Acromegaly Associated with Leukemia: A Case Report

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\textbf{Introduction}

Acromegaly, a clinical syndrome caused by increased levels of growth hormones,\textsuperscript{1} has an incidence of 3-4 per one million people each year, the patients being aged between 40-45 years at time of diagnosis.\textsuperscript{2,3} The most common cause of acromegaly is increased secretion of growth hormone from the pituitary somatotrop cells. Usually there is about a 12-year interval between the appearance of symptoms and diagnosis.\textsuperscript{4} This kind of pituitary adenoma is usually benign, and in 75\% of the patients it is a macroadenoma.\textsuperscript{5} Some of the clinical findings in these patients are enlargement of distal endings, coarse face, large nose, increased dental spaces, joint diseases,\textsuperscript{6} increased bone density,\textsuperscript{5} cardiovascular disorders including cardiomyopathy,\textsuperscript{7} heart failure,\textsuperscript{7,8} pituitary insufficiency,\textsuperscript{5} voice changes, hirsutism,\textsuperscript{5} enlarged visceral organs including the prostate,\textsuperscript{9} and increased incidence of some benign lesions, including uterine leiomyoma,\textsuperscript{10} and polyps in colon.\textsuperscript{11-13}

Manifestations of soft tissue overgrowth include macroglossia, deepening of the voice, and paresthesias of the hands due to carpal tunnel syndrome.\textsuperscript{14} It is also reported that acromegaly results in the increased chance of some cancers, including colon, stomach, esophagus, breast, and hematological malignancies\textsuperscript{13,15} with higher mortality than in the normal population. Some studies have shown
that increased growth hormone level is associated with increased chance of leukemia, and lymphoma. It is reported that there is a 3.2-fold increase in incidence of malignant tumors in patients with acromegaly. The best test for the diagnosis of acromegaly is the measurement of IGF-1 blood level, which differs in various age groups. In addition, the measurement of growth hormone, in particular its dynamic measurement, after glucose tolerance test is necessary for the documentation of the disease. Magnetic resonance imaging (MRI) and dynamic CT scan demonstrate the lesion in most cases.

Trans-sphenoidal resection of adenoma is the treatment of choice in patients with acromegaly. The goal of treatment is to normalize IGF-1 level, and to return growth hormone levels to less than 1 gr/mL after glucose tolerance test; in case this cannot be achieved, medical treatment and radiotherapy may also be considered.

Acute Lymphocytic Leukemia (ALL) is a malignant disorder originating in a single B or T lymphocyte progenitor. The proliferation and accumulation of blast cells in the bone marrow result in the suppression of hematopoiesis and thereafter anemia, thrombocytopenia and neutropenia. The disease is most common in children, but can occur at any age. The relative lack of therapeutic success in adult ALL patients corresponds to a high frequency of cases with unfavorable genetic lesions, such as the BCR-ABL oncogene resulting from the rearrangement of the chromosomes 9 and 22. BCR-ABL expression is associated with an extremely poor prognosis in ALL patients despite treatment using contemporary protocols for high risk disease.

Case Report

In February 2006, a 61 year old man referred to Shahid Beheshti University Hospital of Kashan University of Medical Sciences (KAUMS) for bleeding from a pilonidal cyst and pancytopenia; his history showed admission to hospital for chest pain two months before referring. He received two units of blood for his pallor. He also complained of sweating in upper trunk, weakness, easy fatigability, and bone pain. He had been diagnosed with diabetes since three years, and was on oral medications. He was smoking 40 cigarette packs/yr. He had also had several admissions in the past few months for his heart problem, and bleeding. He appeared very sallow, with pale conjunctivae, and had typical acromegalic features, including prognatism, increased dental spaces, large nose (Fig. 1), broad fingers and toes. He had two skin tags at 6 and 12 o’clock on anus and 5 on neck and upper thoracic region. His liver span was 13 cm, but no splenomegaly, petechia, purpura, or ecchymosis were detected. Lungs were clear. A systolic murmur grade 2/6 was audible.

Fig.1. Photograph of the patient shows acromegalic features such as prognatism, increased dental spaces and large nose

Lab data on admission included: WBC: 2700 μl; Hb:9.6 g/dL; plt:16000 μL; FBS:417 mg/dL. His IGF-1 was 376 ng/mL normal values 78-258 for 50-70 year olds. His random growth hormone level was 75 ng/mL which two hours after glucose tolerance test was 20 ng/mL. A brain CT scan revealed a huge pituitary macroadenoma (Fig. 2).
Analysis of bone marrow aspiration and bone marrow biopsy specimens showed diffuse infiltration of bone marrow with immature cells with heterogeneity in cell size and shape (Fig. 3) with fine chromatin, nuclear indentation and basophilic cytoplasm, a picture more compatible with L2 subtype of acute lymphoblastic leukemia. In flowcytometric analysis, these cells had CD10 and CD19 antigens on the cell surfaces; hence results of aspiration and biopsy of bone marrow and flowcytometric analysis confirmed the diagnosis of Acute Lymphoblastic Leukemia (ALL) pre B cell type. Cytogenetic study of bone marrow aspiration revealed the translocation of 9 and 22 or Philadelphia chromosome (Fig. 4). After two courses of induction chemotherapy the patient attained complete remission; he however refused surgical treatment for his pituitary adenoma, and was hence treated with octreotide, and left the hospital in a good condition.

Discussion
Although the role of growth hormone is well documented in some benign, as well as malignant processes such as uterine tumors, adenomatous polyps in colon, cancers of colon, stomach, esophagus, and breast, there is limited data available regarding this effect in hematological neoplasms. Cohen reported uterine leiomyoma in 81 per cent of patients with acromegaly. Velmhogen reported a five fold increase in adenomatous polyps of colon in comparison to normal populations. This premalignant lesion is seen in 30 per cent of acromegalic patients. It is reported that the stimulating effect of growth hormone results in the increased incidence of colonic
Adenocarcinomas.\textsuperscript{11-13} One study from Hong Kong reported two cases of leukemia in 106 acromegalic patients in a 15-year follow up period; one of the patients had ALL while the other had Acute Myeloblastic Leukemia (AML), suggesting a synergistic effect for growth hormone in the occurrence of leukemia.\textsuperscript{24} Popovic also has reported that in comparison with nonfunctional adenomas and prolactinoma, acromegalic patients are more involved in such diseases as Hodgkin lymphoma, ALL, AML, and thyroid, ovarian, breast, uterus, skin, pancreas, bladder, kidney, and colorectal cancers; he also reported three patients with two cancers, who had 3.39 times more risk of malignant tumors when compared with the normal population.\textsuperscript{25} Frandkin studied the effects of growth hormone in those treated for its deficiency and found that there is a 1.8% increased incidence of leukemia in these patients.\textsuperscript{26} The initiation and progression of ALL is driven by successive mutations that alter cellular functions, including an enhanced ability of self renewal, a subversion of control of normal proliferation, a block in differentiation and an increased resistance to death signals or apoptosis.\textsuperscript{16,19} Many risk factors such as environmental factors, acquired genetic changes, genetic syndromes and alterations in host pharmacogenetics are known to be implicated in the induction of ALL in some patients but the relation of other risk factors with ALL needs to be explored.\textsuperscript{20} It seems that growth hormone with its proliferative and anti-apoptotic effects related to IGF-1 results in the increased incidence of malignant and non malignant diseases.\textsuperscript{17} These effects, as well as cardiovascular consequences of acromegaly, hence mandate surgical treatment of growth hormone secreting pituitary adenomas followed by appropriate medical treatment, and if needed radiotherapy. Also these patients should be thoroughly evaluated for occult malignancies.

On the basis of this report and a review of literature, acromegalic patients have an increased incidence of certain solid tumors and hematological malignancies. Therefore in addition to appropriate management of pituitary tumor, these patients must have regular follow ups and further evaluation for occult malignancies.

References
11. Renehan AG, Shalet SM. Acromegaly and colorectal cancer: risk assessment should be based on
12. Terzolo M, Reimondo G, Gasperi M, Cozzi R, Pi-
14. Jenkins PJ, Sohaib SA, Akker S, Phillips RR, Spil-
15. Delhougne B, Deneux C, Abs R, Chanson P, Fie-
rens H, Laurent-Puig P, et al. The prevalence of co-
lonic polyps in acromegaly: A colonoscopic and pathological study in 103 patients. J Clin Endocri-
16. Puic H, Relling MV, Downing JR. Acute lymphob-
17. Baris D, Gridley G, Ron E, Weiderpass E, Mel-
lemkjaer L, Ekbom A, et al. Acromegaly and can-
19. Gilliland DG, Tallman MS. Focus on acute leuke-
21. Hoelzer D, Gökbüget N, Ottmann O, Pui CH, Rel-
ling MV, Appelbaum FR, et al. Acute lymphobla-
23. Fletcher JA, Lynch EA, Kimball VM, Donnelly M, Tantravahi R, Sallan SE. Translocation (9;22) is associated with extremely poor prognosis in inten-