Thyrotoxicosis With Pegylated Interferon Alfa-2b

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Background: Despite adequate surgery, a diagnosis of stage III melanoma carries a high risk of relapse, and hence mortality. Interferon alfa is the only treatment that has currently been shown to alter the natural history of the disease, delaying relapse-free survival, particularly in patients with micrometastatic disease. There is also recent evidence of a prognostic advantage conferred by the development of autoimmune conditions in patients receiving adjuvant interferon therapy.

Observations: We present the case of a 27-year-old woman with stage IIIa melanoma who was entered into the European Organisation for the Research and Treatment of Cancer 18991 trial of 5-year adjuvant treatment with pegylated interferon (peginterferon) alfa-2b. The patient developed thyrotoxicosis 3 months after commencing treatment, which required treatment with propylthiouracil. The degree of thyrotoxicosis corresponded closely to the dose of peginterferon alfa-2b given. However, in this patient, the hyperthyroidism resolved spontaneously after 4 years when peginterferon treatment was still ongoing. Seven years following the initial diagnosis, the patient has not had disease relapse.

Conclusion: Hyperthyroidism is less common than hypothyroidism as a consequence of interferon therapy, and this case is atypical in that it resolved spontaneously during interferon therapy but is in accordance with the recent evidence of a positive association between interferon-associated autoimmunity and prognosis.

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years but had slowly enlarged over the previous 6 months. Histologic examination showed a superficial spreading malignant melanoma. The melanoma was in vertical growth phase and was filling the papillary dermis (Clark level 3). There was patchy chronic inflammation at the base of the lesion but without a brisk tumor-infiltrating lymphocyte response. The Breslow thickness was 1.5 mm with no ulceration and 2 mitoses per square millimeter. The lesion extended to 2 mm from the closest lateral excision margin. No microvascular invasion and no microsatellites were seen.

On January 16, 2003, the patient underwent wide excision of the area surrounding the lesion and sentinel node lymphoscintigraphy and biopsy. The wide local excision showed fibrosis only, with no residual tumor, but the sentinel lymph node contained 2 foci of cells that stained for S-100 and was considered positive for melanoma. The foci were located at the capsule and were 0.1 mm in diameter. The patient underwent a left groin node dissection in March 2003 in which none of the 12 lymph nodes retrieved contained cancer. A computed tomographic scan in March 2003 showed no evidence of metastatic disease. She was therefore staged as having American Joint Committee on Cancer stage IIIA melanoma (T2aN1aM0).

On April 1, 2003, after signing informed consent, the patient was enrolled in the European Organisation for the Research and Treatment of Cancer (EORTC) 18991 trial of adjuvant peginterferon alfa-2b (PEGINTRON; Schering Corp, a division of Merck & Co, Kenilworth, New Jersey) vs observation and was randomized to 5 years' treatment with peginterferon alfa-2b. Treatment commenced on April 4, 2003, with 6-µg/kg/wk peginterferon alfa-2b for 8 weeks followed by 3-µg/kg/wk peginterferon alfa-2b for 5 years.

After 1 week in the trial, the patient complained of grade 1 fatigue, headache, nausea, and flu-like symptoms. After 3 weeks she also developed grade 1 elevated aspartate aminotransferase levels. Five weeks into the treatment, only grade 1 indigestion and grade 1 fatigue persisted.

On June 27, 2003, 14 weeks into treatment, routine thyroid function test results revealed hyperthyroidism with the following findings: thyroid-stimulating hormone (TSH), less than 0.08 mU/L (reference range, 0.5-6.0 mU/L); total triiodothyronine, 240.26 ng/dL (reference range, 64.94-162.34 ng/dL), and free thyroxine, 3.0 ng/dL (reference range, 0.7-1.9 ng/dL). (To convert total triiodothyronine to nanomoles per liter, multiply by 0.0154; free thyroxine to picomoles per liter, multiply by 12.871.) The patient at that time was experiencing grade 1 fatigue and headaches but no shakes or excessive sweating. She was stable in mood and had no eye symptoms but had lost 1.2 kg body weight since commencing the study. The patient had a low neutrophil count (grade 3 neutropenia) and therefore, on the advice of endocrinologists, received propylthiouracil, 150 mg/d.

One week following commencement of propylthiouracil, the patient was feeling less tired; another week later the patient had regained the 1.2 kg of body weight she had lost and her energy levels had returned to normal. Over the subsequent weeks the patient had intermittent grade 1 to 3 neutropenia. Repeated thyroid function test results in August 2003 showed persisting hyperthyroidism (TSH, 0.02 mU/L), requiring an increase in the propylthiouracil dose to 300 mg/d. Grade 4 neutropenia occurred on September 24, 2003, necessitating a week's interruption of the peginterferon alfa-2b and recommencement 1 week later with a 33% dose reduction (2 µg/kg/wk).

Following this reduction in the peginterferon alfa-2b dose and adjustment of the propylthiouracil dose, the TSH level began to rise, measuring 4.15 mU/L in November 2003 and 6.6 mU/L in January 2004, and therefore, the propylthiouracil was reduced to 150 mg/d. On this lower dose of propylthiouracil, in conjunction with 2-µg/kg/wk peginterferon alfa-2b, the patient's thyroid function test results remained normal for 3 years (TSH: 1.58 mU/L in April 2004; 1.93 mU/L, July 2004; 1.89 mU/L, January 2005; 1.53 mU/L, April 2005; 1.05 mU/L, September 2005; 1.47 mU/L, December 2005; 2.65 mU/L, February 2006; and 2.3 mU/L, August 2006). Thyroid peroxidase antibodies were tested in May 2005 and were positive (463 IU/mL, reference range, 0-60 IU/mL).

In February 2007, the TSH level rose to 32.75 mU/L while the patient remained on peginterferon alfa-2b therapy, and therefore, propylthiouracil treatment was stopped. The TSH level subsequently fell to 5.5 mU/L (reference range, 0.5-6.0 mU/L) in August 2007 and no further propylthiouracil was required.

The patient completed the 5 years of peginterferon alfa-2b at the end of March 2008 and on last follow-up had normal thyroid function and no evidence of recurrence of her melanoma.

The randomized study in which this patient was enrolled involved 1256 patients with resected stage III melanoma randomized to receive peginterferon alfa-2b, 6 µg/kg/wk for 8 weeks, and then 3 µg/kg/wk, or observation, for an intended duration of 5 years. Randomization was stratified for several tumor characteristics including microscopic (43%) vs macroscopic (57%), nodal involvement, and number of positive lymph nodes. The median length of treatment with peginterferon alfa-2b was 12 months. The most common grade 3 or 4 adverse events with peginterferon alfa-2b were fatigue (16%), hepatotoxic effects (11%), and depression (6%); treatment with peginterferon alfa-2b was discontinued because of toxic effects in 191 patients (31%). Data on autoimmunity were not collected in this study. At 3.8 years' median follow-up, 328 recurrence events had occurred in the peginterferon group compared with 368 in the observation group (hazard ratio, 0.82; P = .01); the mean (SE) 4-year rate of RFS was 45.6% (2.2%) in the interferon group and 38.9% (2.2%) in the observation group. The improvement in RFS was more pronounced in patients with micrometastatic disease, particularly in micrometastatic disease with only 1 lymph node involved. Thyrotoxicosis, although less common than hypothyroidism, is a well-documented adverse effect of interferon therapy for melanoma and other conditions such as viral hepatitis. However, evidence has emerged of a prognostic advantage conferred by the development of these autoimmune conditions in patients receiving interferon therapy for melanoma. In a study of 200 pa-
patients receiving adjuvant intravenous interferon alfa-2b, patients were tested for antithyroid, antinuclear, anti-DNA, and antcardiolipin autoantibodies while receiving treatment and were monitored for clinical signs of autoimmunity such as vitiligo and thyrotoxicosis. Autoantibodies or clinical manifestations of autoimmunity were detected in 52 patients (26%) receiving interferon. Antithyroid antibodies were detected in 43 of these 52 patients, and were more common in patients receiving extended therapy with interferon for 1 year rather than induction treatment for 1 month only (27 vs 16 patients, respectively). Hypothyroidism was seen in 11 patients and hyperthyroidism in 2 patients. Other autoimmune manifestations included vitiligo, autoimmune thrombocytopenic purpura, and rheumatoid factor–positive arthritis. After a median follow-up of 46 months, 108 of the 148 patients (72%) without autoimmune symptoms had relapsed compared with 7 of the 52 (13%) with autoimmune activity. The median survival was 38 months for patients without autoimmunity and was not reached in patients with autoimmunity. The development of autoimmunity was an independent prognostic marker for improved RFS and OS, although the retrospective nature of this analysis does introduce a bias. In the trial in which this patient took part, 18% of patients treated with peginterferon alfa-2b developed antithyroglobulin antibodies, but this was found not to be of prognostic or predictive significance.

In the case presented herein, the development of thyrotoxicosis was closely related to the onset and variation in administration of peginterferon alfa-2b. The condition developed 3 months after commencement of treatment with peginterferon alfa-2b, a similar period to the development of autoimmunity in the study by Gogas et al. The degree of thyroid overactivity then lessened, as measured by the dose of propylthiouracil required to keep the TSH in the reference range when the peginterferon alfa-2b dose was subsequently reduced owing to hematological toxic effects. The hyperthyroidism, however, resolved after 4 years of peginterferon alfa-2b treatment (1 year before the cessation of adjuvant peginterferon alfa-2b therapy). Studies of interferon treatment in the hepatitis C population have found similar rates of thyroid dysfunction with standard and pegylated interferons. Hyperthyroidism while receiving interferon is more common in women and takes the form of either a transient flare followed by hypothyroidism or Graves disease with thyroid-stimulating antibodies requiring prolonged therapy. In this patient, the hyperthyroidism followed a prolonged course but resolved spontaneously after 4 years when the peginterferon treatment was still ongoing. Seven years following the initial diagnosis, the patient has not had a relapse of her disease, which is in accordance with the positive association of interferon-associated autoimmunity with prognosis noted by others, and with the microscopic and solitary nodal involvement with melanoma.

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REFERENCES