CASE REPORT

Case of painless thyroiditis that developed during adjuvant chemotherapy for breast cancer

Asumi Iesato¹ · Takaaki Oba¹ · Koichi Ono¹ · Takayuki Watanabe¹ ·
Tokiko Ito¹ · Toshiharu Kanai¹ · Kazuma Maeno¹ · Ken-ichi Ito¹

Received: 10 May 2017 / Accepted: 7 July 2017 / Published online: 10 July 2017
© The Japan Society of Clinical Oncology 2017

Abstract We report a case of painless thyroiditis that occurred during adjuvant chemotherapy for breast cancer. A 41-year-old woman was diagnosed with right breast cancer and underwent surgery followed by adjuvant chemotherapy, given the tumor size and relatively high ratio of Ki-67-positive cells. Three weeks after the first intravenous administration of fluorouracil (500 mg/m²), epirubicin (100 mg/m²), cyclophosphamide (500 mg/m²), and dexamethasone (6.6 mg/body), followed by 3 days of oral dexamethasone (8 mg/day), she complained of continued palpitations. Although Graves' disease was initially suspected, she was diagnosed with painless thyroiditis because of a low free T3:free T4 ratio and low thyroid uptake of iodine. The mechanism of painless thyroiditis, in this case, remains unclear, although supposed etiologic event was the use of cytotoxic drugs (including fluorouracil) or the withdrawal of short-term steroid administration. Painless thyroiditis very rarely occurs during chemotherapy. However, we should consider painless thyroiditis when a patient undergoing cytotoxic chemotherapy for breast cancer experiences continued palpitations. The appropriate diagnosis and treatment of symptoms might avoid an unnecessary dose reduction or discontinuation of chemotherapy and, moreover, may prevent adverse effects associated with the metabolism of anticancer agents.

Keywords Painless thyroiditis · Drug-induced thyroiditis · Thyrotoxicosis · Chemotherapy · Breast cancer

Introduction

Painless thyroiditis is characterized by usually mild-to-moderate thyrotoxicosis, a modest goiter, low radioactive iodine uptake, and reduced thyroid-stimulating hormone (TSH) levels. Although the course of the disease varies, approximately 5–20% of patients with painless thyroiditis exhibit the characteristic sequence of hyperthyroidism followed by hypothyroidism and recovery [1]. Because the symptoms of painless thyroiditis resemble those of early-onset Graves' disease, differentiation between these conditions is important for the selection of an appropriate therapy. Treatments for Graves' disease include antithyroid drugs, radioactive iodine, and thyroidectomy, whereas thyrotoxicosis caused by painless thyroiditis can be managed conservatively. Furthermore, the symptoms of early-onset painless thyroiditis are similar to the adverse events of chemotherapy, particularly as continued palpitations are a known indicator of epirubicin-induced cardiac toxicity.

Multiple reports describe painless thyroiditis in response to drugs such as amiodarone, interferon- α (IFN- α), interleukin-2 (IL-2), lithium, and tyrosine kinase inhibitors [2, 3]. However, few reports have described the development of painless thyroiditis during chemotherapy. A misdiagnosis of the cause of the symptoms might lead to an unnecessary interruption of chemotherapy; furthermore, untreated thyrotoxicosis might affect the metabolism of chemotherapy [4, 5]. Therefore, it is very important to identify the causes of symptoms and thyroid function management during chemotherapy. Here, we report a rare case of painless thyroiditis that developed during adjuvant chemotherapy for breast cancer.

✉ Ken-ichi Ito
kenito@shinshu-u.ac.jp

¹ Division of Breast, Endocrine and Respiratory Surgery,
Department of Surgery (II), Shinshu University School of
Medicine, 3-1-1 Asahi, Matsumoto, Nagano 390-8621, Japan

Case report

A 41-year-old woman with no previous or family history of thyroid disorder was diagnosed with right breast cancer and underwent mastectomy and sentinel lymph node biopsy. The pathological diagnosis was invasive lobular carcinoma (size = 33 mm). No lymphatic or vascular invasion or lymph node metastasis was observed. Although the specimen was human epidermal growth factor receptor 2 (HER2)-negative, 80% of breast cancer cells expressed both the estrogen and progesterone receptors, and 27.8% expressed Ki-67. Considering the tumor size and relatively high ratio of Ki-67-positive cells, we decided to administer an adjuvant combination therapy regimen comprising docetaxel and cyclophosphamide (TC therapy). However, we discontinued TC therapy because of the occurrence of severe peripheral neurotoxicity after the first course, and we switched the treatment to a triple-drug combination of fluorouracil, epirubicin, and cyclophosphamide (FEC therapy).

Three weeks after the first intravenous administration of fluorouracil (500 mg/m²), epirubicin (100 mg/m²), cyclophosphamide (500 mg/m²), and dexamethasone (6.6 mg/body), followed by 3 days of oral dexamethasone (8 mg/day) to prevent chemotherapy-induced emesis, the patient complained of continued palpitations (Fig. 1). Electrocardiography showed sinus tachycardia, which allowed us to rule out epirubicin-induced cardiac toxicity. Her serum concentrations of free T4 (FT4), free T3 (FT3), and thyroid-stimulating hormone (TSH) were 4.02 ng/dL (normal range, 1.00–2.00 ng/dL), 9.48 pg/mL (2.30–4.00 pg/mL), and 0.016 μ IU/mL (0.20–4.00 μ IU/mL), respectively. Her serum level of anti-TSH receptor antibody (TRAb) was slightly elevated (2.35 IU/L), whereas the levels of both antithyroid peroxidase antibody

(TPOAb) and anti-thyroglobulin antibody (TgAb) were within normal ranges (Table 1). Subacute thyroiditis was ruled out because of the absence of fever and thyroid pain. Based on these data and her clinical symptoms, we diagnosed Graves' disease and initiated thiamazole treatment (15 mg/day). However, painless thyroiditis remained a possible diagnosis because of the relatively low ratio of FT3 to FT4 (2.36) and slightly increased TRAb level, which did not fully meet the diagnostic criteria for Graves' disease. Hence, we tested the radioactive iodine uptake (RAIU) of the thyroid. After obtaining a RAIU of 2.22%, which was lower than normal range (10–35%) (Fig. 2), painless thyroiditis was considered to be the cause of the thyrotoxicosis. Thereafter, we gradually decreased the thiamazole dose, and the patient's thyroid function improved.

To confirm the onset of thyrotoxicosis, we measured thyroid hormone and TRAb levels in conserved serum obtained from the patient before the initiation of chemotherapy. Consequently, we confirmed that the painless thyroiditis occurred after the initiation of chemotherapy, as the serum levels of FT3, FT4, and TRAb before the initiation of chemotherapy were within normal ranges (Table 1). After ensuring that her thyroid function had returned to within normal ranges, we reinstituted FEC therapy and the patient completed the planned therapy without an exacerbation of thyroiditis.

Discussion

Thyrotoxicosis is defined as a state of thyroid hormone excess. Several etiologies have been identified in the pathogenesis of thyrotoxicosis, including Graves' disease, toxic nodular goiter, subacute thyroiditis, painless

Fig. 1 Clinical course and thyroid function during chemotherapy for breast cancer. HR heart rate, TSH thyroid-stimulating hormone (μ IU/mL), FT3 free T3 (pg/mL), FT4 free T4 (ng/dL), TC docetaxel and cyclophosphamide, FEC 5-fluorouracil, epirubicin, and cyclophosphamide, DX dexamethasone, G-CSF lenograstim, MMI thiamazole. HR cross symbol, FT3 black diamond, FT4 white square, TSH white triangle

Table 1 Changes in thyroid function and thyroid autoantibody levels during chemotherapy for breast cancer

Hormone or antibody	Normal range	Pre-surgery	Before TC therapy	3 weeks after FEC therapy
FT3 (pg/mL)	2.30–4.00	1.94	3.01	9.48
FT4 (ng/dL)	1.00–2.00	1.92	1.99	4.02
TSH (μIU/mL)	0.200–4.000	0.62	3.59	0.016
TRAb (IU/L)	0–2.0	1.7	1.1	2.35
TPOAb (IU/mL)	0–5.2	1.6	1.8	1.7
TgAb (IU/mL)	0–40.6	<10.0	<10.0	<10.0

TC docetaxel and cyclophosphamide, FEC 5-fluorouracil, epirubicin, and cyclophosphamide, FT3 free T3, FT4 free T4, TSH thyroid-stimulating hormone, TRAb thyroid-stimulating hormone receptor antibody, TPOAb thyroid peroxidase antibody, TgAb thyroglobulin antibody

Fig. 2 ^{123}I thyroid scintigraphy 5 weeks after the initiation of chemotherapy for breast cancer. Almost normal radioactive iodine uptake was detected in the thyroid gland, and the ratio of radioactive iodine uptake after the injection of ^{123}I was 2.22%

thyroiditis, TSH-secreting pituitary adenoma, thyroid hormone resistance syndrome, and some drugs [6]. A differential diagnosis of thyrotoxicosis is essential, as effective treatments have been established for each thyroid disorder.

Some drugs, including tyrosine kinase inhibitors, can directly induce apoptosis of the thyroid follicular cells or may cause inadequate vascularity and gland destruction, leading to the onset of painless thyroiditis and subsequent transient thyrotoxicosis [3, 4]. Other drugs, including interferon, can alter the immune system and thus cause painless thyroiditis [3, 4]. However, few reports have described the development of painless thyroiditis during chemotherapy, and fluorouracil is the only cytotoxic drug reported to induce this condition [5, 7]. Because fluorouracil was administered to our patient, this drug might

have induced thyroiditis, although the mechanisms underlying the injury to the thyroid follicular epithelial cells remain unknown.

We note, however, that several cases in which painless thyroiditis developed after the discontinuation of steroids for autoimmune disease have been reported [8–10]. We administered dexamethasone for 4 days to prevent the side effects of the chemotherapeutic agents in the present case and, therefore, cannot rule out the possibility that activation of the immune system upon withdrawing short-term steroid therapy induced the destruction of thyroid follicular cells.

Furthermore, the symptoms of painless thyroiditis, such as palpitations, weight loss, tremor, tachycardia, and fever, are similar to those caused by anticancer drugs and, therefore, differential diagnosis of the underlying cause is important. A dose reduction or treatment discontinuation is required for symptoms indicative of drug-induced adverse events [4]. However, appropriate treatment should be administered when the symptoms are due to thyrotoxicosis, as untreated thyrotoxicosis may affect the metabolism of administered drugs, including anticancer agents [5].

In the present case, a slight increase in TRAb was observed after the initiation of cytotoxic chemotherapy, which created challenges for the differential diagnosis of the cause of thyrotoxicosis. Morita et al. [11] reported that TRAb positivity was observed in 10–20% of patients with painless thyroiditis and suggested that inflammatory or destructive changes in the thyroid gland might be associated with the transient emergence of this factor. Hence, a RAIU test should be considered when painless thyroiditis is the possible cause of thyrotoxicosis.

Because painless thyroiditis generally occurs from chronic autoimmune thyroiditis, most affected patients have positive serum TPOAb and/or TgAb levels. However, the present case was negative for both antibodies. Drug-induced painless thyroiditis develops in the absence of underlying chronic autoimmune thyroiditis. In a previous study of TPOAb expression, patients with amiodarone-induced thyroiditis were found to be negative, whereas 5–10% of patients with IFN- α - or IL-2-induced thyroiditis

and 33% of patients with lithium-induced thyroiditis were positive [2]. The low TPOAb-positive ratio among patients with drug-induced painless thyroiditis serves as a reminder that painless thyroiditis can occur in a patient without underlying autoimmune chronic thyroiditis as a result of the drug-induced destruction of thyroid follicular cells.

In conclusion, painless thyroiditis is a very rare complication resulting from cytotoxic chemotherapy, and the pathogenic mechanism underlying the painless thyroiditis in the present case is not fully clear. However, painless thyroiditis should be considered when breast cancer patients experience continued palpitations during chemotherapy.

References

- Samuels MH (2012) Subacute, silent, and postpartum thyroiditis. *Med Clin N Am* 96:223–233
- Bindra A, Braunstein GD (2006) Thyroiditis. *Am Fam Physician* 73:1769–1776
- Barbesino G (2010) Drugs affecting thyroid function. *Thyroid* 20:763–770
- Hamnvik OP, Larsen PR, Marqusee E (2011) Thyroid dysfunction from antineoplastic agents. *J Natl Cancer Inst* 103:1572–1587
- Torino F, Barnabei A, Paragliola RM et al (2013) Thyroid dysfunction as an unintended side effect of anticancer drugs. *Thyroid* 23:1345–1366
- Fauci AS, Braunwald E, Kasper DL et al (2008) Disorders of the thyroid gland. *Harrison's principles of internal medicine*, 17th edn. McGraw-Hill Professional, New York, pp 2224–2247
- Beex L, Ross A, Smals A et al (1977) 5-Fluorouracil-induced increase of total serum thyroxine and triiodothyronine. *Cancer Treat Rep* 61:1291–1295
- Morita S, Ueda Y, Yokoyama N (2001) Painless thyroiditis induced by the cessation of betamethasone. *Intern Med* 40:744–746
- Maruyama H, Kato M, Mizuno O et al (1982) Transient thyrotoxicosis occurred after cessation of steroid therapy in a patient with autoimmune thyroiditis and rheumatoid arthritis. *Endocrinol Jpn* 29:583–588
- Haraguchi K, Hiramatsu K, Onaya T (1984) Transient thyrotoxicosis after unilateral adrenalectomy in two patients with Cushing's syndrome. *Endocrinol Jpn* 31:577–582
- Morita T, Tamai H, Oshima A et al (1990) The occurrence of thyrotropin binding-inhibiting immunoglobulins and thyroid-stimulating antibodies in patients with silent thyroiditis. *J Clin Endocrinol Metab* 71:1051–1055