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Keith J. Wroblewski MD Uveitis and Ocular Pathology, Department of Ophthalmology, George Washington University 2150 Pennsylvania Avenue, Suite 2A, Washington, DC 20037

Coauthors: Frank Chin MD (Resident, Ophthalmology), Rim Abdullah MD (Resident, Pathology), Craig Geist MD, Chair, Ophthalmology and Sana Tabbara MD, Staff, Pathologist

[wroboeye@hotmail.com](mailto:wroboeye@hotmail.com) or [kwroblewski@mfa.gwu.edu](mailto:kwroblewski@mfa.gwu.edu)

Protocol and 1 Glass Slide

**History:** 47 year old female presented with a gradual, progressive loss of vision in the left eye, binocular diplopia in all directions of gaze and proptosis of the left eye. Her symptoms began in late September 2017 with sinus pressure, tenderness and nasal congestion and was followed by blurred vision. She had no symptoms of flushing, or diarrhea and no previous history of gastric or respiratory system malignancy. Past Medical History and Review of Systems was negative. CT Scan in late October showed a large sinonasal mass extending into the left orbit. A biopsy was performed and the a photography of the H and E section is shown below:



**Discussion:**

Sinonasal tumors expending into the orbit often present a diagnostic dilemma. Once metastatic carcinomas such as renal cell, prostate, lung and breast are excluded, emphasis must be directed toward trying to use immunstaining to help to decipher clues as to the etiology. Often this is easier said than done in practice. Certainly, granulomatosis and polyangitis needs to be excluded and Vic Elner MD PhD, Carol Shields MD and Diva Salomao MD have presented two very excellent cases of this disorder to our group over the past decade or so and emphasis must be placed on the renal manifestations of this disorder and excluding any dermatologic manifestations. ANCA testing may or may not help in this endeavor. Lymphoid tumors such as the N-K T Cell Lymphomas, albeit a very rare tumor needs to be on the different diagnosis and Woog and colleagues at the Mayo Clinic have presented on this disorder. Large Cell Lymphomas should also be excluded and an association with EBV needs to be elucidated.

The differential diagnosis of small round cell tumor types was presented by Thaddeus Dryja in his most recent presentation of a neuroendocrine carcinoma from the Mass Eye and Ear Group and I include it here: small cell neuroendocrine carcinoma, sinonasal undifferentiated carcinoma, squamous cell carcinoma, Ewing sarcoma-primitive neuroectodermal tumor (PNET), mucosal malignant melanoma, olfactory neuroblastoma (esthesioneuroblastoma), desmoplastic small round cell tumor and rhabdomyosarcoma.

The World Health Organization Classification which divides carcinoid tumors into three main neuroendocrine tumors which include well differentiated, ki-67 ratio of less than 2%, well –differentiated(low-grade) neuroendocrine carcinoma with low grade malignant behavior with a ki-67 ratio between 2% and 15% and the final category which is the poorly differentiated (high-grade) neuro-endocrine carcinoma. These have a ki-67 ratio of greater than 15%.

Generally speaking orbital metastatic carcinoid tumors are typically from the gastrointestinal tract whereas uveal metastatic tumors are typically from the bronchial tracts, but 30% of patients do not have a primary tumor at initial diagnosis which adds to the complexity of making an initial diagnosis. Histopathologically, gastrointestinal carcinoid tumors may have a nesting arrangement and bronchial subtypes may have a trabecular pattern but a mixture may also occur. Chromogranin, synaptophysin, serotonin and calcitonin are useful stains and by EM, there are cytoplasmic neurosecretory granules. PET scanning has been very helpful and blood levels of Chromogranin A and serotonin and urine levels of 5-HIAA are useful.

There are associations with other cancer syndromes such as MEN-1 or MEN-2, NF-1 and von Hippel-Lindau Syndrome.

Ma & Lei reviewed the literature and reported in 2009 on 44 well documented cases of nasal or paranasal neuroendocrine carcinomas (Am J Otolaryngol Head Neck Med Surg 30:54) These tumors are very uncommon at presentation and the clinical presentation is usually nonspecific and include: nasal obstruction, rhinorrhea, or epistaxis and ophthalmic signs include exophthalmos, decreased vision and ocular motility deficits with diplopia, anosmia or regional pain associated with worse disease.

In the past 15 years, EOPS and Verhoeff-Zimmerman members such as Friedman(2004), Shetlar(2106), Milman(2013) and Dryja(20014) have presented different neuroendocrine carcinomas and what I would like to focus on is a recent Survey of Ophthalmology 2015 by Peter MacIntosh MD, Frederick Jakobiec MD and Anna M Stagner MD that looks at high grade neuroendocrine carcinomas. In their case presentation, they present a case with boney erosion and a distracting concomitant Actinomyces infection and they describe the difficulties in separating high-grade neuroendocrine carcinomas with Grade IV Esthesioneuroblastomas. As they mentioned, these tumors often lack lobulation, vascular septae, the Homer Wright and Flexner Wintersteiner Rosettes and the neurophil feltwork of background cellular processes and their biological behavior if often quite similar. I am attaching this article as the host to my USB drives so that you have an opportunity to review this piece.

So in summary, we present a case of a high grade neuroendocrine carcinoma without systemic features of the carcinoid syndrome.