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SHORT COMMUNICATION

Multiple bilateral choroidal metastatic tumors from a small-cell neuroendocrine carcinoma of unknown primary site

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PURPOSE. *To report one case of multiple and bilateral choroidal tumors from a poorly differentiated small cell neuroendocrine carcinoma of unknown primary.*
METHODS. *The case of a 30-years-old white female who developed multiple and bilateral choroidal tumors from a poorly differentiated small cell neuroendocrine carcinoma of unknown primary is presented.*
RESULTS. *The patient had a disseminated disease and died 6 months after. The oncologic work-up, including physical examination, laboratory and radiographic study, fails to identiy the primary site.*
CONCLUSIONS. *Intraocular involvement from a poorly differentiated small cell neuroendocrine carcinoma of unknown primary has not yet reported. We describe thic case together with a review of the literature. (Eur J Ophthalmol 2005; 15: 148-52)*

KEY WORDS. *Metastasis, Small cell carcinoma, Unknow primary, Choroid, Intraocular.*

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INTRODUCTION

A 30-year-old woman who developed multiple and bilateral choroidal tumors from a poorly differentiated small cell neuroendocrine carcinoma of unknown primary site (CUP) is presented. The patient had disseminated disease and died 6 months later. The oncologic work-up, including physical examination and laboratory and radiographic study, failed to identify the primary site. CUP is a common clinical entity, accounting for 2% of all cancer diagnoses in the Surveillance, Epidemiology, and End Results (SEER) registries between 1973 and 1987 (1). Within this category, tumors from many primary sites with varying biologies are represented. We present one case with intraocular involvement and a review of the literature.

Substantial improvements have been made in the management and treatment of some patients with CUP. The identification of specific subgroups of treatable patients has been made possible by the development of specialized immunohistologic techniques that can aid in tumor characterization, and by the recognition of several clinical syndromes that permit prediction of chemotherapy responsiveness.

The typical patient with CUP presents with symptoms referable to a metastatic site. Light microscopic evaluation of biopsy material places the tumor into one of six histologic categories, which then guides further evaluation: adenocarcinoma 70%; poorly differentiated carcinoma 15-20%; poorly differentiated adenocarcinoma 10%; poorly differentiated neoplasm <5%; squamous cell carcinoma 5%; and neuroendocrine carcinoma <5%.

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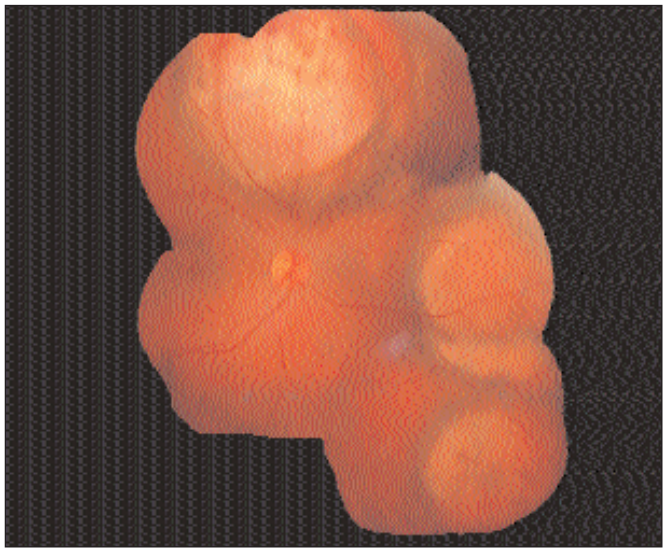

Fig. 1 - *Color photograph of the right eye showing three yellowish choroidal tumors.*

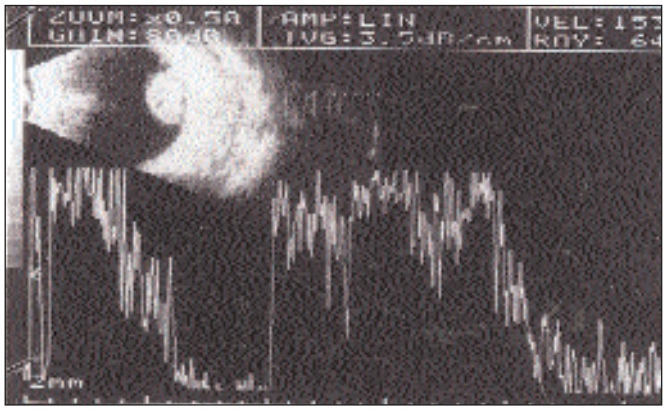

Fig. 2 - *A- and B-scan ultrasonograpy of the largest choroidal tumor.*

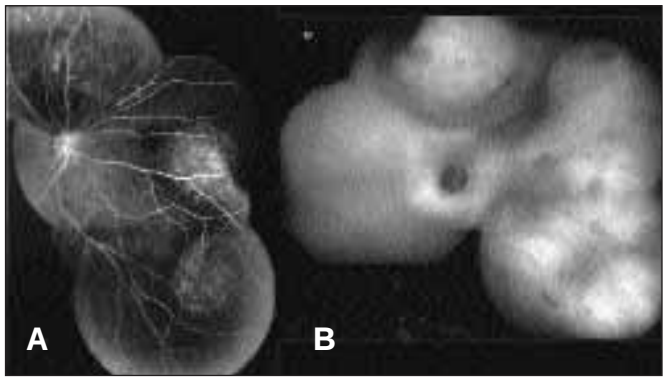

Fig. 3 - *Fluorescein* (**A**) *and indocyanine green* (**B**) *angiography showed pinpoint hyperfluorescence and subtle diffuse staining and leakage in the late frames.*

Case report

On March 28, 1998, a 32-year-old woman was referred to the Retina Service of the University Eye Clinic of Genoa, because of an intraocular mass in her right eye. Four days before, she had been admitted to the Neurology Service of another institution for an epileptic attack.

Funduscopic examination of the right eye revealed three white-reddish choroidal masses at the posterior pole. The largest (Fig. 1) was located superior to the optic nerve, causing an exudative retinal detachment, and measured 6.6 mm in thickness and 11.8 mm in height. The other two lesions (Fig. 2) were located nasally and measured 3 mm in thickness and 7.7 mm in height. Fluorescein angiography showed pinpoint hyperfluorescence while indocyanine green angiography showed subtle diffuse staining and leakage in the late frames (Fig. 3). Fundus examination of the left eye was normal. The patient's visual acuity was 20/20 bilaterally, anterior segment structures were unremarkable, intraocular pressure was 16 mm Hg in the right eye and 14 mmHg in the left.

A complete oncologic work-up performed at the oncology service of another institution revealed multiple lesions located in the brain, liver, right adrenal gland, chest lymph nodes, breast, and thyroid. The

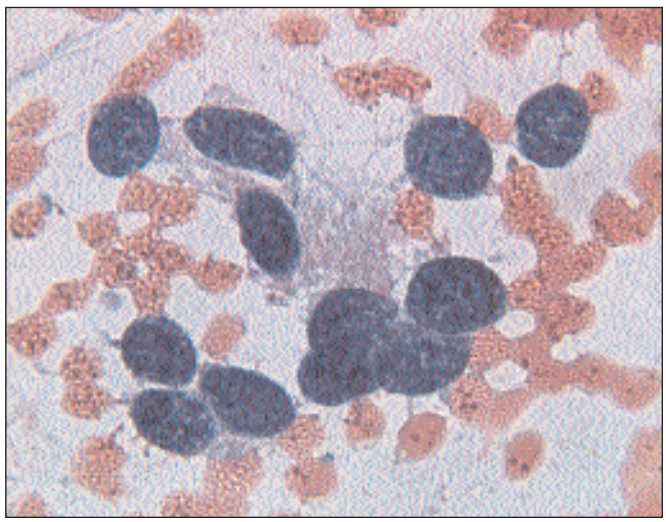

Fig. 4 - *Microphotograph of the fine needle aspiration biopsy of one tumor nodule of the liver.*

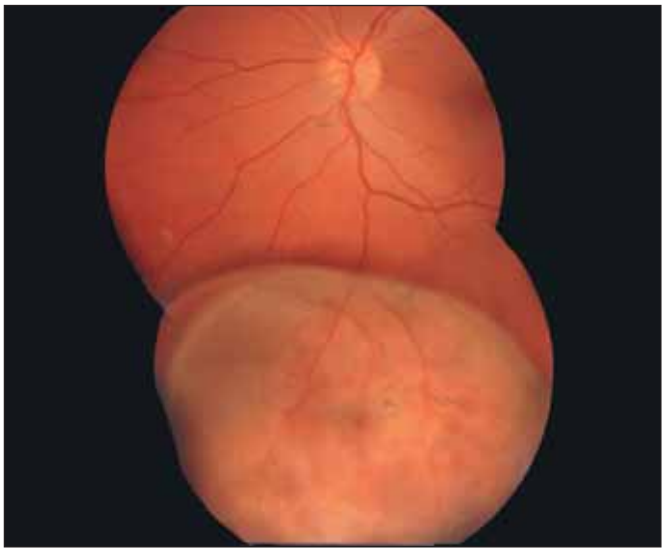

Fig. 5 - *Color photograph of the left eye showing a yellowish choroidal tumor inferiorly to the optic nerve.*

pathologic report of the fine needle aspiration biopsy of the liver was consistent with small cell neuroendocrine carcinoma (Fig. 4), which was also confirmed by the elevated neuroendocrine markers ((chromogranin 250 ng/L (19-98 ng/L) and neuron-specific enolase 150 ng/L (<17 ng/L)) in the blood.

For this reason, the woman underwent four cycles of chemotherapy (vinblastine, cisplatinum, α-interferon, interleukin-2, and dacarbazine). In July 1998, she returned to our clinic. The fundus of the right eye was unchanged while a yellowish choroidal mass was disclosed inferiorly to the optic disc in the left eye, causing a serous retinal detachment (Fig. 5). The patient died in September 1998.

DISCUSSION

The frequency of choroidal metastasis in patients with cancer is estimated to be approximately 2% to 7% (1-4). If all intraocular metastases are considered, this number rises to approximately 12% (1-4). Intraocular metastasis is now considered the most common malignancy of the eye (5). The frequency of ocular metastasis varies significantly among primary sites. Shields et al reported that of 142 patients with ocular diagnosis of uveal metastases and no history of cancer, a subsequent evaluation showed a primary tumor in the lung in 35%, breast 7%, others 6%, and no primary site was found in 51%. Lung cancer was the most common primary tumor detected in patients with no neoplasm at the time of ocular diagnosis (5, 6).

However, there was also a significant percentage of patients in whom no primary site was ever detected (between 8% and 18.3%). Ocular metastasis, and particularly choroidal metastasis, can precede the diagnosis of the primary malignancy. In a study by Ferry and Font (7), 46% of the patients had tumor-related symptoms that preceded the detection of the primary neoplasm. In a study by Shields et al (6), 34% of patients had no history of cancer at the time of ocular diagnosis. Shields et al (6) surveyed 420 consecutive patients with uveal metastases. The tumors were unilateral in 320 patients and bilateral in 100 patients. This proportion of bilateral cases is considerably more than the 4.4% noted by Ferry and Font. The study by Mewis and Young (8) of breast cancer patients noted a 31% incidence of bilaterality. In both the Ferry and Font and Mewis and Young studies, the incidence of subsequent bilaterality was notable (17.6% and 15%, respectively). There seems to be no predilection for metastasis to preferentially affect the right or left eye (3, 6). In each affected eye, more than one metastasis may be noted. Shields et al (6) reported multiple foci in 20% of patients with choroidal metastasis. The mean number of uveal metastasis noted per eye was 2.0, and the maximum number noted was 13.

The site of origin of a histologically documented carcinoma is not identified clinically in approximately 3% of patients; this situation is often referred to as CUP or occult primary malignancy (9-13).

The definition of CUP varies from study to study; however, at a minimum, this determination should include a biopsy of the tumor and a thorough history and complete physical examination that includes head and neck, rectal, pelvic, and breast examinations; chest x-rays; a complete blood cell count; urinalysis; and an examination of the stool for occult blood. When these results do not reveal signs of a potential primary lesion, and the biopsy is not consistent with a primary tumor at the biopsy site, CUP must be assumed. The majority of CUP are adenocarcinomas or undifferentiated tumors; less commonly, squamous cell carcinoma, melanoma, sarcoma, and neuroendocrine tumors can also present with a primary site of origin

that cannot be determined. The most extreme examples occur in the 15% to 25% of patients in whom the diagnosis of the primary site cannot be determined even at postmortem examination (14).

Neuroendocrine tumors are a diverse group of neoplasms that include carcinoid tumors, islet cell tumors, neuroblastoma, and small cell carcinoma of the lung as well as several other less common neoplasms. In 1988, Hainsworth et al (14) identified a previously undescribed group of 29 patients with extrapulmonary undifferentiated small cell neuroendocrine carcinoma (SCNC) metastases of unknown primary site. Extrapulmonary SCNC are rare tumors that show similar histology, aggressiveness, and rapid growth rate of SCNC of the lung. Although choroidal melanoma can shows some similarities with SCNC at cytologic level, usually these tumors are rarely multiple and bilateral, do not have an aggressive outcome, and the blood levels of chromogranin and NSE are not elevated. We excluded a SCNC of the lung because of the young age of the patient, the negative radiologic examination, and the absence of history of tobacco smoking.

The prognosis for patients with CUP is poor. As a group, the median survival is approximately 3 to 4 months in most studies with less than 25% and 10% of patients alive at 1 and 5 years, respectively. CUP is represented by a heterogeneous group of diseases all of which have presented with metastasis as the primary manifestation. Although the majority of diseases are relatively refractory to systemic treatments, there are certain clinical presentations of CUP that carry a much better prognosis. Specifically in this case, the reason we did not perform an irradiation treatment of both eyes was the disseminated metastatic disease and together with the referral oncologist we decided to start chemotherapy. In each instance, there are distinct clinical and pathologic details that require consideration for appropriate, potentially curative, management (15-18). A retrospective review of 657 consecutive patients with CUP (270 additional patients were excluded as a result of identification of a primary malignancy, a noncarcinoma cell type, or no malignancy) reported several variables of significant prognostic importance identified by multivariate analysis. Lymph node involvement and neuroendocrine histology were associated with longer survival; male sex, increasing number of involved organ sites, adenocarcinoma histology, and hepatic involvement were unfavorable prognostic factors (19). Adrenal involvement has also been noted to be a poor prognostic finding (20). Although only a minority of patients will have curable disease or a disease for which there is substantial palliative benefit, the opportunity for treating such patients should not be ignored or lost. This knowledge combined with the appropriate use of special diagnostic pathology and selected radiologic studies will provide the optimal benefit for patients who present with CUP.

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