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Short-term oral albendazole therapy for diffuse unilateral subacute neuroretinitis: A case report

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ABSTRACT

Purpose: To report on a case of diffuse unilateral subacute neuroretinitis (DUSN) that was successfully treated with a short course of oral albendazole.

Observations: A 51-year-old male presented with severe visual loss secondary to DUSN associated with a positive *Toxocara* serology. Because the parasite could not be detected on fundoscopy, first-line treatment with photocoagulation could not be administered. Treatment with a 6-day course of oral albendazole resulted in the resolution of DUSN as well as the restoration of visual acuity.

Conclusion and importance: Although DUSN is characterized by the presence of a parasitic organism in the retina, there are cases in which the parasite is not visible. Albendazole has been used to treat such cases, but a standard treatment regimen has not been determined yet. Our case suggests that the resolution of DUSN can be achieved with short-term albendazole therapy.

1. Introduction

Diffuse unilateral subacute neuroretinitis (DUSN) is an infectious ocular disease that may result in visual-acuity deterioration.[1] Although this disease's pathogenesis remains unclear and a specific causative agent has not been identified, parasitic organisms such as *Baylisascaris procyonis, Ancylostoma caninum, and Toxocara canis* are thought to be involved in its etiology.[1,2] DUSN is more prevalent in young individuals, and most patients present with unilateral disease.[3,4] In the early stages of DUSN, patients may present with a mild loss of visual acuity associated with vitritis, optic disc edema, and gray-white retinal lesions.[1] Because symptoms tend to be more subtle during the early stages, patients may seek medical care later in the course of the disease. Late-stage DUSN is characterized by a severe loss of visual acuity, degenerative retinal pigment epithelium changes, optic atrophy, and retinal arteriole narrowing.[1,4]

DUSN is confirmed when a parasite is identified in the retina of a patient presenting with the disease's classic signs and symptoms.[1,5] However, in many cases, the parasite cannot be identified, making the diagnosis (in those cases) of DUSN a challenge.[2,6] Maintaining a high index of suspicion for this condition is crucial, as early detection and treatment have been associated with better patient outcomes.[5,7–9]

When the parasite is visualized, the first-line treatment of DUSN consists of laser photocoagulation.[1,6] In cases in which the parasite cannot be detected, albendazole has proven to be a valuable second option.[3,10] However, there is no consensus about the specific regimen that should be used to treat DUSN. In this report, we present the case of a 51-year-old male with DUSN that was associated with a positive *Toxocara* serology. Treatment with a 6-day course of albendazole resulted in the resolution of the neuroretinitis and significant improvement in visual acuity.

2. Case report

A 51-year-old Hispanic male reported a 3-week history of constant, severe blurred vision of the right eye. He had been referred to a retina and uveitis specialist for evaluation of his retinal lesions and cystoid macular edema of the right eye. His primary ophthalmologist had also

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noted fine keratic precipitates, vitreous cells, and foci of retinitis in the patient's right eye and had started him on prednisolone acetate 1%, every 2 hours, and ketorolac 0.5%, four times daily, five days before presentation. The review of systems was negative. The patient's past ocular history revealed that he had bilateral cataracts, and his past medical history was remarkable for untreated hypercholesterolemia. The patient denied using alcohol, tobacco, or illicit drug use as well as having traveled outside Puerto Rico. He had a pet dog and a rabbit.

A comprehensive ophthalmological exam revealed a best-corrected visual acuity of finger counting in the right eye and 20/40 in the left eye; the patient's manifest refractions were +0.50–0.50 × 180 (right eye) and +1.50–0.50 × 180 (left eye). His intraocular pressure was 15 mmHg for both eyes. Confrontational visual fields testing revealed a nasal defect in the right eye; visual fields were full in the left eye. Amsler grid testing revealed a central scotoma in the right eye and no abnormalities in the left. The patient's pupils were round and reactive to light, and there was no afferent pupillary defect. His extraocular movements were intact, and the orbits were within normal limits. A slit lamp exam revealed +2 nuclear sclerosis in both eyes but no keratic precipitates, posterior synechiae, or anterior chamber cells in either eye. The vitreous in the right eye had 1+ cells and was clear in the left.

An examination of the right fundus revealed subtle disc edema and an area of retinitis measuring approximately four discs in diameter adjacent to the inferior border of the disc. This area of retinitis had associated exudation with precipitation of hard exudate, inferonasally and within the macula in a star pattern. Additionally, a chorioretinal scar, measuring approximately one disc diameter, was noted approximately 4500 μm superotemporal to the fovea (Fig. 1A). Macular spectral-domain optical coherence tomography (SD-OCT) revealed cystoid intraretinal and sub-foveal fluid.

A presumptive diagnosis of neuroretinitis in the right eye was made, and a workup to rule out such infectious causes as syphilis, *toxoplasmosis*, *bartonellosis*, and tuberculosis was ordered. Empiric treatment with prednisolone acetate 1% and broad-spectrum antibiotics, including doxycycline (100mg twice daily) and trimethoprim/sulfamethoxazole (SMZ-TMP) (800/160 four times daily), was initiated. *Lactobacillus acidophilus* (175mg daily) was also prescribed.

One week after the presentation, his visual acuity had improved to 20/200 in the right eye and remained unchanged in the left eye. The right fundus examination revealed persistent foci of retinitis and macular exudates. The macular SD-OCT showed an improvement of the macular edema, though persistent subfoveal fluid was detected. The initial workup, including a fluorescent treponemal antibody absorption test, a rapid plasma reagin test; Bartonella henselae, Bartonella quintana, and Toxoplasma antibody (IgG and IgM) panels; an HIV-1 and -2 test; and a Mantoux skin test, was negative. The chest X-ray revealed a minimally elongated and calcified aorta, was otherwise within normal limits. A CBC revealed an elevated WBC (10.5×10^3) with a normal differential (5% eosinophils). A comprehensive metabolic panel revealed a slight increase in the albumin/globulin ratio of 1.83, which

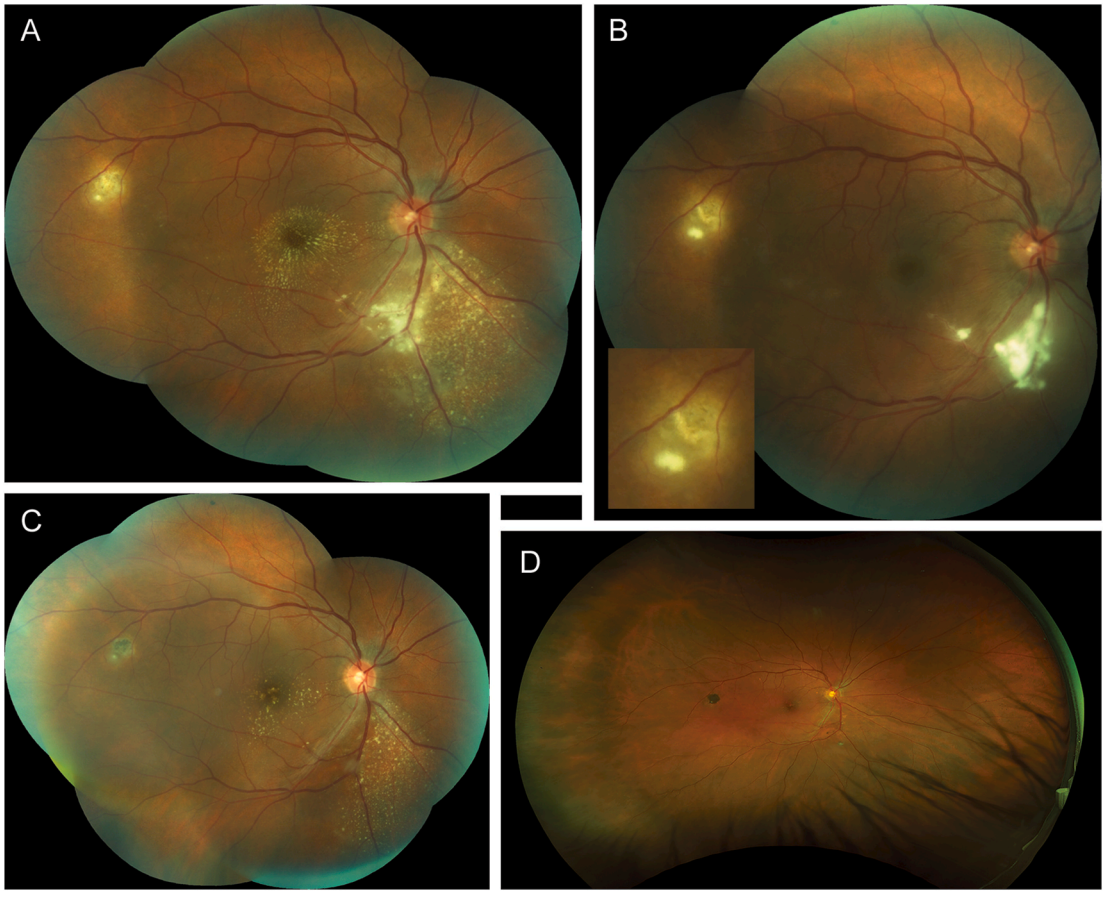

Fig. 1. Color fundus photographs of the right eye. A. Disc edema and hard exudates in a macular star pattern consistent with a diagnosis of neuroretinitis can be seen and were observed at the initial presentation. Additionally, an area of retinitis and a chorioretinal scar inferior to the disc and superotemporal to the macula, respectively, can be seen B. A curved nematode (insert) superotemporal to the macula can be observed, which was present one week before the presentation. Foci of retinitis are noted adjacent to and distant from the nematode. C. After the completion of a six-day course of therapy with systemic albendazole and oral corticosteroids, a significant improvement of the neuroretinitis was noted and can be observed in this photo. D. Four years after the initial presentation, only a small pigmented chorioretinal scar remains in the area corresponding to where the nematode was initially located. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

was otherwise within normal limits.

On the two-week follow-up exam, there were no changes in visual acuity; however, the OCT revealed the complete resolution of the edema. A further workup, which included a test for *Toxocara* antibodies and an examination of a stool sample for ova and parasites, was ordered. After three weeks, the uncorrected visual acuity had improved to 20/100 in the right eye. At this visit, the patient reported a four-day history of fever, headache, and sore throat. He was evaluated in the emergency room and found to have neck lymphadenopathy. A CT scan with contrast enhancement of the neck revealed necrotic lymph nodes with stranding and potential extra-capsular spread. The emergency room physician added oral amoxicillin to the patient's drug regimen. The following day, the patient was evaluated by an otorhinolaryngologist, who found no lesions on performing a flexible laryngoscopy. A neck biopsy and follow-up evaluation were scheduled for two weeks hence, and the amoxicillin was discontinued.

At the four-week follow-up visit, the findings for the right eye remained unchanged, but a white retinal lesion, measuring approximately 750 μm in diameter, was noted along the inferotemporal arcade of the left eye. The lesion was thought to represent a new focus of retinitis (Fig. 2A). The patient's stool was negative for ova and parasites. However, *Toxocara* (total antibody) testing by ELISA was positive. Following this test, ophthalmic images from the referring physician were sought and reviewed. Obtained one week before the retina and uveitis specialist evaluated the patient, these images revealed a curved roundworm, measuring approximately 1000 μm and surrounded by patches of retinitis that were located in the superotemporal region, correlating to where the chorioretinal scar was noted on the patient's initial evaluation (Fig. 1B). The parasite was not visible on the fundus images obtained in subsequent visits.

The patient was admitted to the ward and started on oral albendazole (400mg daily). As only 6-days' worth of albendazole was available in the entire U.S. Commonwealth of Puerto Rico, the patient received treatment for six days. The patient continued to receive SMZ-TMP, while doxycycline was discontinued. He was started on prednisone (40mg daily), after the second day of treatment with albendazole. The pathology service was consulted for a follow-up of the previously detected cervical lymphadenopathy, but as the lymph nodes had decreased in size, a palpation-guided fine-needle aspiration biopsy could not be performed. Further evaluation with a follow-up neck CT scan revealed that the cervical adenopathy had resolved.

Following the inpatient course of therapy, the patient's visual acuity improved to 20/40 (both eyes), and the areas of retinitis showed significant improvement (Figs. 1C and 2B). SMZ-TMP was discontinued, and the patient was discharged home with instructions for a gradual tapering of the prednisone over eleven weeks. At four months after the initial presentation, the patient's visual acuity had improved to 20/20 in his right eye, and a fundus examination revealed the total resolution of the retinitis in both eyes. Four years after the initial presentation, the patient's visual acuity remained 20/20 in the right eye, without any recurrence of the neuroretinitis. A small, pigmented chorioretinal scar superotemporal to the fovea was visible in the patient's right eye (Fig. 1D).

3. Discussion

DUSN is an inflammatory disease capable of involving multiple ocular structures, such as the retina, the retinal vessels, the retinal pigment epithelium, and the optic nerve.[4,9] Its pathogenesis is not fully understood, but it appears to be multifactorial. The presence of a parasite in the retina, the release of toxic products by that parasite, and the host's immune response to the organism generate an inflammatory response.[1,4,6,11] This inflammation is associated with the unilateral loss of visual acuity that characterizes the disease.[9]

Although the patient tested positive for *Toxocara* antibodies, it is possible that his DUSN was not caused by this organism. Serologic studies may be conducted in cases in which the parasite is not visible; however, they have questionable value in the diagnosis of DUSN.[5,8,12] Because it is likely that different nematode species share antigens, the patient's positive *Toxocara* result may not have been specific for this particular organism.[5,8,13] Additionally, a positive test result for a nematode does not mean that this organism is the causative agent of DUSN; another, different, organism that the patient was not tested for may have been involved.[5,13] Serologic testing results depend on factors such as the time the test was administered within the disease course and patient immunity; thus, such results may be falsely negative in patients with *Toxocara*.[4,13]

It has been challenging to identify the etiologic agent in DUSN because few nematodes have been successfully retrieved for histopathologic examination.[14] Even in cases in which a parasite is visualized and then obtained, it often disintegrates, making the accurate identification of the specimen a difficult task.[14,15] Therefore, in most cases of DUSN, clinicians rely on the characteristics revealed by fundoscopy, epidemiologic data, and serology to try to identify the causative agent.[4] *Toxocara canis* nematodes, along with those of *Ancylostoma caninum*, fall within the category of smaller nematodes and are endemic to the Caribbean islands.[4] These smaller worms lead to characteristic retinal lesions, including focal chorioretinal atrophic scars.[16] Using ophthalmic photography, we pinpointed the patient's parasite, identifying it as a large nematode, which measured approximately 1000 μm. However, after completing his treatment the patient developed a residual chorioretinal scar, which is more commonly associated with disease secondary to a small nematode species (Fig. 1D).[4] These seemingly contradictory findings highlight the difficulty of identifying the causative species in cases of DUSN.

Other infectious entities were considered and explored before the

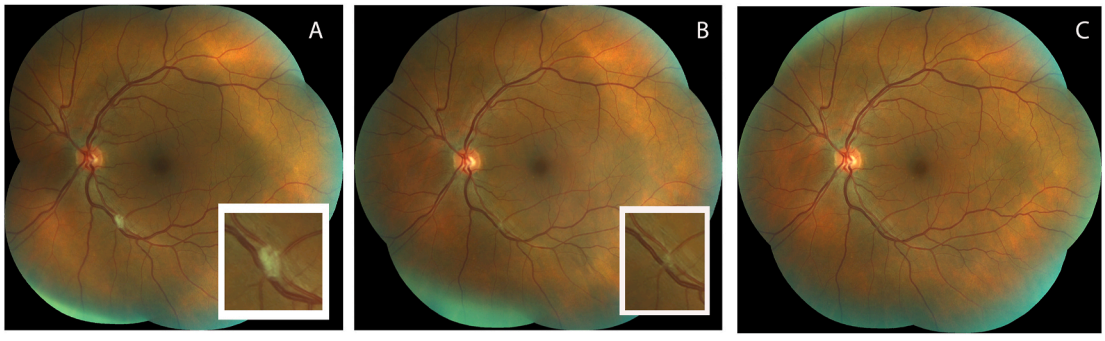

Fig. 2. Color fundus photographs of the left eye. A. The new onset of a white retinal lesion thought to represent a new focus of retinitis can be seen along the inferotemporal arcade (first observed four weeks after the initial presentation). B. After the completion of a 6-day course of albendazole, the lesion improved significantly, which improvement is reflected in the image. C. Three months after the completion of therapy, a complete resolution of the lesion occurred, as can be seen. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

final diagnosis of DUSN was made. It was apparent that the patient's neuroretinitis was due to an infectious cause, as an adjacent area of retinitis was present. Before the initial workup results were available, the patient was empirically treated for toxoplasmosis and bartonellosis. Ocular toxoplasmosis is the most common cause of infectious retinitis.[17] It may be effectively treated with SMZ-TMP, while *bartonellosis* is a common cause of neuroretinitis and may be effectively treated with doxycycline.[17,18] Although serologic testing for *Bartonella* spp. and *Toxoplasma* was negative, the patient's condition appeared to respond to broad-spectrum antibiotic treatment. Given the role of doxycycline and SMZ-TMP in the treatment of other infectious ocular diseases and the patient's favorable response to this treatment regimen, the antibiotic treatment was maintained for a total of 6 weeks.

The patient's posterior uveitis and visual acuity initially improved after doxycycline and SMZ-TMP therapy; however, the appearance of a new lesion in the patient's left eye (Fig. 2A) prompted a search for an alternative treatment. Most patients with diffuse subacute neuroretinitis present with symptoms in one eye, but rare cases of bilateral manifestations have been described in the literature.[3] After albendazole was administered, both eyes showed improvements (Figs. 1C and 2B and C), suggesting that this drug played a significant positive role in treatment. Furthermore, therapy with albendazole resulted in the resolution of his constitutional symptoms and of the neck lymphadenopathy. However, because the patient received treatment with other medications prior to the administration of albendazole, the extent to which these other medications contributed to the successful treatment of DUSN with a short course of albendazole therapy remains unknown.

Corticosteroids were used throughout the course of the patient's treatment. Initially, prednisolone acetate was administered to treat the associated macular edema, which then resolved. Upon the diagnosis of DUSN, oral corticosteroids were prescribed. The rationale behind this treatment was that these drugs decrease the inflammatory process associated with the condition. The role of corticosteroids in the treatment of DUSN has not been established yet, and there is conflicting evidence regarding their efficacy. Corticosteroids appear to both decrease inflammation and prevent the worsening of visual acuity in DUSN.[6,11,15,19] Their use is linked to the suppression of inflammation that occurs after the death of the nematode (secondary to treatment with photocoagulation or systemic medications such as albendazole).[11] Further research is needed to clarify whether or not corticosteroids should be used as adjunctive therapy in the treatment of DUSN.

Studies have shown that albendazole can effectively treat DUSN, particularly in cases in which the parasite cannot be seen and, therefore, photocoagulation cannot be used.[3,6,10] The dose and duration of albendazole therapy for the treatment of DUSN have yet to be established, but a 30-day course has been adapted by some clinicians based on its ability to successfully treat other parasitic infections.[20] A previous case series reported on the successful treatment of 12 patients with 400 mg of oral albendazole (daily) for 30 days, which treatment resulted in improvements in visual acuity, the visual field, and ocular inflammation.[4,10] In 2015, Relhan et al. conducted a case series in which 13 patients with DUSN were first treated with laser photocoagulation, followed by 400 mg of oral albendazole (daily) for 30 days; improvement in the visual acuity in seven patients and the stabilization of the other six were seen.[2] Although parasites were not detected in any of these cases, laser photocoagulation was performed in order to alter the blood-retina barrier, since this treatment has been postulated to increase the ocular penetration of albendazole.[2] Both cases series highlight the role of albendazole in the treatment of DUSN.

Most case series have used 30-day regimens, but others have achieved success with treatments of shorter duration. In Cortez et al.'s case series, six patients with confirmed DUSN were treated with 200 mg of oral albendazole (three times daily) for a total of 10 days.[3] In three of the cases, this regimen resulted in the death and slow reabsorption of the, with no adverse effects.[3] The patients experienced reductions in their existing retinitis and did not develop additional lesions.[3] In 2012, Guan-Fook et al. reported the case of a young patient with late-stage DUSN treated with 400 mg of oral albendazole (daily) for 5 days and with 1mg/kg of oral prednisone, with the patient's tapering off over 6 weeks.[6] The parasite was not seen on physical exam, and serologic studies detected the presence of *Toxocara* IgG. With this treatment, the patient's subretinal lesions resolved and his inflammation decreased; however, visual acuity was not restored in the affected eye.[6] Even in cases of late-stage disease, a short course of albendazole combined with steroids appears to reduce the inflammation associated with DUSN.

4. Conclusions

Our case suggests that there is a role for short-term albendazole therapy in the treatment of DUSN. Although the standard 30-day regimen is effective, short-term therapy may have its benefits: It is associated with better patient compliance and decreases in both treatment costs and drug side effects.[20,21] Although the results of this case support the use of short-term albendazole therapy, further research is needed to investigate whether it can be effective for other patients and to analyze how it compares to the existing treatment modalities. Additionally, the role of adjunct therapy (with agents such as corticosteroids and antibiotics) in the treatment of DUSN must be further explored.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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Authorship

All authors attest that they meet the current ICMJE criteria for authorship.

Declaration of competing interest

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