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Case Report

Bilateral Invasive Orbital Metastases from a Poorly Differentiated Large Cell Neuroendocrine Carcinoma of the Esophagus

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Abstract

We report a case of a 62-year-old man presenting with a right eye tumor and retinal detachment. A magnetic resonance imaging (MRI) of the skull showed hyperintense bilateral orbital masses exhibiting an intraocular component and an extraconal component in the right eye measuring 21.8 x 23.2 mm. Immunohistochemistry studies and histopathology results of our patient following right orbital exenteration confirmed a large cell neuroendocrine carcinoma. A positron emission tomography-computed tomography (PET/CT) scan was performed in an attempt to identify the primary origin detecting a metabolically active tumor located in the distal esophagus and metastases to the bone, liver, pancreas, left kidney, mesentery, abdominal, mediastinal and left axillary lymph nodes, choroid of the left eye and lumbar soft tissues. An upper endoscopy revealed an esophageal infiltrating mass. Immunohistochemical staining confirmed a poorly differentiated, large cell neuroendocrine carcinoma.

Keywords: Large cell neuroendocrine carcinoma, Esophagus, Orbital, Metastasis

Introduction

The prevalence of orbital metastases has increased in the last years and is estimated to range from 2 to 4.7% [1]. Any cancer that can spread through the hematogenous route can metastasize to the orbit and ocular adnexa. The primary cancers that most commonly lead to intraocular metastases include breast cancer, lung cancer, prostate cancer, melanoma and carcinoid tumors [1]. Metastasis from carcinoid tumors tend to become apparent late in the course of malignancy usually from a gastrointestinal site [1-3].

Neuroendocrine tumors (NETs) represent an unusual and complex disease spectrum, which appear to have increased in overall incidence over the past 30 years. The greatest incidence of NETs includes gastrointestinal tract and respiratory system neoplasms. In the gastrointestinal tract, most NETs occur in the small bowel (41.8%), rectum (27.4%), and stomach (8.7%) [4].The presence of NETs in the esophagus is rare but not exotic. Most are poorly differentiated neuroendocrine carcinomas [5-8].

Herein we present a particularly interesting case, to the best of our knowledge, the first case report of orbital metastasis (OM) as the inaugural manifestation of a neuroendocrine carcinoma of the esophagus with widespread metastases.

Summary of Clinical and Pathological Findings

A 62-year-old man, who consulted for a 6-month history of bilateral progressive decrease in vision and acute orbital pain diagnosed as bilateral glaucoma. No other remarkable symptoms were noted. His past history included smoking for 30 years. Ocular examination revealed a right retinal mass with retinal detachment. No mass was evidenced in the contralateral eye. A magnetic resonance imaging (MRI) of the skull showed bilateral hyperintense orbital masses, with an intraocular component (choroid) and extraconal component in the right eye measuring 21.8 x 23.2 mm (Figures 1A and 1B). An optical coherence tomography (OCT) revealed a superior and inferior temporal peripapillary dome shaped lesion, with hypoechoic areas suggestive of necrosis, scleral rupture and orbital infiltration. A 19.2 x 20.3 mm choroidal mass was evidenced in the left eye. The initial clinical impression was bilateral choroidal melanoma with invasive orbital involvement on the right side. Patient underwent right orbital exenteration due to infection of the soft tissues.

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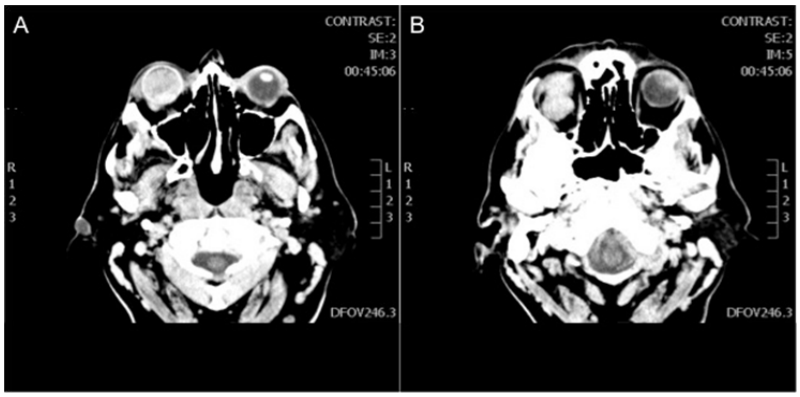

Figure 1: Magnetic resonance imaging of the skull showed bilateral hyperintense orbital masses **(A)** with an intraocular component (choroid) and extraconal component in the right eye **(B)**

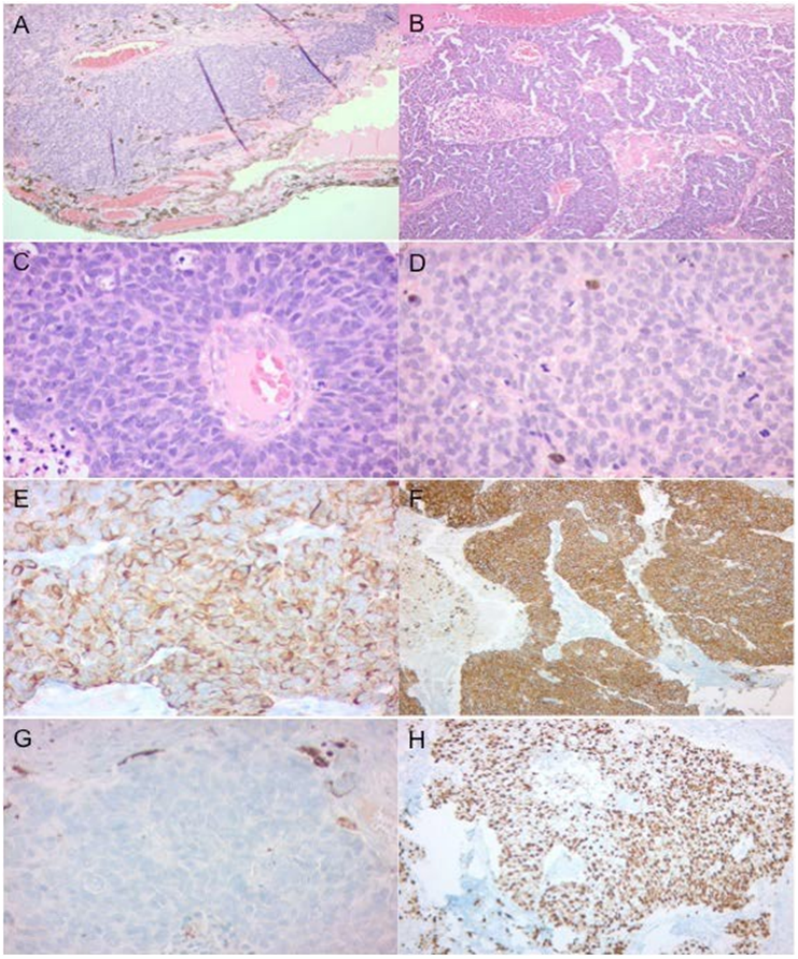

Figure 2: Choroid involvement with a high-grade malignant tumor composed of large cells with poorly defined borders (**A,B)**, focal rosette-like pattern **(C)** and high mitotic activity **(D).** Immunohistochemical staining was positive for Synaptophysin **(E)**, keratins AE1/AE3 **(F)**, and negative for HMB-45 **(G)**. Ki 67 cellular proliferative index was 90% **(H)**.

Histopathological examination showed right eye choroid involvement with a high-grade malignant tumor composed of large cells with poorly defined borders, with high mitotic activity evidencing 32 mitoses per 10 HPF (count by PHH3), focal rosette-like pattern and extensive foci of necrosis. The tumor invaded the sclera, the periorbital fat, optic nerve and surgical margins of resection (Figures 2A-2D). Immunohistochemical staining was positive for keratins AE1/AE3, Chromogranin A and Synaptophysin, and negative for S100, HMB45, MIFT, CDX2, TTF1, CK7 and CK20. The Ki 67 cellular proliferative index was 90%.

These findings supported the diagnosis of a grade 3 poorly differentiated, large cell neuroendocrine carcinoma (Figures 2E-2H).

A PET/CT scan identified a metabolically active tumor in the distal esophagus and metastases to the bone, liver, pancreas, left kidney, mesentery, abdominal mediastinal and left axillary lymph nodes, choroid of the left eye and lumbar soft tissues (Figure 3).

An upper gastrointestinal endoscopy revealed an esophageal ulcerated infiltrating mass with raised margins and a "punched-out" appearance at 40 cm in the distal esophagus, 2 cm in diameter, involving 40% of the circumference and occluding 20% of the lumen. A biopsy was performed. The histopathological examination of the biopsy specimen showed an infiltrating high-grade, large cell, malignant tumor, with high mitotic activity and extensive necrosis. Immunohistochemical staining was positive for keratins AE1AE3, Chromogranin A and Synaptophysin, and negative for S100, p63 and CK34BE12. The Ki 67 index was 90% (Figures 4A and 4B). A diagnosis of a large cell high-grade neuroendocrine carcinoma of the esophagus with bilateral

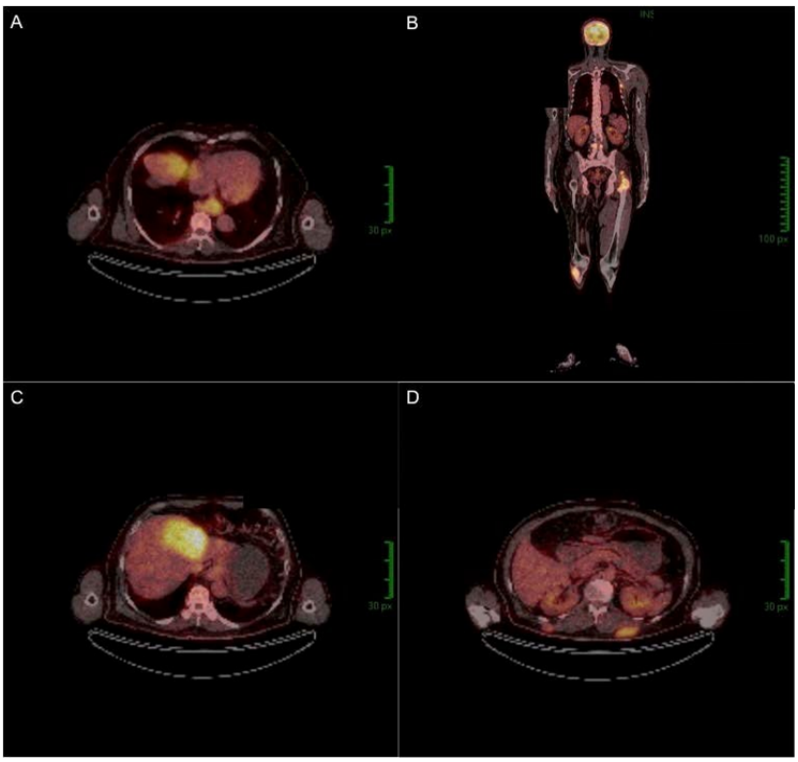

Figure 3: PET-CT scan showed a metabolically active tumor in the distal esophagus **(A)** and metastatic involvement of bone, liver, pancreas, left kidney, mesentery, abdominal, mediastinal and left axillary lymph nodes, choroid of the left eye and lumbar soft tissues **(B,C,D).**

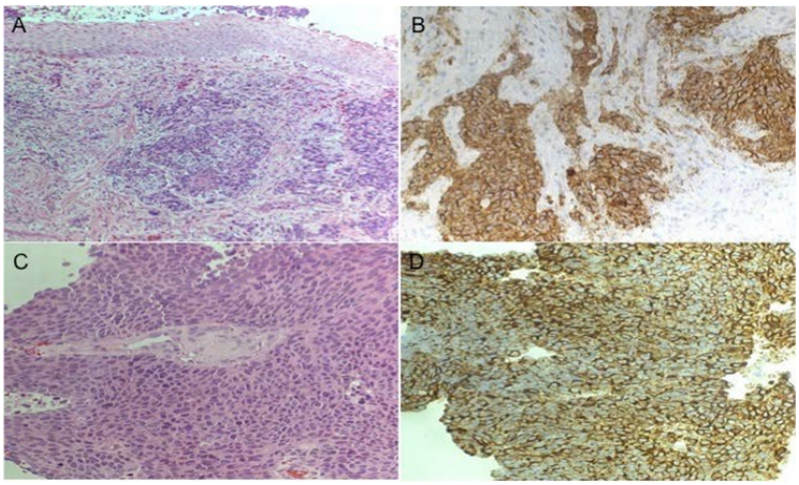

Figure 4: High-grade malignant tumor composed of large cells (**A)** Esophagus. (**C)** Lumbar soft tissues. Immunohistochemical staining was positive for Synaptophysin (**B)** Esophagus. (**D)** Lumbar soft tissues.

orbital, liver, soft tissue and bone metastases was made based on these findings.

An examination of additional biopsies of the lumbar soft tissues (Figures 4C and 4D) and liver resulted in metastases from a poorly differentiated, large cell neuroendocrine carcinoma. At nine months follow-up after the exenteration surgery patient was still alive with impaired functional status. He received combined chemotherapy with cisplatin and etoposide and palliative management with morphine. Unfortunately, he did not respond to chemotherapy and died 11 months after the surgery.

Discussion

The World Health Organization (WHO) has proposed the following classification of gastrointestinal and pancreatic NETs describing three grades based on the proliferation rate of the tumor: (i) Well differentiated (WD) Grade 1 neuroendocrine tumor (WD-NET): mitotic count:: <2 mitoses/10 high-power field (HPF) and / or Ki-67 index: ≤ 2%; (ii) Grade 2 WD-NET: mitotic count: 2–20 mitoses/10 HPF and/or Ki-67 index: 3–20 %; and (iii) Grade 3 poorly differentiated neuroendocrine carcinoma, large cell type or small cell type neuroendocrine carcinoma (PD-NEC), mitotic count:: >20 mitoses/10 HPF and /or Ki-67 index: >20% [5].

Poorly differentiated neuroendocrine carcinoma (PD-NEC) of the esophagus is rare but not exotic [5,6,9]. PD-NECs can be mixed to other subtypes neoplasms, such as adenocarcinoma and squamous cell carcinoma [10]. PD-NEC of the esophagus occurs more frequently in males (3:1), the age at presentation is variable, ranging from 30 to 82 years [5,9,11]. Esophageal NEC typically develops in the lower third of the esophagus and appears as exophytic polypoid and ulcerated lesions. Dysphagia is the most common symptom followed by abdominal pain, melena, and weight loss. Moreover, similar to other esophageal tumors, patients usually present with vague clinical signs such as chest pain and odynophagia [5, 8, 9]. The distant sites of metastases include the liver, abdominal lymph nodes, bone, lung, and brain [6,11]. Metastatic disease is assessed using computed tomography, endoscopic ultrasonography, and PET-CT scan. Esophageal NEC has a poor prognosis correlated to tumor size more than 2.0 cm and lymphovascular or perineural invasion [6, 8,11]. The median overall survival rate varies from 13 to 28.5 months even in those patients who receive treatment. A high percentage of esophageal NETs are metastatic at diagnosis [6, 9, 12] such as the case reported herein. Chemotherapy with cisplatin and etoposide regimen is given either in the adjuvant setting or as palliative intent therapy for inoperable or metastasized NETs. Irinotecan-plus-cisplatin appears to be a feasible chemotherapy for extensive-disease esophageal NETs with respect to efficacy, toxicity, and availability in the clinical setting [8,13,14].

An OM from a primary esophageal tumor is rare. This type of metastasis has been reported from primary adenocarcinoma [15] and melanoma [16] but not from primary NETs. A metastasis of a primary NET to the orbit is rare. Less than 40 cases of OM have been reported in the medical literature [2] usually from gastrointestinal sites and more than two-thirds of NET metastasis to the orbit had a previously established diagnosis [1]. Typically they are slow growing and may manifest as a mass causing proptosis, diplopia, or less commonly, inflammatory symptoms [1].

On the other hand, OM is usually associated with an extremely poor prognosis. The choroid is the most common ocular site for metastatic disease owing to abundant vascular supply. OM occurs in 4-12% of patients with solid tumors, preferentially breast and lung carcinomas. Bilateral, multifocal metastases are most often secondary to breast cancer, whereas unilateral, unifocal metastases are more commonly found with lung cancer [17,18].

Histologically, WD-NETs display cell organoid arrangements usually with nesting or trabecular patterns. The cells have granular eosinophilic cytoplasm. The nuclei show coarsely granular salt and pepper chromatin. Mitosis and necrosis are not present. The histologic appearance of poorly differentiated large cell neuroendocrine carcinomas (PD-NECs) is characterized by neoplastic cells forming large nests with central necrosis. These cells exhibit moderate amount of cytoplasm and round to oval nuclei; coarsely granular open chromatin and prominent nucleoli. Numerous mitoses are present [19]. Immunohistochemical studies are an important tool for diagnosis or differential diagnosis to distinguish primary tumors from metastatic lesions from melanoma, breast carcinoma, lung carcinoma, prostate carcinoma [1] or even from a lymphoma. Thus, we recommend performing an immunohistochemical profile in all cases of OM to identify the primary tumor when the origin is not known. Orbital lesions from a neuroendocrine tumor require identifying a gastrointestinal tract or lung primary tumor.

Conflict of Interest

The authors declare no conflict of interests.

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