The Prostate 10:19–24 (1987)

Complete Response of Lung Metastases Caused by Prostatic Cancer After Chronic Administration of a Gonadotropin-Releasing Hormone Analog, Buserelin (HOE 766)

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A stage D_2 prostate cancer patient with biopsy-proven lung metastases and negative work-up for metastases is discussed. Treatment consisted of hormonal therapy in the form of chronic administration of an analog of gonadotropin-releasing hormone (GnRH-A), Buserelin, with follow-up for 24 months. The complete response of the patient to GnRH-A therapy provides an interesting and unusual case in the understanding of the biological behavior of prostate cancer.

Key words: LHRH, pulmonary metastasis, soft tissue metastases, cancer, prostate, stage D_2, Gn RH-A

INTRODUCTION

Stage D_2 prostatic cancer is a designation assigned to patients with histologically proven adenocarcinoma of the prostate and clinically proven distant metastatic disease. Although the vast majority of metastatic disease is found in bones, after the lymphatics, the lungs are the most common site of soft tissue lesions [1]. Pulmonary metastases caused by prostatic cancer are usually the findings of already widely disseminated disease in the skeleton [2,3]. There have been a few reported cases where metastatic soft tissue disease was found only in the lungs and without evidence of bony disease [4–7]. Interestingly, all these cases were associated with a positive response to hormone manipulation (orchiectomy and/or estrogens) and with long patient survival.

This report describes a patient, with metastatic prostate cancer detected only in the lung, who shows complete and long-term remission on treatment with Buserelin GnRH-A.

CASE REPORT AND METHODS

A 71-year-old white male was hospitalized in June 1983 with obstructive urinary symptoms. He had complained of obstructive symptoms for 1 year prior to admission

Received October 23, 1985; accepted May 9, 1986.

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and had a progressive deterioration of his obstructive symptoms in the latter months. No hematuria was reported.

Medical history included varicose vein stripping (1975), a right renal mass found on ultrasound to be a cyst (1981), and well-documented coronary artery disease. Physical examination was unremarkable except for mild obesity with no abdominal masses and a rock hard, large, irregular prostate gland. Hemogram and SMA-16 were within normal limits. Prostatic acid phosphatase (PAP) by radioimmunoassay (RIA) was elevated to 20 ng/ml (normal range 0–4.6), chest X rays showed evidence of two or three small nodules believed at the time to be granulomata. A bone scan and metastatic bone survey showed no evidence of metastatic disease. A CAT scan showed no adenopathy in the pelvis or in the abdomen, but it confirmed the presence of an irregular and large prostate. On June 20, 1983, he underwent a transurethral resection of the prostate (TURP). Pathological examination of the specimen revealed moderately differentiated adenocarcinoma with areas showing an endometrioid pattern. His obstructive symptoms improved, and he was followed bimonthly with clinical and radiological evaluation of the suspicious pulmonary nodules. In February 1984, changes were noted on chest X rays, with multiple nodular densities throughout both lungs, suggestive of metastatic disease (Fig.1). The patient was readmitted to the hospital, and on March 3, 1984, he underwent an open lung biopsy, which showed metastatic adenocarcinoma, consistent with a prostatic primary. Liver and spleen scans at the time were normal, and the work-up for metastatic bone disease was again negative. Alkaline phosphatase was normal, and the PAP by RIA was found again to be elevated 22 ng/ml.

On March 15, 1984, the patient began therapy in the form of Buserelin. He received an injection of 500 μg subcutaneously every 8 hours, daily, for 7 days, and then was switched to 3 $\times$ 400 μg daily, treatments given intranasally. Buserelin (HOE 766) was provided by Hoechst Pharmaceuticals Canada Inc. The protocol used has been approved by the McGill Ethics Committee and the Canadian Health Protection

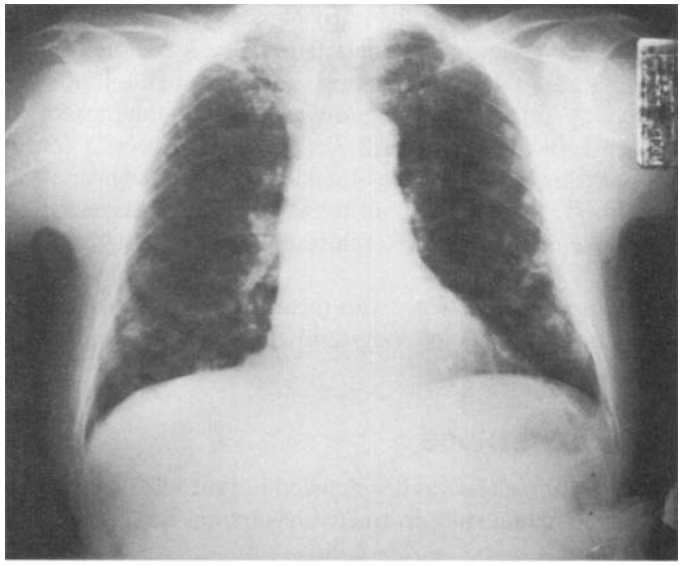

Fig. 1. Status of lung metastatic disease before the initiation of Buserelin treatment.

Branch. Hormone measurements were done by standard radioimmunoassays. The size of the prostate was evaluated by transabdominal ultrasound [8]. Response to treatment was evaluated according to the criteria established by the National Prostatic Cancer Project (NPCP). The patient was seen every week for the first month and every 2 weeks for the second month and subsequently at monthly intervals.

Prior to therapy, and thereafter, the follow-up consisted of hematological, biochemical, hormonal, radiological, nuclear imaging, CAT scan, and tumor marker evaluations performed every 1 to 3 months. Plasma testosterone (T) was measured at weekly intervals for the first month, biweekly during the second month, and monthly thereafter.

RESULTS

Hormonal Data

Plasma testosterone (T), estrone (E), and estradiol (E_2) levels significantly decreased after Buserelin treatment. After the sixth week, plasma T, E, and E_2 levels fluctuated within castrate limits. That is, T dropped from 650 to 80 ng/dl by the sixth week, E dropped from 3.8 to 1.1 ng/dl, and E_2 dropped from 3.1 to 0.9 ng/dl; castrate values for T, E, and E_2 were $\leqq$ 100, $\leqq$ 1.5, and $\leqq$ 2 ng/dl, respectively.

Patient Response

The patient's urinary symptoms improved remarkably after the TURP (June 1983), but he remained symptomatic. Three months following initiation of Buserelin treatment the patient's urinary frequency disappeared.

Radiological Findings

Both the size and the number of pulmonary metastatic foci reduced significantly within 2 months. Eight months later metastatic disease had disappeared (Fig. 2). Evaluation in February 1986 with plain films and tomograms showed complete lung clearance. Radiological and nuclear imaging as well as CAT scan reevaluation remained negative for metastatic disease. Transabdominal ultrasound demonstrated a progressive decrease in the size of the postprostatectomy prostate, and at last assessment the prostate was reported as undetectable ultrasonically and by rectal examination.

Enzyme Markers

Alkaline phosphatase has remained within the normal range throughout follow-up. PAP levels normalized within 2 months after treatment and have continued in the normal range.

Clinical Response

The patient experienced a complete clinical response. Lung metastases disappeared, PAP levels normalized, and the prostate is clinically undetectable by ultrasound and CAT scan.

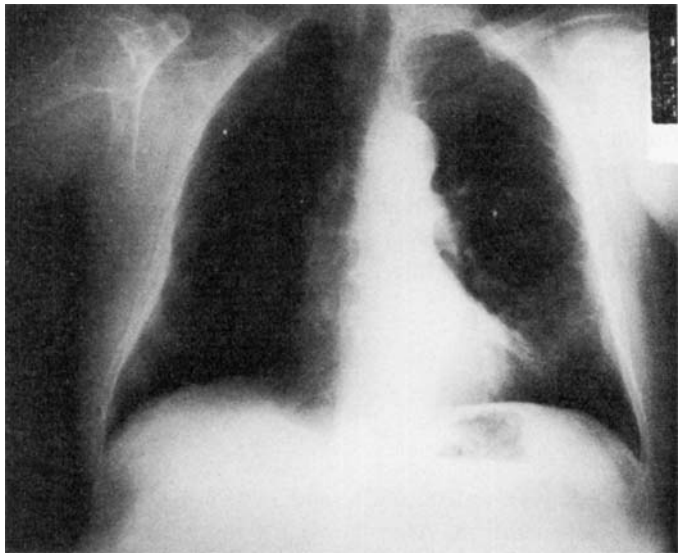

Fig. 2. Clearance of metastatic nodules from the pulmonary fields within 8 months of treatment with Buserelin.

Side Effects

The patient complained of hot flushes and loss of libido. Hot flushes began 4 weeks after treatment, and they were reported as severe between the third and ninth months of follow-up. Since then the patient has complained of mild hot flushes on an irregular basis. Complete loss of libido was reported 1 week after Buserelin treatment began.

DISCUSSION

The vast majority of metastatic prostatic cancers present in the form of osteoblastic and/or osteolytic bony metastases. Other than the lymphatics, the most common soft tissue metastatic site is the lungs. It is unusual to find multiple pulmonary metastatic disease in the absence of any other detectable disease either in soft tissue sites or in bones. This report documents an infrequent case that has been treated successfully with an LHRH super agonistic analog, Buserelin.

There has been a recent report of complete response of pulmonary metastatic sites in patients with demonstrated skeletal metastatic disease responding to D-tryptophane G LHRH analog [9]. However, long-term follow-up, remission, and survival data are not reported.

According to previous reports [3–7], pure lung metastases, as in the present case, are always associated with a dramatic and complete response as well as long-term patient survival following estrogen therapy or castration. This is strikingly different from that observed in stage D_2 patients with bone involvement with or without lung metastases, where survival is generally poor [3,10–15], although a satisfactory initial response is seen in approximately 80–90% of cases [10,12,14,15–18]. This may indicate that tumor subclones responsible for the lung metastatic sites

are biologically different from those found in the bones. This is in agreement with current concepts regarding tumor heterogeneity [19-22].

Recently, considerable attention has been focused on whether or not tumor responsiveness and escape from therapy is determined by heterogeneous nature of tumor cell subclones [22,23]. In the case of prostatic cancer, responsiveness and relapse from hormonal therapy have been explained by either the preexistence of hormonally responsive and unresponsive cells or the evolution of nonresponsive cell clones during treatment [24,25]. There is increasing evidence to support the former concept [26]. In addition, the identification of variables that may define clinically the behavioral pattern of cell subclones would improve the accuracy of predictions on hormonal responsiveness and long-term patient survival [14,15]. Presumably, the explanation of complete response to therapy described in this case is due to the existence of only hormone-sensitive cell subpopulations.

We have presented an unusual case of well-documented prostatic metastatic disease confined to soft tissue that has had a complete response at the metastatic site, as well as the primary tumor now lasting more than 2 years. This case serves to illustrate some aspects of the poorly understood variable biological behavior patterns of cell lines found in prostatic adenocarcinoma.

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