

Sarcoidosis Optic Neuropathy

Optometric Retina Society Residency Award

Delia Groshek, OD

*White River Junction VA Medical Center
Ocular Disease Residency 2010-2011*

6244 North Knox Avenue
Chicago, IL 60646
(773) 620-5993
delia.groshek@gmail.com

Abstract

Sarcoidosis is a multi-systemic granulomatous disease of unknown etiology that can affect almost every organ in the body, though it typically affects the lung, lymph nodes, skin, liver and eyes. The diagnosis of sarcoidosis is based on histological evidence of noncaseating epithelioid cell granulomas, bilateral hilar lymphadenopathy, and exclusion of other diseases that produce a similar clinical and/or histological picture. Ocular involvement may be the presenting sign of the disease and can involve any ocular structure. In this case, a 67 year old Caucasian male presents with blur, photopsia, papillitis, and periphlebitis. This case report reviews the diagnosis, treatment and management of ocular sarcoidosis.

Key words: *angiotension converting enzyme, bilateral hilar lymphadenopathy, noncaseating granuloma, papillitis, periphlebitis, sarcoidosis*

Case Report

A 67 year old Caucasian male presented to the VA eye clinic with a chief complaint of central blurring of his vision in his left eye, which happened twice the previous night lasting for five minutes each time. Afterwards, he saw blue spots. In the exam, he stated his left eye felt like it had a dull, aching pain of a 2-3 on a scale of 10. He reported itching and tearing of his left eye. Upon further questioning, the patient denied scalp tenderness, jaw claudication, or recent weight loss. The patient did report neck pain, which has been stable for years due to his arthritis. He also reported fatigue and shortness of breath for the last twelve months with an associated dry cough. The last three primary care doctors and a pulmonologist had not been able to uncover a diagnosis for these symptoms, but the symptoms had gotten worse over the last two to three months.

The patient's medical history included hypertension, osteoarthritis, xerotic eczema, and sciatica. It also included personal history of tuberculosis diagnosed at the age of two with treatment. He had chest x-rays on a yearly basis since he was a teenager with no lung lesions found. His last yearly x-ray was in May 2010. The patient denied a history of tobacco use.

Visual acuity uncorrected measured 20/30+2 OD with pinhole of 20/20 and 20/40 OS with pinhole of 20/30. Pupils were equal, round and minimally reactive to light without an afferent pupillary defect. Extraocular muscles, confrontational visual fields, and anterior segment evaluation were unremarkable. Intraocular pressure measured with Goldmann was 14 mm Hg OD and 14 mm Hg OS. The patient was dilated using 1% tropicamide and 2.5% phenylephrine. He dilated poorly. The fundus examination was unremarkable OD. The left optic nerve was swollen with dense hemorrhages 360 degrees and a small blood clot floating above the optic nerve inferior which appeared to be attached to the optic nerve. The veins were dilated and tortuous with many arteriovenous crossing changes. There were a few scattered hemorrhages in

the posterior pole, greatest in the inferior temporal arcade (*see* Figure 1). Blood pressure was taken right arm sitting at 150/82 (stage 1 hypertension). The temporal arteries were palpated and were soft with bilateral pulse, no tenderness, swelling, or induration. Fundus photos were taken. The differential diagnoses considered in this case include: anterior ischemic optic neuropathy, diabetic papillopathy, malignant hypertension, tuberculosis, syphilis, sarcoidosis, optic neuritis due to multiple sclerosis, and compressive optic neuropathy.

The exact diagnosis of this patient was unable to be determined until further testing was completed. The laboratory tests ordered were erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complete blood count (CBC), hemoglobin A1C and chest x-ray. Syphilis testing was not done at this time and was to be ordered if the above testing came back normal. The patient was educated on the clinical findings and was instructed to continue taking daily aspirin 81mg.

The chest x-ray performed the same day revealed enlarged right pulmonary hilum with possible enlargement of the left hilum (*see* Figure 2). The differential diagnosis from the chest x-ray included sarcoidosis, tuberculosis and lymphoma. Blood work came back normal with only slightly elevated ESR and CRP.

The follow-up CT scan revealed hilar and mediastinal lymphadenopathy with a few pulmonary nodules. The patient was seen by gastroenterology due to fatty liver seen on the CT scan. His liver enzymes were tested and were elevated. The patient had a lung biopsy with endobronchial ultrasound. The patient's lung biopsy of the right (R11) lymph node came back negative for malignancy but revealed necrotizing granulomatous inflammation. Flow cytometry showed CD4 to CD8 ratio of 10:1. Acid fast bacillus and fungus stains were both negative. This pathology report was most consistent with sarcoidosis.

The patient was seen in the eye clinic throughout his diagnosis for follow-up examinations. Fluorescein angiogram of the left eye revealed an increase in hyperfluorescent telangiectasia on the optic nerve 360 degrees during the study with a hypofluorescent hemorrhage inferior nasal to the optic nerve and a few scattered hyperfluorescent dot hemorrhages inferior temporal (*see* Figure 3 & 4). At about one minute faint hyperfluorescent periphlebitis was seen superior temporal and inferior temporal which increased in fluorescence around two minutes (*see* Figure 5). The patient was diagnosed with papillitis with periphlebitis secondary to sarcoidosis.

B-scan of the left eye revealed very minimal elevation of the left optic nerve due to the edema; no signs of infiltration or uveal thickening were present. Exophthalmometry, color vision, and Humphrey visual field 30-2 were all normal. Optical coherence tomography of the retinal nerve fiber layer of the left eye showed elevation superior and inferior quadrant with the nasal and temporal quadrants within normal limits (*see* Figure 6). A MRI of the head and orbits was ordered to rule out any central nervous system involvement. The MRI was normal (*see* Figure 7).

After discussion of the eye findings with pulmonology/rheumatology/infectious disease, it was decided oral prednisone should be started with 40mg daily for 1 month and then 20mg daily for 1 month and then 10mg daily for 6 months. One month after starting oral prednisone, the fundus examination revealed resolved papillitis and periphlebitis (*see* Figure 8).

Discussion

Sarcoidosis commonly affects young and middle aged adults with peak incidences in the third to fourth decade and again in the fifth to seventh decade.^{5,6,7} In the United States, sarcoidosis is more prevalent in African Americans with a slight female predilection.^{6,7,8} It

frequently presents with bilateral hilar lymphadenopathy (90% patients), pulmonary infiltrates, ocular signs, and skin lesions.⁵ Overall mortality is 5% due to complications such as pulmonary insufficiency and cardiac involvement.^{5,9} Mortality doubles to 10% in patients with neurosarcoidosis.⁶

There is controversy over the exact etiology of sarcoidosis. One theory suggests a genetic link.^{5,1} Other theories include environmental factors, infectious agents (viruses, bacteria, and mycobacteria), drugs, chemicals, or an autoimmune dysfunction without any clear answers.^{5,6}

In sarcoidosis, there is an increased accumulation of CD4+ T cells of Th1 type, which interacts with macrophages, monocytes, and other inflammatory cells to contribute to granuloma formation at the sites of inflammation.^{5,6} Patients taking interferon for treatment of other diseases may trigger or exacerbate sarcoidosis due to the drug increasing the Th1 response.¹¹

Pulmonary involvement is the most common systemic manifestation of sarcoidosis.^{1,5,6,9} Symptoms are dry cough, dyspnea, chest pain, and rare haemoptysis.^{5,6} Smoking can increase the severity of the disease.⁵ An abnormal chest x-ray is found in 90% of patients.¹ Multiple studies have demonstrated that the most important marker for prognosis is the initial chest x-ray.¹ Stage zero is a normal chest x-ray, stage one is bilateral hilar lymphadenopathy (BHL), stage two is bilateral hilar lymphadenopathy and diffuse parenchymal reticulonodular infiltrates (upper lobe predominance), stage three is reticulonodular infiltrates alone, and stage four is pulmonary fibrosis.^{1,5} Other diseases that may produce similar radiographic results and should be ruled out include tuberculosis, lymphoma, and carcinoma.⁶

Biopsy proven sarcoidosis gives a definitive diagnosis.³ The recommended lung biopsy procedure is transbronchial lung biopsy with an 80-90% diagnostic yield.⁵ Broncho-alveolar lavage (BAL) with a CD4/CD8 ratio of greater than 3.5-4.0 has a specificity of 94-96%.^{5,12}

CD4/CD8 ratios tend to be higher in patients with radiographic evidence of sarcoidosis and evidence of acute inflammation than in asymptomatic patients.¹³

Skin lesions occur in twenty five percent of patients.⁶ Erythema nodosum, which are tender subcutaneous red nodules most common on the lower extremities, is often a presenting sign of acute disease typically in Caucasians with good prognosis.^{3,5,6} Lupus pernio, which are purplish plaque like lesions around the mouth, nose, lids, and ears, is a more common presentation in African Americans and often associated with a more chronic course.^{5,6,9} Other skin lesions can occur including infiltration of old scars by granulomas.⁶ Skin biopsy is useful in diagnosis of sarcoidosis due to the accessibility of the lesions; however biopsy of erythema nodosum is not useful since it does not contain granulomas.^{3,5} In the past, the Kveim-Siltzbach skin test was utilized to diagnose sarcoidosis. For this test, antigen from proven sarcoidosis spleens was injected intradermally and diagnosis was made three to six weeks later.^{1,3} The nodule that formed was biopsied for noncaseating granulomas. However, this is not commercially available and is rarely used anymore due to fear of transmitting infectious agents.^{3,6,15}

Ocular manifestations occur in 25-50% of patients with sarcoidosis.^{1,4,6} Ocular involvement may be the presenting sign of the disease and can involve any ocular structure.^{4,6} The most common ocular manifestation (two-thirds of patients) is unilateral or bilateral anterior uveitis with cells and flare, mutton fat keratitic precipitates or small fine keratitic precipitates. In addition, patients may present with iris nodules at the pupillary margin (Koeppe) and/or iris stromal nodules (Busacca).^{1,3,6,16} Secondary complications include anterior and posterior synechiae, trabecular meshwork nodules, secondary glaucoma, secondary cataract, band keratopathy (due to chronic uveitis or hypercalcemia), or cystoid macular edema.^{1,6,16} Patients

who require cataract surgery are at risk for severe ocular inflammation post-operatively and often require systemic corticosteroids.³ Other anterior segment involvement includes keratoconjunctivitis sicca and conjunctival granulomatous nodules, which often resemble follicles.⁶ Conjunctival biopsies are positive in 25-57% patients.¹ Lid and adnexal findings include granulomatous lid lesions and lacrimal gland enlargement, which can cause displacement of the globe.^{6,8}

The most common signs of posterior segment involvement are periphlebitis and posterior uveitis with vitreal opacities described as strings of pearls or snowballs, commonly located inferiorly on the retinal surface anterior to the equator.^{1,3,9,16} Patients may also present with chorioretinitis or choroidal granulomas, neovascularization of the disc or retina, or rarely occlusion of the retinal veins.^{1,6,9,16} Branch retinal vein occlusions are more common than central retinal vein occlusions.¹ Deep yellow choroidal lesions and mottling of the pigment epithelium are more common than true elevated choroidal granulomas.³ High resolution ultrasound biomicroscopy can show uveal thickening.¹⁷

Neurosarcoidosis occurs in 5-15% of cases.¹⁸ The most common sign of neurosarcoidosis is facial nerve palsy, usually lower motor neuron dysfunction.^{6,7} Other cranial nerve palsies may lead to extraocular muscle dysfunction causing diplopia.^{1,6,7,16} Pupillary abnormalities such as unilateral or bilateral tonic pupil can be found in neurosarcoidosis.¹⁹ It is suspected that this patient has bilateral tonic pupil given his poor response to light and poor dilation. Syphilis should be ruled out in cases of bilateral tonic pupil without a known cause. Optic nerve involvement may be unilateral or bilateral.⁷ There can be papilledema secondary to intracranial sarcoid lesions causing increased intracranial pressure, disc edema secondary to intraocular inflammation, and granulomatous involvement of the optic nerve, tract, or intracranial path.^{1,6,7,16} Optic disc

swelling occurs in 39% of patients, usually without visual dysfunction.³ Isolated optic neuropathy may be the first manifestation of neurosarcoidosis.¹ Optic atrophy may result after compression of the nerve.⁶

When sarcoidosis is suspected as a cause of intraocular inflammation diagnostic tests should be ordered such as serum angiotension-converting enzyme (ACE), complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), chest x-ray, PPD with energy level, syphilis serology, antinuclear antibody, and toxoplasmosis titers (in cases of posterior uveitis). If there is cranial nerve, optic nerve or lacrimal gland involvement then a CT, MRI, or gallium scan of the head and orbits should be ordered.⁶ In the gallium scan, gallium 67 accumulates in areas of inflammation and is useful in detecting lacrimal gland, parotid gland and lung involvement.^{3,6} MRI manifestations are non-specific with a predilection for the base of the brain and midline structures, such as hypothalamus and pituitary gland.^{5,20} Neurosarcoidosis can mimic multiple sclerosis (MS) findings on a MRI. Granulomatous processes will often present with persistent enhancement of parenchymal or meningeal lesions which is not expected in MS.^{5,7,21} MRI may also show enhancement of the optic nerves with or without enlargement.²¹ This can lead to an incorrect diagnosis of optic nerve glioma.¹⁹ Fluorescein angiography and indocyanine green angiography are useful tests in the evaluation of neovascularization and chorioretinal involvement.⁶

ACE, an enzyme that converts angiotension I to angiotension II (a potent vasoconstrictor), is elevated in 60-90% of patients with active sarcoidosis.^{3,15} Serum ACE, which reflects the total body granuloma content, is useful in monitoring the course of the disease.^{1,5,22} Studies have demonstrated that measuring soluble interleukin-2 receptor (sIL2R) is the best marker for predicting disease severity.^{22,23} Serum ACE levels may be elevated in other

diseases such as tuberculosis, active histoplasmosis, alcoholic cirrhosis, diabetes mellitus, idiopathic pulmonary fibrosis, leprosy, Gaucher's disease, Hodgkin's disease, myeloma, primary biliary cirrhosis, amyloidosis, hyperthyroidism, scleroderma, and pulmonary embolism.¹⁵ ACE is not useful in diagnosis of sarcoidosis in younger patients, since patients under the age of 20 normally have very high ACE levels.^{15, 16} ACE inhibitor antihypertensive medications will decrease ACE levels, so for these patients it is useful to order serum lysozyme.^{15, 16} Patients with sarcoidosis may also have hypercalcemia, hypercalciuria, lymphopenia (associated with chronic disease), and elevated liver enzymes.^{3, 16, 24} The first international workshop on ocular sarcoidosis in 2006, included liver function testing as a laboratory investigation to include when sarcoidosis is suspected due to the liver being a site frequently involved.^{2, 16, 25} In this case, the patient's liver enzymes were significantly elevated.

Tuberculosis is important to rule out in cases where ocular sarcoidosis is suspected, but not yet diagnosed.² In this case, the patient had a reported history of tuberculosis at age two. Therefore, a chest x-ray was ordered at the initial visit. Tuberculosis may also present as bilateral hilar lymphadenopathy. However, chest x-ray patterns can be varied. Often in pulmonary tuberculosis the apices of the lungs show infiltrates and cavitation. Diagnosis of tuberculosis is confirmed with isolation of *M. tuberculosis* in the sputum or lung tissue. *M. tuberculosis* is an aerobic, acid-fast staining bacillus (AFB).²⁶ A positive smear for acid fast bacillus along with a positive culture gives a positive diagnosis of tuberculosis. Acid-fast bacillus is used to monitor treatment for tuberculosis.²⁷ In this case, the smear was negative for acid-fast bacillus.

For stage one pulmonary sarcoidosis as was the case in this patient, initial follow-up for pulmonology is every six months along with chest x-rays.^{5, 6} Often stage one disease is not treated with therapy and will spontaneously resolve within one to two years.⁶ However,

treatment is initiated when there is disease progression or other organ involvement.^{5,6} Often in cases with anterior uveitis, the standard protocol of topical steroids and cycloplegic agents are used along with anti-glaucoma medications in cases of secondary glaucoma. Also intralesional steroid injections may be used for lid lesions and periocular steroid injections for severe anterior uveitis.¹ Since there was only posterior involvement in this case, systemic steroids was the route of choice. Due to the multiple organ systems involved in sarcoidosis, it is important to co-manage the patient with a pulmonologist and/or an internist.

Optimal dose and duration of corticosteroids has not been adequately studied in randomized, prospective trials. Treating the cause of sarcoidosis is not possible due to unknown etiology. The initial dose of prednisone is usually 20-40mg/day, which is tapered to 5-10mg/day over 2-3 months. Treatment is continued for a minimum of 12 months and then patients are monitored for 3 years after therapy discontinued.⁵ Higher initial doses of corticosteroids may be necessary in patients with chronic ocular inflammatory disease.³ Practitioners should monitor patients closely for complications of steroids, such as weight gain, diabetes mellitus, hypertension, glaucoma, and cataracts.⁶

Patients who suffer from major side effects of corticosteroids or require long term therapy are usually put on either methotrexate 10-25mg/week or azathioprine 100-150mg/day.^{1,5,6} Methotrexate, a folate analog that inhibits dihydrofolate reductase, is usually the drug of choice.²⁸ However, it may take up to six months for methotrexate to take effect so patients are often kept on a maintenance dose of corticosteroids.³ Antimalarial drugs, such as chloroquine and hydroxychloroquine, are used as first line therapy for lupus pernio, other disfiguring skin disease and hypercalcaemia.^{5,6} In the rare case, where chronic sarcoidosis is refractory to all other treatments, anti-TNF alpha may be considered.⁵

Conclusion

This case shows the complexity involved in diagnosing sarcoidosis. The most important radiological evidence for sarcoidosis is bilateral hilar lymphadenopathy. Diagnosis is confirmed with histological evidence of noncaseating epithelioid cell granulomas. It is important to exclude other diseases that produce a similar clinical and histological picture, such as tuberculosis. In progressive pulmonary disease or other organ involvement, systemic corticosteroids are the drug of choice. Co-management of sarcoidosis patients is important due to multiple organ systems involved.

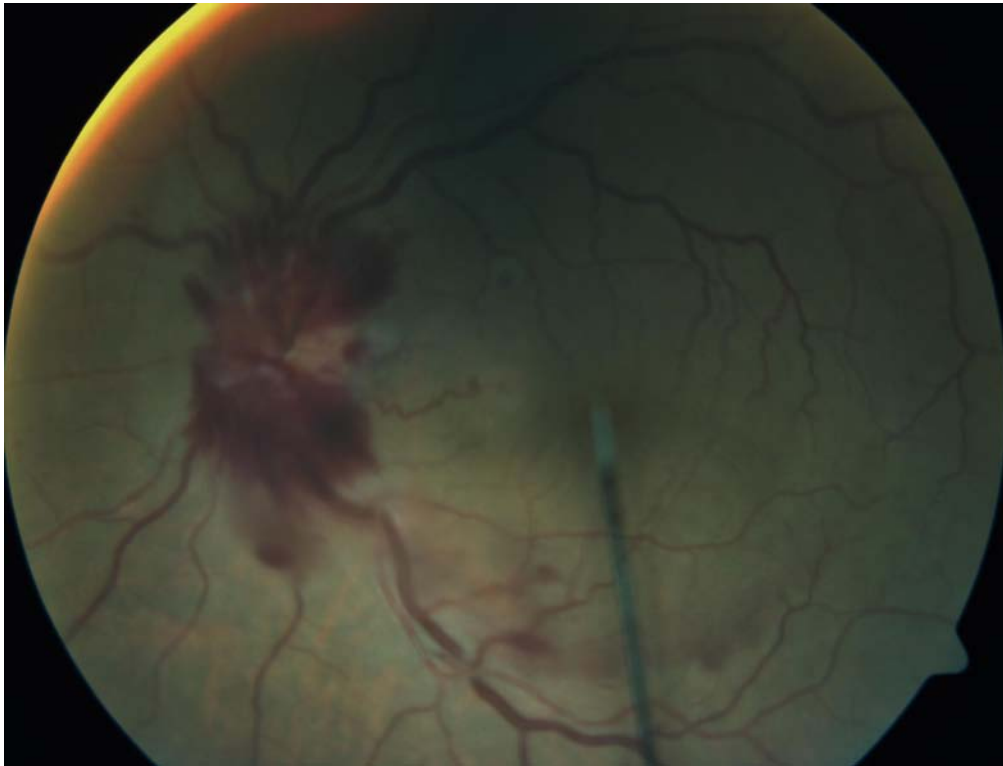


Figure 1 Fundus photo of the left eye at the initial visit. This shows papillitis with dense hemorrhages 360 degrees, dilated retinal veins with arteriovenous crossing changes greatest in the inferior temporal arcade.

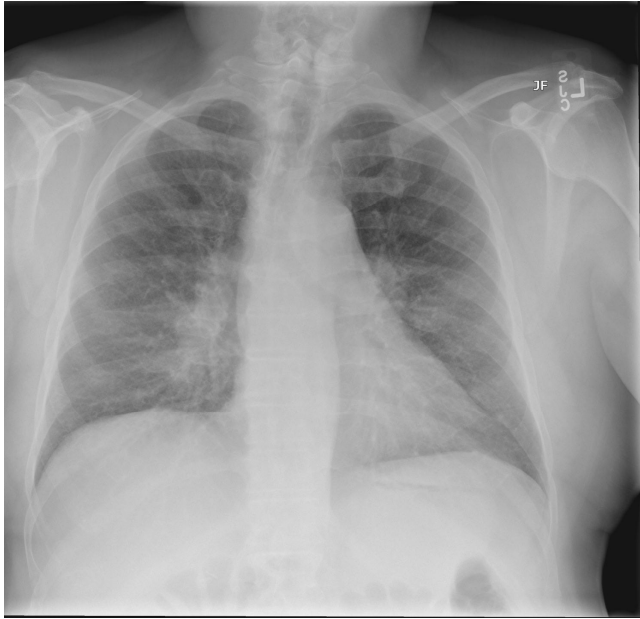


Figure 2 Initial chest x-ray showing stage one bilateral hilar lymphadenopathy



Figure 3 This shows papillitis with periphlebitis in the inferior temporal and superior temporal arcades.



Figure 4 Intravenous fluorescein angiography (IVFA) arteriovenous phase that shows hyperfluorescent telangiectasia on the optic nerve 360 degrees, hypofluorescent hemorrhage inferior nasal to the optic nerve and a few scattered hyperfluorescent dot hemorrhages inferior temporal.

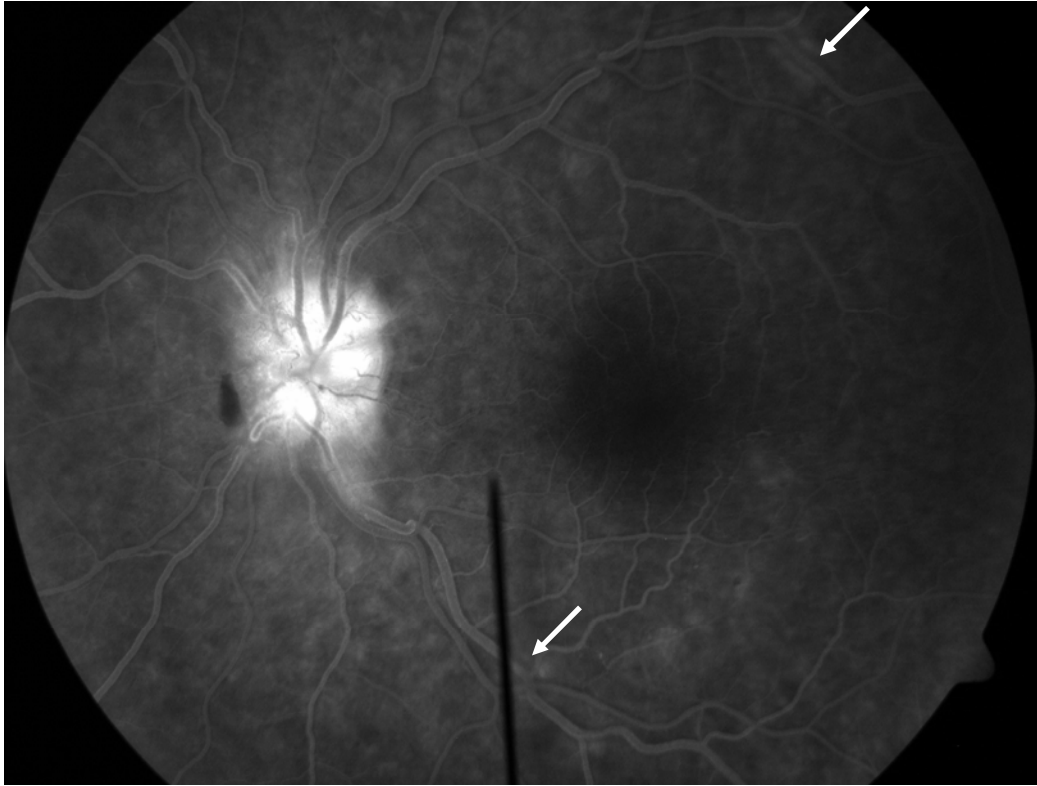
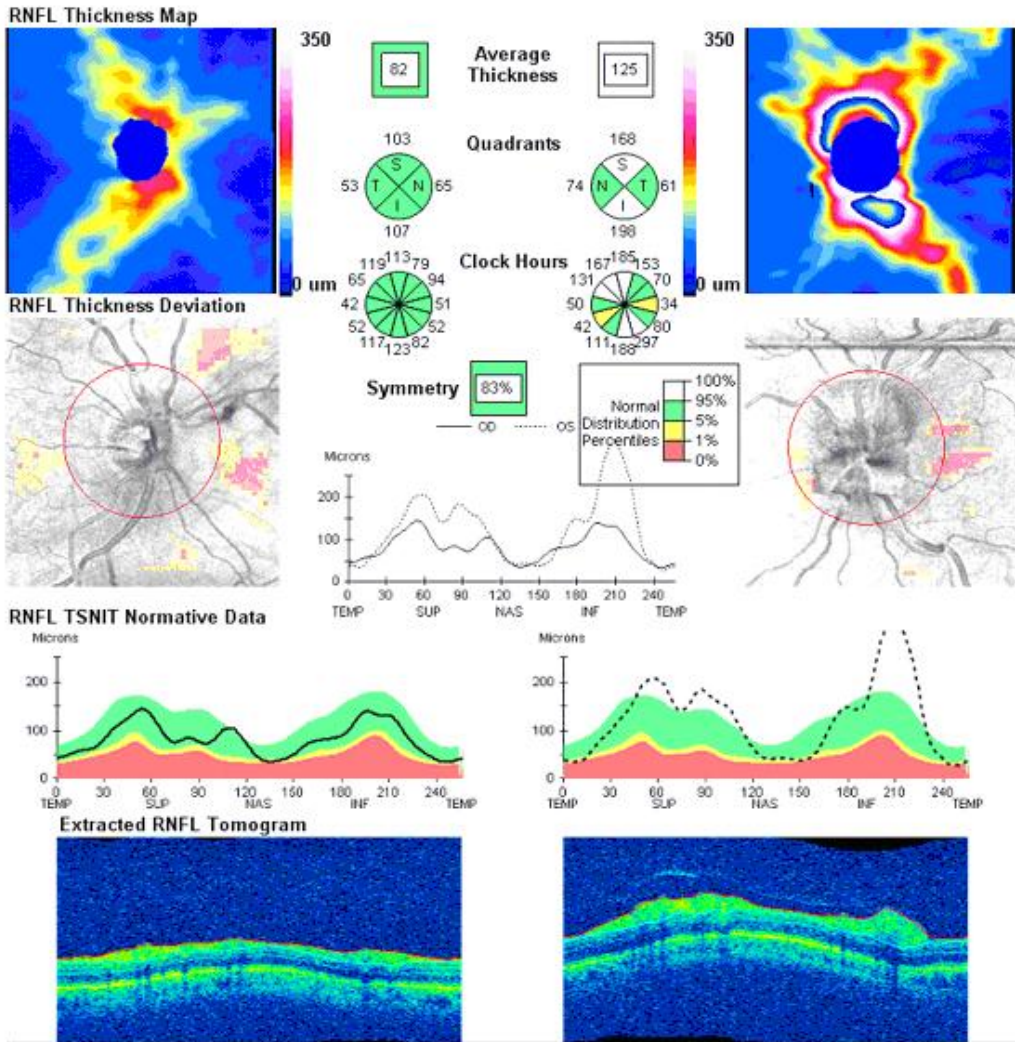


Figure 5 IVFA late phase that shows an increase in hyperfluorescence of the optic nerve head and hyperfluorescent periphlebitis superior temporal and inferior temporal.

OD OS
 Exam Time: 1:52 PM 1:51 PM CZMI
 Signal Strength: 6/10 6/10
 Exam Date: 1/24/2011
 Technician: Operator, Cirrus
 DOB: 6/27/1943
 Gender: Male
 Physician:



Optic Disc Cube 200x200 OD ● OS



Comments

Physician's Signature

SW Ver: 3.0.0.64
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Figure 6 Cirrus™ (Carl Zeiss Meditec) spectral domain high definition optical coherence tomography (OCT) of the retinal nerve fiber layer shows elevation of the superior and inferior quadrant of the left eye.

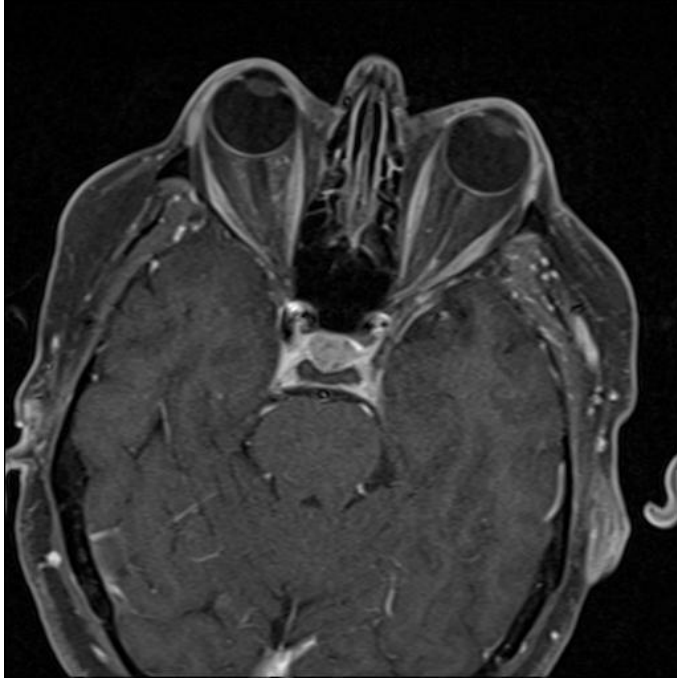


Figure 7 Normal Magnetic Resonance Imaging (MRI)

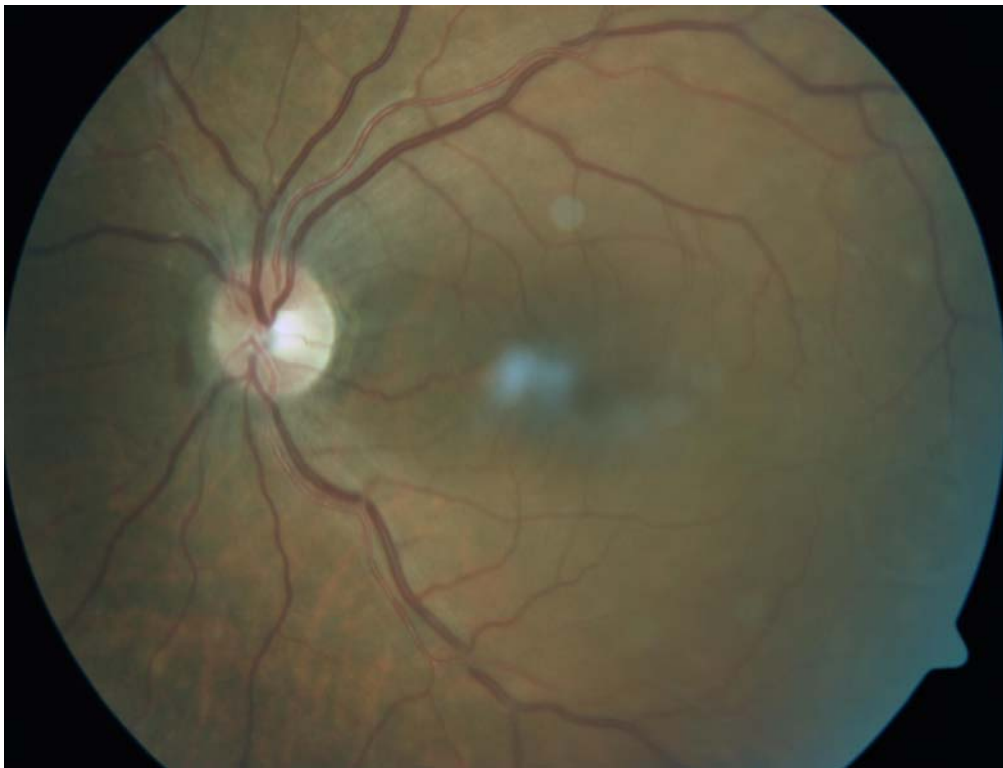


Figure 8 This shows resolved papillitis and periphlebitis one month after starting oral prednisone. (Note: there is an artifact in the center of the picture over the macula)

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