Hepatocellular Carcinoma Metastatic to the Orbit

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We report a rare case of orbital metastasis from hepatocellular carcinoma and review previously documented cases of this condition. The clinical, histopathological, and immunohistochemical characteristics of hepatocellular carcinoma metastatic to the orbit are described. Results from histopathological examination and histochemical findings of the orbital mass established the diagnosis. A review of 10 cases of metastatic hepatocellular carcinoma to the eye and orbit disclosed painful proptosis as the most common clinical sign of hepatocellular carcinoma metastatic to the orbit. In 5 (56%) of the 9 cases that had orbital metastasis (including the present case), the diagnosis was made after the patient first was examined with symptoms from the orbital mass. Metastatic hepatocellular carcinoma should be considered as a rare cause of painful proptosis. While patients usually are seen with signs and symptoms of widespread metastatic carcinoma, patients with hepatocellular carcinoma with orbital involvement may be first examined by the ophthalmologist because of the clinical manifestations of the disease, proptosis and pain. Other orbital lesions associated with painful proptosis are discussed briefly.

Tumor metastasis to the orbit is generally uncommon. In a review of 227 cases of metastatic carcinoma to the eye or orbit, no cases of primary liver carcinoma were recorded. Recently, the incidence of orbital metastasis appears to have increased, possibly because of the prolonged survival of patients. The report by Ferry and Font noted that while tumors from the breast and lung metastatic to the orbit were responsible for more than 68% of the metastases, the primary lesion was unknown in 18% of the cases.

The purpose of the current report is to document a histologically confirmed metastatic hepatocellular carcinoma to the orbit and to review the literature. To our knowledge, only 10 cases of metastatic hepatocellular carcinoma to the eye and orbit have been documented previously. The salient histological features and immunohistochemical findings are discussed.

REPORT OF A CASE

A 79-year-old white woman was first seen with a 3-month history of decreasing vision, progressive proptosis, and inferior displacement of the right globe (Figure 1). The patient noted a constant dull pain localized to the right side of the forehead over the last 4 weeks. Her medical history was notable for hypertension, chronic hepatitis C infection, and age-related macular degeneration. On ophthalmologic examination, the patient had a visual acuity of counting fingers at 2 ft OD. A solid, compressible mass could be palpated on the lateral aspect of the right orbit. The right globe had 9 mm of proptosis and 5 mm of inferior displacement. The patient had an afferent pupilary defect in the right eye. The right upper and lower eyelids were erythematous and swollen. Diffuse conjunctival chemosis was noted on slitlamp examination. Ocular motility was significantly decreased in all fields of gaze, in the right eye. Findings from ophthalmoscopic examination showed retinal striae in the posterior pole. Retinal pigment epithelial atrophy and
pigment mottling consistent with nonexudative age-related macular degeneration was evident in the foveal region. Visual acuity OS was counting fingers to 6 ft. Findings from ophthalmoscopic examination of that eye were noteworthy for advanced, nonexudative macular degeneration.

Computed tomographic scans of the orbits disclosed an oval to fusiform mass of a maximal horizontal diameter of 37 × 27 mm vertical diameter involving the posterolateral right orbital wall with destruction of the orbital roof and extension into the right cranial fossa (Figure 2 and Figure 3). Magnetic resonance imaging revealed an elongated mass that was located superior to the globe and extended through the orbital roof into the anterior cranial fossa. Findings from an incisional biopsy of the orbital mass were interpreted as metastatic hepatocellular carcinoma. Laboratory studies revealed abnormal findings for the liver function tests, and subsequent computed tomographic scans of the abdomen showed multiple filling defects in the liver. A biopsy of the liver mass was not performed. No evidence of other metastatic lesions was present. The patient underwent palliative radiation therapy to the orbit with improvement of ocular symptoms and a reduction in proptosis. The patient was reported alive with tumor 3 years after the diagnosis was made.

PATHOLOGIC FINDINGS

Histopathological findings of the orbital mass showed large polygonal cells with granular acidophilic cytoplasm and large nuclei with prominent single nucleoli (Figure 4). In some areas, the tumor cells exhibited a distinct trabecular pattern delineating open sinusoidal spaces lined by a single layer of flat endothelial cells. Periodic acid–Schiff stains revealed the presence of numerous periodic acid–Schiff–positive granules (glycogen) in the cytoplasm of the tumor cells (Figure 4). A low-power view of the tumor showed ductular structures with small central lumens (Figure 5, top). These ductular structures represent the formation of bile canaliculi that are highly characteristic of hepatocellular carcinoma. No bile thrombi were observed within the canaliculi. Oblique sectioning of the tumor demonstrates more vividly the canaliculi that are stained strikingly positive for polyclonal carcinoembryonic antigen (CEA) (Figure 5, bottom). The cell membranes of the neoplastic cells also showed immunoreactivity against a low-molecular-weight cytokeratin (CAM 5.2). Table 1 summarizes the results of the immunohistochemi-
cal findings. The tumor was studied for DNA ploidy and cell cycle analysis by flow cytometry and demonstrated an aneuploid stem line with a DNA index of 1.16. The S-phase fraction (for proliferative activity) could not be determined.

**COMMENT**

Patients with hepatocellular carcinoma commonly are seen with a triad of fever, right upper quadrant pain, and a palpable abdominal mass. Occasionally, the tumor manifests with signs and symptoms related to metastasis to the regional lymph nodes or lungs. Less common metastatic sites include the skin, supraclavicular lymph nodes, gums, and bone. Orbital metastases of hepatocellular carcinoma are rare. Only 8 cases have been recorded previously.

Table 2. Results of Immunohistochemical Stains From the Right Orbital Mass

<table>
<thead>
<tr>
<th>Stain Performed</th>
<th>Result</th>
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<tr>
<td>Low-molecular-weight keratin (CAM 5.2)</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>Polyclonal carcinoembryonic antigen</td>
<td>Positive (outlining bile canaliculi)</td>
</tr>
<tr>
<td>α-Fetoprotein</td>
<td>Negative</td>
</tr>
<tr>
<td>Keratin cocktail (AE1/AE3)</td>
<td>Negative</td>
</tr>
<tr>
<td>Epithelial membrane antigen</td>
<td>Negative</td>
</tr>
<tr>
<td>α1-Antitrypsin</td>
<td>Negative</td>
</tr>
<tr>
<td>HMB-45</td>
<td>Negative</td>
</tr>
<tr>
<td>S100 protein</td>
<td>Negative</td>
</tr>
<tr>
<td>Chromogranin</td>
<td>Negative</td>
</tr>
<tr>
<td>Neuronal specific enolase</td>
<td>Negative</td>
</tr>
<tr>
<td>Vimentin</td>
<td>Negative</td>
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</table>

Metastasis to the eye and orbit is usually associated with advanced disease and early mortality. In our review of the literature, only 2 of the 7 patients for whom follow-up data were available survived more than 1 year. It is remarkable that the patient described herein is still alive with tumor 3 years after the histopathological diagnosis of the orbital mass was established.

About half of the cases of metastatic hepatocellular carcinoma to the orbit are associated with proptosis and pain. Clinicians should be aware that some primary neoplasms of and metastatic tumors to the orbit may cause proptosis and pain. Among the primary orbital neoplasms associated with painful proptosis one must include adenoid cystic carcinoma of the lacrimal gland, malignant peripheral nerve sheath tumor (malignant schwannoma) arising from the supraorbital nerve and its branches, and direct orbital invasion by neurotropic squamous cell carcinoma from the skin of the eyelid and peri-

Figure 5. Top, Lower-power view of the tumor showing ductular structures with small central lumina (arrow). The latter structures represent bile canaliculi that are highly characteristic of hepatocellular carcinoma (hematoxylin-eosin, original magnification × 345). Bottom, Trabecular pattern of neoplastic hepatocytes delineating bile ducts cut obliquely (arrowheads). No bile thrombi were observed in the lumen of the canaliculi. The presence of bile ducts is virtually pathognomonic of hepatocellular carcinoma (polyclonal carcinoembryonic antigen, original magnification × 692).
orbital region. Among the metastatic lesions to the orbit one may include prostatic adenocarcinoma, especially if bone involvement is present as well as some cases of Langerhans cell histiocytosis (R.L.F., unpublished observations, 1997).

In summary, the diagnosis of hepatocellular carcinoma with orbital metastasis requires a thorough clinical and radiological examination of the patient as well as a careful histopathological examination of the tumor with an appropriate panel of immunohistochemical stains. Metastatic hepatocellular carcinoma should be considered in the differential diagnosis of orbital tumors from an uncertain primary site. The role of the ophthalmic pathologist is essential for establishing the correct diagnosis.

As with other metastatic neoplasms to the orbit, once the diagnosis of metastatic hepatocellular carcinoma to the orbit is established, the prognosis is dismal. In these patients, palliative radiotherapy to the orbit appears to be the best mode of therapy.

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REFERENCES