

hormone-related peptide associated with hypercalcemia in a patient with Graves' disease and thymus enlargement. Because levels of both anti-thyrotropin-receptor antibody and parathyroid hormone-related peptide decreased during antithyroid treatment, we hypothesize that anti-thyrotropin-receptor antibody induced the release of parathyroid hormone-related peptide in this patient. From a clinical point of view, it is important to recognize that thymus enlargement and parathyroid hormone-independent hypercalcemia may occur simultaneously in Graves' disease and that both may respond to antithyroid treatment.

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Primary Ovarian Insufficiency Associated with Imatinib Therapy

TO THE EDITOR: Imatinib acts through selective inhibition of tyrosine kinases, which are constitutively activated in a number of cancers. Some of the drug's adverse reactions are presumably caused by the inhibition of normal kinases in various tissues. Ovarian failure is not a recognized complication of imatinib treatment, and successful conception and pregnancy have occurred in women receiving the drug.^{1,2} This outcome is at variance with what might theoretically be expected, given that kinases that are inhibited by imatinib (c-kit, c-abl, and platelet-derived growth factor receptor) are expressed in mammalian ovaries and appear to be important in multiple aspects of the growth and development of oocytes and follicles.^{3,4} We report the development of ovarian insufficiency in a young woman who was treated with imatinib for chronic myeloid leukemia (CML).

A 28-year-old woman with no personal or family history of gynecologic, endocrine, or developmental disorders was found to have Philadelphia chromosome-positive CML in January 2005, when she was in the fourth month of her first pregnancy. The pregnancy was terminated, and treatment with imatinib mesylate, at a dose of 400 mg per day, was started, with a good hematologic response. The dose was increased to 600 mg per day in July 2006, owing to persistent residual disease. Imatinib was well tolerated; the only undesirable effects were skin discoloration and

occasional muscle cramps. The patient's menstrual periods were normal, and she was taking no other medication. In December 2006, a complete cytogenetic and molecular remission was confirmed.

In February 2007 (2 years after the start of imatinib therapy and about 6 months after the dose was increased), the patient noticed oligomenorrhea, which subsequently evolved into amenorrhea. In November 2007, a diagnosis of primary ovarian insufficiency was made on the basis of characteristically high serum levels of follicle-stimulating hormone (median, 73 mIU per milliliter) during a 4-week period, combined with a greatly diminished follicle count, as seen on transvaginal ultrasonography of the ovaries.

These findings suggest that prolonged administration of imatinib may have profound effects on female fertility. The significance of the relatively high dose that the patient received is not known, but a young man in whom oligospermia developed during imatinib treatment for the hypereosinophilic syndrome was also receiving a high dose of the drug (800 mg daily).⁵ The true incidence, possible dose dependence, and reversibility of imatinib-induced ovarian failure should be examined in future studies. Awareness of this potential complication will enable physicians to offer patients appropriate counseling and to consider strategies of preserving fer-

tility and ovarian function before embarking on imatinib therapy.

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