Diplopia resulting from metastatic Renal Cell Carcinoma

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Abstract: A 62-year-old male with a history of metastatic renal cell carcinoma presented for complaints regarding horizontal diplopia, and further testing revealed aberrant regeneration of cranial nerve 3 and a cranial nerve 6 palsy.

I. Case History:

A. Patient Demographics: 62 year old Caucasian male

B. Chief Complaint: Patient presents to Portland VA Ocular Polytrauma clinic for a follow up regarding previously prescribed prism glasses. The patient has been wearing the glasses for two weeks. The patient notes improved clarity with glasses; however, he continues to experience diplopia at both distance and near with glasses. The diplopia is relieved when one eye is covered. He states that the diplopia is mostly horizontal; however, sometimes the image will skew vertically. He notes that he diplopia is more bothersome at near.

C. Ocular/Medical History:

i. Ocular:

   (+) Diplopia 03/2016 status post pituitary tumor surgery
   (+) Renal Cell Carcinoma Metastasis to Choroid OS temporal to macula
   (+) Visual Field Loss: Bitemporal hemianopsia resulting from metastasis to pituitary
   (+) Orbital Fracture ~1995: has history of occasional diplopia in right superior temporal gaze

ii. Medical:

   (+) Clear Cell Renal Cell Carcinoma (RCC) diagnosed ~ 1996, history of metastasis to bones and lungs, pituitary and left choroid
   (+) Pituitary tumor second to renal cell carcinoma. First surgery performed in March 2016. Another surgery scheduled for August 2016 due to regrowth of tumor.
   (+) Post surgical hypothyroidism
   (+) Right Frontal Lobe Metastasis
   (+) Anemia
   (+) Gastritis
   (+) Type 2 Diabetes
   (+) Hypertension
   (+) Depression
   (+) Post Traumatic Stress Disorder

D. Medications:

   Acarbose 50 mg
   Alfuzosin hcl 10 mg
Bisacodyl 10 mg
Calcium 500 mg
Clindamycin 300 mg
Diphenhyramine
Docusate 100 mg
Fluticasone
Guaifenesin 400 mg
Hydrocortisone 5 mg
Levothyroxine
Loratadine 10 mg
Magnesium oxide 420 mg
Morphine sulfate 60 mg
Omeprazole 20 mg
Oxybutynin chloride 5 mg
Oxycodone hcl 5 mg
Polyethylene glycol 3350 powder
Pravastatin 20 mg
Prochlorperazine 5 mg
Sennosides 8.6 mg
Sertraline hcl 100 mg
Terbinafine hcl
Tuberculin syringe 1ml 27g
Urea 20% cream

E. Other salient information: The patient is being treated by the Portland VA for metastatic renal cell carcinoma (RCC). He is being followed by Casey Eye Institute for a metastatic lesion in the left choroid. The patient will be undergoing anti-VEGF injections to reduce fluid surrounding the choroidal lesion. The patient will be undergoing a second pituitary tumor surgery.

II. Pertinent Findings:

A. Clinical:

BCVA (Distance):
  OD: 20/40+   PH: NI
  OS: 20/350-   PH: 20/200-

BCVA (Near):
  OD: 20/80
  OS: 20/200
  OU: 20/50

Cover Test (Distance) with correction: 4XP
Cover Test (Near) with correction: 8 XP’

Confrontation Visual Fields: (+)Field loss superior temporally OU
Pupils: (+) Anisocoria. Poor reactivity, OD reacts more than OS.

Extraocular Motility: retraction of the superior lid OS during downgaze—indicates aberrant regeneration of cranial nerve 3 most likely due to post-surgical healing from pituitary tumor surgery. Limited mobility in superior and lateral gazes. Limited mobility in lateral gaze indicates cranial nerve 6 palsy.

Exophthalmometry:
- Base: 125 mm
- OD: 15 mm
- OS: 19 mm

Habitual Rx (Distance):
- OD: +1.75 2BI
- OS: +1.75 2BI

Habitual Rx (Near):
- OD: +4.25 6BI
- OS: +4.25 6BI

B. Physical: Clear Cell RCC, Bone Metastasis, Pituitary Metastasis, Right Frontal Lobe Metastasis, Anemia, Gastritis, Type 2 Diabetes, Hypertension, PTSD, Depression, Post-surgical Hypothyroidism

C. Laboratory Studies: Pituitary tumor biopsy revealed clear cell RCC. Left Kidney Biopsy was performed to confirm clear cell RCC.

D. Radiology Studies: Initial MRI in February 2016 revealed 2.1 centimeter by 2.4 centimeter mass affecting the floor of the 3rd ventricle and optic chiasma. The MRI also revealed a right frontal extra axial mass. The frontal mass has remained stable; however, after the transphenoidal approach for the sellar tumor resection a residual mass remained in the sella and suprasellar cistern that has increased in size since March of 2016. After multiple MRI’s the mass has shown growth and is currently 1.7 centimeters by 1.8 centimeters.

E. Other (Information from Casey Eye Institute): Monthly B-Scans beginning in January 2016 regarding size and reflectivity of choroidal lesion. Lesion shows increasing thickness. Initial B-Scan reveals 0.75 mm thick lesion, most recent B-Scan reveals 1.7 mm thick lesion.

III. Differential Diagnosis:

A. Primary/Leading: Diplopia resulting from multiple cranial nerve palsies due to metastatic renal cell carcinoma

B. Others:
- Acquired exotropia
- Convergence Insufficiency
IV. Diagnosis and Discussion:

A. Elaborate on condition:

1. Renal Cell Carcinoma (RCC) is the most common type of kidney cancer, if caught early and treated the prognosis is generally good. However, prognosis becomes much poorer once metastasis has occurred.
   a. 5 subtypes of renal cell carcinoma, this patient has clear cell which accounts for 80% of all RCC
      - Clear Cell RCC
      - Papillary RCC
      - Chromophobe RCC
      - Collecting Duct RCC
      - Unclassified RCC
   b. Most common in patients between the ages of 50 -70
   c. Risk Factors include: smoking, family history of Von-Hipple Landau disease, obesity and exposure to certain dyes, asbestos, cadmium (a metal), herbicides, and solvents
   d. Symptoms: lump on lower back or abdomen, blood in urine, lower back pain, unintentional weight loss, fever, malaise, night sweats, high blood pressure and increased levels of calcium in the blood
   e. Diagnosis: urine and blood analysis, ultrasound, CT scan further tests including: MRI, bone scan, and chest x-ray may be warranted to determine metastasis and staging
   f. Treatment options: Surgery or ablation of tumor, biologic drugs, or targeted therapy which focuses on attacking the tumor’s vascular supply or proteins. This patient is currently taking Nivolumab which is a targeted therapy drug. Unfortunately he is not responding well to this drug.
   g. The TNM system is used to stage cancer, this patient’s cancer is considered to be stage 4 due to distant metastasis.
      - T indicates the tumor size and is scaled from 0 to 4 with a higher number indicating a larger tumor
      - N indicates if the tumor has spread to the lymph nodes
      - M indicates if there has been metastasis. Common sites of metastasis include: bones, lungs, and brain

B. Expound on unique features of case:

1. When a patient has a history of metastatic cancer and complaints of diplopia a thorough evaluation of extraocular motor function and pupils becomes paramount.
2. When multiple palsies are noted there is likely cavernous sinus involvement
3. Cranial Nerve 3 palsy with aberrant regeneration
   a. For this patient, the palsy is due to a lesion of the oculomotor nerve with infiltration into the cavernous sinus with pupil involvement.
b. Caused by clear cell RCC pituitary tumor metastasis. Other lesions that may infiltrate the cavernous sinus include: multiple myeloma, metastatic carcinoma, and nasopharyngeal carcinoma.
c. The oculomotor nerve palsy may present as the initial sign of the causative disease when the lesion infiltrates the cavernous sinus.
d. Lesions with infiltration to the cavernous sinus may present with isolated oculomotor nerve dysfunction, but often cause a polyneuropathy, which was seen in this case.
e. Following injury to the oculomotor nerve, aberrant regeneration of the peripheral nerves may develop. For this patient there was likely injury to the oculomotor nerve during the surgery involving removal of the pituitary tumor.
   i. The process of aberrant regeneration involves regeneration of the peripheral motor and sensory nerves.
   ii. During the regenerative process more axons are produced.
   iii. If peripheral nerves innervate more than one muscle, misdirection of the regenerating nerve fibers can occur. Therefore, regenerating sprouts of axons that innervated one muscle group prior to injury, can ultimately innervate a different muscle group.
      ex. The levator palpebrae superioris can receive fibers that were originally innervating the medial rectus muscle.
   iv. Although this is most common after acute oculomotor nerve palsies, it can also occur as a primary phenomenon without preexisting acute oculomotor nerve paresis. When this occurs it is usually due to a slow growing lesion in the cavernous sinus or subarachnoid space. Because the lesion grows so slowly the damage to the oculomotor nerve is mild and does not produce visual symptoms, and allows regeneration to occur.
v. Signs of aberrant regeneration:
   - Horizontal gaze-eyelid synkinesis: elevation of the involved eyelid in adduction of the eye. This was one sign observed for this patient during EOM evaluation, the left superior lid elevated in right gaze.
   - Pseudo-Grafe sign: retraction and elevation of the eyelid during downgaze. This may be more obvious during a combination of downward gaze and adduction. This was the second sign observed during EOM evaluation for this patient.
   - Restriction during elevation and depression of the eye. This was yet another sign observed during EOM evaluation for this patient.
   - Adduction of the involved eye during elevation or depression movements
   - Pseudo-Argyll Robertson pupil: the involved pupil does not react or reacts poorly to light stimulation. Will constrict during adduction.
- Monocular vertical optokinetic responses: The involved eye has suppressed vertical responses

4. Cranial Nerve 6 palsy
   a. A cranial nerve 6 palsy may present for a variety of reasons. In this case because of the presence of the cranial nerve 3 palsy, the cranial nerve 6 palsy is likely due to a lesion of the abducens nerve in the cavernous sinus. The lesion is metastatic RCC.
   b. Tumors that infiltrate the cavernous sinus include: meningioma, metastatic carcinoma, nasopharyngeal carcinoma, Burkitt’s lymphoma, pituitary adenoma, and craniopharyngioma.
   c. If a tumor becomes large enough it can affect both sides of the cavernous sinus and manifest as a bilateral cranial nerve 6 palsy.

V. Treatment and Management:

A. Treatment and response to treatment:

2. Typically onset of these findings warrant immediate MRI imaging; however, patient’s oncology team is already aware of pituitary tumor status and involvement with cranial nerves. Recommended patient continue to seek care with his neuro-ophthalmologist, neurologist, and oncologist.
3. In regard to patient’s glasses and diplopia, patient was educated on diplopia management options including: prism, mono-vision, and central stipple clear contact paper occlusion. Changing prism is not recommended due to patient’s upcoming pituitary surgery and anti-VEGF injections. Monovision is not recommended at this time due to poor VA OS at distance and near. Central stipple occlusion/patching OS was recommended to help relieve diplopia until after surgery and injections.
4. Patient is to follow up with ocular polytrauma clinic as needed. If patient desires further diplopia treatment after surgery and ocular injections a reverse prism OS could be evaluated to move blurry image into non-seeing peripheral field so that it could be more easily ignored.

B. Refer to research where appropriate

C. Bibliography

**Conclusion:**
When managing patients with diplopia, especially for patients with a history of cancer, a thorough case history, evaluating pupils, visual fields, and extraocular motility becomes paramount in order to determine if MRI imaging is warranted to evaluate for possible tumors or aneurysms. If the above mentioned tests reveal normal results, prism evaluation may be pursued. However, prism may not be the best option for alleviating diplopia in these patients and other options including: monovision and central stipple occlusion must be considered.