Long-term course and predictive factors of elevated serum thyroglobulin and negative diagnostic radioiodine whole body scan in differentiated thyroid cancer

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ABSTRACT. Following the initial management, some patients with differentiated thyroid cancer (DTC) develop a state of high thyroglobulin (Tg) and negative diagnostic radioactive iodine (RAI) whole body scan (DxWBS). The predisposing factors and outcome of this condition are unclear. In this study, our objectives were to determine the predictive factors for the development of high Tg and negative DxWBS (Tg+/scan-) and to study the long-term course of the disease in patients with this condition. Methods: We, retrospectively, reviewed the medical records of a cohort of 105 non-selected DTC patients (26 males and 79 females; median age 37.7 yr, range 7-72). None of these patients had positive Tg antibodies or distant metastases. All Tg levels were obtained off thyroid hormone therapy. At the first follow-up visit after RAI ablation (13±7.6 months), patients were classified into those with low Tg (<2 ng/ml off L-T₄) and negative DxWBS (control group) and those with high Tg (≥2 ng/ml off L-T₄) and negative DxWBS (Tg+/scan- group). Using univariate and multivariate logistic regression analyses, we evaluated a number of parameters (see results) for their association with the development of Tg+/scan-. In addition, the long-term course of the disease in Tg+/scan- group was analyzed. Results: In univariate analysis, the following factors were found to be significantly associated with Tg+/scan-: perithyroidal tumor extension (p=0.025), soft tissue invasion (p=0.001), cervical lymph node metastases (p=0.014) and Tg level before RAI ablation (p=0.015). In multivariate analysis, only soft tissue invasion remained significantly associated with Tg+/scan- [p=0.001, odds ratio, 15.6 (95% CI, 2.96-82.06)]. Age, sex, duration of goiter before surgery, pressure symptoms, tumor size, tumor multifocality, lymph node dissection at initial surgery, tumor-node-metastasis (TNM) stage, and RAI ablative dose were not associated with Tg+/scan-. In 53 patients with Tg+/scan-, 42 cases were followed without any therapeutic intervention; over a median follow-up of 71.6 months (range, 13-144.7), 31 cases had a spontaneous remission and 11 cases continued to have a persistent disease (Tg ≥2 ng/ml, negative DxWBS, and no palpable disease or distant metastases); Tg declined from 9.32±9.91 ng/ml at first visit after RAI ablation to 1.59±5.39 ng/ml at last visit (p<0.0001). In the other 11 cases of Tg+/scan-group, one or more therapeutic interventions (RAI, surgery, or external radiotherapy) were undertaken. Over a median follow-up of 98.4 months (range, 6-147), Tg decreased from 110.2±147.5 to 23.5±41.2 ng/ml (p=0.026); 4 cases achieved remission, 5 cases continued to have persistent disease, and 2 cases had progression of their disease, which led to their death. Conclusion: Soft tissue invasion on original surgery strongly predicts the development of Tg+/scan- in DTC patients. The long-term course of the disease is mostly favorable especially when the Tg level is only modestly elevated.


INTRODUCTION

Following thyroidectomy and radioactive iodine (RAI) ablation, about 10-15% of patients with differentiated thyroid cancer (DTC), continue to have or develop an elevated serum thyroglobulin (Tg) despite negative diagnostic RAI whole body scan (DxWBS) (1-3).
The management of this condition is far from clear (2, 4). RAI therapy has been reported to induce variable reduction in Tg level (5, 6, 3), and surgery has not been consistently effective (7). Despite the initial doubt about the significance of elevated Tg in the absence of any discernable pathological uptake on DxWBS (Tg+/scan-), many studies have shown that patients with Tg+/scan- often have persistent/recurrent disease (2, 3, 5, 6). Several mechanisms have been proposed to explain the persistence or development of Tg+/scan-, including inadequate uptake by tumor cells which have lost their ability to trap RAI but continued to produce Tg, too small residual or metastatic tumor tissue to be visualized on conventional DxWBS, and saturation of thyroid tissue by non-RAI (8). None of these proposed mechanisms have, however, been clearly demonstrated. In addition, it is unclear what clinical and pathological parameters are associated with the development of Tg+/scan-. In this study, we evaluated a number of clinical, pathological, and radiological factors for their association with the development of Tg+/scan- in patients with DTC. Furthermore, in the absence of long-term prospective studies, retrospective evaluation of patients with Tg+/scan- provides valuable information on the natural course of the disease especially in those patients who have, for whatever reason, not received any additional therapy after the initial surgery and RAI ablation. We describe the long-term course of the disease in a cohort of patients with this condition; most of them have been followed-up over a long period of time without intervention.

MATERIALS AND METHODS

Patients

We retrospectively screened the medical records of 178 non-selected cases of DTC. We excluded patients with distant metastases, no further follow-up DxWBS and Tg subsequent to the first follow-up DxWBS and Tg after RAI ablation, positive Tg auto-antibodies, or whose follow-up data were significantly missing or incomplete. Based on these exclusion criteria, we reviewed the medical records of the remaining 105 patients with DTC who were seen during the period 1990-1999 (26 males and 79 females; median age, 37.7 y; range, 7-72). At the initial presentation, all patients had goiter with a mean±SD duration of 37.4±46 months (range, 1-200). Ninety-nine patients had total or near-total thyroidectomy, while the other 6 patients underwent subtotal thyroidectomy. Of all cases, 20 patients (19%) had unilateral, 66 patients (62.9%) had bilateral modified neck dissection, and 7 patients (6.7%) had lymph node sampling. Pathological diagnosis showed papillary thyroid cancer (PTC) in 89 cases (84.8%), follicular variant of PTC in 13 cases (12.4%), tall cell variant of PTC in 2 cases (1.9%) and minimally invasive follicular thyroid cancer in 1 case. The median tumor size was 3 cm (range, 0.2-9). The tumors showed multifocality in 41 cases (39%), perithyroidal extension in 22 cases (21%), and soft tissue invasion in 28 (27.7%). Cervical lymph node metastases were present in 42 cases (40%) but none of the patients had distant metastases. Seventy-eight cases (75%) were in tumor-node-metastasis (TNM) classification stage 1, 7 cases (6.6%) in stage 2, 15 (15%) in stage 3, 2 (1.9%) in stage 4, and 3 could not be staged due to lack of information on tumor size (9). With the exception of 2 patients (one had undetectable Tg and negative DxWBS after surgery and one was a low-risk patient), all patients had 131I ablation (mean±SD, 477±1221 MBq). The mean±SD Tg and TSH levels just before patients received 131I ablative dose were 36±127 ng/ml and 114.7±78.5 mIU/l, respectively. Following 131I ablation, patients were treated with suppressive doses of LT4 in order to achieve TSH<0.01 mIU/l with normal FT4. At a mean duration of 13±7.6 months, patients were evaluated with Tg and DxWBS off LT4 for at least 5 weeks and T3 for at least 2 weeks. Patients were prescribed a low iodine diet for at least one week before DxWBS. All DxWBS were negative and the median Tg was 2 ng/ml (range, undetectable-508). At this point of follow-up, we classified patients into 2 groups: group 1, which acts as a control group (those with low Tg (<2 ng/ml) and negative DxWBS (52 cases)) and group 2, which acts as cases (those with high Tg (≥2 ng/ml) and negative DxWBS (53 cases)). We used a cut-off limit Tg value of 2 ng/ml, since it is now widely accepted that patients with stimulated (either after T4 withdrawal or with recombinant TSH) Tg level of ≥2 ng/ml have persistent/recurrent disease (10). We assessed a number of clinical, pathological and radiological parameters for their association with the development of Tg+/scan- in patients with DTC. These parameters are: age, sex, duration of goiter before initial surgery, the presence of pressure symptoms prior to surgery (pain, dysphagia, or change of voice), tumor size, tumor multifocality, perithyroidal tumor extension (extension of the tumor outside the thyroid capsule in the surrounding fibrofatty tissue without involvement of muscles, trachea, esophagus, or vessels), soft tissue invasion by the tumor (involvement of the surrounding muscles, trachea, esophagus, or vessels), the presence of lymph node metastases, TNM stage of the disease, unilateral vs bilateral modified neck dissection, Tg level before the first RAI ablative dose, RAI percentage uptake on pre-ablation DxWBS, and RAI ablative dose. We also analyzed the long-term outcome of the disease in patients with Tg+/scan-. We defined outcome as follows: a) remission: no clinical or radiological evidence of local or distant disease, negative DxWBS, and Tg<2 ng/ml; b) persistent disease: no evidence of locally palpable disease or distant metastases on radiological studies (chest X-rays, CT scan of the chest, or FDG-PET WBS), negative DxWBS, and Tg ≥2 ng/ml; c) progression: appearance of locally palpable disease or new distant metastases.

Diagnostic radioiodine whole body scans (DxWBS)

DxWBS at our institution, we routinely use iodine-123 isotope (I-123). We and others have shown a high diagnostic accuracy and comparability to 131I isotope (11, 12). In preparation for DxWBS, patients were kept off L-T4 for at least 5 weeks and off T3 for 2 weeks. Patients were prescribed low 131I diet for at least 1 week before obtaining DxWBS. Two diagnostic I-123 activities were used. Between January 1990 and December 1993, the diagnostic activity used was 185 MBq. Because of the easy access to obtaining I-123 (our institution has a cyclotron), the lack of stunning effect, and in order to increase the rate of detection of metastatic disease, I-123-scanning dose was increased to 370-555 MBq as of January 1994. The scanning was performed 24 h after oral ingestion of I-123 diagnostic doses. DxWBS included planar WBS and dedicated films of the neck and chest regions.