemberton JD, Fay A. Idiopathic sclerosing orbital inflammation: a review of demographics, clinical presentation, imaging, pathology, treatment, and outcome. *Ophthal Plast Reconstr Surg*. 2012;28(1):79–83.
28. Deshpande V, Zen Y, Chan JK, et al. Consensus statement on the pathology of IgG4-related disease. *Mod Pathol*. 2012;25(9):1181–1192.
29. Chang SY, Keogh K, Lewis JE, Ryu JH, Yi ES. Increased IgG4-positive plasma cells in granulomatosis with polyangiitis: a diagnostic pitfall of IgG4-related disease [published online ahead of print April 11, 2012]. *Int J Rheumatol*. doi:10.1155/2012/121702.
30. Stone JH, Merkel PA, Spiera R, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med*. 2010;363(3):221–232.
31. Taylor SRJ, Salama AD, Joshi L, Pusey CD, Lightman SL. Rituximab is effective in the treatment of refractory ophthalmic Wegener's granulomatosis. *Arthritis Rheum*. 2009;60(5):1540–1547.
32. Martinez Del Pero M, Chaudhry A, Jones RB, Sivasothy P, Jani P, Jayne D. B-cell depletion with rituximab for refractory head and neck Wegener's granulomatosis: a cohort study. *Clin Otolaryngol*. 2009;34(4):328–335.
33. Blum M, Andrassy K, Adler D, Hartmann M, Volcker HE. Early experience with intravenous immunoglobulin treatment in Wegener's granulomatosis with ocular involvement. *Graefes Arch Clin Exp Ophthalmol*. 1997;235(9):599–602.
34. Lee R, D'Cruz D. Novel therapies for anti-neutrophil cytoplasmic antibody-associated vasculitis. *Drugs*. 2008;68(6):747–770.
35. Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus standard therapy for Wegener's granulomatosis. *N Engl J Med*. 2005;352(4):351–361.