THERAPEUTIC ADVANCES in
Rare Disease

Case Report

Papilledema and retinopathy lead to diagnosis of IgA nephropathy: a case report

Ther Adv Rare Dis

2023, Vol. 4: 1–8

DOI: 10.1177/
26330040231152957

James T. Kwan*, **Erin Lanzo***, **David J. Ramsey**, **Aarti Kalra** and **Geetha K. Athappilly-Rolfe**

Abstract

This case features a young healthy male who was diagnosed with immunoglobulin A (IgA) nephropathy after presenting with blurry vision that was caused by hypertensive retinopathy and papilledema. In this report, we examine the relationship between hypertension and increased intracranial pressure (ICP), along with the ocular signs of IgA nephropathy that may present in the setting of kidney disease.

Plain Language Summary

Immunoglobulin A (IgA) nephropathy is an immune-mediated inflammatory condition that affects the kidneys and is characterized by deposits of IgA antibodies across the body. Nephropathy in general is defined as the deterioration of kidney function. Hypertension is a common complication because of the resultant kidney damage. IgA can also deposit widely across the body, including within the eyes, and may lead to various inflammatory manifestations affecting the front and back of the eyes.

We present a case of a 38-year-old male with 2 weeks of worsening vision and headaches. His blood pressure was extremely high (206/116 mmHg) and he was found to have acute kidney injury. Examination of his eye revealed hypertensive retinopathy but also significant swelling of both of his optic discs, concerning for increased intracranial pressure (ICP), which is unusual in a young, otherwise healthy male. The investigation for the cause of increased ICP led to the diagnosis of IgA nephropathy. Treatment of his increased ICP and blood pressure resulted in improvement of his vision.

It is important to consider increased ICP as a cause of optic disc swelling in patients with very high blood pressures. Prompt evaluation and management of elevated ICP is important to preserve vision, prevent brain complications and diagnose the underlying disease process. Especially important is the communication and coordination across medical specialties to ensure safe treatment given the multisystem organ involvement. In this article, we also review the eye findings associated with IgA nephropathy, as well as other immune-mediated complications of this rare disease.

Keywords: case report, hypertensive retinopathy, IgA nephropathy, malignant hypertension, papilledema

Received: 23 May 2022; revised manuscript accepted: 4 January 2023.

Correspondence to:
Geetha K. Athappilly-Rolfe
Department of Ophthalmology, Atrius Health, Medford MA, USA

Department of Ophthalmology, Lahey Hospital & Medical Center, Burlington, MA, USA

Harvard Vanguard Medical Associates Medford, Medford, MA, USA
athappl@gmail.com

James T. Kwan
Erin Lanzo
David J. Ramsey
Department of Ophthalmology, Tufts Medical Center, Boston, MA, USA

Department of Ophthalmology, Lahey Hospital & Medical Center, Burlington, MA, USA

Aarti Kalra
Department of Pathology, Lahey Hospital & Medical Center, Burlington, MA, USA

*Co-first authors.

Introduction

Patients with malignant hypertension often report blurred vision or symptomatic visual spots. Associated retinal findings include flame hemorrhages, cotton wool spots, choroidal infarcts, macular edema with hard exudates, and optic disc swelling with disc hemorrhages. Chronic hypertensive changes are frequently also evident, including segmental arteriolar narrowing, wall opacification, arteriovenous crossing changes, and microaneurysms.[1]

Bilateral disc edema can occur with hypertensive retinopathy but when severe, raises concern for increased intracranial pressure (ICP) and necessitates evaluation with neuroimaging, confirmatory lumbar puncture with opening pressure, and relevant cerebrospinal fluid (CSF) studies. There are reports in the literature of concurrent increased ICP with papilledema in the setting of malignant hypertension.[2–4]

We present a case of a patient with acute blurred vision secondary to malignant hypertension and increased ICP, found to have immunoglobulin A (IgA) nephropathy. This unique case illustrates the concurrent development of malignant hypertension and papilledema, which have each been reported to occur as separate manifestations of severe IgA-associated disease.[4] We also review the literature related to the pathophysiology of the ocular manifestations of IgA disease. Finally, we discuss treatment challenges in these complex cases of vision loss from kidney disease with hypertension and elevated ICP.

Case

A previously healthy 38-year-old male presented to the emergency room with 2 weeks of progressive, bilateral blurry vision associated with retro-orbital headaches. He had no previous ocular history. Medical, family, social, and occupational history were noncontributory. He took no medications.

In the emergency room, his blood pressure was 206/116 mmHg. Other vital signs were normal. His electrocardiogram (ECG) showed nonspecific T-wave inversions. Pertinent laboratory work-up revealed a creatinine of 2.4 mg/dl and glomerular filtration rate of 34 ml/min. Serial troponins were 0.06, 0.47, and 0.40 ng/ml. Complete blood count showed mild normocytic anemia. Toxicology screen and COVID-19 testing were negative. Chest X-ray was normal and computed tomography of the head without contrast showed no acute intracranial abnormality.

Ocular examination was significant for near visual acuity of Jaeger (J) 3 in the right eye (OD) and J7 in the left eye (OS) using the Rosenbaum Jaegar Near Vision Card. Pupils were reactive without afferent pupillary defect. Intraocular pressure (IOP) measured by iCare rebound tonometry was 15 mmHg OD and 13 mmHg OS. His efferent pathways were intact. All Ishihara color plates were correctly identified. In addition to decreased central vision, he was noted to have reduced peripheral vision on confrontation in both eyes.

Anterior segment examination was unremarkable. Posterior segment examination revealed severe bilateral optic disc edema with splinter hemorrhages and cotton wool spots emanating from both discs. He also had retinal venous enlargement with increased tortuosity. Subretinal fluid with hard exudates arranged in a star shape around the fovea with scattered cotton wool spots and dot blot hemorrhages throughout the periphery of both eyes were demonstrated. These findings observed at the time of hospitalization showed mild improvement on fundus imaging obtained 1 month post-discharge (Figure 1).

Upon further questioning, he reported ‘dimming of his vision’ and transient visual obscurations. He denied tinnitus or auditory sensations, diplopia, positional headache, recent weight fluctuation, pain with extraocular movement, or other focal neurologic symptoms. The patient denied taking new medications, including those associated with increased ICP. He did not have exposure to cats, risk factors for sexually transmitted infections, or illicit drug use.

He was admitted for management of hypertensive emergency and acute kidney failure. On hospital day 1, his blood pressure was maintained at a goal of 140–160 mmHg on a nicardipine drip, and his headache and visual symptoms improved. His troponin leak and associated ECG findings were thought to be a mild non-ST-elevation myocardial infarction in the setting of kidney failure.

Although features of hypertensive retinopathy were noted, his fundus examination and symptoms were concerning for coexisting increased ICP.

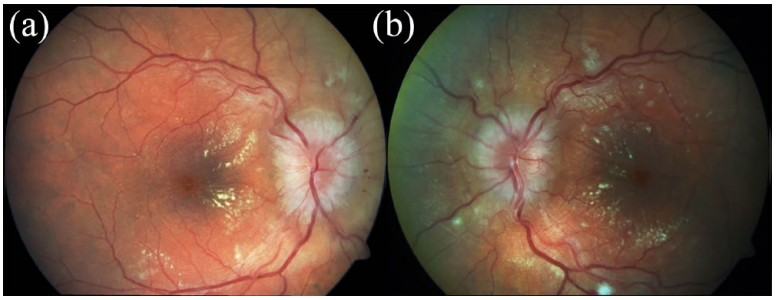

Figure 1. Color fundus photos of right eye (a) and left eye (a) showing severe optic disc edema in both eyes with peripapillary hemorrhages and cotton wool spots emanating from the disc and macular exudates obtained at 1 month post-discharge.

Magnetic resonance imaging (MRI) of the head and orbit and magnetic resonance venography (MRV) of the brain showed confirmatory findings of a partially empty sella, flattening of the posterior globes, and distention of subarachnoid fluid surrounding the optic nerve sheaths (Figure 2). No other acute abnormalities were noted on MRI. He underwent lumbar puncture with an opening pressure of 37 cmH_2O (normal: 6–25 cmH_2O).[5] CSF studies were normal, including white blood cell count, protein, and glucose levels.

Other studies evaluating secondary causes of optic nerve edema were also unrevealing, including CSF IgG index, oligoclonal bands, cytology, and flow cytometry. Serum testing for Aquaporin-4, bartonella, syphilis, Lyme disease, antinuclear antibodies, anti-Sjogren's-syndrome-related antigen A antibodies, angiotensin-converting enzyme, rheumatoid factor, and myelin oligodendrocyte glycoprotein antibodies was negative. Urine studies showed increased proteinuria (600 mg/dl), moderate blood, amorphous crystals, and mucous thread, consistent with nephrotic syndrome and acute tubular necrosis.[6] Subsequent kidney biopsy revealed severe IgA-dominant glomerulonephritis with sclerosing and membranoprolife6rative pattern of injury. Selective immunofluorescence staining for IgA showed increased signal intensity throughout the entirety of the glomeruli.

The patient was transitioned to oral anti-hypertensive medications and was treated for increased ICP with 1000 mg daily of acetazolamide, in coordination with the nephrology team.

One month after discharge, his Snellen vision at distance was $20/20^{-2}$ and color vision (Ishihara plates) was full in both eyes. Despite good central vision, severe papilledema with visual field changes of enlarged blind spots and paracentral changes correlating to his macular pathology persisted (Figure 3). After 8 months, his papilledema nearly resolved, and acetazolamide was stopped. Repeat optic nerve height and retinal nerve fiber layer analysis of both eyes 13 months later demonstrated significantly decreased thickness compared with initial measurements (Figure 4(a)). Ganglion cell and inner plexiform layer thickness corroborated the improvement in papilledema and intact optic nerve function, demonstrating normal values in all sectors bilaterally (Figure 4(a)). Visual fields showed continued constriction of the enlarged blind spots.

Discussion

This case illustrates that even when plausible explanations for bilateral disc and macular edema

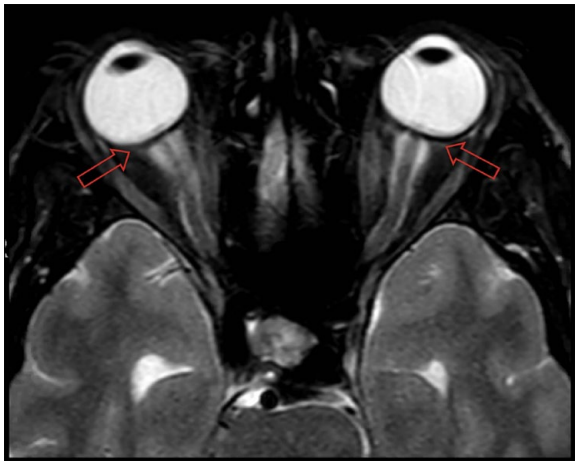

Figure 2. Axial T2-weighted MRI orbits showing features of increased ICP with flattening of posterior globes (arrows) and bilateral perioptic nerve sheath distention.

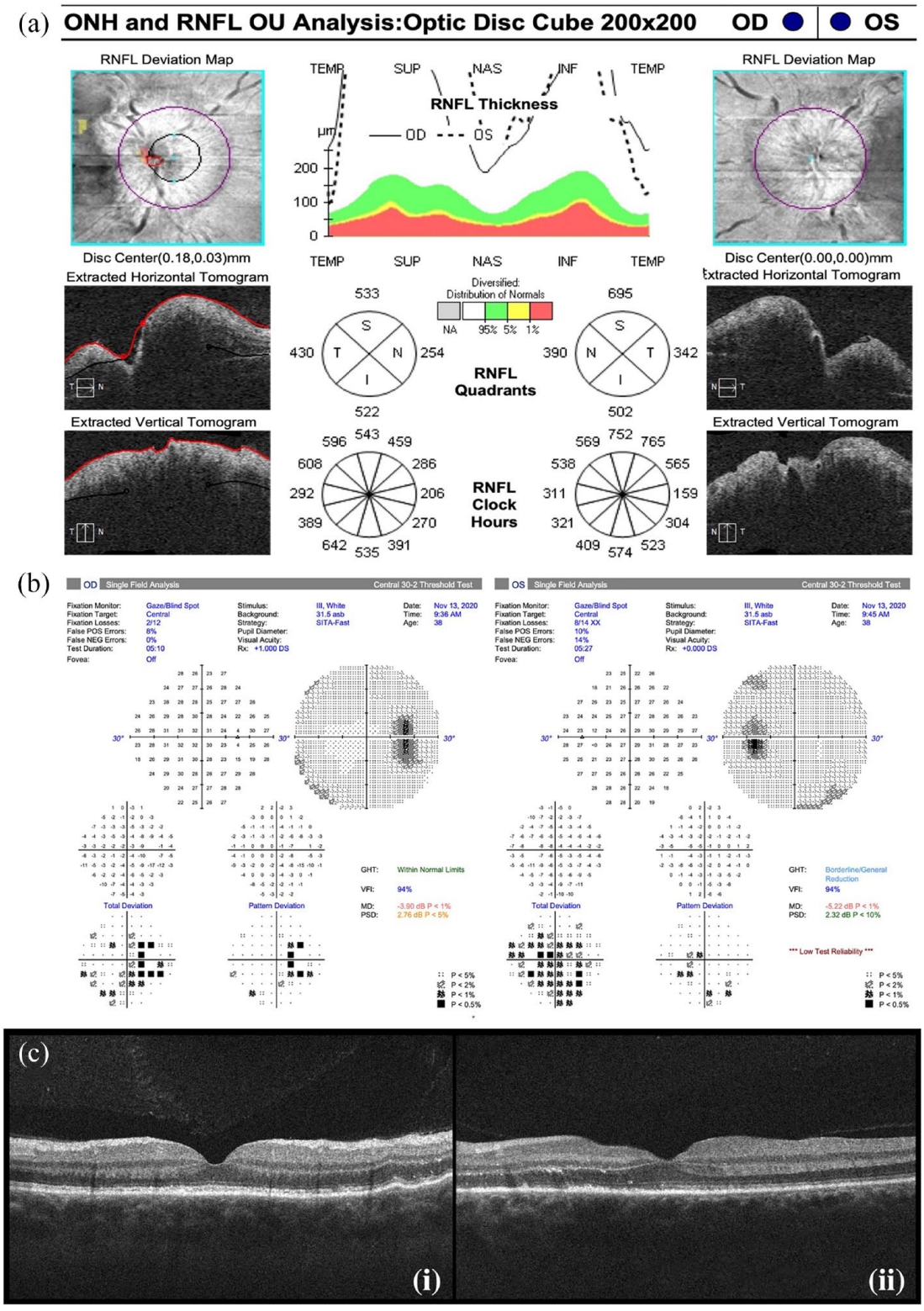

Figure 3. Findings 1 month after presentation. OCT of the retinal nerve fiber layer (RNFL) of both eyes showed severe papilledema with average RNFL thickness of 435 and 483 µm, respectively (a). Humphrey Visual Field 30-2 showed a corresponding enlargement of the blind spots and paracentral changes in both eyes (b). Macular OCT scans of the right (i) and left (ii) eyes demonstrate symmetrical irregular outer retinal thinning with disruption of the photoreceptor ellipsoid zone (c).

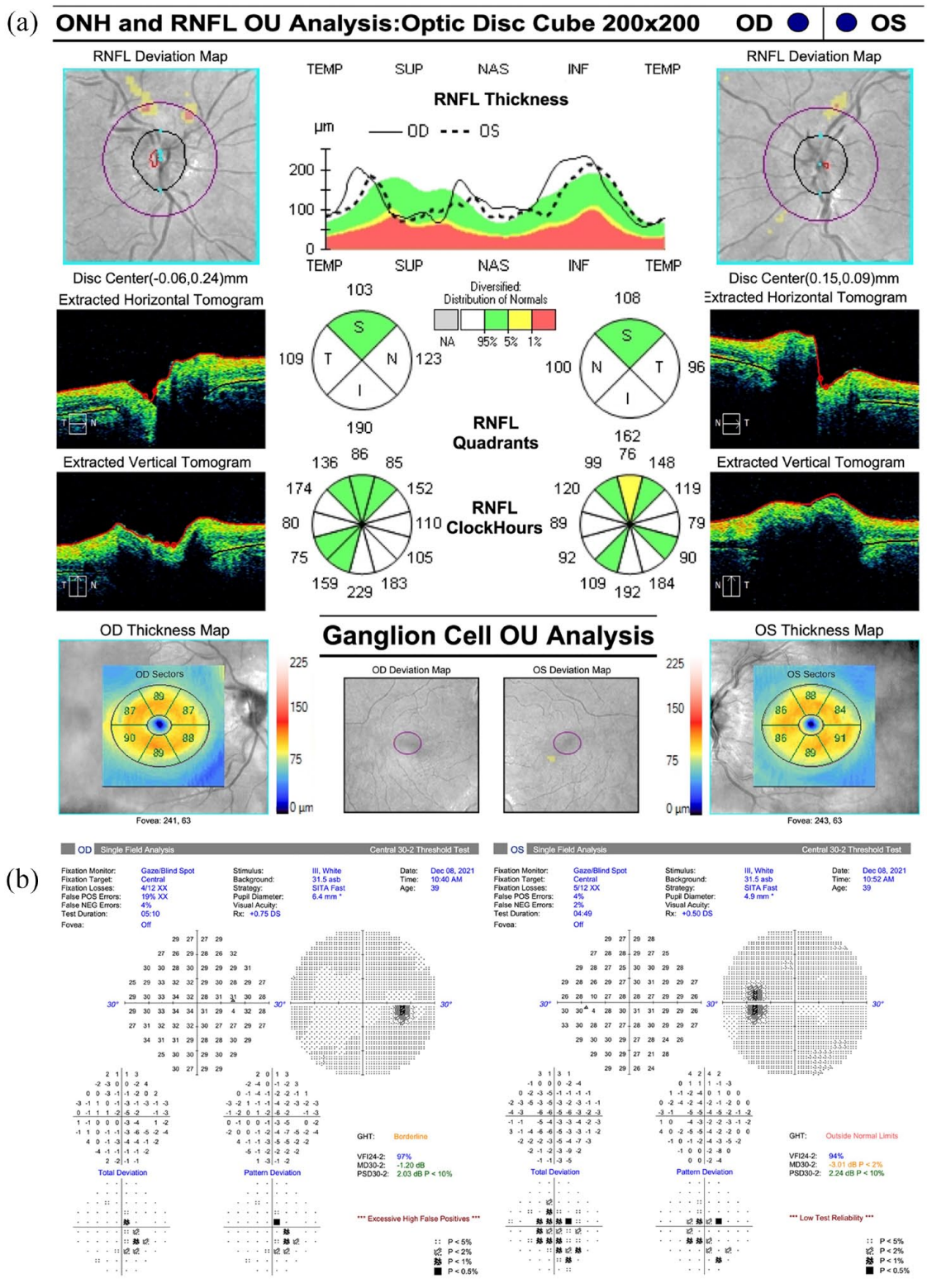

Figure 4. Findings 13 months after presentation. OCT of the RNFL of the right and left eyes demonstrated significant reduction in papilledema when compared with 1 month after presentation. Average RNFL thickness was 131 and 116 µm, respectively. Ganglion cell analysis of the right and left eyes also demonstrated normal ganglion cell layer and inner plexiform layer thickness, averaging 88 and 87 µm in the right and left eyes, respectively (a). Humphrey Visual Field 30-2 similarly showed a reduction in blind spots (b).

are present, signs of coexisting increased ICP warrants investigation. Fundus examination findings most suggestive of increased ICP are (1) severe, bilateral disc edema, (2) cotton wool spots and hemorrhages around the disc, and (3) retinal venous engorgement with tortuosity. Notably, macular edema with hypertensive retinopathy can also occur with significant papilledema. Bilateral disc edema should prompt consideration and evaluation of primary and secondary causes of intracranial hypertension. Primary intracranial hypertension, also known as idiopathic intracranial hypertension (IIH) or pseudotumor cerebri, is commonly seen in obese women during their fertile years. Secondary intracranial hypertension has many causes, including central nervous system (CNS) processes such as intracranial vascular lesions, infections, inflammation, infiltrative processes, spinal cord tumors, medications, malignant hypertension, and kidney disease.

The intersection between systemic hypertension and optic disc edema is complex and may be in part explained by: (1) excessive cerebral blood flow leading to vasogenic edema and increased ICP, (2) ischemia leading to fibrinoid necrosis and cytotoxic edema, and/or (3) hypertension leading to retinopathy with optic nerve involvement.[1] The connection between kidney failure and increased ICP has been reported with primary IIH. Animal and pathology studies have demonstrated elevated ICP with kidney impairment[7–10] and suggest this could be due to fluid overload, anemia, and increased cerebral blood flow.[11]

In the presence of bilateral disc edema suggestive for increased ICP, neuroimaging with MRI of the orbits and brain should be obtained. These studies can corroborate clinical evidence of increased pressure within the craniospinal compartment with findings such as posterior flattening of the globes, distention of the subarachnoid space around the optic nerves, and an 'empty' sella. If suspicion for increased ICP persists, a lumbar puncture to check opening pressure and CSF studies should be undertaken provided there is no mass lesion or concern for herniation.[12]

The case we describe posed a diagnostic and treatment challenge for the interdisciplinary care team. Although ophthalmology was initially consulted to evaluate the problems of visual pathway, it became apparent that the problem was more than typical malignant hypertension, prompting the work-up for increased ICP. Even after it was determined that IgA nephropathy was the underlying cause of the patient's disease, the question remained whether the ocular findings were the result of IgA deposition or secondary to resultant kidney injury causing malignant hypertension and increased ICP.

IgA nephropathy is the most prevalent primary glomerular disorder.[13] It is a systemic inflammatory condition marked by high serum IgA levels and IgA immune complex deposition within glomerular tissue; this inflammation causes leaky vessels with resulting hematuria and proteinuria.[13]

IgA deposits and inflammation can also occur systemically, especially in the intestines and ocular tissues.[3,14–19] The most common ocular findings in patients with IgA nephropathy are inflammatory, including episcleritis,[15,16] keratoconjunctivitis, anterior uveitis,[20–22] nodular scleritis,[23] panuveitis,[24] retinal vasculitis,[25] serous retinal detachment,[14,25] uveal effusion syndrome,[26] and Vogt-Koyanagi-Harada disease.[27,28]

Our case postulates a connection between chronic kidney disease secondary to IgA nephropathy and increased ICP. Treatment of papilledema in the setting of kidney disease requires coordination with our medicine and nephrology colleagues. Blood pressure control must be performed gradually in the setting of elevated ICP to prevent the development of ischemic optic neuropathy. Steroids, occasionally used for treating IgA disease, can further elevate ICP and exacerbate papilledema, requiring close ophthalmic follow-up. Acetazolamide, the first-line treatment for increased ICP, presents a special challenge in patients with kidney dysfunction as it is renally cleared, presenting concern for toxicity. If pharmacologic treatment for visual decline from papilledema is unsuccessful or cannot be safely continued, surgical interventions such as cerebral stenting, ventriculoperitoneal shunting, or optic nerve sheath fenestration should be considered without delay.[29]

Conclusion

This case highlights the importance of considering increased ICP among the potential causes for bilateral optic disc edema. Even in cases of malignant hypertension with evidence of hypertensive retinopathy, significant optic disc edema warrants a work-up to identify the presence and cause of

increased ICP. Diagnosing increased ICP is important not only for visual preservation but also in preventing neurologic complications and detecting underlying systemic disease processes. A multidisciplinary approach is essential for accurate diagnosis and safe management of these complex conditions.

Declarations

Ethics approval and consent to participate

Our study adheres to the tenets of the Declaration of Helsinki and was deemed exempt by the Institutional Review Board of the Lahey Hospital & Medical Center by virtue of being a single case report. CARE guidelines were followed when preparing this manuscript.

Consent for publication

Informed consent for publication of clinical details and images was verbally obtained from the patient and documented in the electronic medical record as required under the circumstance of the COVID-19 public health emergency.

Author contributions

James T. Kwan: Investigation; Writing – review & editing.

Erin Lanzo: Conceptualization; Writing – original draft; Writing – review & editing.

David J. Ramsey: Investigation; Supervision; Writing – original draft; Writing – review & editing.

Aarti Kalra: Investigation; Writing – original draft.

Geetha K. Athappilly-Rolfe: Conceptualization; Formal analysis; Investigation; Methodology; Supervision; Writing – original draft; Writing – review & editing.

Acknowledgements

The authors thank Dr Shiyoung Roh, Tim Tivan, and Carol Spencer, Lahey Hospital Librarian, for research support. David J. Ramsey is the Harry N. Lee Family Chair in Innovation at the Lahey Hospital & Medical Center, Beth Israel Lahey Health.

Funding

The authors disclosed receipt of the following financial support for the research, authorship and/or publication of this article: D.J.R. is supported by the Harry N. Lee Family Chair in Innovation at the Lahey Hospital & Medical Center, Beth Israel Lahey Health.

Competing interests

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Availability of data and materials

No relevant data and materials are available separate from the clinical data presented in this case.

ORCID iDs

James T. Kwan https://orcid.org/0000-0001-8754-3179

David J. Ramsey https://orcid.org/0000-0002-5504-812X

References

1. Shah BM, Sadaka A, Berry S, *et al*. Bilateral disc edema in hypertensive emergency. *Can J Ophthalmol* 2018; 53: e113–e115.
2. Abbasi HN, Brady AJ and Cooper SA. Fulminant idiopathic intracranial hypertension with malignant systemic hypertension: a case report. *Neuroophthalmology* 2013; 37: 120–123.
3. Taban M, Chand D and Sears JE. Ocular findings in IgA nephropathy with renal failure and hypertension. *J Pediatr Ophthalmol Strabismus* 2006; 43: 378–380.
4. Chang D, Nagamoto G and Smith WE. Benign intracranial hypertension and chronic renal failure. *Cleve Clin J Med* 1992; 59: 419–422.
5. Lee SC and Lueck CJ. Cerebrospinal fluid pressure in adults. *J Neuroophthalmol* 2014; 34: 278–283.
6. Lana-Peixoto MA and Talim N. Neuromyelitis optica spectrum disorder and anti-MOG syndromes. *Biomedicines* 2019; 7: 42.
7. Rodriguez E, Delucchi A and Cano F. [Neurotoxicity caused by cyclosporin A in renal transplantation in children]. *Rev Med Chil* 1992; 120: 300–303.
8. Gilliland KG and Hegstrom RM. The effect of hemodialysis on cerebrospinal fluid pressure in uremic dogs. *Trans Am Soc Artif Intern Organs* 1963; 9: 44–50.
9. Olsen S. The brain in uremia. A patho-anatomical study of brains from 104 patients

dying in renal insufficiency, with reference to the influence of complicating factors, especially ischemia of the brain. *Acta Psychiatr Scand Suppl* 1961; 36: 1–128.

10. Raskin NH and Fishman RA. Neurologic disorders in renal failure (first of two parts). *N Engl J Med* 1976; 294: 143–148.
11. Ahmed US, Bacaj P, Iqbal HI, *et al*. IgA nephropathy in a patient presenting with Pseudotumor Cerebri. *Case Rep Nephrol* 2016; 2016: 5273207.
12. Engelborghs S, Niemantsverdriet E, Struyfs H, *et al*. Consensus guidelines for lumbar puncture in patients with neurological diseases. *Alzheimers Dement (Amst)* 2017; 8: 111–126.
13. Wu MY, Chen CS, Yiang GT, *et al*. The emerging role of pathogenesis of IgA nephropathy. *J Clin Med* 2018; 7: 225.
14. Avila SA, Golshani C and Friedman AH. Hypertensive crisis with massive retinal and choroidal infarction: a case update. *Am J Ophthalmol Case Rep* 2019; 13: 22–24.
15. Sirbat D, Saudax E, Hurault de Ligny B, *et al*. [A new etiology of episcleritis: nephropathies with IgA and/or isolated C3 deposits]. *J Fr Ophtalmol* 1983; 6: 921–925.
16. Hegde V, Mitrut I, Bennett H, *et al*. Episcleritis: an association with IgA nephropathy. *Cont Lens Anterior Eye* 2009; 32: 141–142.
17. El Matri K, Amoroso F, Zambrowski O, *et al*. Multimodal imaging of bilateral ischemic retinal vasculopathy associated with Berger's IgA nephropathy: case report. *BMC Ophthalmol* 2021; 21: 204.
18. Wegmann-Burns M, Gugger M and Goldblum D. Hypertensive retinopathy. *Lancet* 2004; 363: 456.
19. Wolfensberger TJ, Piguet B, Gregor ZJ, *et al*. [Retinal vasculopathy associated with Berger's IgA nephropathy]. *Klin Monbl Augenheilkd* 2000; 216: 334–338.
20. Moller-Jensen J, Marthinsen L and Linne T. Anterior uveitis in IgA nephropathy. *Am J Ophthalmol* 1989; 108: 604–605.
21. Yamabe H, Ozawa K, Fukushi K, *et al*. IgA nephropathy and Henoch-Schonlein purpura nephritis with anterior uveitis. *Nephron* 1988; 50: 368–370.
22. Pascual J, Liano F, Mampaso F, *et al*. IgA nephropathy and acute interstitial nephritis in a patient with relapsing uveitis and longstanding AS. *J Rheumatol* 1991; 18: 942–945.
23. Garza-Leon M, Flores D, Alarcón-Galván G, *et al*. Bilateral scleritis and sclerokeratitis associated with IgA nephropathy. *J Ophthalmic Inflamm Infect* 2012; 2: 207–210.
24. Takhar JS and Gonzales JA. IgA nephropathy-associated uveitis: a case presentation. *Ocul Immunol Inflamm* 2020; 28: 1125–1128.
25. Kwok AK, Cheng LL, Bhende P, *et al*. Tear of the retinal pigment epithelium and serous retinal detachment in a case of IgA nephropathy after renal transplantation. *Arch Ophthalmol* 2000; 118: 582–583.
26. Pavlin CJ, Easterbrook M, Harasiewicz K, *et al*. An ultrasound biomicroscopic analysis of angle-closure glaucoma secondary to ciliochoroidal effusion in IgA nephropathy. *Am J Ophthalmol* 1993; 116: 341–345.
27. Zhang Q, Fan X, Tian M, *et al*. A case presentation of an IgA nephropathy patient with Vogt-Koyanagi-Harada syndrome. *BMC Nephrol* 2020; 21: 272.
28. Matsuo T, Masuda I, Ota K, *et al*. Vogt-Koyanagi-Harada syndrome in two patients with immunoglobulin A nephropathy. *Acta Med Okayama* 2007; 61: 305–309.
29. Bouffard MA. Fulminant idiopathic intracranial hypertension. *Curr Neurol Neurosci Rep* 2020; 20: 8.