

# Uveitis and autoimmune hepatitis, a real entity? A case report with review of the literature

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## Abstract:

A 63-year-old man presented with a 10-day history of severe pain, redness of the right eye, and reduced vision in both eyes. In addition, he had been diagnosed incidentally with liver cirrhosis and splenomegaly 1 week before he was admitted to our center. The patient was found to have severe intraocular inflammation that initially involved the right eye and then progressed to bilateral panuveitis. The presenting visual acuity was 20/60 for the left eye and lumbar puncture (LP) for the right eye. Vitreous tap revealed a nonturbid, yellow fluid that was negative for organism culture, polymerase chain reaction (PCR), and tumor markers. Oral prednisolone significantly improved the clinical status of both ocular and hepatic inflammation. During the admission period, the patient developed several medical comorbid complications that temporarily altered the management of our case. After a full evaluation of uveitis causes, the patient was diagnosed with biopsy-proven autoimmune hepatitis. In addition to a high-dose oral steroid, azathioprine was given for 3 months before the patient developed decompensated liver failure, which was successfully managed with a liver transplant. The patient was stable for 1 year following the transplant but eventually developed blindness of the right eye and visual acuity of 20/30 in the left eye.

## Keywords:

Autoimmune hepatitis, blindness, ocular immunology, panuveitis, uveitis

## INTRODUCTION

Uveitis is an intraocular inflammation that primarily affects the uvea, which includes the iris, ciliary body, and choroid. The term uveitis may also include inflammation of other intraocular tissues, such as the retina, optic disc, and vitreous. Uveitis is a potentially blinding condition that accounts for approximately 10% of all legal blindness worldwide.<sup>[1]</sup> In Saudi Arabia, the estimated prevalence of uveitis is 1.5%, with an incidence of 129 cases per year.<sup>[2]</sup>

Uveitis usually occurs due to an infectious process such as herpes simplex, varicella-zoster virus, tuberculosis, or toxoplasmosis. Moreover, several systemic autoinflammatory diseases, such as ankylosing spondylitis, inflammatory bowel disease (IBD), reactive arthritis, sarcoidosis, and Behcet's disease, are well known as causative factors of uveitis.<sup>[3]</sup>

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Autoimmune hepatitis (AIH) primarily affects all age groups and ethnicities, with a strong female predilection. In Saudi Arabia, AIH is responsible for 14.3% of all cases of liver transplantation.<sup>[4]</sup> It is estimated that 20% of all AIH patients present with another autoimmune disease, with diabetes and thyroid disorders being the most common in Saudi Arabia.<sup>[5]</sup> Interestingly, few reports addressed the unusual association between AIH and uveitis. Here, we present the course and clinical manifestations of uveitis associated with AIH.

## CASE REPORT

A 63-year-old male was incidentally diagnosed with liver cirrhosis and splenomegaly in another hospital 1 week before he was admitted to our center in Riyadh for further investigation and management. In addition, the patient complained of a painful red right eye and vision loss for 10 days before admission.

On clinical examination, the patient was jaundiced with stable vital signs. An ultrasound

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of the abdomen showed a cirrhotic liver with portal hypertension. Magnetic resonance cholangiopancreatography (MRCP) showed an uncomplicated stone with no dilatation in the common bile duct or intrahepatic duct. His FibroScan score was F4 with Child A status. Initially, there were no signs suggestive of decompensated liver failure. History of alcohol intake, ingested herbs, and hepatotoxic medications was all negative. His brother had previously received liver transplant.

He presented with a visual acuity of 20/60 in the left eye and light perception in the right eye. Intraocular pressure at presentation was 22 mmHg for the right eye and 14 mmHg for the left eye. Extraocular muscles were full. Ophthalmic examination of the right eye showed severe conjunctival congestion, shallow anterior chamber with occasional cells, central corneal haze, mature lens cataract with posterior synechiae, and mitotic nonreactive pupil. B-scan was suggestive of severe vitritis [Figure 1].

Initially, the patient was started on a topical steroid and mydriatic agents, which partially relieved his eye discomfort. Ten days after, the patient developed severe nongranulomatous bilateral panuveitis that further involved the left eye. Fundus photography and fluorescein angiography of the left eye showed peripapillary arteritis with a single Roth spot temporal to the macula. Fundus examination was not applicable for the right eye. Since infection, particularly endogenous endophthalmitis, could not be ruled out initially, intravitreal vancomycin, ceftazidime, and dexamethasone with intravenous acyclovir were administered.

Full uveitis and rheumatology workups were performed to rule out differential diagnoses, such as giant cell arteritis, polyarteritis nodosa, systemic lupus erythematosus (SLE), sarcoidosis, lymphoproliferative disease, masquerade syndrome, or infectious causes. Vitreous sampling revealed a clear yellow fluid, which came back negative for organism culture, PCR, and tumor markers. Cytology of the vitreous fluid was suggestive of a chronic inflammatory process, as pus and neutrophils were

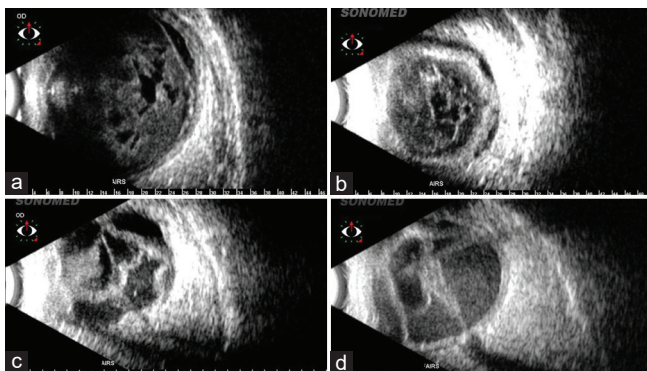
not evident. Cultures from blood, synovial fluid, and urine were all negative. There was no previous history suggestive of IBD or connective tissue disease. Chest computed tomography was negative for sarcoidosis features. In addition, the patient denied any previous history of oral or genitalia ulcers.

Blood tests were unremarkable except for elevated ESR (130 mm/h) and CRP (150 mg/dL), aspartate transaminase 83 IU/L, alanine aminotransferase 59 IU/L,  $\gamma$ -glutamyl transpeptidase 384 IU/L, alkaline phosphatase 359 IU/L, total bilirubin 20  $\mu$ mol/L, and conjugated bilirubin 14  $\mu$ mol. Infectious causes such as tuberculosis, herpes simplex virus, viral hepatitis, brucellosis, and HIV were ruled out with serological tests. Rheumatoid factor, cytoplasmic antineutrophil cytoplasmic antibodies, perinuclear antineutrophil cytoplasmic antibodies, antimitochondrial antibodies, and liver-kidney microsome type 1 antibodies were all negative. Serological tests were remarkable for antinuclear antibodies of indirect immunofluorescence assay at a titer of 1:40, anti-smooth muscle antibodies at a titer of 1:320, HLA B51 B52, and high IgG 2260 mg/dL and IgA 648 mg/dL.

After ruling out infectious causes, autoimmunity etiology was suggested. Therefore, the patient was started on 40 mg oral prednisolone with intravitreal dexamethasone injection while fortified antibiotics were stopped. The patient then developed a prostatic abscess with sepsis, which was managed accordingly. As a consequence, oral steroids were temporarily stopped, and a liver biopsy was delayed until clinical stability had been achieved. As the biochemical evaluation was suggestive of AIH, a liver biopsy was performed and revealed lymphoplasmacytic infiltrate with moderate interface hepatitis.

After ophthalmology reassessment and biopsy-proven AIH, oral prednisolone dose was increased to 60 mg, and azathioprine 50 mg was added to the regimen. One week after initiating the treatment regimen, visual acuity of the left eye improved and became 20/30, while the right eye remained LP. B-scan showed a shrunken right eye with resolved inflammation, and a choroidal detachment was noticed. The patient was discharged after agreeing to taper oral prednisolone and gradually increase azathioprine to 75 mg.

After 4 months, the patient presented with a decompensated liver failure and was labeled as Child B status. A diagnosis of AIH was considered definite [Table 1]. After 6 months of managing the patient's comorbidities, a liver transplant from a living donor was successful, and the patient remained stable for 1 year following the transplant. Ophthalmic follow-up was unremarkable, but his right eye appeared to be irreversibly blind [Figure 2].



**Figure 1:** B-scan of the patient's right eye. (a) Moderate organized vitreous opacity with retinal detachment involving the macula at first presentation. (b) Dense vitreous with peripheral choroidal detachment 1 month after the first presentation. (c) Prephthisis with total retinal detachment three months after the first presentation. (d) Dense vitreous and sub-retinal hemorrhage 6 months after the first presentation

## DISCUSSION

Uveitis is an intraocular inflammation that results from a variety of specific local or systemic inflammatory triggers. Uveitis primarily affects people between the ages of 20 and 60, but it can also occur in young children. Usually, uveitis

**Table 1: Autoimmune hepatitis: Revised scoring system**

Criteria element	Score
Gender: Male	0
ALP/AST: >3	-2
ALP/ALT: >3	
IgG assay: >2	3
ANA, SMA, or LKM1: SMA positive	3
AMA: Negative	0
Hepatitis markers: Negative	3
Hepatotoxic drug: Negative	1
Alcohol intake: Negative	2
Liver biopsy: Lymphoplasmatic infiltrates with moderate interface hepatitis	4
Autoimmune disease: Negative	0
Response to therapy: Relapse	3
Total score: 15 pretreatment, 17 posttreatment	
Status of AIH	
Pretreatment AIH: Definite	
Posttreatment: Definite	

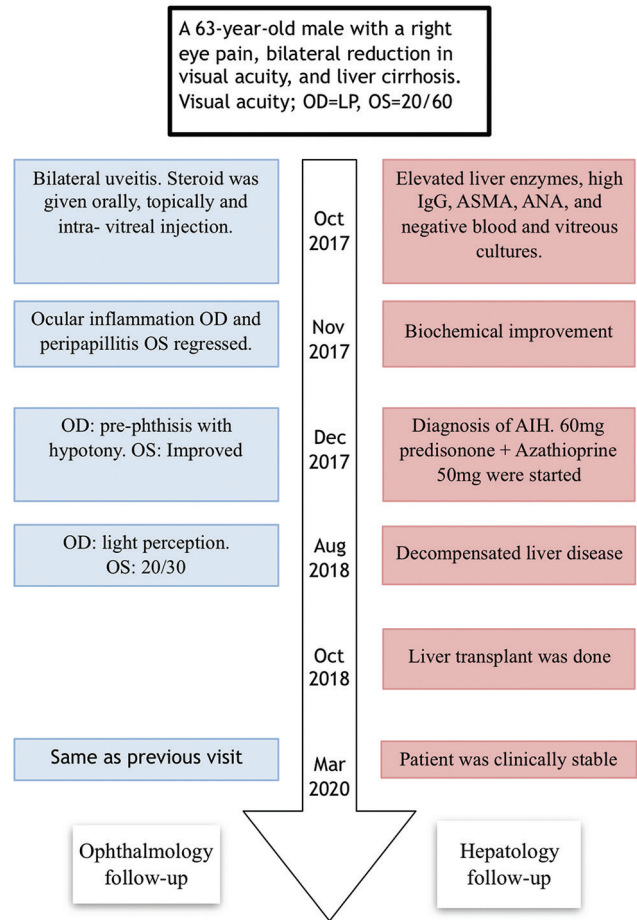
ALP: Alkaline phosphatase, AST: Aspartate aminotransferase, ALT: Alanine transaminase, SMA: Smooth muscle antibodies, ANA: Antinuclear antibodies, LKM1: Liver kidney microsome type 1, AMA: Anti-mitochondrial antibody, AIH: Autoimmune hepatitis

leads to serious sight-threatening complications if not detected and treated early. Many infectious and inflammatory causes have been linked to uveitis.<sup>[1]</sup> In the Middle East and Northern Africa, the most common infectious etiologies of uveitis were herpetic infection, toxoplasmosis, and tuberculosis. Behcet’s disease and Vogt–Koyanagi–Harada disease were the most common noninfectious causes of uveitis in the Middle East and Northern Africa.<sup>[3]</sup>

The course and severity of AIH tend to be highly variable, ranging from mild hepatic disease to massive hepatocellular necrosis.<sup>[4]</sup> Our patient first presented with jaundice, which is the most reported clinical feature among AIH patients and liver cirrhosis.<sup>[6]</sup> AIH is associated with other extrahepatic immune-mediated disorders, including thyroiditis, type-1 diabetes, ulcerative colitis, SLE, Sjögren syndrome, and rheumatoid arthritis.<sup>[4]</sup> However, the possibility of uveitis being an extrahepatic manifestation of AIH remains unclear.

Both AIH and uveitis have been described in terms of their associations with other systemic conditions but not with one another. To the best of our knowledge, there have only been 11 reported cases worldwide that suggested the presence of AIH as an etiology of uveitis [Table 2]. Before 1989, several reports discussed the association between uveitis and chronic active hepatitis. However, these cases were likely to be attributed to type-C viral hepatitis, which had not been discovered by that time; hence, they were excluded from our review.

Despite the wide spectrum of differential diagnosis, the clinical course of this case seems to be highly attributed to AIH. An intraocular infection was suspected but not proven, as vitreous came back negative. The intraocular inflammation seemingly responded to steroid and azathioprine therapy. Thus, it is indeed presented as autoimmune uveitis presumably associated with



**Figure 2:** Timetable demonstrating the sequence of events and case progression

AIH. Moreover, the patient’s biomarkers were suggestive of competent immunity. Lim *et al.*<sup>[9]</sup> have described the pattern of uveitis that is linked to AIH as a chronic, bilateral, and persistent uveitis with sight-threatening complications. Uveitis associated with AIH can present suddenly as anterior uveitis or insidiously as intermediate or panuveitis. Interestingly, we observed a chronic long-standing course of bilateral panuveitis in our case, which started in the right side before involving the left eye. Lim *et al.* concluded that the rarity of uveitis and AIH occurring simultaneously, the consistent pattern of uveitis, and the shared concept of immune dysregulation in both conditions are suggestive of a real association.<sup>[9]</sup>

This assumption is limited by the few reports and the possibility of overlap syndromes, which might make the association of uveitis and AIH appeared coincidental. For example, the second case reported by Kamal *et al.*<sup>[7]</sup> was diagnosed with primary biliary cirrhosis (PBC) and treated with oral ursodeoxycholic acid. In addition, the case reported by Kim *et al.*<sup>[10]</sup> was likely to be an overlap syndrome that showed features of PBC and AIH.

To overcome such an obstacle, we applied the revised diagnostic criteria published by the International Autoimmune

**Table 2: Summary of all reported uveitis cases associated with autoimmune hepatitis in the literature**

Author name	Gender	Age	Clinical features	Complications	Treatment	
Kamal <i>et al.</i> <sup>[7]</sup>	Female	33	Unilateral panuveitis Persistent	N/A	Topical steroid Oral prednisolone Azathioprine	
	Female	39	Unilateral panuveitis Persistent	N/A	Topical steroid Ursodeoxycholic acid	
Romanell <i>et al.</i> <sup>[8]</sup>	Male	38	Unilateral anterior uveitis	Corneal stromal scar	Topical steroid Oral prednisolone	
Lim <i>et al.</i> <sup>[9]</sup>	Female	31	Bilateral sudden anterior uveitis Persistent	Glaucoma	Topical steroid Oral prednisolone Azathioprine	
	Female	34	Bilateral sudden anterior uveitis Persistent	Cataract Posterior synechiae Cystoid macular edema Epiretinal membrane hypotony	Topical steroid Oral prednisolone Azathioprine	
	Male	65	Bilateral gradual intermediate uveitis Persistent	Cataract	Topical steroid Oral prednisolone Azathioprine	
	Female	18	Bilateral gradual panuveitis Persistent	Cataract Posterior synechiae Glaucoma Cystoid macular edema	Topical steroid Oral prednisolone Azathioprine Mycophenolate mofetil Cyclophosphamide Chlorambucil	
	Male	8	Bilateral gradual panuveitis Persistent	Cataract Glaucoma Peripheral anterior synechiae Hypotony Band keratopathy Phthisis bulbi	Topical steroid Oral prednisolone Cyclosporine	
	Male	67	Bilateral gradual panuveitis Persistent	Cystoid macular edema	Topical steroid Oral prednisolone Azathioprine	
	Female	40	Bilateral sudden anterior uveitis Persistent	Cataract Posterior synechiae	Topical steroid Oral prednisolone Azathioprine	
	Kim <i>et al.</i> <sup>[10]</sup>	Female	50	Unilateral sudden anterior uveitis Started in the right then involved the left eye	N/A	Topical steroid Ursodeoxycholic acid

N/A: Not applicable

Hepatitis Group [Table 1]. This scoring system identifies AIH as “definite” or “probable” with a 97%–100% sensitivity and 96%–100% specificity.<sup>[11]</sup> The diagnosis and management of this case were challenging for the following reasons. First, the patient presented late, as he came from another hospital that is 160 km far from the city of Riyadh. Second, the presence of several comorbidities caused a significant delay in performing a biopsy and liver transplant, which necessitate good clinical stability. In addition, the color of the vitreous fluid was unusually frank yellow, which should have been sent earlier for chemical analysis to rule out bilirubin accumulation.

Both uveitis and liver hepatitis significantly improved as we introduced oral steroids. To salvage the patient’s vision, intravitreal steroid was injected. Clinically, the pain was vanished and the inflammation resolved. However, the retrolental membrane, as expected, pulled and detached the peripheral choroid and ciliary body. This resulted in a

permanent hypotony, which indicated an aggressive response to a long-standing severe vitreous inflammation. In fact, intravitreal steroid accelerated the shrinkage of the vitreous membranes, but the eye still went into a phthisical phase, as the patient presented too late. The left eye inflammation resolved as we introduced the immunosuppressant.

## CONCLUSION

The clinical pattern of uveitis associated with AIH tends to be chronic and bilateral with serious ocular complications. The higher likelihood of facing diagnostic dilemmas and devastating complications while approaching uveitis associated with autoimmune hepatitis is a clear reason for hepatologists and ophthalmologists to further explore such an entity.

## Declaration of patient consent

The authors certify that they have obtained all appropriate

patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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