

## Brief Report

## ACROMEGALY CAUSED BY SECRETION OF GROWTH HORMONE BY A NON-HODGKIN'S LYMPHOMA

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**A**CROMEGALY is a systemic disorder caused by sustained hypersecretion of growth hormone. The typical features include thickening of the skin, enlargement of the hands, feet, and mandible, and visceromegaly.<sup>1,2</sup> Active disease is indicated by the presence of excessive sweating and soft-tissue swelling.<sup>1,2</sup> Most patients with acromegaly have a growth hormone-secreting pituitary adenoma,<sup>3</sup> but a few (less than 1 percent) have hypothalamic or other tumors that secrete growth hormone-releasing hormone.<sup>4</sup> Isolated ectopic secretion of growth hormone has been reported only once, in a patient with a pancreatic islet-cell tumor.<sup>5,6</sup> Here we describe a patient with recurrent non-Hodgkin's lymphoma and acromegaly caused by ectopic production of growth hormone by the lymphoma.

### CASE REPORT

In October 1994, a 57-year-old woman was referred to another hospital for evaluation of malignant lymphoma. She had a six-month history of excessive sweating, bone pain, swelling and stiffness of the hands, and weight loss of 7 kg, followed by a weight gain of 5 kg. In July 1994, she underwent bilateral decompression of the median nerve because of carpal tunnel syndrome. Abdominal lymphadenopathy was detected by ultrasonography and verified by abdominal computed tomography, which suggested the presence of a malignant lymphoma; a lymph-node biopsy revealed follicular non-Hodgkin's lymphoma grade I (according to the classification system of the World Health Organization<sup>7</sup>). Although her symptoms suggested that the patient had an excess of growth hormone secretion, the presence of acromegaly was not recognized at that time.

The patient was treated with four cycles of cyclophosphamide, vincristine, doxorubicin, etoposide, and prednisolone. The lymphoma responded well to treatment, and the symptoms and signs of active acromegaly resolved. The patient was well until the end

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of 1997, when excessive sweating and swelling and stiffness of her hands and feet gradually reappeared (Fig. 1A). She also noticed enlargement of her nose, lips, and jaw (Fig. 1B). She was hospitalized at our institution in July 1998 and evaluated for growth hormone excess.

The physical examination was normal except for the features of acromegaly and axillary and inguinal lymphadenopathy. Serum growth hormone concentrations were high (Table 1), with little diurnal variation, as were serum concentrations of insulin-like growth factor I (IGF-I) and insulin-like growth factor-binding protein 3 (IGFBP-3). Plasma growth hormone-releasing hormone (GHRH) concentrations were below the limit of detection. Growth hormone secretion did not change after the oral administration of 75 g of glucose, the subcutaneous administration of 100  $\mu$ g of octreotide (Sandostatin, Novartis Pharma, Nuremberg, Germany), or the intravenous administration of 200  $\mu$ g of thyrotropin-releasing hormone (Relefact TRH, Hoechst Marion Roussel, Bad Soden, Germany) and 1  $\mu$ g of GHRH per kilogram of body weight (Ferring, Kiel, Germany).

The results of magnetic resonance imaging of the pituitary gland were normal (Fig. 1C), and jugular venous sampling did not reveal a pituitary-to-peripheral gradient in the serum growth hormone concentration. Abdominal computed tomography revealed enlargement of the liver, spleen, and multiple lymph nodes in the para-aortic region compressing the vena cava (Fig. 1D). Inguinal lymph-node biopsy revealed follicular non-Hodgkin's lymphoma with characteristic expression of the B-cell markers CD20 and CD79a. Indium-111 pentetreotide scintigraphy revealed no uptake in the pituitary or in the lymphoma tissue.

After one cycle of cyclophosphamide, vincristine, and prednisone, clinical and biochemical signs of acromegaly persisted, and the lymphoma was unchanged in size. The patient was therefore treated with fludarabine, mitoxantrone, and dexamethasone, which resulted in rapid clinical improvement and a rapid decrease in the serum concentration of growth hormone and IGF-I (Fig. 2). The patient has since remained in remission.

### METHODS

#### Assays

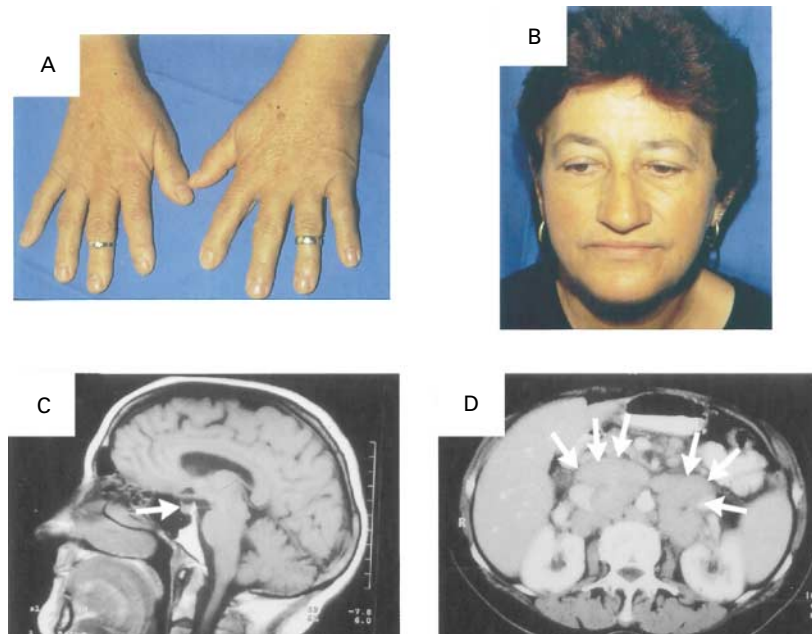
Serum growth hormone was measured by a commercial radioimmunoassay (Sorin Biomedica, Düsseldorf, Germany). To determine whether the tumor secreted the pituitary or placental growth hormone isoforms,<sup>9</sup> both serum and cell-culture supernatants were analyzed in an immunofunctional assay,<sup>10</sup> which recognizes pituitary and placental growth hormone equally well, and by a sandwich immunoassay specific for pituitary growth hormone.<sup>11</sup> Serum IGF-I (Mediagnost, Tübingen, Germany) and GHRH<sup>12</sup> were measured by radioimmunoassay, and IGFBP-3 by enzyme-linked immunosorbent assay (Diagnostic Systems Laboratories, Webster, Tex.).

#### Tissue and Cell Studies

Portions of the inguinal lymph node were subjected to primary cell culture or immediately frozen and stored at  $-80^{\circ}\text{C}$ . Frozen sections of growth hormone-producing pituitary adenoma, normal liver, and normal lymph node from patients without acromegaly served as controls. The use of tissue samples for research was approved by the ethics committee of the University of Freiburg, and the patient gave written informed consent for the studies.

#### Reverse-Transcriptase Polymerase Chain Reaction

Total RNA was extracted with use of RNeasy Mini Kit (Qiagen, Hilden, Germany). The reverse-transcriptase polymerase chain reaction was performed according to the manufacturer's instructions (Perkin-Elmer Cetus), with 35 cycles of amplification (each consisting of 1 minute at  $95^{\circ}\text{C}$ , 1 minute at  $55^{\circ}\text{C}$ , and 1 minute at  $72^{\circ}\text{C}$ ), followed by a final extension cycle of 10 minutes at  $72^{\circ}\text{C}$ . The primer sequences for pituitary growth hormone were 5'-GT-CAGTTCCCTCAGGAGTGTCT3' and 5'-GAGTAGTGCGTCA-TCGTTGTGT3'. The primers for the growth hormone recep-



**Figure 1.** Photographs and Computed Tomographic and Magnetic Resonance Images of a Patient with Acromegaly and Lymphoma.

The patient's hands (Panel A) and face (Panel B) show clinical signs of acromegaly. In Panel C, the pituitary gland (arrow) has a normal appearance on magnetic resonance imaging. Multiple enlarged para-aortic lymph nodes (arrows) are evident on computed tomography of the abdomen (Panel D).

**TABLE 1.** SERUM AND CELL-CULTURE CONCENTRATIONS OF HORMONES IN A PATIENT WITH ACROMEGALY AND LYMPHOMA.

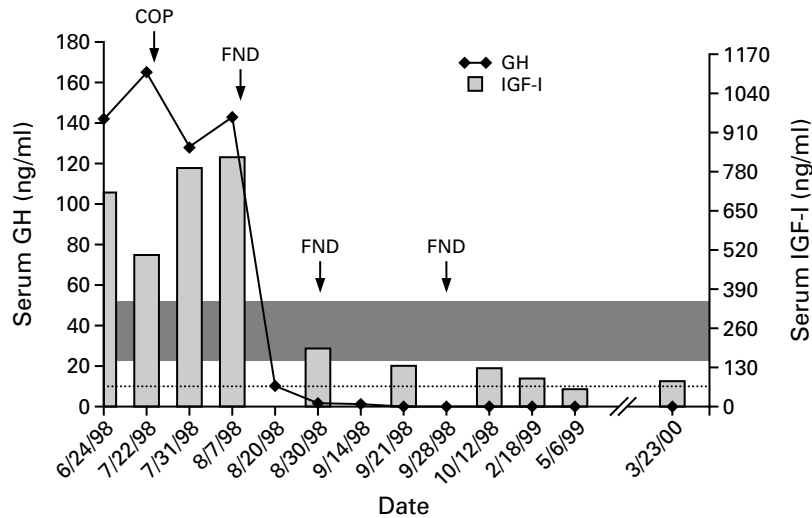
HORMONE	SERUM*		CELL-CULTURE MEDIUM†			
	PATIENT	NORMAL VALUE	LYMPHOMA CELLS FROM PATIENT	LYMPHOMA CELLS FROM CONTROL 1	LYMPHOMA CELLS FROM CONTROL 2	LYMPHOCYTES FROM NORMAL SUBJECT
Growth hormone	143–174	<1‡	102±28	0.3±0.1	0.4±0.1	0.4±0.1
Insulin-like growth factor I	645–782	142–380§	6.6±0.1	6.2±0.4	6.4±0.8	7.3±1.2
Insulin-like growth factor–binding protein 3	8514	2333–5705§	ND	ND	ND	ND
Growth hormone–releasing hormone	<0.02	<0.1	<0.02	<0.02	<0.02	<0.02

\*For the serum growth hormone determinations, blood was drawn hourly from 8 a.m. to 4 p.m., and the minimal and maximal values are shown. Serum insulin-like growth factor I was measured on three days.

†Values shown are in vitro secretion of growth hormone by the patient's lymphoma cells and the concentrations of the hormone in medium from cultures of peripheral-blood lymphocytes from a normal subject and two non-Hodgkin's lymphomas grown under identical conditions (controls 1 and 2). All values were measured at 12 hours. For the cell-culture experiments, the mean (±SD) of at least three independent samples is given. ND denotes not determined.

‡The lowest serum growth hormone concentration detected in repeated samples obtained throughout the day in normal subjects is shown.<sup>8</sup>

§The age-adjusted normal range is shown.



**Figure 2.** Serum Concentrations of Growth Hormone (GH) and Insulin-like Growth Factor I (IGF-I) during Treatment in a Patient with Acromegaly and Lymphoma.

Chemotherapy with cyclophosphamide, vincristine, and prednisone (COP) had no effect on the tumor or on serum growth hormone concentrations; symptoms of acromegaly persisted. Chemotherapy with fludarabine, mitoxantrone, and dexamethasone (FND) induced a rapid and sustained remission of the lymphoma and a decline in serum concentrations of growth hormone and insulin-like growth factor I. The dotted line indicates the upper limit of the normal range of serum growth hormone values. The shaded band shows the age-adjusted normal range of serum insulin-like growth factor I. Intervals between dates are not drawn to scale.

tor<sup>13</sup> and GHRH<sup>14</sup> have been reported previously. To characterize the growth hormone receptor amplification product, we hybridized it with a full-length [<sup>32</sup>P]- $\alpha$ -cytosine triphosphate-labeled insert of pcDNA1 growth hormone-receptor plasmid, as described elsewhere.<sup>15</sup> An ovarian-cancer cell line expressing GHRH messenger RNA (mRNA) served as a positive control for the amplification of GHRH.<sup>14</sup>

#### Immunofluorescence Microscopy

Ten-micrometer cryostat sections were fixed in cold acetone and dried overnight. After incubation with methanol-hydrogen peroxide (0.6 percent) to inhibit endogenous peroxidase activity, the sections were washed in 0.05 M TRIS-hydrochloric acid and 0.15 M sodium chloride at a pH of 7.6 and incubated at 4°C overnight with a rabbit polyclonal antibody against growth hormone (Dako Diagnostika, Hamburg, Germany) at a concentration of 30  $\mu$ g per milliliter in phosphate-buffered saline containing 3 percent bovine serum albumin. Bound primary antibody was visualized with a fluorescein isothiocyanate-conjugated sheep F(ab')<sub>2</sub> fragment directed against rabbit IgG (Boehringer, Mannheim, Germany).

#### Cell-Culture Experiments

Lymphoma tissue was placed in RPMI 1640 medium containing 10 percent fetal-calf serum, 2 percent L-glutamine, gentamicin (50  $\mu$ g per milliliter), amphotericin B (1  $\mu$ g per milliliter), and interleukin-4 (10 ng per milliliter); the tissue was mechanically dispersed until a suspension of single cells was obtained. The cells were grown in serum-free RPMI 1640 medium in six-well plates at a density of about 100,000 cells per well. The medium was changed every 12 hours, and the supernatant was stored at -20°C for measurement of growth hormone, IGF-I, and GHRH. As controls, peripheral-blood lymphocytes obtained from a normal subject after separation on a Ficoll-Hypaque gradient and cells from two

patients with low-grade non-Hodgkin's lymphomas were grown under identical conditions, and the culture medium was subjected to hormone analysis.

## RESULTS

#### Expression of mRNA in Lymphoma Tissue

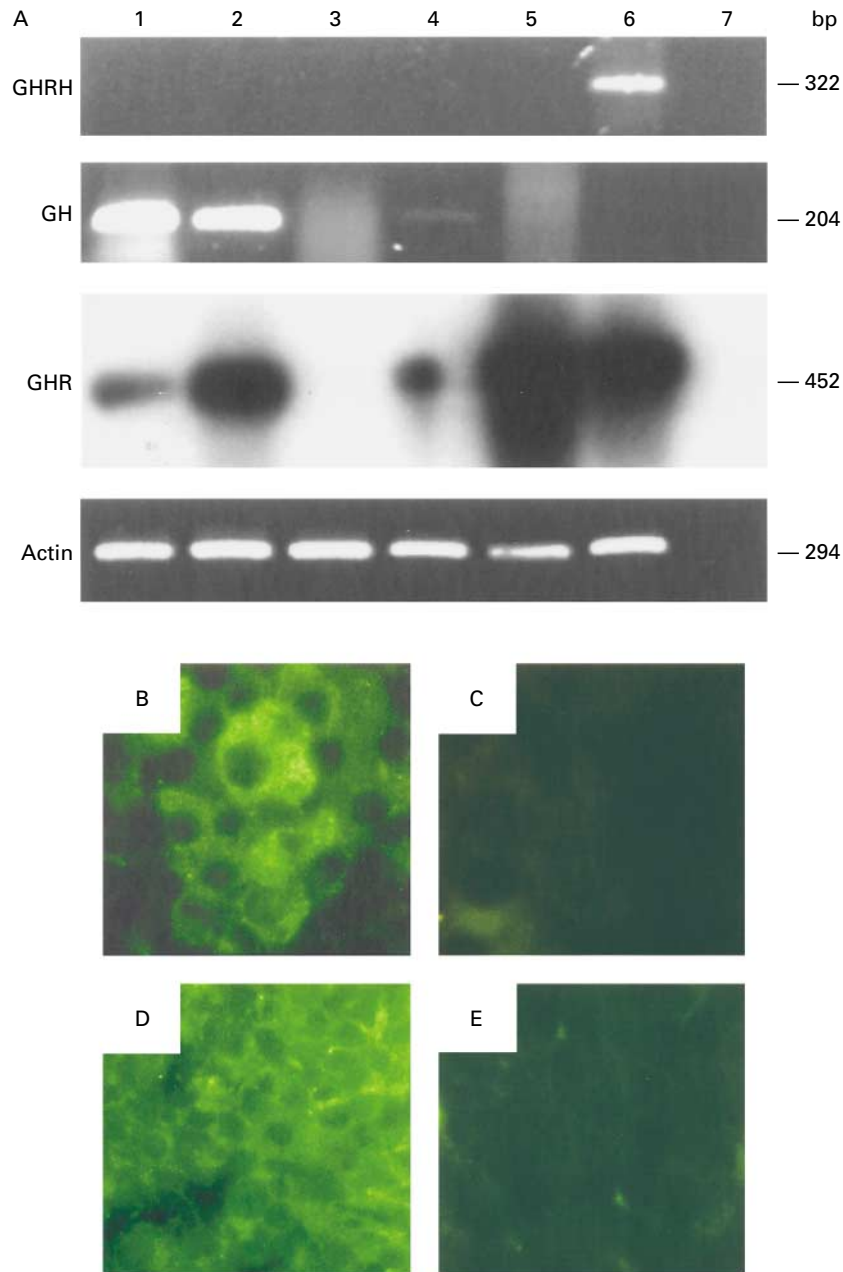
We detected mRNA encoding growth hormone and growth hormone receptors in the patient's lymphoma tissue (Fig. 3, top), whereas GHRH mRNA was undetectable.

#### Immunofluorescence Microscopy

The patient's lymphoma tissue showed strong immunoreactivity to growth hormone; the immunoreactivity was similar to that of tissue from a growth hormone-secreting pituitary adenoma from another patient with acromegaly (Fig. 3, bottom). Nearly all the patient's tumor cells stained for growth hormone. At the cellular level, the immunoreactivity in the patient's lymphoma was restricted to the cytoplasmic compartment.

#### In Vitro Secretion of Growth Hormone

The cultured lymphoma cells from the patient secreted large amounts of growth hormone into the medium (Table 1). By comparison, no growth hormone was detected in the medium from the cultures of peripheral-blood lymphocytes from the normal subject



**Figure 3.** Results of Molecular and Imaging Studies.

Panel A shows the results of reverse-transcriptase–polymerase-chain-reaction (RT-PCR) amplification of messenger RNA (mRNA) from growth hormone–releasing hormone (GHRH), growth hormone (GH), growth hormone receptor (GHR), and beta-actin in various tissues: lane 1, growth hormone–producing lymphoma (from the patient); lane 2, growth hormone–producing pituitary adenoma; lane 3, inactive pituitary adenoma; lane 4, normal lymph node; lane 5, normal liver tissue; lane 6, human ovarian cancer-cell line; and lane 7, water (control). RT-PCR products were separated by electrophoresis on a 1.2 percent agarose gel and stained with ethidium bromide. To prevent coamplification of genomic DNA, the RNA samples were subjected to digestion with DNase. All primers were designed as intron-spanning pairs. Amplification of the desired gene product was verified by digestion with appropriate restriction enzymes (data not shown). Control reactions included samples without template, samples without reverse transcriptase, and samples without DNase digestion.

Panels B, C, D, and E show the results of immunofluorescence microscopy for the localization of growth hormone immunoreactivity in the growth hormone–producing lymphoma (Panel B,  $\times 400$ ) and in a patient with a growth hormone–producing pituitary adenoma (Panel D,  $\times 400$ ). Negative control sections (Panels C and E) were incubated with a nonrelevant monoclonal antibody supplied by the manufacturer (Dako). In addition, control sections of an inactive pituitary adenoma showed no growth hormone immunoreactivity (data not shown).

or the two other lymphomas. The patient's lymphoma secreted only pituitary growth hormone and no placental growth hormone. GHRH was not detected in any sample of culture medium.

### DISCUSSION

Ectopic secretion of growth hormone has been suggested by the *in vitro* detection of immunoreactive growth hormone in some endocrine and non-endocrine tumors.<sup>16-22</sup> However, most reported cases have not met the criteria for the diagnosis of ectopic growth hormone secretion<sup>5</sup>: marked arteriovenous gradients of serum growth hormone concentrations across the ectopic source, cure of acromegaly after the removal of the tumor, and evidence of the expression of growth hormone gene by tumor tissue. We evaluated a patient with acromegaly due to the secretion of growth hormone by a non-Hodgkin's lymphoma. That the patient's lymphoma produced and secreted growth hormone was demonstrated by the decrease in serum growth hormone concentrations during chemotherapy, the presence of growth hormone mRNA and growth hormone immunoreactivity in tumor cells, and the secretion of growth hormone by tumor cells *in vitro*. GHRH mRNA or protein was not detected. Magnetic resonance imaging of the pituitary did not reveal somatotroph hyperplasia, a feature of ectopic GHRH secretion, and selective venous sampling did not reveal a pituitary-to-peripheral gradient in serum growth hormone concentrations.

Ectopic hormone secretion is a typical feature of neuroendocrine tumors and many others. Although we are not aware of other cases in which there was ectopic growth hormone secretion from the lymphatic system, a growing body of evidence suggests that growth hormone is a paracrine growth factor within the immune system.<sup>23</sup> The hormone has immunomodulatory properties, is required for development and function of the immune system,<sup>24-26</sup> and has a profound influence on both cellular and humoral immunity.<sup>22</sup> For example, the secretion of thymulin, a hormone produced by thymic epithelial cells, is up-regulated by growth hormone.<sup>27</sup> In aging rats, the administration of growth hormone increased the total number of thymocytes.<sup>28,29</sup> Normal lymphocytes have receptors for growth hormone,<sup>30,31</sup> and both rodent and human mononuclear cells synthesize and secrete growth hormone-like molecules.<sup>32-35</sup> Growth hormone mRNA has been detected in normal lymphoid tissues and in B-cell and T-cell lymphomas.<sup>36</sup> These findings support the concept of an autocrine or paracrine effect of growth hormone produced by the lymphoma cells on tumor proliferation. In this context, so-called ectopic growth hormone production by the lymphoma is not genuinely ectopic but, rather, a modification of normal cell function.<sup>37</sup>

The mechanisms by which growth hormone gene expression was up-regulated in the patient's lympho-

ma are not known. Amplification of the growth hormone gene locus or chromosomal translocation causing gene rearrangement or mutations in the growth hormone promoter could have contributed to the hypersecretion of growth hormone by the lymphoma. The majority of malignant lymphomas express somatostatin receptors and can be visualized by pentetreotide scintigraphy.<sup>38,39</sup> In our patient, the pentetreotide scan was negative, despite the extensive lymphoma. In addition, the patient's serum growth hormone concentrations did not decrease after the administration of octreotide. The absence of the expression of somatostatin receptors may have contributed to growth hormone excess because of the lack of inhibitory effects of endogenous somatostatin.

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