MULTIPLE NEOPLASMS IN PATIENTS WITH UVEAL
MELANOMA
NEOPLASIAS MÚLTIPLES EN PACIENTES AFECTOS DE
MELANOMA DE ÚVEA
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ABSTRACT

Purpose: To study the prevalence of multiple neoplasms in patients affected by uveal melanoma in Spain and to relate these with survival.

Method: We carried out a longitudinal prospective study of the prevalence of multiple neoplasms in patients diagnosed to have a uveal melanoma during the years 1984-2005. The data has been analysed for the following variables: age, sex, date of diagnosis, affected eye, origin and tumoral size, classification according to COMS (Collaborative Ocular Melanoma Study), time of follow-up, presence of other neoplasms, current clinical state, date and cause of death.

Results: Three hundred and five patients affected by uveal melanoma have been studied in the Ocular Oncology Unit of our institution; 24 patients (7.9%) had evidence in their medical reports of one or more additional neoplasms. Excluding cutaneous neoplasms originating in basal cells, this number reduced to 22 patients (7.2%). We did not find any statistically significant differences among the presentation age, sex or localization of the melanoma (ciliary body or choroid) and the presence or absence of a second neoplasm. When we analysed the proportion of patients with metastatic disease (both alive and dead) who presented with a second neo-

RESUMEN

Objetivo: Estudiar la prevalencia de neoplasias múltiples en pacientes afectos de melanoma de úvea en nuestro medio y relacionarlo con la supervivencia.

Método: Para ello se ha realizado un estudio prospectivo longitudinal de prevalencia de múltiples neoplasias en pacientes diagnosticados de melanoma de úvea entre los años 1984-2005. Se han analizado entre otras las variables clínicas: edad, sexo, fecha de diagnóstico, ojo afecto, origen y tamaño tumoral, clasificación según el COMS (Collaborative Ocular Melanoma Study), fecha del último control, tiempo de seguimiento, presencia de otras neoplasias, estado sistémico actual, fecha y causa de muerte.

Resultados: Se han estudiado 305 pacientes afectos de melanoma de úvea en la Unidad de Oncología Ocular de nuestro centro. 24 pacientes (7,9%) presentaron en su historia médica una o más neoplasias malignas. Excluyendo las neoplasias cutáneas de origen en células basales, esta proporción fue del 7,2% (22 pacientes). No se ha encontrado diferencias estadísticamente significativas entre la edad de presentación, sexo y la localización del melanoma (cuerpo ciliar o coroides) y la presencia o no de segundas neoplasias. Cuando se analizó la proporción de pacientes con enfermedad metastásica (tan-
plasm (40.9%), we found a statistically significant relationship between these variables (Chi-square test, p=0.004).

Conclusions: We have observed a percentage of second neoplasms similar to that described in other international studies. We did not find a larger proportion with a second neoplasm according to the sex, age, or tumoral localization, nor did we observe a higher frequency of any particular second neoplasm. We have defined a relationship between metastatic uveal melanoma, and the development of a second neoplasm, which clearly indicates a need for increased systemic follow-up in such patients (Arch Soc Esp Oftalmol 2007; 82: 535-540).

Key words: Uveal melanoma, multiple neoplasm, second neoplasm, prognostic factor, choroidal tumor.

INTRODUCTION

The existence of multiple primary cancers in the same subject has been known since the late 1800’s. Since then, and in particular when in 1889 Billroth established the initial criteria to characterize Multiple Neoplasms (MN), interest in this area has progressively increased. This has been enhanced by two facts: a) Their growing frequency: from 3.7% of all neoplasms (1926 to 1931) to 6.8% (1932 to 1943) and b) Patients with multiple neoplasms are of great interest to study etiological issues such as genetic predisposition, and cancer pathogeny (1). It is possible that this proportion of patients with secondary neoplasms has been increasing probably as a reflection that with their greater survival the chance of developing a secondary neoplasm is also higher.

Compared to the general population, the risk of developing a secondary neoplasm for males and females with a primary cancer is 1.3 and 1.6 respectively (2).

Uveal melanoma is a relatively rare tumor, with an incidence of 5-6 cases per million inhabitants (3). Not considering metastatic tumors, uveal melanoma is the most frequent intraocular malign tumor in adults. 80% of uveal melanomas are located in the choroids, 12% in the ciliary body and 8% in the iris. There is a clear racial predilection in the development of this tumor with a one-to-eight ratio for Afro-Americans versus the Caucasian population. Some cases of clear family incidence have been published (4,5).

Several authors have published about the presence of multiples primary cancers in patients affected by uveal melanoma (6,7), which would suggest a greater risk of developing other types of neoplasms (8,9). However, some of these results have not been confirmed by other authors (10,11).

Different studies published in existing literature show that the proportion of secondary neoplasms in patients affected by uveal melanoma ranges from 8 to 14% (12-14).

To date, no studies have been conducted with data from Spanish patients, therefore the objective of this paper is to learn about the prevalence of multiple neoplasms in patients affected by uveal melanoma in our country, as well as the type of neoplasms more frequently associated, and to try to determine whether this conditions a worse chance of survival.
SUBJECTS, MATERIAL AND METHODS

A descriptive longitudinal prospective study of the prevalence of multiple malign neoplasms was conducted in patients diagnosed with uveal melanoma.

We included all patients diagnosed with this pathology at the Ocular Oncology Unit of the Department of Ophthalmology in our site from 1984 to 2005. We included both patients in the area covered by this hospital, and those referred from other regions in Spain.

For each patient we recorded age, sex, date of diagnosis of uveal melanoma, location of tumor, physical condition at the end of the study, cause of death, presence of other neoplasms before, at the time of diagnosis and during follow-up. Lesions were classified as synchronous if diagnosed within a period of 6 months before or after diagnosis of uveal melanoma and as metachronous if the diagnosis was conducted in a period of over 6 months.

A statistical analysis was carried out with the software suite SPSS version 10.0 (SPSS by Windows, SPSS Inc, Chicago, USA) and Chi-square or Fische statistics were used, as pertinent.

RESULTS

A total of 305 patients were diagnosed as affected by uveal melanoma, at the Ocular Oncology Unit of our site, during the study period, of which 170 (55.7%) were female and 135 (44.3%) were male. Age at the first visit ranged from 25 to 89, with an average of 58.6. In 51% of the patients the tumor affected their right eye and in 49% the left one. In 256 cases (83.9%) the melanoma affected the choroids, in 40 cases (13.1%) the ciliary body and in seven cases (2.3%) the iris.

Average follow-up of our series was 1144.6 days (CI 1041-1248.2). Out of the total of 305 patients studied, 24 of them (7.9%) presented in their medical history one or more malign neoplasms. When we excluded cutaneous basal cell neoplasms, the proportion was 7.2% (22 patients).

Table I. Localization of second neoplasiae diagnosed in 24 patients with uveal melanoma

<table>
<thead>
<tr>
<th>Type of neoplasia</th>
<th>Number of neoplasiae</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast carcinoma</td>
<td>5</td>
<td>17.8%</td>
</tr>
<tr>
<td>Prostate adenocarcinoma</td>
<td>2</td>
<td>7.1%</td>
</tr>
<tr>
<td>Colon/sigma adenocarcinoma</td>
<td>2</td>
<td>7.1%</td>
</tr>
<tr>
<td>Skin melanoma</td>
<td>2</td>
<td>7.1%</td>
</tr>
<tr>
<td>Bladder carcinoma</td>
<td>2</td>
<td>7.1%</td>
</tr>
<tr>
<td>Squamous larynx carcinoma</td>
<td>2</td>
<td>7.1%</td>
</tr>
<tr>
<td>Squamous skin carcinoma</td>
<td>2</td>
<td>7.1%</td>
</tr>
<tr>
<td>Basocellular carcinoma</td>
<td>2</td>
<td>7.1%</td>
</tr>
<tr>
<td>Squamous lung carcinoma</td>
<td>1</td>
<td>3.5%</td>
</tr>
<tr>
<td>Kidney carcinoma</td>
<td>1</td>
<td>3.5%</td>
</tr>
<tr>
<td>Cerebellum Hemangioblastoma</td>
<td>1</td>
<td>3.5%</td>
</tr>
<tr>
<td>Waldenström macroglobulinemia</td>
<td>1</td>
<td>3.5%</td>
</tr>
<tr>
<td>Esophagus carcinoma</td>
<td>1</td>
<td>3.5%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>1</td>
<td>3.5%</td>
</tr>
<tr>
<td>T-cell skin lymphoma</td>
<td>1</td>
<td>3.5%</td>
</tr>
<tr>
<td>Squamous penis carcinoma</td>
<td>1</td>
<td>3.5%</td>
</tr>
<tr>
<td>Squamous tongue base carcinoma</td>
<td>1</td>
<td>3.5%</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>100%</td>
</tr>
</tbody>
</table>

Of the 24 patients affected by multiple malign neoplasms, in 18 cases (81.8%) the melanoma affected the choroids, in four cases (18.2%) the ciliary body and in no cases, the iris. Average age of the patients affected by multiple neoplasms was 63.45, with a range from 30.79 to 85.24, with no evidence of sex-related differences. The proportion of females and males was 54.2% (13 patients) and 45.8% (11 patients) respectively.

As for the number of neoplasms present taking into account uveal melanoma, it was two neoplasms in 21 patients (87.5%), three neoplasms in two patients (8.3%) and four neoplasms in one patient (4.1%).

In the 21 patients presenting two multiple neoplasms, we found four cases in which the neoplasm was synchronous (19%). For the rest of the patients the diagnosis of the neoplasms was metachronous (81%).

No statistically significant differences were found regarding age of presentation, sex and location of melanoma (ciliary body or choroids) and the presence or not of secondary neoplasms.

When we analyzed the type of secondary neoplasms present in patients in our series, we found that the most frequent cancer was breast adenocarcinoma (17.8%), followed in the same proportion by prostate adenocarcinoma, colon, cutaneous melanoma, bladder carcinoma, larynx carcinoma, squamous cutaneous carcinoma and basal cell carcinoma (7.1% for each) (table I). When analyzing data by patient sex, in females the most frequent secondary neoplasm was breast carcinoma and colon adenocarcinoma, and in males prostate adenocarcinoma, urinary bladder carcinoma and squamous larynx carcinoma (tables II and III).
When we analyzed the proportion of patients with metastatic disease (both living and dead) who did not present a secondary neoplasm (14.3%) compared to those who did (40.9%), through Chi-square test, we found a statistically significant relation with p=0.004 (fig. 1).

**DISCUSSION**

Uveal melanoma is not a very prevalent tumor with an annual incidence of six new cases per million inhabitants in the United States (3). Even so, it is the most frequent primary intraocular malignant tumor. Many aspects such as epidemiology, pathogenesis or treatment of this neoplasm continue being controversial. We conducted this study to examine the epidemiology of this neoplasm, specifically we wanted to know the prevalence of other associated neoplasms in patients affected by uveal melanoma diagnosed at the Ocular Oncology Unit of our site. There are no publications in our community describing epidemiological aspects of the patients affected by uveal melanoma. Also trying to find associations between different types of cancers could help demonstrate potentially similar causes and identify populations presenting worse possibilities of survival.

Our percentage of patients with more than one neoplasm was 7.2%, a similar value to that described in COMS (Collaborative Ocular Melanoma Study), which was 7.7% (excluding in both cases basal cell cutaneous tumors). This percentage did not differ much from the probability of developing invasive cancer between the age of 40 to 59 both for males and females, which is between 8 to 9% in the United States, based on data from 1998 to 2000. These percentages are not completely comparable since in our study we recorded all secondary neoplasms presented by patients before, during and after diagnosis of uveal melanoma, whereas the COMS only considered neoplasms appearing after diagnosis (15). In other studies, prevalence of secondary neoplasms in patients with uveal melanoma ranges from 11% to 14% (12-14).

Location of the most frequent secondary neoplasms was breast carcinoma, followed by prostate adenocarcinoma, colon, cutaneous melanoma, bladder, larynx and lung carcinoma. In other studies, the most frequent locations were breast and prostate (15).

Some authors have found a greater prevalence of gynecological neoplasm (uterus and cervical can-
cer) among women with uveal melanoma compared to a control group (13). A Danish study of 2,018 patients affected by uveal melanoma, found a greater risk of secondary neoplasms in males compared to females, and both presented a higher risk of developing a primary liver cancer, not related to metastatic disease (12). In our series we found no evidence of any of these associations, neither did we observe a greater prevalence of a specific type of secondary neoplasm, either in males or females, similar to other studies (14).

We were surprised to see the presentation of more than one secondary tumor aside from the melanoma in nearly 1% of our series (three patients), a fact which leads us to believe that there is an individual predisposition to the genesis of neoplasms, probably genetic. In fact, this predisposition to the development of multiple neoplasms has been described, and over 30 genes related to a higher susceptibility to cancer have been identified (1). The presence of secondary neoplasms can also be associated to treatments that are potentially carcinogenic, such as external radiotherapy (teleradiotherapy) or chemotherapy, however in our patients this possibility was very remote, since they were usually treated with laser photocoagulation, surgery or localized radiotherapy (brachytherapy).

We did not find statistically significant differences between age of presentation, sex and location of the melanoma (ciliary body or choroids) and the presence or not of secondary neoplasms.

We observed a greater presence of metastatic disease among those patients with secondary neoplasms than those without, with a statistically significant difference (p=0.004, Chi-square test). This association represents a worse survival for those patients who developed a secondary neoplasm before diagnosis of uveal melanoma or for those in whom it appeared during follow-up and it is probably due to a greater genetic predisposition to develop cancer.

The limitations of this study were due to the fact that prevalence of secondary neoplasms could be greater than those recorded, since medical histories could be incomplete or patients did not properly explain their cancers during the first visit or follow-up. Also, since secondary neoplasms are located in regions distant from the eye, early diagnosis of these lesions is difficult during standard systemic screening for metastatic analysis of patients affected by uveal melanoma.

Neither could we establish a relationship between a greater prevalence of specific neoplasms in our population of patients.

As a conclusion, we can state that in our study population, we observed a percentage of secondary neoplasms similar to that described in other international series. We did not find a higher proportion of secondary neoplasms by sex, age, tumor location. Neither did we observe a higher frequency of certain secondary neoplasms. But we did find evidence of a greater predisposition to develop metastatic disease in patients presenting secondary neoplasms, so that these patients require increased systemic follow-up.

References

