Case report

Autoimmune retinopathy and optic neuropathy associated with enolase-positive renal oncocytoma

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ABSTRACT

Purpose: To report a case of autoimmune retinopathy and optic neuropathy associated with an enolase-positive renal oncocytoma.

Observations: A 41-year-old man presented with subacute, painless, bilateral vision loss. On initial examination, visual acuity measured 20/125 OD and 20/1250 OS, and telangiectatic vessels were noted on the optic nerves and in the maculae. Goldmann perimetry showed bilateral, cecocentral scotomas, and electroretinography demonstrated reduced photopic and scotopic signals, concerning for autoimmune retinopathy. Serum testing showed multiple positive anti-optic nerve and anti-retinal antibodies, including to alpha-enolase. Extensive systemic workup was negative except for a large, exophytic, right renal mass. Biopsy was consistent with a benign oncocytoma, and immunohistochemical staining showed diffusely positive alpha-enolase staining. The patient was treated with a five-day course of intravenous methylprednisolone and plasmapheresis with minimal improvement. Surgical excision of the oncocytoma was performed. At 9-months post-operatively, visual acuity had improved to 20/40 OU, with corresponding improvement on visual field and electroretinography testing.

Conclusions and importance: To our knowledge, this is the first report of autoimmune retinopathy and optic neuropathy associated with a renal oncocytoma. The case highlights the importance of a thorough systemic workup in cases of suspected autoimmune retinopathy and reminds clinicians that even tumors considered benign can have distal effects on other organs.

1. Introduction

Autoimmune retinopathy and optic neuropathy are poorly-understood diseases thought to be the result of an immune reaction to autoantigens. Cancer-associated, or paraneoplastic, retinopathy is considered a subset of autoimmune retinopathy secondary to a tumor as the source of antigens. Among many potential antigens, alpha-enolase is a well-described 46 kD protein known to cause cancer-associated and autoimmune retinopathy. Oncocytomas are benign tumors rarely associated with paraneoplastic syndromes. Here, we present a case of profound vision loss secondary to autoimmune retinopathy and optic neuropathy associated with an alpha-enolase-positive renal oncocytoma, with remarkable improvement of vision after tumor resection.

2. Case report

A 41-year-old man presented with 2 weeks of bilateral, painless vision loss in the absence of any systemic symptoms. On initial examination, visual acuity measured 20/125 OD and 20/1250 OS, and telangiectatic vessels were noted on the optic nerves and in the maculae. Goldmann perimetry showed bilateral, cecocentral scotomas, and electroretinography demonstrated reduced photopic and scotopic signals, concerning for autoimmune retinopathy. Serum testing showed multiple positive anti-optic nerve and anti-retinal antibodies, including to alpha-enolase. Extensive systemic workup was negative except for a large, exophytic, right renal mass. Biopsy was consistent with a benign oncocytoma, and immunohistochemical staining showed diffusely positive alpha-enolase staining. The patient was treated with a five-day course of intravenous methylprednisolone and plasmapheresis with minimal improvement. Surgical excision of the oncocytoma was performed. At 9-months post-operatively, visual acuity had improved to 20/40 OU, with corresponding improvement on visual field and electroretinography testing.

Conclusions and importance: To our knowledge, this is the first report of autoimmune retinopathy and optic neuropathy associated with a renal oncocytoma. The case highlights the importance of a thorough systemic workup in cases of suspected autoimmune retinopathy and reminds clinicians that even tumors considered benign can have distal effects on other organs.
mitochondrial DNA testing was negative for mutations at nucleotide pairs 3460, 11778, and 14484. An MRI of the brain and orbits was pursued, showing bilateral optic nerve enhancement and white matter T2/FLAIR hyperintensities, concerning for demyelinating disease. A lumbar puncture with analysis of the cerebral spinal fluid was unrevealing, including negative neuromyelitis optica antibodies. On laboratory testing, he was incidentally noted to have an elevated creatinine (4.0 mg/dL). An abdominal CT revealed a large, heterogeneous, exophytic right renal mass, suggesting paraneoplastic syndrome as the cause of vision loss.

An autoimmune retinopathy panel was obtained and demonstrated multiple anti-optic nerve and anti-retinal autoantibodies (40-kDa, 46-kDa [alpha-enolase], and 70-kDa), with binding of the patient’s serum to bipolar cells on human retinal tissue. Full-field electroretinography (ERG) demonstrated reduced photopic greater than scotopic signals (Table 1; Fig. 4). PET-CT demonstrated hypermetabolic activity only at the known right renal mass (Fig. 5A). Biopsy of the renal mass was consistent with a benign oncocytoma, confirmed by positive CD117 immunohistochemical staining. Additional immunohistochemical staining was negative for CK7, distinguishing the tumor from renal cell carcinoma, and positive for alpha-enolase (Fig. 5B). Extensive additional investigations, including serum and CSF paraneoplastic panels, as
well as for rheumatologic (ANA, ANCA, SS-a/b antibodies, complement levels, ACE), infectious (tuberculosis, lyme, Bartonella, syphilis, HIV, hepatitis A and B) and demyelinating causes (multiple sclerosis, neuromyelitis optica), were negative.

The patient was treated with a five-day course of intravenous methylprednisolone (1 g/day), followed by five rounds of plasmapheresis with minimal improvement. Surgical excision of the oncocytoma with partial nephrectomy was thus performed 3 months after diagnosis. Histologic inspection of the tumor confirmed a benign oncocytoma throughout the sample. The patient experienced gradual, progressive improvement in vision following tumor resection. By 9 months post-operatively, visual acuity had improved to 20/40 OU, with recovery of the I2e isopter OU (Fig. 1C and D), improved waveforms with reduced latencies on ERG (Table 1, Fig. 4), and consolidation of the outer plexiform layer irregularities on OCT (Fig. 3C and D).

3. Discussion

We report a case of presumed autoimmune retinopathy and optic neuropathy associated with an alpha-enolase-positive renal oncocytoma. Definitive associations between autoimmune retinopathy and distant tumors can be difficult to demonstrate. However, in this case, the patient's serum had multiple, positive anti-retinal and anti-optic nerve antibodies, including to alpha-enolase. The patient's serum showed binding to the bipolar layer of human retina, consistent with the irregularities of the outer plexiform layers seen on OCT. The patient's ERG was strongly consistent with autoimmune retinopathy and MRI showed enhancement of both optic nerves. An extensive workup for autoimmune retinopathy or optic neuropathy was negative except for the large renal oncocytoma, which was positive for alpha-enolase throughout the biopsy sample on immunohistochemistry. Despite initial immunosuppression, the patient only improved after oncocyto ma resection, further supporting this potential link.

Enolase associated autoimmune retinopathy has been well described. Multiple reports have shown the association of both alpha-enolase and gamma-enolase antibodies in serum to autoimmune retinopathy. Serum anti-enolase antibodies can be found in other inflammatory conditions and their presence does not prove causality in the context of autoimmune retinopathy. However, in this case, an extensive workup for autoimmune retinopathy was negative except for the large renal oncocytoma, which was positive for alpha-enolase throughout the biopsy sample on immunohistochemistry. Hence, we postulate in this case that the large burden of alpha-enolase expressed by the tumor was the inciting antigen for the autoimmune retinopathy and optic neuropathy.

To our knowledge, this is the first report of an oncocytoma expressing alpha-enolase or causing autoimmune retinopathy and optic neuropathy. Although generally considered benign, oncocytomas have rarely been associated with paraneoplastic syndromes, including tumor-induced hypertension, erythrocytosis, and ataxia. Prior histologic studies have demonstrated that oncocytomas can produce known retinal antigens, including recoverin and neuron-specific (gamma) enolase. This patient did not have anti-recoverin or anti-gamma enolase antibodies in his serum, and staining of the oncocytoma was negative for gamma enolase.

Treatment of autoimmune retinopathy is challenging, in part due to delay and ambiguity in diagnosis. Currently, immunosuppression is standard care, but the efficacy of such treatments is unclear, with studies showing variable degrees of improvement in cancer-associated retinopathy and inconsistent responses in other sub-types of autoimmune retinopathy. In general, improvement even with immunosuppression or tumor resection is unusual. This patient did not respond to initial treatment with intravenous methylprednisolone and plasmapheresis, and tumor resection was therefore pursued. Remarkably, the patient noted subjective improvement within weeks of tumor resection, and by 9 months post-operatively, he demonstrated improved visual acuity, visual fields, and ERG waveforms confirming his response to treatment.

4. Conclusion

This case highlights the importance of a comprehensive workup in patients with autoimmune retinopathy and optic neuropathy. Clinicians should be aware that even tumors regarded as benign may have paraneoplastic effects on other organ systems.

Patient consent

The patient consented to publication of the case in writing.

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Table 1
Electroretinography on presentation and 10 month follow-up.

| Electroretinography | Presentation | Follow-Up (10 months) | Change on Follow-Up vs. Presentation | Normal Range |
|---------------------|--------------|-----------------------|--------------------------------------|--------------|
|                     | OD | OS | OD | OS | OD | OS | OD | OS | uV | ms | uV | ms |
| Dark Adapted 0.01 (Rod Response) | 85.69 | 92.00 | 64.50 | 92.00 | 73.25 | 95.00 | 111.20 | 90.00 | -12.44 | 3.00 | 46.7 | -2.00 | 61.30-334.70 | 75.12-108.02 |
| Dark Adapted 3.0 B-wave (Maximal Combined Response) | 199.40 | 63.00 | 118.10 | 63.00 | 132.50 | 45.00 | 147.50 | 45.00 | -6.90 | -18.00 | 29.50 | 18.00 | 115.00-446.20 | 29.98-50.30 |
| Dark Adapted 3.0 A-wave (Maximal Combined Response) | -61.52 | 19.00 | -65.21 | 17.00 | -79.17 | 16.00 | -90.61 | 17.00 | -17.65 | -3.00 | -25.40 | 0.00 | -194.95-(-196.45 | 12.20-15.22 |
| Light Adapted 3.0 B-wave (Cone Response) | 39.25 | 40.00 | 24.34 | 34.00 | 53.56 | 35.00 | 50.95 | 35.00 | -14.31 | -5.00 | 26.61 | 1.00 | 86.14-205.26 | 25.81-29.61 |
| Light Adapted 3.0 A-wave (Cone Response) | -10.82 | 15.00 | -18.03 | 18.00 | -13.85 | 16.00 | -17.70 | 14.00 | 2.97 | 1.00 | 0.33 | -4.00 | -59.78-(-24.44 | 10.80-14.00 |
| 30 Hz Flicker (Cone Response) | 37.43 | 33.04 | 41.55 | 46.37 | 4.12 | 13.33 | 68.43-147.53 |

uV = microvolts; ms = milliseconds.
Gray boxes denote abnormal values.
Light blue boxes show values that have improved on follow-up relative to presentation.
Electroretinography was performed on Diagnosys Desktop E3 according to International Society for Clinical Electrophysiology of Vision 2008 standards.
Electroretinography at presentation and 10 month follow-up.

Electroretinography at presentation shows reduced cone and rod responses, with decreased amplitudes and delayed latencies, suggesting cone greater than rod dysfunction in both eyes. On follow-up, dark adapted (rod response) amplitudes are low normal, with overall improved b-wave amplitudes and latencies (best seen in the combined and cone responses).
Conflict of interest disclosures

None of the authors have conflicts of interests to report.

Authorship

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

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ajoc.2018.09.005.

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Fig. 5. Computed tomography imaging and immunohistochemical analysis.
(A) Positron emission tomography-computed tomography (PET-CT) shows intensively hypermetabolic uptake by the right renal mass (arrow), without other lesions. (B) Immunohistochemical staining of the renal oncocytoma shows positive alpha-enolase staining (yellow) throughout the biopsy sample. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)