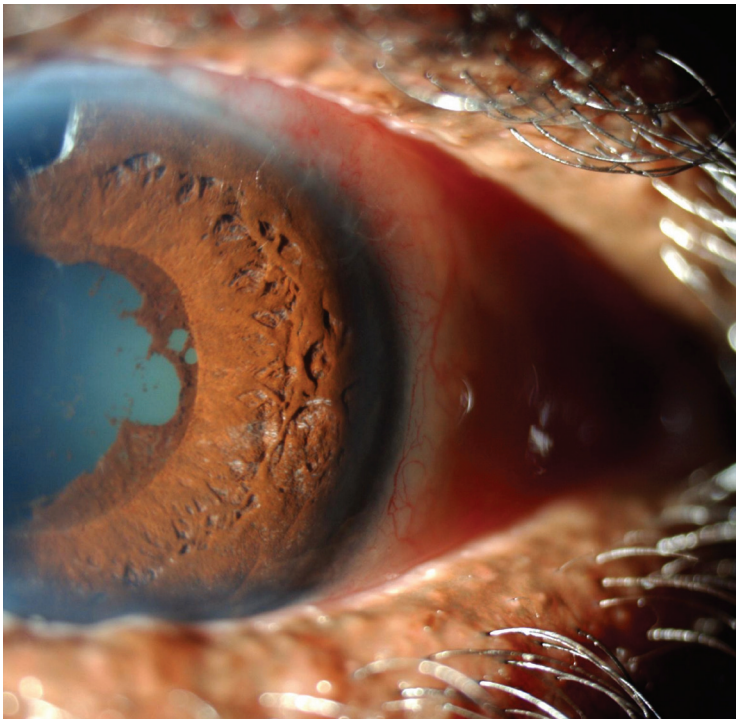


Woman, 64, With Eye Pain, Swelling, and Tearing

Jacqueline B. Broadway-Duren, DNP, MSN, FNP-BC



Credit: Paul Whitten/Science Source

Anterior uveitis—an inflammation of the iris, choroid, and ciliary body—is often associated with systemic inflammatory diseases and infections.

A 64-year-old woman presented to the clinic with a two-to-three-week history of significant pain, swelling, and excessive tearing of the left eye. The patient had a persistent cough but denied wheezing or shortness of breath.

Medical history was remarkable for uveitis, severe recurrent sinusitis, and allergic rhinitis. The patient reported that she had been exposed to benzene and burning paint fumes about 10 years ago but had no known symptoms or problems at the time.

Vital signs included a temperature of 97.0°F; respiratory rate, 18 breaths/min; pulse, 100 beats/min; and blood pressure, 144/80 mm Hg. Her height was 65 in; weight, 122 lb; and O₂ saturation, 100% on room air.

Physical examination revealed a left palpebral lacrimal mass with an enlarged lacrimal gland. The left lacrimal

gland and conjunctiva were mildly erythematous, with a cobblestone appearance. The right eye was stable, with no significant inflammation. Pupils were equal, round, and reactive to light and accommodation. Extraocular movements were intact. Nasal turbinates were swollen and mildly erythematous. Oropharynx was stable and tonsils absent. Left parotid gland was slightly swollen and tender.

The neck was supple with no jugular venous distension. Palpable cervical and supraclavicular lymphadenopathy, measuring approximately 1.5 x 1.5 cm bilaterally, was present. The lungs were clear to auscultation and percussion. The heart rate and rhythm were regular, with normal S₁ and S₂ sounds. The abdomen was soft, nontender, and without hepatosplenomegaly. Extremities were stable, with no rashes, lesions, or cutaneous skin nodules.

Jacqueline B. Broadway-Duren is a family nurse practitioner in the Department of Leukemia at MD Anderson Cancer Center, Houston.

TABLE 1
Patient's Laboratory Test and Tissue Evaluation Results

Angiotensin-converting enzyme (ACE) level	85 U/L (normal range, 9-67)
Biopsy Nasal tissue; parotid gland (left) Palpebral lacrimal gland (left)	Noncaseating granulomas Noncaseating granulomatous inflammation with infiltrates, composed of lymphocytes and epithelioid histiocytes, with nodular formation
CT and x-ray: Chest	Mediastinal and bilateral hilar lymphadenopathy and bilateral pulmonary nodules, approximately 1 cm in diameter
CT: Orbit, head, neck	Enlarged left lacrimal gland, 2 x 2 cm; contrast-enhancing lesion in left nasopharynx, 1.8 cm
Lactate dehydrogenase (LDH)	675 U/L (normal range, 313-618)
Tuberculosis test	Negative

The patient was referred to a specialist for a complete ophthalmologic examination and further work-up. This included a complete blood count, comprehensive metabolic panel, tissue biopsies of the affected lacrimal gland and parotid gland, CT, and x-rays; results are shown in Table 1. In addition, the patient's persistent nasosinus congestion was determined, by otolaryngologic consultation, to be the result of a deviated septum, for which she underwent endoscopic nasal septal repair with tissue biopsy.

The lacrimal gland biopsy led to a diagnosis of chronic noncaseating granulomatous dacryoad-

enitis, with an extensive area of necrosis. Significant findings included histiocytes and discrete nodules in the gland. Biopsies of the parotid gland and nasal tissue also identified noncaseating granulomas.

The patient's test results suggested several possible diagnoses, including

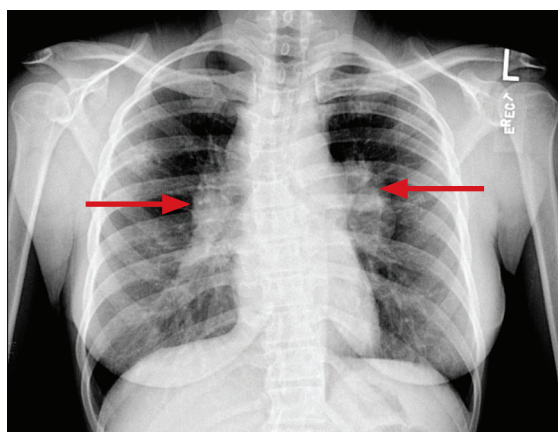
- Granulomatosis with polyangiitis
- Tuberculosis (TB) or similar pulmonary infectious disease
- Sarcoidosis (ocular and/or pulmonary)

DISCUSSION

Differential diagnosis

Granulomatosis with polyangiitis. GPA, also known as *Wegener granulomatosis*, is characterized by necrotizing granulomatous inflammation with necrotizing vasculitis, usually of small and medium vessels; ocular involvement is frequent.¹ Ocular granulomas of GPA can be mistaken for those caused by other diseases, such as mycobacterial or syphilitic infection or idiopathic uveitis.²

Tuberculosis. Common symptoms of TB include fever, cough, dyspnea, weight loss, malaise, and fatigue. Granulomas are typically necrotizing but are occasionally nonnecrotizing.³ TB can manifest with hilar and diffuse lymphadenopathy,⁴ which the patient's chest imaging revealed (see Figure 1). Granulomas produced by *Mycobacterium tuberculosis* and atypical mycobacteria are similar histopathologically to sarcoidosis granulomas, complicating the diagnostic process.⁵

FIGURE 1

Bilateral hilar lymphadenopathy can be seen in both tuberculosis and sarcoidosis.

Credit: Medical Body Scans/Science Source

Sarcoidosis. Sarcoidosis is a multisystem inflammatory disease characterized by noncaseating epithelioid granulomas in affected organs.⁶ More than 90% of patients with sarcoidosis present with pulmonary symptoms, including shortness of breath, cough, and pleuritic chest pain.⁶⁻⁸ Ocular manifestations, such as uveitis, iritis, or conjunctivitis, are less common, developing in 30% to 60% of patients.^{2,9,10} In addition, rashes, lesions, or cutaneous skin nodules, including erythema nodosum and lupus pernio, are seen in 25% to 35% of patients.^{2,6}

In up to two-thirds of patients, sarcoidosis resolves spontaneously²; in others, it may become chronic and progressive.⁴ Patients may have few or no symptoms; some require no treatment, while others may be severely affected by the disease.

Ocular involvement in sarcoidosis generally manifests as uveitis, most commonly in the anterior chamber (see photo on page 43). Uveitis is a potentially vision-threatening inflammatory disease involving both the uveal tract and adjacent structures.¹¹ In a review of records for 2,619 patients with uveitis, 59.9% had anterior disease, of whom 2.1% were diagnosed with sarcoidosis.¹¹

While the etiology of sarcoidosis continues to be studied,⁷ the prevailing theory is that, in genetically predisposed individuals, sarcoidosis is a cell-mediated immune response to as-yet unknown antigen triggers that leads to granuloma formation.^{3,6,7}

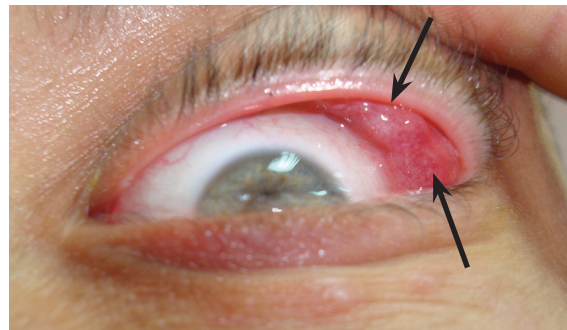
CD4+ activated T-cells stimulate the immune reaction against an antigen, producing cytokines that activate immune cells (eg, B cells, macrophages, monocytes, and neutrophils).² Immune cells accumulate and aggregate at antigen sites in an exaggerated response, resulting in the formation of granulomas (see Figure 2).^{7,12,13}

Infectious agents have long been investigated as possible causative agents in sarcoidosis, with *Mycobacterium* species most frequently identified.⁵ Additional possibilities include *Propionibacterium acnes* (found predominantly in skin lesions) and herpesviruses, although viruses are not known to cause epithelioid granulomas.¹⁴

Environmental triggers have also been explored. One large study found a possible association between exposure to insecticides, agricultural environments, and microbial bioaerosols and sarcoidosis.¹⁵

The difficulty of pinpointing a single etiology for sarcoidosis—with its varying clinical manifestations, severity, and disease course—suggests that sarcoidosis may be a spectrum of disorders caused by the

FIGURE 2



Red, swollen lacrimal gland can be seen on eversion of the eyelid, with granulomas visible in the conjunctiva.

Used with permission from the University of California Davis Medical Center.

interaction of genetic, immunologic, infectious, and environmental factors.¹⁴

Diagnosis

The diagnosis of sarcoidosis is based on clinical and radiologic features, histologic evidence of noncaseating granulomas, and exclusion of other possible causes of granulomas.^{2,12} In addition, when ocular sarcoidosis is suspected, other possible causes of uveitis must be excluded.

In an effort to address these challenges, the International Workshop on Ocular Sarcoidosis (IWOS) developed a standardized approach to diagnosis.⁹ The group first identified seven intraocular signs of ocular sarcoidosis and then five laboratory or imaging tests that are of value in making the diagnosis in patients with these signs. Last, they established four levels of certainty for the diagnosis of ocular sarcoidosis, based on these signs, tests, and biopsy results, if available (see Table 2, page 46).

Treatment

Anterior uveitis in sarcoidosis is usually treated initially with a topical corticosteroid (eg, prednisolone or difluprednate drops), particularly if the patient's symptoms are mild. In more severe cases (eg, posterior or bilateral uveitis) or when topical corticosteroids are ineffective, systemic (oral) corticosteroids (eg, prednisone) may be initiated. Topical therapy can also be added to an oral regimen as a means of decreasing the oral dosage and thereby reducing the adverse effects of systemic corticosteroids. When the patient's disease is refractory to corticosteroids or

TABLE 2
Diagnosis of Ocular Sarcoidosis

Based on combinations of presenting signs and test results, the diagnosis of ocular sarcoidosis can achieve one of four **levels of certainty**:

Definite: Biopsy-supported diagnosis of sarcoidosis, with a compatible uveitis

Presumed: Biopsy not done but chest x-ray or CT is positive for bilateral hilar lymphadenopathy (BHL), with a compatible uveitis

Probable: Biopsy not done and chest x-ray is negative for BHL, but 3 suggestive intraocular signs and 2 supportive laboratory or imaging test results are present (see below)

Possible: Negative lung biopsy, but at least 4 suggestive intraocular signs and at least 2 supportive laboratory or imaging test results are present (see below)

Intraocular signs of ocular sarcoidosis	Laboratory/imaging tests
Mutton-fat or small granulomatous keratic precipitates and/or iris nodules (Koeppe/Busacca)	Negative tuberculin (TB) test in a BCG-vaccinated patient or in a patient with a positive TB skin test previously
Trabecular meshwork nodules and/or tent-shaped peripheral anterior synechiae	Elevated serum angiotensin-converting enzyme (ACE) levels and/or elevated serum lysozyme
Snowballs/string of pearls vitreous opacities	Chest x-ray revealing BHL
Multiple chorioretinal peripheral lesions (active and/or atrophic)	Abnormal liver enzyme tests (any two of ALP, AST, ALT, LDH, or GGT)
Nodular and/or segmental periphlebitis (with or without candlewax drippings) and/or retinal macroaneurysm in an inflamed eye	Chest CT in a patient with a negative chest x-ray
Optic disc nodule(s)/granuloma(s) and/or solitary choroidal nodule	
Bilaterality	

Note: Other possible causes of uveitis must be eliminated first.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCG, Bacillus Calmette-Guerin;

GGT, gamma-glutamyl transpeptidase; LDH, lactate dehydrogenase.

Source: Herbort et al. *Occ Immunol Inflamm*. 2009.⁹

there are concerns about long-term adverse effects, chronic cases may be treated with immunosuppressive agents (eg, methotrexate, azathioprine, mycophenolate mofetil). Finally, refractory cases of ocular sarcoidosis may be treated with anti-tumor necrosis factor α (TNF- α) biologic agents such as infliximab and adalimumab.^{10,17}

OUTCOME FOR THE CASE PATIENT

Histologic evaluation of tissue from the lacrimal gland, parotid gland, and sinus cavity revealed inflammatory noncaseating granulomas, strongly suggestive of sarcoidosis. Diagnosis of ocular sarcoidosis was based on the noncaseating granulomas in

the lacrimal gland.^{9,16} Pulmonary sarcoidosis was also diagnosed, based on the presence of hilar and mediastinal lymphadenopathy.⁷

The mass in the patient’s lacrimal gland was surgically removed. She was treated with a combination of topical and oral corticosteroids tapered over two weeks, which induced remission of her ocular disease. The patient will be seen annually by an ophthalmologic specialist and was advised to contact her clinician immediately if acute ocular symptoms recurred.^{10,17}

The patient’s persistent cough was determined to be secondary to acute bronchitis, rather than to her pulmonary sarcoidosis, which required no treat-

ment. She received a short course of antibiotics and antitussives for her bronchitis. Systemic corticosteroid treatment of her ocular sarcoidosis also had the benefit of decreasing the size of her pulmonary nodules. She will be followed with annual CT and chest x-rays to monitor the status of her hilar and mediastinal lymphadenopathy and the nodules.³ Periodic pulmonary function testing will also be performed.⁷

CONCLUSION

The elusive nature of the diagnosis of sarcoidosis is well documented in the medical literature. In this case, histologic evaluation of biopsied tissue, correlated with clinical symptoms and radiographic findings, were essential in making the diagnosis.

Primary care providers may be the first to evaluate patients with ocular sarcoidosis and will oversee long-term management. Patients who present with symptoms of eye pain, visual disturbances, abnormal inflammatory ocular features, or swollen lacrimal glands should be referred to an ophthalmologic specialist for further evaluation. **CR**

REFERENCES

1. Jennette JC, Falk RJ, Bacon PA, et al. 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum*. 2013;65(1):1-11.
2. Culver DA. Sarcoidosis. *Immunol Allergy Clin North Am*. 2012;32(4):487-511.
3. Spagnolo P, Luppi F, Roversi P, et al. Sarcoidosis: challenging diagnostic aspects of an old disease. *Am J Med*. 2012;125(2):118-125.
4. Dempsey OJ, Peterson EW, Kerr KM, Denison AR. Sarcoidosis. *BMJ*. 2009;339:620-625.
5. Brownell I, Ramirez-Valle F, Sanchez M, Prystowsky S. Evidence for mycobacteria in sarcoidosis. *Am J Respir Cell Mol Biol*. 2011;45(5):899-905.
6. Iannuzzi MC, Fontana JR. Sarcoidosis: clinical presentation, immunopathogenesis, and therapeutics. *JAMA*. 2011;305(4):391-399.
7. Baughman MD, Culver DA, Judson MA. A concise review of pulmonary sarcoidosis. *Am J Respir Crit Care Med*. 2011;183(5):573-581.
8. Koyama T, Ueda H, Togashi K, et al. Radiologic manifestations of sarcoidosis in various organs. *Radiographics*. 2004;24(1):87-104.
9. Herborg CP, Rao NA, Mochizuki M; for the Scientific Committee of First International Workshop on Ocular Sarcoidosis. International criteria for the diagnosis of ocular sarcoidosis: results of the first International Workshop on Ocular Sarcoidosis (IWOS). *Ocul Immunol Inflamm*. 2009;17(3):160-169.
10. Jamilloux Y, Kodjikian L, Broussolle C, Seve P. Sarcoidosis and uveitis. *Autoimmun Rev*. 2014;13(8):840-849.
11. Barisani-Asenbauer T, Maca SM, Mejdoubi L, et al. Uveitis—a rare disease often associated with systemic diseases and infections—a systematic review of 2619 patients. *Orphanet J Rare Dis*. 2012;7:57.
12. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. *New Engl J Med*. 2007;357(21):2153-2165.
13. Fontenot A, King T. Pathogenesis of sarcoidosis. www.uptodate.com/contents/pathogenesis-of-sarcoidosis?source=search_result&search=Pathogenesis+of+sarcoidosis&selectedTitle=1%7E150. Accessed February 17, 2015.
14. Saidha S, Sotirchos ES, Eckstein C. Etiology of sarcoidosis: does infection play a role? *Yale J Biol Med*. 2012;85(1):133-141.
15. Newman LS, Rose CS, Bresnitz EA, et al; for the ACCESS Research Group. A case control etiologic study of sarcoidosis. Environmental and occupational risk factors. *Am J Respir Crit Care Med*. 2004;170:1324-1330.
16. Kawaguchi T, Hanada A, Horie S, et al. Evaluation of characteristic ocular signs and systemic investigations in ocular sarcoidosis patients. *Jpn J Ophthalmol*. 2007;51(2):121-126.
17. Bodaghi B, Touitou V, Fardeau C, et al. Ocular sarcoidosis. *Presse Med*. 2012;41(6 Pt 2):e349-e354.

Clinician Reviews®

Interested in PEER REVIEWING for us?

If you would like to share your talents and expertise
as a *Clinician Reviews* peer reviewer, please e-mail your
CV to CRNewsEditor@frontlinemedcom.com