The American Journal of Surgery 194 (2007) 323–327
Clinical surgery–American

Hyperparathyroidism after radioactive iodine therapy

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Manuscript received February 7, 2007; revised manuscript April 16, 2007

Abstract

Background: Radioactive iodine (RAI) treatment has been suggested to cause primary hyperparathyroidism (HPT). We describe a series of patients with HPT and a history of RAI exposure.
Methods: Patient demographic and clinical information was evaluated, including the latency time to the development of HPT after RAI exposure.
Results: We treated 11 patients with HPT and a history of RAI exposure. RAI treatment was administered for benign thyroid disease in 9 (82%) cases. Thirty-six cases of HPT after RAI exposure in the English literature were compiled for further analysis. In this collective experience, the average latency time to the development of HPT after RAI treatment was 13.5 ± 9.1 years and was found to be inversely correlated with age at RAI exposure.
Conclusions: Patients who undergo RAI treatment are at risk of developing HPT, and this risk appears to increase in elderly patients. Serum calcium surveillance is recommended for patients who have undergone RAI treatment.

Keywords: Primary hyperparathyroidism; Radioactive iodine

The causal effect of localized external-beam ionizing radiation exposure and subsequent development of primary hyperparathyroidism (HPT) has been extensively described and studied since it was first suggested by a case report in 1975 [1–17]. The treatment of thyroid disease with iodine 131 (^{131}I) and its possible effect on the subsequent development of HPT was noted almost a decade later [7,18,19]. Several case series describing patients with HPT and a history of ^{131}I treatment followed these initial observations [20–25]. The authors of some of these reports noted that younger patients may have increased susceptibility to ^{131}I and advised periodic calcium surveillance in patients with a history of ^{131}I exposure [19,22,24].

The safety of ^{131}I therapy for benign thyroid disease in young patients has been shown, and some clinicians have advocated its use in this patient population [26–29]. However, previous studies fail to document or address the development of HPT in these young patients. This has motivated the retrospective review of our own experience of patients with a history of ^{131}I treatment referred to us for surgical management of HPT. We also performed an extensive review of the medical literature and analyzed the resultant collective experience.

Materials and Methods

We conducted a retrospective analysis of patients undergoing parathyroidectomy for primary HPT at the University of California San Francisco (UCSF) Medical Center from 1996 to 2004. In these patients, the diagnosis of primary HPT was established by an elevated serum parathyroid hormone in the setting of hypercalcemia. Each patient completed a standard questionnaire at the initial preoperative visit and again postoperatively. Demographic and clinical information collected with the questionnaire included age at the time of treatment for HPT, sex, symptoms commonly associated with thyroid and parathyroid disorders, history of thyroid disease treated with RAI therapy, dose of radioiodine received, and age at the time of RAI therapy. We reviewed the medical records of the hyperparathyroid patients who reported a history of RAI treatment for any reason. The operative notes and pathology reports provided information regarding the number and location of the abnormal parathyroid glands and coexistent thyroid pathology. Patients with 1 enlarged parathyroid gland were considered to have a parathyroid adenoma, whereas patients with 2 enlarged parathyroid glands were considered to have a double adenoma. Parathyroid hyperplasia was diagnosed

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0002-9610/07/$ – see front matter
doi:10.1016/j.amjsurg.2007.04.005

when all glands were abnormal, although the size was variable.

Next, we performed a comprehensive literature search to identify the previously reported cases of patients who developed functional parathyroid adenomas after receiving RAI treatment for any reason. To our knowledge, there have been 36 cases reported to date in the English-language literature. Information from these cases regarding the age and sex of patients presenting with primary HPT, age at the time of radioiodine treatment, and the reason for RAI treatment were recorded and combined with the data obtained from our patient series.

In this collective experience, analysis was performed for 3 groups of patients: (1) all patients, (2) patients who were treated with RAI for benign thyroid disease, and (3) patients who were treated with RAI for malignant thyroid disease. The age distribution and the mean age at the time of RAI treatment were calculated. The latency period was defined as the time (in years) between RAI treatment and the diagnosis of primary HPT. If the patient received multiple courses of RAI, the year of the earliest treatment was used to calculate the latency period. When appropriate, variables were compared between groups 2 and 3 by using the 2-sided Student *t* test or analysis of variance. The association between age at the time of RAI treatment and the latency period was explored by scatterplot, nonparametric, and parametric correlation analyses and linear regression analysis. A P value of $<.05$ was considered significant for all analyses. Statistical analysis was performed by using SPSS for Windows (version 12.0; SPSS, Inc, Chicago, IL).

Results

Eleven patients were identified in the UCSF clinical database who underwent surgical treatment for primary HPT after being treated with RAI for any reason. The demographic characteristics of these patients are presented in Table 1. Nine of the 11 patients were women (82%), and 2 were men (18%). The parathyroid resections were performed in patients who were 48 to 84 years of age (mean age, 63.3 ± 10.6 years). This was 2 to 35 years after their earliest treatment with RAI or a mean latency period of 16.0 ± 12.0 years. Nine of the 11 patients were treated with RAI for benign thyroid disease (82%). Eight of these patients received RAI therapy for Graves' disease, and 1 received RAI therapy for multinodular goiter. The remaining 2 of the 11 patients were treated with RAI after undergoing a total thyroidectomy for papillary thyroid carcinoma (18%).

An additional 36 patients who received RAI therapy and subsequently underwent surgical treatment for primary HPT were identified in the English-language literature. The available demographic characteristics of these patients are presented in Table 1. Female sex predominated similarly to the UCSF cohort of patients. Out of 27 patients, there were 26 women (96.3%) and 1 man (3.7%). The parathyroid resections were performed in patients who were 26 to 80 years of age (mean age 59.0 ± 13.8 years). This was 3 to 30 years after their earliest treatment with RAI or a mean latency period of 12.7 ± 8.3 years. The reason for receiving RAI therapy was available for 35 patients, and, like the UCSF cohort, the majority of the patients were treated for benign thyroid disease. Of the 30 patients (85.7%) treated for benign thyroid disease, 17 received RAI therapy for Graves' disease, 5 for toxic multinodular goiter, and 8 for hyperthyroidism of an unknown origin. The remaining 5 out of 35 patients (14.3%) were treated with RAI for thyroid carcinoma.

Combining the data obtained from the literature with the data obtained from our patient series resulted in a total of 47 patients; however, patient characteristics were not available for all 47 patients. Thirty-four of the 38 patients were women (89.5%) and 4 were men (10.5%). The parathyroid resections were performed in patients who were 35 to 85 years of age (mean age 59.4 ± 13.5 years; n = 38). Postsurgical pathological analysis revealed 38 single adenomas (32 benign and 6 malignant), 2 double adenomas, and 4 cases of parathyroid hyperplasia (n = 43). The mean age of the patients at the time of RAI therapy was 45.5 ± 17.5 years (n = 35), resulting in a mean latency period of 13.5 ± 9.1 years (n=37) before the onset of primary HPT.

A statistically significant association was found between the age of the patient at the time of RAI therapy and the latency period before the development of primary HPT (Kendall's correlation coefficient = -0.473, $P < .0001$; Spearman's rho = -0.648, $P < .0001$). Linear regression showed a negative correlation between these 2 variables (slope = -0.361, $R^2 = 0.4406$, $P < .0001$). As age at the time of RAI treatment increased, the latency period decreased (Fig. 1).

The effects of the amount of RAI on the development of HPT could not be determined because the RAI dosage was not known for most patients. We thus assumed that patients treated for benign disease received a lower dose of RAI than those treated for malignant thyroid disease. In patients with a history of RAI treatment for benign thyroid disease (including Graves' disease, a toxic multinodular goiter, and hyperthyroidism), surgical treatment for primary HPT occurred at a mean age of 58.9 ± 12.8 years (n = 31). The mean latency period between RAI therapy and theonset of primary HPT in this group of patients was 12.9 ± 8.8 years (n = 30). In patients with a history of RAI treatment for thyroid malignancy (mostly papillary carcinoma), surgical treatment for primary HPT occurred at a slightly older mean age of 61.4 ± 17.0 years (n = 7). The mean latency period between RAI therapy and the onset of primary HPT in these patients when compared with those patients treated for benign thyroid disease was also increased at a mean of 16.3 ± 10.5 years (n = 7). However, the differences in age at the time of parathyroidectomy and latency period between patients who were treated with RAI for benign versus malignant thyroid disease were not significant as determined by analysis of variance ($P = .665$ and .379, respectively).

Comments

It is not surprising that many patients diagnosed with primary HPT have been previously exposed to localized external-beam ionizing radiation. External ionizing radiation has been shown to cause parathyroid adenomas in numerous cases since the first published case report in 1975