SFO COMMUNICATION

Uveal metastasis revealing lung cancer☆

Métastases uvéales révélatrices de cancer du poumon

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Summary

Background. — Uveal metastases (UM) are the most common intraocular malignancies and can be the first manifestation of a disseminated disease. The purpose of this study is to determine the frequency with which uveal metastasis results in a diagnosis of lung cancer, to describe the clinical characteristics of patients with lung cancer metastatic to the uvea, as well as diagnostic difficulties that may be encountered.

Patients and methods. — We carried out a single-center retrospective study of the medical records of all patients who presented with a UM between 1999 and 2010 at the institut Curie in Paris. From these patients, we retrospectively studied UM secondary to lung cancer. A work-up including thoracic-abdominal-pelvic CT was performed for each patient in whom the primary source of choroidal metastasis was unknown.

Results. — Of 109 patients presenting with UM, 43 were diagnosed with primary lung cancer (39.4%). Of those 43 patients, the UM was observed prior to the lung cancer in 31 patients (72.1%). Demographic data included 61% male and 39% female, mean age 59.1 years (range: 31–78), and mean life expectancy after diagnosis of UM was 7.5 months (range: 0.7–29). Other metastatic sites were associated with UM in 90.7% of the patients. In all, 90.7% of the patients presented with blurred vision, and 25.6% with pain or inflammation. UM were located within the choroid for 39 patients (90.7%), the iris for three patients (7.3%) and the vitreous for one patient. Seventy percent of patients had a solitary lesion, 76.7% had unilateral involvement, and

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23.3% of cases were bilateral. Mean thickness on B-scan ultrasonography was 3.61 mm (range: 1–8.5 mm). In all, 81.4% of UM were unipigmented, while 18.6% showed pigment mottling. In all, 20.9% of patients were referred with the diagnosis of choroidal melanoma from their regular ophthalmologist, and three of the 43 patients (6.9%) were initially misdiagnosed and treated for melanoma at Curie. Chest X-ray was unremarkable in 18.9% of patients.

**Conclusion.** — UM is often the first manifestation of disseminated disease and requires a search for the primary tumor, in particular lung cancer. Standard chest X-ray cannot rule out the diagnosis. Metastases may be solitary with heterogenous pigmentation, and the differential diagnosis from uveal melanoma may be difficult, requiring the expertise of a referral center.

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**Résumé**

**Introduction.** — L’objectif de l’étude est de déterminer dans quelle proportion la découverte d’une métastase uveale est révélatrice d’un cancer du poumon et de décrire les caractéristiques cliniques des patients atteints de cancer du poumon métastatique à l’uvée et les difficultés diagnostiques pouvant être rencontrées.

**Patients et méthodes.** — Nous avons réalisé une étude rétrospective, monocentrique, sur les dossiers médicaux des patients ayant eu des métastases uveales de 1999 à 2010. Les patients présentant une tumeur choroidienne suspecte ont bénéficié d’un scanner thoraco-abdomino-pelvien.

**Résultats.** — Sur 109 patients atteints de lésions métastatiques uveales, 43 patients avaient un primitif pulmonaire (39,4%). Parmi ces patients, le diagnostic de la lésion uveale a permis de révéler le cancer primitif chez 31 patients soit dans 72,1 % des cas. La population était composée de 61 % d’homme et 39 % de femme, l’âge moyen au diagnostic était de 59,1 ans ; la durée moyenne de survie après diagnostic de métastase uveale de cancer du poumon a été de 7,5 mois. Dans 90,7 % des cas les métastases choroidiennes étaient associées à d’autres localisations métastatiques. La plupart des patients ont consulté pour une baisse d’acuité visuelle. Les lésions étaient choroidiennes dans 90,7 % des cas, iriennes dans 7,31 %. Elles étaient uniques dans 70 % des cas et bilatérales dans 23,3 % des cas. Elles avaient une épaisseur moyenne de 3,61 mm en échographie mode B. Elles étaient totalement achromes dans 81,4 % des cas mais dans 18,6 % des cas elles avaient des remaniements pigmentaires de surface pouvant orienter à tort vers un mélanome. Au total, 20,9 % des patients étaient adressés pour suspicion de mélanome et trois patients sur 43 (6,9 %) ont été traités pour un mélanome. La radiographie de thorax n’a pas révélé de lésion suspecte dans 18,9 % des cas.

**Conclusion.** — La découverte d’une lésion choroidienne évocatrice de métastase peut révéler un cancer disséminé et nécessite la recherche de la tumeur primitive, en particulier pulmonaire. Une radiographie standard normale ne permet pas d’éliminer le diagnostic. Des remaniements pigmentaires de surface peuvent orienter à tort vers un mélanome.

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**Introduction**

Uveal metastasis (UM) are the most common intraocular malignancies [1—6] and are becoming an increasing issue due to the enhanced survival of patients with advanced stage cancer. Prompt diagnosis and treatment are important to preserve patient quality of life. In studies based on eye bank populations, the frequency of ocular metastasis in patients who died from cancer can reach 12.6% [3]. Most of the time, intraocular metastasis are located within the choroid [6,7]. The most common primary cancer origin of UM is breast and lung adenocarcinoma [7,8]. Choroidal metastasis incidence from metastatic lung cancer was reported between 2% to 6.7% [4,9]. Choroidal metastasis usually appears as one or more white/yellow lesions, plateau or dome shaped, infiltrating, rapidly progressing, associated with secondary retinal detachment with sub retinal fluid and are generally located at the posterior pole. Bilateral and multiple choroidal tumors are very suggestive of CM [6,10—12]. However, in some cases, the diagnosis can be difficult when the tumor is unique, has some pigment mottling, or when it is mushroom shaped [13,14]. Therefore, the tumor cannot be easily distinguished from an achronic choroidal melanoma especially when the primary cancer is not known at the time of ophthalmologic examination. In 1997, Shield et al. [7] have demonstrated that one third of the patients with choroidal metastasis have no history of primary cancer at the time of diagnosis. In 1994, Beati–Zografos et al., have showed that metastasis from lung carcinoma were often diagnosed before the primary tumor compared to the other primary cancer [15]. Unlike the breast cancer, which can be diagnosed very early thanks to the screening and the auto palpation, the diagnosis of lung cancer is often late, and discovered at a disseminated stage [16].

The aim of this study is to describe the frequency in this series of UM of pulmonary cancer diagnosed before the
primary tumor. We also describe the clinical characteristics of the CM. And we finally report the difficulties the clinicians can meet to establish the diagnosis of choroidal metastasis and to find the primary cancer.

Patients and methods

In this retrospective study, we reviewed the medical charts of all the patients referred for UM between January 1, 1999 and December 31, 2010 in the department of Ophthalmology of the institut Curie in Paris (French Onco Ophthalmology referral center). Every patient was recorded with the diagnosis of UM based on concordant clinical findings and past medical history in the Curie database.

Only the patients presenting a choroidal metastasis arising from a lung cancer were included. Clinical diagnosis criteria of UM have been published by Shields [17]. The diagnosis was established on Ophthalmologic examination, ocular ultrasonography findings, and a positive history of pulmonary cancer or the detection of a primary cancer during the follow-up (proved histologically). Fundoscopic findings required for the diagnosis were: a white/yellow tumoral lesion located in the choroid, ciliar body or iris, rapidly progressing, plateau-shaped or dome shaped, single or multiple, unilateral or bilateral.

The diagnosis was made after a choroidal biopsy in one patient, a vitrectomy in one patient and an anterior chamber paracentesis in one patient. If the patient had no history of cancer, thoracic X-ray, thoraco-abdominal tomography and mammography were performed.

For each patient a complete clinical evaluation was performed and was recorded: age, sex, symptoms, best corrected visual acuity, location, clinical characteristics and number of lesions, presence of retinal detachment, ultrasonography findings, past medical history of cancer, other metastatic sites and characteristics of the thoracic X-ray.

Results

Between 1999 and 2010, we identified 109 patients with UM. The primary cancer was a lung cancer in 43 cases (39.4%). Among them, 12 patients (27.9%) reported a history of primary cancer and 31 patients (72.1%) had no known history of cancer at the time of diagnosis of UM.

Mean age at diagnosis was 59.1 years (range 31 to 78 years). Seventeen were women (39%) and 26 were men (61%). The mean follow-up period was 10.4 months (range 0.7 to 84 months, standard deviation [SD] = 14.5). At the end of follow-up, eight patients were still alive, six patients were lost of follow-up, and 29 patients have died. Mean life expectancy after diagnosis of choroidal metastasis was 7.5 months (range 0.7 to 29 months) in these 29 patients.

For the patients who already had a history of cancer, the diagnosis of UM was done after a mean interval of 26.6 months (range: 1 month–8 years) between the diagnosis of the cancer and UM.

Clinical features

The UM were located within the choroid for 39 patients (90.7%), the iris for three patients (7.31%) and the vitreous for one patient (2.3%) (Table 1).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical findings of 43 patients with uveal metastasis from lung cancer.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (a)</td>
<td>59.1 (range: 31–78) (%)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>26</td>
</tr>
<tr>
<td>Female</td>
<td>17</td>
</tr>
<tr>
<td>Known lung cancer</td>
<td>12</td>
</tr>
<tr>
<td>Unknown lung cancer</td>
<td>31</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
</tr>
<tr>
<td>Blurred vision</td>
<td>39</td>
</tr>
<tr>
<td>Pain/inflammation</td>
<td>11</td>
</tr>
<tr>
<td>Photopsia</td>
<td>3</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>2</td>
</tr>
<tr>
<td>None</td>
<td>4</td>
</tr>
<tr>
<td>Location</td>
<td></td>
</tr>
<tr>
<td>Choroid</td>
<td>39</td>
</tr>
<tr>
<td>Iris</td>
<td>3</td>
</tr>
<tr>
<td>Vitreous</td>
<td>1</td>
</tr>
<tr>
<td>Laterality</td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>33</td>
</tr>
<tr>
<td>Bilateral</td>
<td>10</td>
</tr>
<tr>
<td>Number of lesions</td>
<td></td>
</tr>
<tr>
<td>Solitary</td>
<td>30</td>
</tr>
<tr>
<td>Multiple</td>
<td>11</td>
</tr>
<tr>
<td>Diffuse</td>
<td>2</td>
</tr>
<tr>
<td>Color</td>
<td></td>
</tr>
<tr>
<td>Totally achromic</td>
<td>35</td>
</tr>
<tr>
<td>Pigment mottling</td>
<td>8</td>
</tr>
<tr>
<td>Thickness (a) (mm) ± SD</td>
<td>3.61 ± 2.08 (range 1–8.5 mm)</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td></td>
</tr>
<tr>
<td>Localized</td>
<td>9</td>
</tr>
<tr>
<td>Diffuse</td>
<td>16</td>
</tr>
<tr>
<td>Unknown</td>
<td>4</td>
</tr>
</tbody>
</table>

a = mean; SD = standard deviation.

For 37 patients (86.1%) UM were associated to other metastatic locations. For four patients (9.3%), choroid was the only metastatic site detected, and for two patients (4.6%) their metastatic status was unknown. In the 37 patients with other metastatic locations, 13 had only one other metastatic location (35.1%), 15 had two others metastatic sites (40.5%), and nine had more than two other sites (24.3%). The most frequent associated metastatic locations were bones (59.5%), lung (48.6%), liver (35.1%) and brain (24.3%) (Fig. 1).

The most common symptoms included blurred vision in 39 patients (90.7%) and ocular pain or inflammation in 11 patients (25.6%). The other symptoms were photopsia in three patients (6.9%), and glaucoma in two patients (4.6%). Four patients were totally asymptomatic (9.3%) and were diagnosed fortuitously. Glaucoma was associated with an iris metastatic location in two-thirds of the patients.

Lesions were unilateral in 33 patients (76.7%). Most of the patients (30 patients, 69.7%) had a solitary lesion. Eleven patients (25.6%) had multiple lesions: eight patients had
two UM, and three patients had more than two lesions. Two patients (4.6%) had a diffuse eye infiltration with vitreous or anterior chamber spreading. For 81.4% of the patients the lesion was totally achromic (35 patients), and 18.6% (eight patients) had some pigment motting in the lesions. Most of the patients had only some pigment motting on the surface of the lesion (with a "tiger aspect") (Fig. 2). But three patients had a real pigmentation at the basis of the lesion with a very misleading aspect (Figs. 3 and 4). On ultrasound, the mean thickness was 3.61 mm (range 1 to 8.5 mm, SD = 2.08). The echogenicity analysis was possible for only seven patients: five tumors were isoechoic, one was heterogenic, and one was hypoechoic. A retinal detachment was present in 25 patients (58.1%). It was localized for nine patients, diffuse for 16 patients.

**Thoracic imaging**

Every patient had a chest X-ray at the diagnostic of UM. Of the 43 patients with primary lung cancer, seven patients (19%) had an unremarkable thoracic X-ray and 30 (69%) patients had a suspicious lesion on the X-ray. (The X-ray results were not available for six patients). Thoracic CT failed to detect pulmonary primary cancer in two patients.

**Diagnostic mistakes**

Nine of 43 patients (21%) were addressed by their regular ophthalmologist with the diagnostic of choroidal melanoma. Three patients (7%) have been misdiagnosed and treated as a choroidal melanoma (proton beam irradiation) at the beginning of the management. The correct diagnosis of choroidal metastasis has been done secondarily after the appearance of other homolateral or controlateral suspect lesions at the fundoscopy few weeks later and after the diagnosis of pulmonary cancer at the thoracic X-ray or tomography (which is systematically done for each patients with achromic or partially pigmented choroidal melanoma).

**Atypical aspects**

Two patients had very atypical presentation. The first presented a granulomatous anterior uveitis with iris nodules and elevated eye pressure. The diagnosis was done after anterior chamber tap. The other one had posterior uveitis with...
nodular deposit on the retina. The diagnosis was done after a diagnostic vitrectomy.

Another patient had a very typical aspect of choroidal metastasis, but the primary cancer wasn’t detected by the imaging (thoraco-abdominal tomodensitometry, PET scan). A choroidal biopsy was performed and the histological examination found a lung cancer choroidal metastasis. Repeated CT scan and pulmonary fibroscopy confirmed lung cancer few weeks later.

Discussion

Lung is the first primary cancer site of UM for the males, and the second one after breast for the females. In the literature, very few series have studied the population of patients with UM secondary to lung cancer specifically. Only Shields et al., 1997 [7] and Kreusel et al., 2008 [14] had series with a consequent number of patients (respectively 90 and 22 patients). Kreusel et al., 2008 [14] report that UM reveal a lung cancer in 64% of the patients.

Shields et al., 1997 [7] showed that for all patients who present an isolated UM, a lung cancer is found in most of the cases, representing 35% of these cases, whereas breast cancer is revealed by a choroidal metastasis in only 7% and all other cancers individually accounted for 1% or less. More recently, Wang TJ et al., 2005 [18] showed that UM can reveal a cancer whatever the location in 22% of the cases. Our study confirms that the ocular diagnosis of UM is mostly established before the diagnosis of pulmonary cancer (72% of the patients). This is consistent with series previously published.

Concerning breast cancer, the proportion of revealing UM is totally different and represents only 3% according to Demirci et al., 2003 [19].

This difference between UM from lung cancer and breast cancer can be explained by the fact that breast cancer can be diagnosed at an early stage thanks to the organized screening politics in developed countries [20]. Lung cancers are diagnosed very late, and in a lot of cases diagnosed at a disseminated stage of the disease. Metastases are often the first manifestation of pulmonary cancers [21].

Our study also showed that UM of lung cancer have a strong tendency to be unilateral (77%) and unique (70%), whereas the classical description of choroidal metastasis is a multiple and bilateral achromatic lesion. Shields et al., 1997 [7] already described that the CM from lung cancer was more often unilateral and unifocal. In their study, the choroidal metastases from lung cancer were unilateral in 67% of the cases, and the mean number of lesions was 1 whereas they showed that CM from breast cancer had a strong tendency to occur as a multifocal and bilateral tumor.

The differential diagnosis between metastasis and achromic choroidal melanoma can be challenging, particularly in cases without known primary tumor. We observed in our study that almost 20% of the lesions were not totally achromic and were initially diagnosed as choroidal melanoma by their regular ophthalmologist. For most of the patients, the correct diagnosis was established by careful clinical examination, ultrasonography findings, and repeated extensive work-up. Very selected patients required a biopsy. There can be some pigment motting on the surface of a choroidal metastasis (Fig. 1) but it’s not the same pigmentation compared to melanoma, which is more homogenous [22]. For three of our patients the aspect of the fundus and the pigmentation was very misleading and we initially diagnosed and treated them as a choroidal melanoma.

The correct diagnosis was established after the discovery of a lung cancer. Other authors have already described the presence of different degree of pigmentation on the surface of the choroidal metastasis. For example, in the series of Kreusel et al., 2008 [14], of 27 affected eyes, 19 lesions had different degree of pigmentation on the tumor surface.

We also found that pain and ocular inflammation was suggestive of metastasis of lung cancer representing 25% of all the patients. This data is consistent with Shields et al. [7] in their study pain was associated with lung metastasis in 13% when breast metastasis was painful in only 2% of the cases. In this retrospective study, the number of atypical or challenging cases may be over-estimated. Many bias can be discussed in a tertiary center specialized in Onco Ophthalmology that is part of a Cancer institute.

Conclusion

Uveal metastases of lung cancer are often the first manifestation of a disseminated disease. They can be solitary unilateral with a heterogenous pigmentation. The differential diagnosis with achromic uveal melanoma may be difficult requiring expertise in referral centers. Repeated extensive work-up with chest CT scan, bronchoscopy, and bone scintigraphy will help ophthalmologists to reach the correct diagnosis.

Disclosure of interest

The authors declare that they have no conflict of interest concerning this article.

References

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