Radiation-induced cerebral meningioma: a recognizable entity

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The authors retrospectively analyzed the clinical and histopathological findings in 201 patients with intracranial meningiomas operated on in the period 1978 to 1982. Forty-three of the patients (21.4%) had at some previous time received radiation treatment to their scalp, the majority for tinea capitis. The findings in these 43 irradiated patients were compared with those in the 158 non-irradiated patients. Several distinctive clinical and histological features were identified in the irradiated group, which suggest that radiation-induced meningiomas can be defined as a separate nosological subgroup.

The use of irradiation in large numbers of children with tinea capitis in the era prior to the availability of griseofulvin may be responsible for a significantly increased incidence of intracranial meningiomas.

Key Words: meningioma, scalp irradiation, tinea capitis, radiation therapy

Although reports as early as 1915 warned against the dangers of ionizing radiation, it remained an acceptable treatment for fungal infections of the scalp during the first half of this century. Albert, et al., in 1966 reported the late effects of radiation therapy for tinea capitis, and disclosed a higher incidence of tumors of the head and neck. In 1969, Munk, et al., presented a group of five cases from Israel and pointed out the link between radiation treatment for tinea capitis and the late appearance of intracranial meningiomas. In 1972, Beller, et al., described a further 16 cases, also from Israel. Subsequently, Modan, et al., found a significantly higher risk of both benign and malignant head and neck tumors among 11,000 children undergoing irradiation for tinea capitis in Israel. The chance of the irradiated patients developing a meningioma was found to be four times greater than for those in the control group. An increased incidence of mental disorders and psychiatric hospitalization, as well as long-term electroencephalographic changes and permanent functional damage to the central nervous system, as reflected by the visual evoked response, were also reported in follow-up studies on these irradiated patients.

Recently, Iacono and co-workers reviewed 38 cases of radiation-induced meningiomas reported in the literature and noted that these patients were of a younger age and showed a male predominance when compared to other series of patients with meningiomas that had not been treated with irradiation. They also emphasized an important clinical sign apparent in the irradiated group: namely, the presence of radiation-induced atrophic skin changes in the scalp overlying the area of the tumor. Very recently, Soffer, et al., studied a group of 42 post-irradiation meningiomas, also from Israel. They suggested that these tumors differ from other meningiomas in their location, multiplicity, and more aggressive biological behavior.

In this retrospective study, we analyzed the clinical and histopathological findings in 201 patients with intracranial meningiomas, 43 (21.4%) of whom had at some previous time received radiation treatment to their scalp. The findings in this group of 43 irradiated patients were compared with those in the 158 non-irradiated patients. The observations made in this study, in conjunction with those in other reported series, suggest that radiation-induced meningiomas may be defined as a separate nosological subgroup with distinctive clinical and histological stigmata.

Clinical Material and Methods

The series consisted of 201 surgically verified cases of intracranial meningiomas treated in our department over the 4-year period, January, 1978, to January, 1982.
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The patients' records and operative summaries were reviewed, with special attention to previous radiation exposures to the scalp, the clinical course, location of the tumor, and operative findings. A reevaluation of the histological specimens was undertaken. In order to verify the history concerning radiation treatment to the scalp, the case records were confirmed by questioning the patients at follow-up examination and by means of a questionnaire that was sent to all 201 patients.

Summary of Cases

Patient Population

During the period of the study, 600 patients with primary intracranial tumors were operated on in our department. Of these, 201 (33.5%) had histologically verified meningiomas. Forty-one of the patients with meningiomas had received low-dose irradiation during their early childhood for fungal scalp infections according to the Kienböck-Adamson method. The radiation doses used varied in the different centers in which the children were treated, but the total dose was small, usually under 850 rads. The brain doses ranged from 175 rads at the surface to 70 rads at the base. Several of the patients were irradiated on more than one occasion, and some even required a third course of treatment because of relapse. One patient, in addition to receiving irradiation for tinea capitis in childhood, subsequently (at the age of 61 years) received 2500 rads to the skin of her right temple for a basal cell carcinoma. Five years thereafter she presented with a meningioma over the convexity of the right frontotemporal region.

Two other patients were given radiotherapy for malignant intracranial lesions. One received 1500 rads at the age of 2 years, following the resection of a right frontal astrocytoma. At the age of 20 years he presented with a massive right frontotemporal meningioma. The second patient received 1500 rads at the neuraxis at the age of 10 months as part of a curative regimen for the management of acute lymphoblastic leukemia. At the age of 6 years she presented with a meningioma in the right cerebellum pontine angle.

About half of the patients who received radiation therapy for tinea capitis were Jews of North African and Middle Eastern origin; they had either immigrated in childhood or were born in Israel, and had received their radiation treatment in Israel. The remainder were Jews of Central and East European origin and most of them received radiation treatment in their countries of origin. Despite the fact that our department receives a large number of Arab patients, it is noteworthy that only one patient in the entire series of 201 patients with meningiomas was of Arab descent.

Age and Sex

The ages at admission of the patients who had previously received radiation therapy for tinea capitis ranged from 25 to 63 years, with a mean of 45 years. The age range of those patients who had not received irradiation was from 34 to 78 years, with a mean of 58 years. The difference in mean age between the two groups was statistically significant (p < 0.005).

There were 23 males and 20 females in the group that had received irradiation to the scalp, for a male to female ratio of 1:0.9. In the control group there were 59 males and 99 females, a ratio of 1:1.7.

Latent Period

The latent period was defined as the time that had elapsed from administration of scalp irradiation until the appearance of clinical symptoms. The period ranged from 16 to 58 years, with a mean of 38 years. These data include all 41 patients who were irradiated for fungal scalp infection. The latent periods for the two children who received irradiation for reasons other than tinea capitis were 5 years for the child with leukemia, and 18 years for the child who underwent resection of an astrocytoma.

Clinical Presentation

Almost all the patients who had received irradiation showed trophic changes in the scalp: a characteristic patchy alopecia which could be easily identified; atrophy and scarring of the skin; telangiectases; and occasional keratoses. In none of the patients in the non-irradiated group were these skin changes apparent. Neither group showed the cafr-au-lait spots or other cutaneous manifestations of von Recklinghausen's neurofibromatosis. On analysis of the various modes of clinical presentations, four main categories could be identified: convulsive disorders, focal motor and sensory deficits, symptoms and signs of increased intracranial pressure, and an organic mental syndrome (Table 1).

Characteristics of the Tumor

Location

The site of the lesion in the great majority of the irradiated patients was either in the falx and parasagittal area or over the convexity (51% and 44%, respectively). Only 4.6% of the tumors were situated over the base of the skull.

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of the skull. This is in contrast to the location of meningiomas in the non-irradiated group, in which one-third of the patients had meningiomas arising from the base of the skull (Table 2). This difference in location is statistically significant \( p < 0.001 \).

**Operative and Histopathological Findings**

Although meningiomas in the irradiated group appeared to have more complex adhesions and vascular connections with the adjacent brain than in the non-irradiated group, there were no differences between the groups regarding frequency of invasion of bone, dura, or parenchyma.

 Forty-three histological preparations from the irradiated patients and a like number from the non-irradiated patients were reexamined and reviewed. No significant difference was found in the relative frequencies of the four histological categories of meningiomas, based on the classification of Russell and Rubinstein.24

Of the 43 specimens from irradiated patients, 26 (60.5%) were classified as syncytial (meningotheliomatous), eight (18.6%) were fibroblastic, five (11.6%) were transitional, and four (9.3%) were angioblastic in type.

In 35 (81%) of these 43 histological preparations from the irradiated patients, certain distinctive microscopic features were present and striking in their prominence (Fig. 1): 1) The tumors showed a very high degree of cellularity. 2) The cell nuclei were pleomorphic, varying greatly in their size, shape, and chromatin density. 3) Numerous giant cells, some with a single nucleus and some multinucleated, could be seen in every field, sometimes as many as six cells per high-power field. Their nuclei were monstrous in size and bizarre in shape, containing large hyperchromatic nucleoli. These nucleoli were often equal in size to the nuclei of the meningioma cells of the non-irradiated patients. 4) Many of the meningioma cell nuclei were vacuolated, showing clear nuclear vacuoles. Nuclear inclusions were also frequent. Mitoses, psammoma bodies, foam cells, and blood vessels of which the walls were very thick and hyaline in appearance were prominent. These vessels, however, showed negative staining for amyloid. The high cellularity, the numerous giant cells, and the gross nuclear pleomorphism were not seen in the specimens from the non-irradiated patients \( p < 0.001 \).

In the irradiated group, one patient was considered, on histological grounds, to have an unequivocally malignant meningioma, and two other tumors were considered to be borderline. No instance of malignant meningioma was found in the non-irradiated patients.

**Multiplicity of Tumors**

Two cases with multiple meningiomas were encountered in the irradiated group and one in the non-irradiated group. Thus, the incidence was 4.6% in the

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**TABLE 2**

Location of meningiomas in 201 irradiated and non-irradiated patients with meningioma

<table>
<thead>
<tr>
<th>Tumor Location</th>
<th>Irradiated Patients</th>
<th>Non-Irradiated Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Percent</td>
</tr>
<tr>
<td>falx/parasagittal area</td>
<td>22</td>
<td>51.2</td>
</tr>
<tr>
<td>convexity</td>
<td>19</td>
<td>44.2</td>
</tr>
<tr>
<td>base of skull</td>
<td>2</td>
<td>4.6</td>
</tr>
<tr>
<td>total cases</td>
<td>43</td>
<td>100</td>
</tr>
</tbody>
</table>

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**FIG. 1.** Photomicrographs of meningioma tissue from patients with prior scalp irradiation showing the distinctive histological features of these cases. H & E, \( × 200 \). *Left:* Bizarre hyperchromatic nuclei. *Right:* Large giant cells and nuclei, vacuolated nuclei, and giant nucleoli.
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irradiated group compared to 0.6% in the non-irradiated group (p > 0.05), and was 1.5% for the whole series. The multiple meningiomas encountered in the two irradiated patients were all situated supratentorially whereas, in the patient who had not received irradiation, one meningioma was situated over the convexity and the second in the posterior fossa.

Recurrence Rates

In view of the relatively short follow-up period of some of the patients in this study, the final data concerning various aspects of recurrence are not yet available. As of June, 1983, 11 (25.6%) of the 43 patients in the irradiated group had developed a local recurrence of the meningioma, whereas 18 (11.4%) of the 158 patients who had not received radiation therapy had developed recurrences (p < 0.05). In calculating the recurrence rates, we have excluded nine patients in whom the primary resection of the meningioma was considered to be incomplete at operation or on computerized tomography scanning in the immediate postoperative period. All nine were from the non-irradiated group.

Five of the 11 patients with recurrent tumors in the irradiated group (11.6% of the 43 patients) had two or more recurrences; three of the 18 patients with recurrent tumors in the non-irradiated group had two or more recurrences (1.9% of the 158 patients). Comparison of these groups resulted in a p value of less than 0.05.

Discussion

Numerous authors have attempted to implicate low-dose radiation to the scalp for tinea capitis and other skin lesions, as well as high-dose cranial irradiation for brain tumors, as an etiological factor in the development of meningiomas. The patients in those reports, as well as those in our present series, fulfilled the criteria of Cahan, et al., regarding radiation-induced tumors. In all our patients, the tumor appeared within the irradiated area following a latent period of at least 5 years.

In reviewing the clinical details and histopathological data of the 43 patients in our series who developed meningiomas following irradiation, we have been impressed by several features that may serve to define such meningiomas as a distinct neurological entity.

During the period of our study, 201 (33.5%) of the 600 consecutive cases of primary intracranial tumors operated on were characterized as having meningiomas. Compared to the usually quoted figures of 13% to 19%5 this is an exceptionally high incidence of meningiomas. No less than 21.5% of the 201 patients operated on in our department for intracranial meningiomas during the survey period had a history of previous irradiation to the scalp. This extraordinary figure reflects a particular choice of dermatological management of tinea capitis that was popular worldwide between 1910 and 1959 and was favored in Israel during the 1950's. The relatively uncontrolled and uncritical use of irradiation in large numbers of children suffering from ringworm of the scalp in the era prior to the availability of griseofulvin may now be responsible for the high incidence of meningiomas that we are encountering.

The average age of the patients undergoing operation for meningioma, and who had previously received scalp irradiation for tinea capitis, was 45 years, whereas the average age of those in the non-irradiated group was 58 years. This earlier age of presentation is significant, and is a feature that might be clinically useful in defining this particular group.

The ratio of males to females in the irradiated group in our series was 1:0.9 (23 males and 20 females) in contrast to the ratio of 1:1.7 (59 males and 99 females) in the non-irradiated group. This preponderance of males among the irradiated patients is also seen in the series reviewed by Iacono, et al., namely, 19 males and 15 females (a ratio of 1:0.8). These figures contrast with the generally reported male:female ratio for meningiomas of about 1:1.8.35

The scalp changes due to radiation damage observed in almost all of our irradiated patients have been emphasized in several earlier reports. These readily observed skin changes were so striking and occurred so frequently in the irradiated patients as to constitute a hallmark of this entity. When observed in any patient with a history of radiation therapy to the scalp who presents with neurological complaints, they should suggest the possibility of an underlying meningioma.

The radiation fields used in the Kienböck-Adamson technique of irradiation for ringworm of the scalp were directed to the entire convexity of the calvaria. Should a cause-and-effect relationship exist between the development of meningiomas and prior irradiation, one might expect radiation-induced meningiomas to be localized to these regions. This, in fact, was observed in the present study. In our irradiated patients, the frequency of calvarial meningiomas was 95%, the remaining 5% being distributed along the base of the skull (see Table 2). This is in marked contrast to the greater distribution ratio between the base and calvaria observed in our non-irradiated group as well as in the general literature. Interestingly, Preston-Martin, et al., have noted that early exposure to full-mouth diagnostic dental x-ray films constitutes a potential risk factor for the development of basal meningiomas.

The high prevalence of convulsive disorders observed in the irradiated group in comparison with the non-irradiated control patients (see Table 1) may, in part, be explained by the predominantly supratentorial location of the tumors in the former group.

The meningiomas encountered in the irradiated group of patients appear to exhibit certain distinctive pathological and biological features. Some of the striking histological changes that were seen in many of the
post-irradiation meningiomas have also been encountered, albeit less frequently, in meningiomas of non-irradiated patients. The prominent histological characteristics include: high cellularity, pleomorphism, and the presence of giant cells with monstrous nuclei, which occur singly or several at a time. The biological features examined in the present study included multiplicity of tumors and recurrence rates. If radiation-induced meningiomas can be regarded as a distinct clinicopathological entity, one would expect to find the incidence of multiple meningiomas to be higher in the irradiated patients. Our results are consistent with this expectation in that the multiplicity rate in the irradiated group (4.6%) was greater than that in the non-irradiated group (0.6%). The multiplicity rates described in the general literature are of the order of 2%. In view of the prediction shown by the meningiomas in the irradiated group for the meninges over the convexity rather than at the base of the skull and, hence, their greater surgical accessibility, one would expect that the recurrence rate of these tumors after apparently complete resection at the base of the skull and, hence, their greater surgical accessibility, one would expect that the recurrence rate of these tumors after apparently complete resection would be smaller than in the non-irradiated group. In fact, the irradiated group in our series exhibited a significantly greater recurrence rate (25.6%) and a greater multiple-recurrence rate (11.6%) than did the non-irradiated group (11.4% and 1.9% for single and multiple recurrences, respectively). The higher recurrence rate in the irradiated group reflects an intrinsic difference in tumor behavior. This assumption is also consistent with the difference in the histological appearance between the meningiomas in the irradiated and non-irradiated patients.

Conclusions

Radiation-induced meningiomas appear to have several salient clinicopathological features with regard to their epidemiology, location, presenting symptoms, multiplicity, recurrence rate, and histopathology, which enable them to be recognized as a distinct entity among the meningiomas of unknown etiology. Similar biological features were also reported by Soffer, et al., in a recent survey of 42 cases of meningiomas occurring in patients who had received low-dose cranial irradiation for tinea capitis. In that study, as in the present series, the mean latency period between the time of irradiation and the clinical presentation was approximately 36 to 38 years.

Until 1959, cranial irradiation was employed worldwide as treatment for tinea capitis. In addition, many other patients underwent radiation therapy for various disorders of the head and neck. In light of the above findings, it appears reasonable to anticipate an increased incidence of meningiomas in those patients who have previously undergone such exposure to radiation. Serial screening examinations of that sector of the population who have received cranial irradiation may lead to the earlier discovery of radiation-induced meningiomas, and thereby may minimize the morbidity and mortality associated with late detection. In view of the high prevalence of post-irradiation meningiomas among the Jewish population in Israel, future studies should address the possibility that genetic factors may predispose to the development of this entity.

References

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