Acromegaly and Large Cell Lymphoma

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Acromegaly is a disorder characterized by an increased pituitary production of growth hormone (GH). Many of the clinical manifestations are produced by GH-dependent factors, such as somatomedin C or insulin-like growth factor I (IGF-I) [1]. These peptides have insulinlike activity, being able to stimulate cell growth in many tissues and are implied in tumor pathogenesis [2]. Acromegaly is associated with an increased risk of cancer [3]. GH appears to stimulate the development of plasma cell tumors and lymphosarcoma in mice [4] and multiple myeloma has been described in patients with acromegaly [5].

We report the association between acromegaly and large cell lymphoma. A 58-year-old man was referred for evaluation and treatment of acromegaly. He had a history of active acromegaly of 13 years. Since the patient refused to undergo surgery, he was treated with bro-mocriptine and pituitary irradiation (5,100 rad). High GH levels and a noninvasive pituitary microadenoma persisted. Three years after radiotherapy a nontender tumor beneath the right zygomatic arch was discovered. A CT scan revealed the presence of a round formation in the right maxillary sinus that produced a rupture of the floor of the orbit and the inferior sinus wall and invaded neighboring structures. The tumor was resected by transorbital surgery and a large cell lymphoma was diagnosed by histology. Other lymphoma foci were looked for, but none were found.

Eighteen months later, when he was first seen again at our hospital, he still had clinical symptoms of active acromegaly, increased GH plasma levels (38 ng/ml) and increased IGF-I plasma levels (9.56 IU/ml; normal 0.28-2.07 IU/ml). There was no evidence of recurrence of the lymphoma. Despite irradiation, the immunological evaluation showed normal levels of total T lymphocytes in the blood (1,104/mm³) and their subpopulations (720 CD4+ lymphocytes/mm³ and 208 CD8+ lymphocytes/mm³) and a somewhat elevated value of B cells (320 surface Ig+ lymphocytes/mm³), without evidence of clonality. Serum interleukin 1 (IL-1), IL-4 and IL-6 were increased (540, 300 and 80 pg/ml, respectively – normal values are undetectable), and tumor necrosis factor was not detected (< 1.8 pg/ml).

These findings suggest an association between acromegaly and a large cell lymphoma. It is interesting to speculate about the cause of the large cell lymphoma in this patient, and its unusual localization. Human GH promotes the growth of bone, muscle and other tissues [1] and may

also stimulate the proliferation as well as the transformation of normal and leukemic human lymphocytes in vitro [6]. The role of GH in the modulation of the immune response has been reviewed [7]. The detection of the corresponding mRNA and immunoreactivity has established the production of GH and IGF-I by lymphocytes. The presence of GH and IGF-I receptors on normal human lymphocytes and on human lymphoblasts has been reported [8]. GH acting either directly or indirectly has been implied in the process of acute lymphoblastic leukemia [9, 10]. It is noteworthy that in our patient the large cell lymphoma developed after radiotherapy for the pituitary GH-secreting adenoma. It is possible that GH or GH-dependent factors may influence the development of lymphomas after radiation injury.

Several cytokines are able to stimulate the proliferation of B lymphocytes, including IL-1, IL-4 and IL-6 [11]. The detection of these cytokines in the serum of the patient after there was no longer evidence of lymphoma, but still active acromegaly, suggests that GH (or GH-associated factors) probably could have been implicated in their production. Consistent with this hypothesis, we found IL-6 in the serum of most acromegalic patients [unpubl. data]. The hypothetical participation of B-promoting cytokines in the immunopathology of lymphoma has been postulated and currently needs to be investigated. On the other hand, large cell lymphomas have been reported in immunosuppressed patients, such as organ transplant recipients [12]. Recently, we reported that patients with active acromegaly presented a decreased B cell function [13, 14].

Certain conditions such as age (> 50 years), long duration of disease (> 10 years), and the number of skin tags (> 3) appear to be positive predictors of colonic neoplasia in patients with acromegaly [2]. Interestingly our patient presented all three conditions. It is tempting to speculate that these markers, considered to be specific for the development of colonic neoplasia, should perhaps be considered risk factors for any type of neoplasia. Further studies are needed to clarify this situation.

Three other cases of lymphomas/leukemia have been reported in patients with acromegaly [15]. Bengtsson et al. [15] do not specify the type of the lymphoma or the relationship to previous radiation. The development of meningiomas after radiotherapy for pituitary GH-secreting adenomas has been reported in patients with active acromegaly. It appears that the incidence of intracranial tumors in acromegaly is only increased in association with radiotherapy [3]. In summary, our report adds evidence of the increased risk of developing neoplasia in patients with acromegaly. This suggests that GH, acting directly or indirectly, may be involved in the process of tumorigenesis. Moreover, GH could potentiate the action of other transforming agents, such as irradiation. The need to achieve an absolute biochemical cure, and maintain a long-term follow-up after radiotherapy in order to prevent the various complications associated with acromegaly is highly recommended.

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