Intracranial meningiomas following low-dose irradiation to the head

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Earlier reports have suggested that low-dose ionizing irradiation might be involved in induction of intracranial meningiomas. One of the problems in evaluating irradiation-induced neoplasms is the belief that these tumors have no distinguishing features to indicate their etiology. In an attempt to identify such features in meningiomas following irradiation, a group of 42 post-irradiation meningiomas (PIM's) has been compared with a group of 84 non-PIM control meningiomas. These 42 PIM's included all the intracranial meningiomas diagnosed at the Hadassah University Hospital during the years 1952 to 1981 in individuals treated in childhood with low-dose x-ray therapy for tinea capitis. Although the individual PIM does not seem to differ from a "spontaneous" meningioma, this study indicates that PIM's as a group have distinct characteristics, namely, their location at the site of maximal irradiation, and features suggesting rapid growth and aggressive biological behavior. There was a significantly higher number of calvarial tumors (p < 0.001), a high proportion of multiple meningiomas, a higher recurrence rate following apparent complete excision (p < 0.02), and an increased number of histologically malignant meningiomas (p < 0.01). The demonstration of features that distinguish PIM's from meningiomas of other etiology supports the suggestion that low-dose ionizing irradiation was involved in the pathogenesis of these tumors.

KEY WORDS • radiation therapy • meningioma • epidemiology • malignant meningioma • tinea capitis

The etiology of meningiomas, like the etiology of most other neoplastic diseases, is still unknown. Cushing and Eisenhardt suggested trauma as a possible etiological factor. However, apart from a few anecdotal case reports, there is no convincing evidence favoring the role of trauma in meningioma induction. Two separate reports from Israel have called attention to the occurrence of intracranial meningiomas in individuals who were exposed to low-dose ionizing irradiation during childhood. Low-dose x-ray irradiation was applied to the scalp of those individuals for the treatment of tinea capitis. An epidemiological study subsequently confirmed the increased incidence of intracranial meningiomas in this group of patients, suggesting a causative role for low-dose irradiation in the development of meningiomas.

One of the problems in evaluating irradiation-induced neoplasms is the long interval (many years or decades) between the time of irradiation and the time at which the tumor is diagnosed. Another problem is that irradiation-induced tumors allegedly have no distinguishing features by which they can be recognized as such. The demonstration of certain features characteristic of neoplasms following irradiation but not seen in other "spontaneous" neoplasms would support the assumption that irradiation is involved in the genesis of these tumors. In an attempt to identify such common denominators for post-irradiation meningiomas (PIM's), we compared a group of 42 PIM's with a group of 84 "spontaneous" control meningiomas. Our data suggest that PIM's differ from other meningiomas in their location, multiplicity, and more aggressive biological behavior.

Clinical Material and Methods

A search was made through the files of the department of neurosurgery at the Hadassah University Hospital in Jerusalem, for patients with intracranial meningiomas and a history of low-dose therapeutic x-ray irradiation to the head. Forty-two such patients were identified, treated between 1952 and 1981, who fulfilled...
the above criteria and whose medical records and histological material were available for reevaluation. Non-Israeli residents were excluded. These 42 patients with PIM’s comprised the study group. All were irradiated during childhood and, in most cases, history of irradiation was supported by objective physical signs such as partial alopecia, scars, and pigmentary changes in the scalp. For each PIM two control cases were selected, the latter being the two intracranial meningiomas submitted to the pathology department preceding each PIM specimen. It was assumed that this would ensure that both the PIM and the control meningiomas would have been handled in a similar way, usually by the same pathologist. In most cases, the pathologist initially examining the material had no previous knowledge whether he was dealing with a PIM or with a meningioma of different etiology.

Clinical and demographic data on the patients were obtained from the medical charts, and the operative reports were reviewed. Tumor removal was judged from the surgeon’s statement in the operative report. Follow-up data were incomplete, as most patients were lost to follow-up review after a short period of time, unless they came back to seek medical advice on their own initiative.

The histological sections of all the meningiomas were reexamed, without prior knowledge of whether they belonged to the PIM or to the control group. Special attention was given to the following morphological features: degree of cellularity, nuclear pleomorphism, mitotic rate, and the existence of focal necrosis, bone invasion, and tumor invasion of the brain. Meningiomas were divided into major subtypes according to the classification and criteria of Russell and Rubinstein. Intracranial sarcomas that had no demonstrable pattern of meningioma, whether or not they were attached to the dura, were not included. Likewise, pure intracranial hemangiopericytomas were excluded. The cellularity of the tumor was graded on a scale of 1 to 4. Tumors displaying cellularity of Grade 3 or 4 were considered highly cellular tumors. Mitotic rate was determined by counting the number of mitotic figures in 10 random high-power microscopic fields. The presence of more than two mitotic figures per 10 microscopic fields was considered a high mitotic rate.

Results

Patients’ Age, Sex, and Ethnic Group

Data concerning age, sex, and ethnic group of the patients are presented in Table 1. Although PIM and control patients were not individually matched, the two groups did not differ significantly in age, sex, or ethnic origin. Mean age of PIM patients at the time of diagnosis was 45.5 years (range 22 to 63 years), somewhat younger than the mean age of the control patients, which was 50.9 years (range 9 to 80 years). Both groups showed a slight female preponderance, somewhat more pronounced in the control patients. The mean time from irradiation to diagnosis of the meningioma was 36.8 years (range 15 years to 52 years).

Location of Tumors

Meningiomas were divided into two large groups based on their location: meningiomas of the base of the brain and meningiomas of the calvaria. Calvarial meningiomas included falcial, parasagittal and convex meningiomas. Basal meningiomas were located at the olfactory groove, sphenoid ridge, paraseptal region, tentorium, posterior fossa, and cerebellopontine angle; there was also one intraventricular meningioma (in the control group). In two cases (both control patients) the exact location of the tumor was not clearly stated, and they were not considered in the evaluation.

The location of the meningiomas is shown in Table 2. It is apparent that PIM and control tumors differ significantly in their location. The PIM’s had a statistically significant tendency to present in a calvarial location ($p < 0.001$), while there were significantly more control meningiomas in the basal regions ($p < 0.001$). Meningiomas of both groups were similarly distributed on the right and the left side, as well as in the anterior and posterior compartments of the skull.

Multiplicity and Recurrence

Six cases of multiple meningiomas were diagnosed in the PIM group and none in the control group. Each
case of multiple meningiomas involved two tumors. In five instances, the two neoplasms were diagnosed simultaneously, and in the sixth a second meningioma was identified (at a distant location) 14 years after excision of the first meningioma. None of the patients with multiple meningiomas had features of neurofibromatosis.

Local recurrence after apparent complete removal of tumor was noted in six PIM patients and in two control cases. One PIM recurred twice and another recurred three times. The mean time from resection of the tumor to the first recurrence was 6.2 years in the PIM group (range 2 to 14 years), and 10.5 years in the control group (9 and 12 years). In addition, six and 10 meningiomas recurred in the PIM and control groups, respectively, following incomplete resection of the tumor. Thus, with exclusion of the postoperative deaths (four PIM and eight control cases) and the incompletely removed tumors, the recurrence rate of PIM's after complete excision was 18.7% (six of 32 cases), compared with 3.0% (two of 66 cases) in the control group (p < 0.02). The overall recurrence rate for completely and incompletely removed tumors combined was 21.0% (31.6% in PIM and 15.8% in control cases). It should be emphasized that all figures dealing with recurrence must be considered as minimum figures. As stated previously, follow-up information was not available for many cases and, in fact, was available only for those patients who were readmitted to the Hadassah Hospital. Thus, it is still possible that additional patients succumbed to their disease or were treated for recurrence in another hospital. However, there is no reason to believe that PIM and control patients were handled differently in any way.

Pathological Findings

The distribution of meningiomas by main histological subtypes is shown in Table 3. The distribution of syncytial, transitional, fibroblastic, and angioblastic meningiomas was similar in the PIM and control groups. More PIM's than control tumors displayed morphological features, indicating rapid growth and aggressive biological behavior. This included high cellularity, nuclear pleomorphism, increased mitotic rate, focal necrosis, bone invasion, and tumor infiltration of the brain (Table 4). However, with the exception of high cellularity (p < 0.05), these differences did not reach statistical significance (although the p values for nuclear pleomorphism, increased mitotic rate, and focal necrosis were close to 0.05). Nevertheless, there were significantly more histologically malignant meningiomas in the PIM group compared with control tumors (p < 0.01). Malignant meningioma, as defined by Russell and Rubinstein, Zülch and Mennel, Tytus, et al., and others, was characterized by loss of typical architecture, high cellularity, pleomorphism, increased mitotic rate, focal necrosis, and brain infiltration accompanied by marked glial proliferation. No papillary pattern was observed in our series, and there were no distant metastases.

### Discussion

The results of our study indicate that meningiomas following low-dose irradiation have a distinct biological behavior, different in certain aspects from meningiomas of other etiology. The irradiated patients in our series received low-dose x-ray radiation therapy during childhood for the treatment of tinea capitis. X-ray epilation used to be a standard therapy for tinea capitis and was used extensively, worldwide, between 1910 and 1959, utilizing the Kienböck-Adamson points. It should be emphasized that the term “low-dose irradiation” used by us implies a low therapeutic dose of irradiation, and is completely different from the same term used for very small doses of unintentional radiation (less than 5 rads per person according to United States Government Regulations). The latter was the subject of intensive investigations in recent years and is not the issue in our study.

Although the individual PIM does not seem to differ from a “spontaneous” meningioma, our study indicates that PIM's as a group had certain distinguishing characteristics. These included: a tendency to present in a calvarial location, a high proportion of multiple tumors, a high recurrence rate, and an increased number of histologically malignant meningiomas. In all these aspects, PIM's were significantly different from control meningiomas. One might argue that the differences

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**TABLE 3**

<table>
<thead>
<tr>
<th>Type of Meningioma</th>
<th>PIM Group</th>
<th>Control Group</th>
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<tbody>
<tr>
<td>syncytial</td>
<td>11</td>
<td>26.20</td>
</tr>
<tr>
<td>transitional</td>
<td>22</td>
<td>52.38</td>
</tr>
<tr>
<td>fibroblastic</td>
<td>2</td>
<td>4.76</td>
</tr>
<tr>
<td>angioblastic</td>
<td>1</td>
<td>2.38</td>
</tr>
<tr>
<td>malignant*</td>
<td>6</td>
<td>14.28</td>
</tr>
<tr>
<td>total cases</td>
<td>42</td>
<td>100</td>
</tr>
<tr>
<td>Percent</td>
<td>31</td>
<td>36.90</td>
</tr>
</tbody>
</table>

*P < 0.01.

**TABLE 4**

<table>
<thead>
<tr>
<th>Histological Features</th>
<th>PIM Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>high cellularity*</td>
<td>10</td>
<td>23.8</td>
</tr>
<tr>
<td>nuclear pleomorphism</td>
<td>9</td>
<td>21.4</td>
</tr>
<tr>
<td>increased mitotic rate</td>
<td>10</td>
<td>23.8</td>
</tr>
<tr>
<td>focal necrosis</td>
<td>9</td>
<td>21.4</td>
</tr>
<tr>
<td>bone invasion</td>
<td>9</td>
<td>21.4</td>
</tr>
<tr>
<td>brain invasion</td>
<td>6</td>
<td>14.2</td>
</tr>
<tr>
<td>reactive gliosis</td>
<td>5</td>
<td>11.9</td>
</tr>
<tr>
<td>total cases</td>
<td>42</td>
<td>84</td>
</tr>
</tbody>
</table>

*P < 0.05.
Post-irradiation meningiomas

between the two groups are not real but due to the fact that our control group is not representative. However, our control cases were selected randomly, PIM's and control meningiomas were handled similarly both clinically and pathologically, and patients in both groups did not differ significantly in age, sex, or ethnic origin. In addition, our control tumors were similar in their main features to many other large series of meningiomas reported in the literature, whereas PIM's were distinct from other series also.

Thus, 46.3% of our control meningiomas were calvarial tumors and 53.7% were located at the base of the brain. Similar distribution was noted in the large series of Yamashita, et al.,36 (54.6% basal meningiomas out of all intracranial meningiomas), Simpson39 (46% basal meningiomas), and Bockhorn5 (46% basal tumors). Although some authors quoted higher rates of calvarial meningiomas, including Tedeschi, et al.,44 (65%), and Sattlegger, et al.,46 (72%), our figures are comparable to those reported in the major series.

The incidence of multiple meningiomas following irradiation in our series (18.7%) was higher, not only than the incidence in our control patients, but also considerably higher than the 1% to 2% rate widely accepted in the literature1-12,20,32,48,56 (see the review by Nahser, et al.,36). Likewise, the rate of histologically malignant meningiomas in the irradiated patients (14%) was significantly higher than the rate in our control patients and in the rate of about 2% cited in most series.11,13,19,24,39,44

Recurrence rates of meningiomas vary widely in the literature. The incidence of recurrence following apparent complete resection was stated as 0%,34 2%,13 6%,17 8%,36 9%,39 11%,33,44 14%,19 15%,40 and 19%.9 The 3% recurrence rate of our control meningiomas, although falling within the range of other series, probably underestimates the true recurrence rate in those cases, as the follow-up study of the patients was incomplete. This rate, therefore, should not be regarded as an absolute figure, but rather as a base for comparison with the rate seen in the PIM group. In fact, the recurrence rate of our PIM's was significantly higher than the rate in our control patients, although the numbers in both groups were relatively small. All these data demonstrate that the differences in biological behavior between meningiomas following irradiation and "spontaneous" meningiomas are authentic.

Nevertheless, the possibility that the differences between PIM's and control meningiomas were not related to irradiation, but were rather the result of the different ethnic composition of the two groups, should also be considered. Most of the children treated with x-ray epilation therapy in Israel were of Afro-Asian origin,27 and it might be argued that Jews of Afro-Asian origin are particularly prone to develop meningiomas. However, our PIM group is different from the series of Modan, et al.27 Our series contained Jews of diverse ethnic origin, most of whom were treated outside Israel. In fact, the ethnic origin of our PIM and control groups was similar (Table 1). In addition, earlier epidemiological studies did not reveal any significant differences in the incidence rates of meningiomas in the various ethnic groups in Israel.8,22,23 It must be concluded, therefore, that ethnic origin by itself cannot account for the differences between the two groups of meningiomas, although it may be a contributing factor.

The high proportion of calvarial meningiomas following irradiation deserves a comment. Dosimetry studies of the irradiation technique which was used for epilation showed that with that technique the brain received a dose of 150 to 175 rads at its surface, decreasing to 70 rads at the base of the brain.37,34 Thus, the higher incidence of calvarial meningiomas may be related to the fact that the calvaria was exposed to a considerably higher dose of radiation than the basal area.37,34 Many data suggest that tumor induction is approximately proportional to dose within certain irradiation limits.28 Therefore, more meningiomas are expected on the convexity than at the base, as was indeed the case. The average interval from irradiation to diagnosis of the meningioma was 36.8 years in our cases. Iacono, et al.,18 reviewing the literature on meningiomas following irradiation, noted that the interval from irradiation to diagnosis was significantly shorter in meningiomas following high-dose irradiation compared with meningiomas following low-dose irradiation. If we extrapolate Iacono's observation to our PIM's, we might expect to find a longer induction time in basal meningiomas which were exposed to smaller doses of irradiation, and a shorter induction time in convexity meningiomas which were exposed to a higher radiation dose, although both groups were in the low-dose range. However, no significant difference was found between the average interval from irradiation to diagnosis in convexity and basal meningiomas in our series. It is still possible that, with the passing of time, additional basal meningiomas will be identified. Yaar, et al.,44 stated that in irradiated individuals the left side of the head was exposed to a higher radiation dose than the right side. Our PIM's were equally distributed on the left and right side, presumably because the difference in irradiation dose between the two sides was of small magnitude and had no effect on our relatively small series. It is noteworthy that the first five reported PIM's were all located on the left side.29 In addition, all the intracranial tumors (two meningiomas included) reported in the New York series of Shore, et al.,38 of patients treated with x-ray epilation during childhood were also located on the left side.

Conclusions

Meningiomas following irradiation are rare, but they have been reported in patients exposed to low-dose irradiation4,6,7,14,27,29,35,38,41,47,52 as well as to high-dose radiation.5,16,18,25,31,34,41,43,44 Three cases of meningiomas were also reported following intrathecal introduction of
Thorotrast (thorium dioxide).\textsuperscript{21,26,42} Data suggesting that irradiation plays a role in induction of meningiomas have been found in epidemiological and experimental studies. A statistically significant increase in the incidence of meningiomas was found in individuals exposed to low-dose x-ray irradiation during childhood.\textsuperscript{27,28} Irradiated patients had a higher incidence of head and neck tumors and also an excess of psychiatric disorders\textsuperscript{33} and permanent electroencephalographic\textsuperscript{55} and visual evoked response abnormalities.\textsuperscript{54} Dimant, et al.,\textsuperscript{12} were able to produce meningiomas in rabbits by implanting radioactive cobalt needles into the spinal subdural space. Our study, which indicates that meningiomas following irradiation have several distinct biological characteristics, gives further support to the suggestion that low-dose irradiation is an etiological factor in the induction of meningiomas. Further epidemiological and experimental studies are needed in order to substantiate this proposition.

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