A Possible Association between Ionizing Radiation and Pituitary Adenoma

A Descriptive Study

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BACKGROUND. Despite the recognition of ionizing radiation as a causal risk factor for a variety of solid tumors (including brain tumors), to date, such an association with pituitary adenoma (PA) has not been demonstrated.

METHODS. To evaluate a possible association between past exposure to radiation and the occurrence of PA, the authors reviewed about 4900 medical records of patients who had been irradiated in childhood for *tinea capitis*. An additional search for patients was performed using the Israel Cancer Registry. The average radiation dose to the pituitary gland was estimated as 0.56 grays, and, for all patients, a meticulous validation of the irradiation was performed.

RESULTS. A group of 16 patients who developed symptomatic PA after childhood exposure to radiotherapy were identified. Overall, the clinical and demographic characteristics of these patients were similar to other series reported in the literature. There was an apparently high rate of second primary tumors (25%), all of them in the irradiated area, diagnosed among this group. The methodologic issues that limit the demonstration of a possible association between radiation and PA and the epidemiologic and experimental findings in the literature are discussed.

CONCLUSIONS. In view of the ample amount of evidence identifying low-dose ionizing radiation as a risk factor for a number of intracranial tumors as well as for tumors arising in endocrine organs, a *radiation immunity* of the pituitary gland is difficult to accept. Hence, the authors suggest that this series should be considered as preliminary observation that supports the role of ionizing radiation in the development of this tumor. ***Cancer* 2002;95:397–403.**

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Pituitary adenoma (PA), the most frequent primary tumor of this gland, is a benign neoplasm that arises in adenohypophyseal cells.[1] Compared with asymptomatic PAs, which are a relatively common finding in unselected adult autopsies and imaging series, ranging from 2% to 23%,[2–4] symptomatic PAs are a rather rare neoplasm, with a reported annual incidence rate ranging between 11 and 25 per 10^6 population.[5–7] Other than a clear association with MEN 1 syndrome (with parathyroid, pituitary, and pancreatic involvement the most common), no other genetic conditions have been known to alter predisposition to this rare illness, and no risk factors have been identified to date.

For nearly 50 years, ionizing radiation has been recognized as a definite risk factor for a variety of solid tumors.[8,9] However, in the first half of the 20th century, irradiation was considered good medical

practice for the treatment of a number of benign diseases. Accordingly, up until the 1960s, *tinea capitis*, a fungal infection of the scalp, was treated with radiotherapy. Although studies assessing neoplasm development among this population have shown excessive risk for a number of malignant and benign tumors, and especially for tumors of the brain, thyroid, and salivary gland,[10] an association between ionizing radiation and the occurrence of PAs has not been shown to date. Due to its very low incidence rate, any study that aspires to detect disease pattern changes and risk factors for PA would have to examine a very large population. Therefore, current studies may fail to demonstrate such an association due to insufficient population size. In addition, many studies examining tumors risk after irradiation are based on either mortality data or linkages with cancer registries, and both methods are inappropriate for PA detection.

To assess a possible association between past exposure to ionizing radiation and the occurrence of PAs in humans, we reviewed records of clinically symptomatic patients with PA among a group of individuals who, as children, were treated with ionizing radiation to the head area for *tinea capitis*. This report presents the description of 16 such patients and discusses the findings in the literature.

MATERIALS AND METHODS

During the 1950s, treatment with ionizing radiation for *tinea capitis* was given in an organized way and en mass to subpopulations in Israel. This irradiated group was comprised mostly of immigrants coming from North Africa and the Middle East as well as Israeli-born citizens. The irradiation treatment applied in Israel took place mainly in one of four major radiation treatment centers. A subgroup of 10,836 irradiated individuals with 2 nonirradiated matched control groups, known as the *Tinea Capitis* Cohort, have been followed for over 45 years by our group for radiation sequelae. Using one of the original X-ray machines and a phantom skull from an individual age 7 years, radiation doses to different parts of the brain were estimated. The average dose to the brain ranged from 1.0 grays (Gy) to 2.0 Gy (mean, 1.4 Gy).[11] The pituitary gland was exposed to a radiation dose of 48–66 centigrays (cGy).[12]

Although official figures suggest that about 20,000 individuals, mostly children, were irradiated in Israel, it has been advocated lately that the total size of the exposed group was much larger, because a considerable number of immigrants were irradiated abroad in their countries of origin.[13] According to a law legislated in 1994, compensation is given to irradiated individuals who developed specific, delayed effects that were proven to result from exposure to radiation (i.e., mainly head and neck tumors). Irradiation treatment for *tinea capitis* as a basis for inclusion in the framework of this law is being determined by a special expert committee that decides on the validity of the irradiation of each individual.[14]

To evaluate a possible association between past exposure to ionizing radiation and the occurrence of adenomas of the pituitary gland, we reviewed the compensation claim files searching for patients with PA. In addition, records on all patients with a diagnosis of PA among the *Tinea Capitis* Cohort were retrieved from the Israeli National Cancer Registry. A total of 18 patients with PA were identified among individuals approved by the expert committee to be irradiated. In accordance with this study's strict criteria, two patients were excluded due to insufficient data ascertaining past irradiation, and the remaining 16 patients were divided as follows: *definite past exposure* (n = 12 patients) and *highly probable past exposure* (n = 4 patients). Definite past exposure to head irradiation was considered in the following circumstances: 1) appearance in the original *Tinea Capitis* Cohort (n = 5 patients), 2) documentation of the exposure (n = 1 patient), or 3) a definite approval of the irradiation according to clinical pathognomonic dermatologic signs (n = 6 patients). The remaining four individuals whose validity of past irradiation was confirmed by the expert committee but did not meet our criteria for *definite past exposure* were regarded as having *highly probable past exposure*.

The diagnosis of PA was based on histologic reports (n = 8 patients), imaging studies and hormone profiles (n = 7 patients), and imaging studies supported by adequate clinical findings (n = 1 patient). All patients who were included in the study were symptomatic, that is, they presented with initial complaints and/or clinical symptoms that could be attributed to an adenoma of the pituitary gland prior to diagnostic work-up. Therefore, over-diagnosis due to an incidental nonsymptomatic pituitary lesion was avoided. Each file reviewed contained demographic and clinical data as well as details on the date and place of irradiation treatment. Medical data included clinical presentation of PA, diagnostic work-up, histologic type, treatments, recurrence, presence of other tumors, and concomitant illnesses, if any.

RESULTS

The main characteristics of the study population are presented in Table 1. The patients were born between 1939 and 1955; five patients (31%) were Israeli born, three patients (19%) were born in Iraq, and each of the remaining eight patients (50%) was born in a North

TABLE 1
Description of Selective Characteristics of the Study Population

Patient	Irradiation validity	Year of birth	Country of birth	Gender	Age at irradiation treatment (yrs)	Age at diagnosis (yrs)	Latent period (yrs)	Clinical phenotype	Modes of treatment
1[a,b]	Definite-dermatologic signs	1939	Egypt	Male	10	54	44	Macroprolactinoma (greatest mean dimension ≅ 1.8 cm)	Bromocriptine
2	Definite-dermatologic signs	1944	Morocco	Male	10	51	41	Macro NFPA	Pituitary hormonal replacement therapy
3[b]	Definite-*Tinea Capitis* Cohort	1944	Morocco	Male	10	40	30	Invasive NFPA (greatest dimension ≅ 4 cm)	Right frontal craniotomy, resection of tumor
4	Highly probable	1944	Morocco	Male	11	45	34	GH-secreting microadenoma	Bromocriptine, transsphenoidal resection of tumor
5	Definite-dermatologic signs	1944	Israel	Female	7	36	29	Microprolactinoma	Bromocriptine, transsphenoidal resection of tumor
6[a]	Definite-early physician documentation	1945	Libya	Male	7	45	38	Invasive macroprolactinoma (2 cm × 3.5 cm × 2.5 cm)	Bromocriptine
7	Definite-dermatologic signs	1946	Iraq	Male	7	48	41	Invasive NFPA	Transsphenoidal resection of tumor, radiation therapy
8[a]	Definite-*Tinea Capitis* Cohort	1948	Iraq	Female	3	20	17	NFPA	Radiation therapy, bromocriptine, pituitary hormonal replacement therapy
9	Definite-dermatologic signs	1948	Iraq	Female	4	41	37	ACTH-secreting adenoma (Cushing disease)	Transsphenoidal resection of tumor
10	Highly probable	1948	Libya	Female	6	47	41	GH-secreting microadenoma (greatest dimension ≅ 0.3 cm)	Transsphenoidal resection of tumor, bromocriptine
11	Highly probable	1950	Israel	Male	4	38	34	Macroprolactinoma	Transsphenoidal partial resection of tumor, bromocriptine
12[a]	Definite-*Tinea Capitis* Cohort	1951	Israel	Female	6	35	29	Prolactinoma	Bromocriptine
13	Definite-*Tinea Capitis* cohort	1951	Morocco	Female	6	24	18	Macroprolactinoma	Transsphenoidal resection of tumor
14	Highly probable	1953	Tunisia	Male	5	30	25	Micro NFPA (0.7 cm × 0.8 cm)	Observation
15	Definite-*Tinea Capitis* Cohort	1954	Israel	Female	5	27	22	GH-secreting microadenoma	Transsphenoidal resection of tumor
16	Definite-dermatologic signs	1955	Israel	Male	3	40	37	Macroprolactinoma (greatest dimension ≅ 1.4 cm)	Bromocriptine

NFPA: nonfunctioning pituitary adenoma; GH: growth hormone; ACTH: adrenocorticotropic hormone.
[a] Developed a second neoplastic disease
[b] Not alive.

African country. The female-to-male ratio was 0.77. Of the 16 patients, 14 were irradiated in Israel, and 2 were irradiated in Morocco prior to their immigration. The mean age at exposure to head irradiation was 6.5 years ± 2.6 years (range, 3–11 years), the mean age at the time patients were diagnosed with PA was 38.8 years ± 9.7 years (range, 20–54 years), and the mean latent period from radiation exposure to diagnosis was 32.3 years ± 8.4 years (range, 17–44 years).

The distribution of PAs according to clinical phenotype was as follows: Seven patients (44%) had prolactin-secreting adenomas, 5 patients (31%) had nonfunctioning PAs (NFPAs), 3 patients (19%) had growth hormone-secreting PAs, and 1 patient (6%) had an adrenocorticotropic hormone-secreting adenoma. Nine patients (56%) underwent surgery. Complementary treatments, if given, are listed in Table 1.

Recurrent disease developed in four patients

(25%). Of these, three patients (Patients 3, 4, and 9) had undergone a second surgery 5 years, 10 years, and 6 years after the first surgical procedure, respectively. One patient (Patient 10) developed a recurrent acromegaly stigmata 1 year after undergoing transsphenoidal resection of the adenoma, and treatment with bromocriptine was initiated.

None of the 16 patients presented had a personal history of another neoplastic disease at the time of their diagnosis with PA. Throughout the years after their PA diagnosis, four patients (25%) were diagnosed with a second neoplastic disease (acoustic neurinoma in Patient 1, follicular carcinoma of the thyroid in Patient 6, meningioma in Patient 8, and neurofibroma of the cervical region in Patient 12). It is interesting to note that all these of second primary tumors occurred in the irradiated area. Other than hypothyroidism, which occurred in one patient (Patient 13), no other endocrine abnormalities (that were not related directly to adenoma of the pituitary gland or to the treatment applied) have been recorded.

The survival rate (mean follow-up, 13.2 years) was 87.5%. The deaths of two patients (Patients 1 and 3) were due to immediate complications after they underwent cranial surgery.

DISCUSSION

In this study we described a group of 16 patients who developed a symptomatic PA after childhood exposure to ionizing radiation to the head area. For more than half a century, vigorous attempts have been made to fully assess the detrimental effects of ionizing radiation. To date, the vast majority of epidemiologic studies did not show an association between ionizing radiation and PA. Although several studies support the role of previous radiation exposure in the development of brain tumors, most of them do not specifically mention PAs.[10,15–21] This also holds true for the Israeli *Tinea Capitis* Study, in which comparisons between the rate of tumors in the irradiated group and the nonirradiated control group showed a significant excess risk for various tumors arising in the irradiated area, including benign and malignant brain tumors.[20] However, to date, an excessive risk for PA has not been indicated.

Our series includes five patients with PA from the original *Tinea Capitis* Cohort. Because benign lesions like PAs are under-documented in cancer registries (as demonstrated by the fact that only three of these five patients were known to the cancer registry), and because the cancer registry was our only source for identifying patients with tumors among control participants, an association between ionizing radiation and PA could not be demonstrated using this methodology.

The New York *Tinea Capitis* Study, which based its findings on 2215 irradiated individuals who were exposed to brain doses of 175 rads at the surface to 70 rads at the base, showed that, after an average follow-up of 20 years, 6 brain tumors arose in the irradiated group and no brain tumors arose among the control group ($P = 0.07$): No tumors were PAs.[21]

The lack of findings with regard to PAs in the studies mentioned above led some authors to conclude that, unlike the thyroid or salivary glands, the pituitary gland is relatively resistant to the tumorogenic effect inflicted by radiation.[22] Conversely, a thorough review of related articles identified two publications that pointed to an association between PAs and previous exposure to ionizing radiation. The first article reports 2 patients with PAs among 239 inhabitants of the Marshal Islands who were exposed accidentally to radioactive fall-out in 1954.[23] Both patients were female, and their estimated total body absorbed doses were 190 cGy and 11 cGy. This close follow-up yielded PA incidence rates that were 13.6 times higher than the rates found in a comparable group from Olmsted County, Minnesota. It is noteworthy that one of the two patients presented actually had an asymptomatic PA that was diagnosed during skull X-rays performed due to prior illness. Therefore, it may have been inappropriate to include this patient in the analysis, and the results obtained should be examined cautiously.

The second study was a pooled analysis of two Swedish cohorts comprised of 26,949 individuals who were irradiated for skin hemangiomas during infancy (mean intracranial dose, 7 cGy) in whom 83 intracranial tumors were observed, yielding a standardized incidence ratio of 1.43 (95% confidence interval, 1.14–1.78).[24] Of these tumors, 33 were gliomas, 20 were meningiomas, 9 were PAs, and 9 were nerve sheath tumors. Although the relative risks for specific tumors were not published, we found great importance in the results of Karlson et al., who presented an impressive series of nine individuals who developed PAs after receiving childhood irradiation.

Although the question of the human pituitary response to low-dose ionizing radiation remains debatable, we propose an alternative explanation for the lack of evidence regarding increased adenoma formation in those exposed. The annual incidence of symptomatic PA reported in the literature is very low, as discussed above, ranging from 11 per 10^6 population to 25 per 10^6 population.[5–7] Hence, and in accordance with the view raised by Ron and Saftlas,[22] we believe that the size of populations exposed to a possible risk

factor would have to be very large to make detection of such a risk possible.

Assuming that head irradiation at low doses is a causal risk factor that elevates the incidence rate of PA among those irradiated and makes it, for instance, four times greater than the incidence rate among the general population, and assuming that the highest reported annual incidence rate is 25 per 10^6 population, power calculations (using Poisson distribution) show that it would require 168,000 individuals in each group to obtain a significant elevation of risk (two sided $P = 0.1$) with a power of 0.8.[25] Similarly, employing the same calculations for a relative risk of 2.5 dictates more than 440,000 individuals in each group. Most studies addressing the subject at hand presented their results based on cohorts of thousands. Even the 1994 atomic bomb report,[26] which was one of the largest and most comprehensive studies, was based on a total cohort of only 79,972 individuals. Even by combining the populations from a number of studies, the artificially combined cohort attained still would fall short regarding population size. Only with a very powerful risk factor would detection among smaller cohorts be possible (e.g., using a similar approach, a cohort of 10,000 radiation-exposed individuals would demand a relative risk of > 10).[25]

In addition, even the largest studies conducted will have great difficulties pointing to an association between ionizing radiation and PAs as long as their data are retrieved from cancer and mortality registries, which, as mentioned above, have limited information with regard to most benign tumors. Even though information on benign tumors among atomic bomb survivors is still insufficient,[27] a number of recent studies that employed a different, more active methodology (screening programs that included clinical evaluations and laboratory assessments) already have identified a significant increase in incidence rates of uterine myomas[28] and hyperparathyroidism (most patients who underwent surgery had proven parathyroid adenomas).[29] Based on these specific methodologic limitations, and considering the low incidence of PA, the conclusions regarding the insensitivity of the pituitary gland to low-dose ionizing radiation may have been premature and, in our view, should be reconsidered until further data are accumulated.

Several investigators have pointed at characteristics that differentiate radiation-induced tumors from spontaneous tumors[18]; therefore, comparing our patient group with other series is of interest when discussing the possibility of past irradiation involvement in the pathogenesis of these tumors. Overall, the clinical phenotype distribution in our series of patients with PA appears to be in accordance with the literature.[3,30–32] In our study, the peak incidence of prolactinoma was during the 3rd decade of life, in accordance with the findings of Mindermann and Wilson, which were based on a series of 2230 patients with PA.[32] Although most individuals who received irradiation during childhood for *tinea capitis* have not yet entered the 7th decade of life, a relatively early age at the time of diagnosis may be noticed in our series for patients with NFPA (i.e., endocrine-inactive adenomas; ages 20 years, 30 years, 40 years, 48 years, and 51 years vs. a reported peak occurrence during the 6th decade of life).[32] It is interesting to note that, for patients with meningiomas, for whom low-dose irradiation is a proven risk factor, relatively young age at the time of diagnosis is considered one of the characteristics of postirradiation tumors compared with nonirradiation-related tumors.[18]

The lack of a reported female predominance observed in our group (female/male: overall, 0.77; prolactinomas, 0.75; NFPAs, 0.25 vs. 1.73, 4.4, and 0.65, in a large series of patients with non-radiation induced PAS, respectively[32]) may not be a genuine finding that reflects different sensitivities to low-dose irradiation among men and women but, rather, represents a higher percentage of males among individuals who apply for compensation. Nevertheless, this characteristic also was observed for radiation-induced meningiomas.[18]

The biologic behavior of these tumors in terms of aggressiveness, judged by recurrences and postoperative deaths, does not seem to differ from previously published results.[30,31] We find it extraordinary that 25% of this study group later developed a second primary tumor, and, furthermore, that all of these neoplasms occurred in the irradiated area (head and neck). Although none of these four different tumors has ever been associated directly with PAs, it has been shown that ionizing radiation has a major effect on the development of all four types.[20,24,33–35]

Although there have been reports linking patients with acromegaly or NFPA with an increased risk of developing secondary neoplastic disease, prolactin-secreting adenoma has not been associated with such a risk.[36] In our study, three of four individuals who developed a second primary tumor had Prolactinomas (Patients 1, 6, and 12), and only one (Patient 8) had NFPA and was subjected consequently to high-dose radiotherapy as a selected mode of treatment. Because the overall risk of developing any second tumor after treatment for most first primary tumors is only 10–50% higher than the risk expected in the general population,[37] a second primary tumor incidence rate of 25% seems extremely high, and, in addition to the specific location in which the second primary tumors

arose, supports the etiologic role of previous head irradiation in the development of both the secondary tumor and the primary tumor. Furthermore, it may indicate greater sensitivity of certain individuals to the radiation that initiated both tumors.

The mean latent period in our study was 32.3 years ± 8.45 years (range, 17–44 years), which resembles the latent period reported by Soffer et al. for patients with meningioma after childhood irradiation for *tinea capitis* (mean, 36.8 years; range, 15–52 years).[18] The latency reported for most other series of patients with benign solid tumors in this group seems shorter (e.g., thyroid adenomas: mean, 17.9 years; range, 5.1–23.7 years; benign salivary gland tumors: mean, 21.5 years).[35,38] A relatively long latent period, like what was seen in our study, may add to the obstacles of relating higher rates of neoplasms to exposure that occurred many years earlier.

Although most studies examining ionizing radiation-exposed populations failed in establishing a clear association between past exposure and PA formation in humans, such a link has been established in animals.[39–41] Numerous studies have examined alterations in rodent pituitary glands induced by ionizing irradiation at different doses. One of the latest and more comprehensive studies that addressed the issue of a dose-response relation for the induction of solid tumors[41] showed that female mice that were irradiated neonatally with a single dose of gamma rays developed pituitary tumors in excess with a significant difference in all irradiated groups, with 48 cGy the lowest dose tested. It is interesting to mention that a dose dependent increase in the observed incidence was found up to 1.43 Gy.

The fact that animal models are considered reliable in cancer research and have been used in the past to clarify physiologic as well as many pathologic processes in humans does not support the notion of a low-dose radiation resistance related to the pituitary gland. The pituitary gland is an intracranial endocrine organ, and, in view of the ample amount of indisputable evidence identifying low-dose ionizing radiation exposure as a definite risk factor for a number of intracranial tumors[18,20,24] as well as tumors arising in endocrine organs,[29,35] the possibility of a *radiation-immune* pituitary gland is rather difficult to accept.

At the heart of each of those associations between ionizing radiation and tumors, there are preliminary observations and mere case reports, usually dating back substantially, that cautiously suggest what became evident later.[42,43] Hence, it is our view that this series of 16 patients with PA who previously received irradiation should not go unnoticed, and it stresses the need to elucidate further the possible effects of low-dose ionizing radiation on the pituitary gland.

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