

## Paradoxical response of prostate cancer skeletal metastases to androgen deprivation therapy

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We report a marked geographically inconsistent response of prostate cancer skeletal metastases to androgen deprivation therapy. Such inconsistent response to therapy has not been described previously in the literature and should be correlated with individual patient history. Further understanding of the mechanism of geographic responses to hormone deprivation therapy may have implications in the targeting of specific regions of disease for treatment in the future.

### Case report

The patient is an 84-year-old male with a history of prostate carcinoma. At the time of diagnosis, he had a Gleason sum of 5 and received radioactive seed brachytherapy. Due to subsequent biochemical failure (rising PSA) approximately eight years later, he presented for a nuclear medicine bone scan, which showed diffuse osteoblastic metastatic skeletal disease (Fig. 1). The patient was started on luteinizing hormone-releasing hormone (LHRH) agonist and antiandrogen therapy at that time and returned for a followup bone scan approximately six months after initiation of continuous hormone deprivation therapy (Fig. 2).

For both the pretherapy and post-therapy bone scans, the patient was injected intravenously with approximately 25 mCi of Technetium-99m MDP. Anterior and posterior planar images of the body were obtained four hours after injection. The pretherapy bone scan showed multiple areas of intense focal radiotracer uptake consistent with osseous metastases including the sternum, multiple bilateral ribs, multiple levels of the thoracic and lumbar spine, bilateral iliac bones, acetabula, sacrum, and left superior pubic ra-

mus. Intense focal uptake in the glenoid of bilateral scapula was also suspicious for metastatic involvement. Increased uptake at the left knee joint and medial knee compartment on the right was most likely related to degenerative change.

The post-therapy bone scan revealed a remarkable mixed pattern of interval change. The majority of identified foci of intensely increased uptake throughout the upper thoracic spine demonstrated considerable interval decrease in intensity and extent along with concordant decrease in intensity and extent of multiple foci of increased uptake involving the anterior and posterior upper ribs bilaterally.

In contrast to the above findings, there was interval progression of foci of increased uptake involving the lower ribs bilaterally, lower thoracic spine, lumbar spine, and pelvis, including significant interval progression involving the sacrum, right iliac bone, and right ischium; and significant interval increase in intensity and extent of uptake involving the right acetabulum and surrounding pelvic bones. In addition, there was interval progression of increased uptake involving the left acetabulum and surrounding pelvic bones. There was interval development of three new foci of increased uptake involving right femoral neck, right lesser trochanter, and right proximal medial femoral shaft. Again there were findings suggestive of degenerative disease involving the knee joints bilaterally.

In summary, when compared to the pretherapy bone scan, the post-therapy bone scan demonstrated an overall mixed pattern of interval change, with significant interval improvement involving the upper thoracic spine and upper ribs bilaterally in contrast to significant interval progression in the lower thoracic spine, lumbar spine, pelvis, and right femur, as described in detail above.

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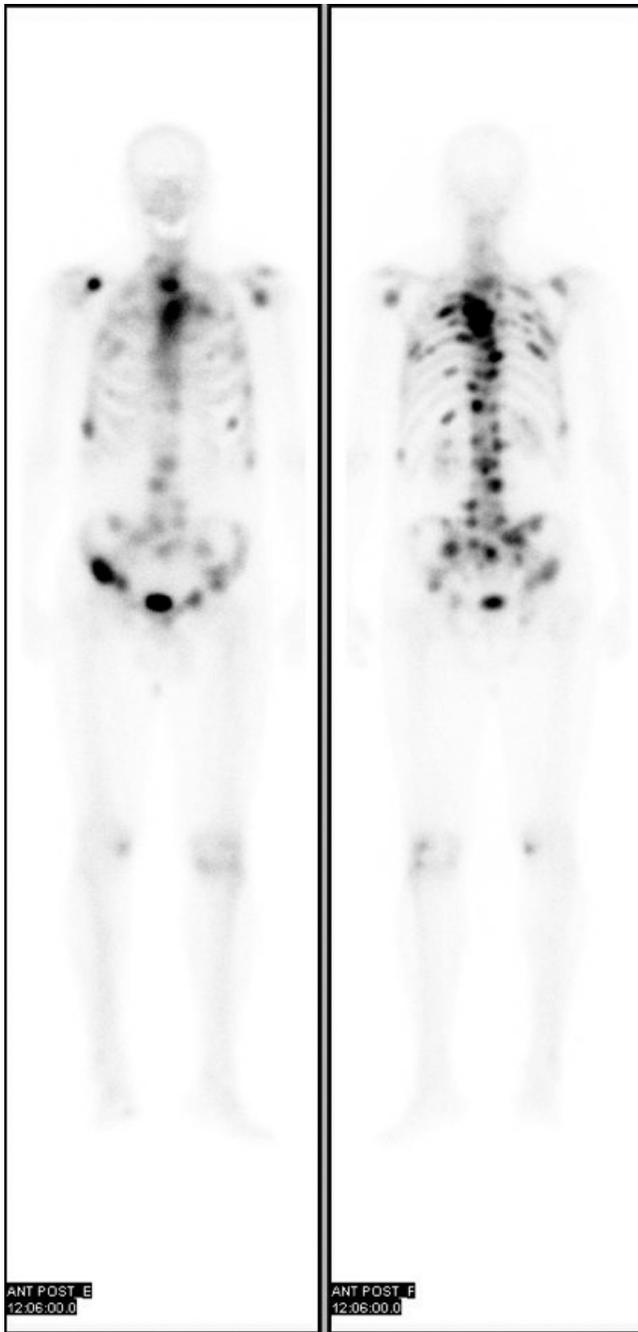


Figure 1. 84-year-old male with prostate cancer. After rising PSA, nuclear medicine bone scan shows diffuse disease metastatic to the skeleton. The left image shows the anterior projection, and the right image shows the posterior projection.

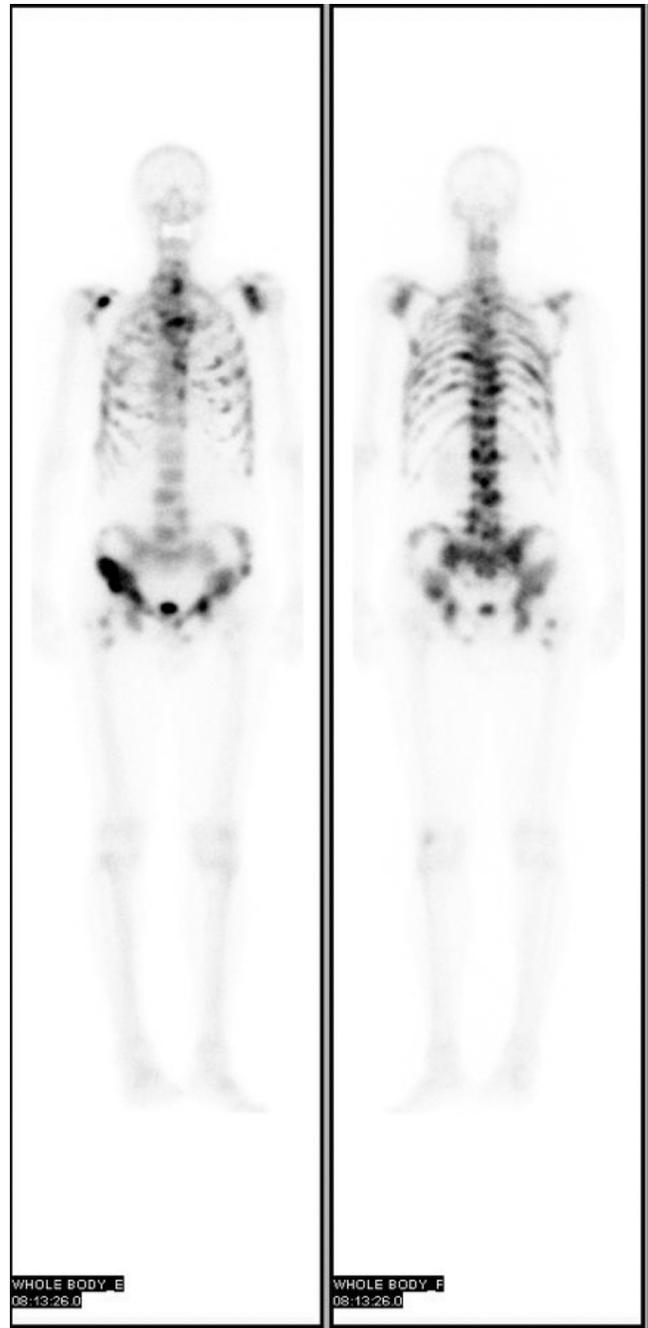


Figure 2. 84-year-old male with prostate cancer. Nuclear medicine bone scan approximately six months after continuous hormone deprivation therapy demonstrates a mixed pattern of improvement and progression of skeletal metastases. Improvement of skeletal metastases is best appreciated in the upper thoracic region. The left image shows the anterior projection, and the right image shows the posterior projection.

### Discussion

Bone is one of the most common sites of metastasis from prostate cancer, and bone metastasis greatly affects the quality of life and prognosis of patients with prostate cancer. Androgen deprivation therapy (ADT) is a mainstay of prostate cancer management for patients with evidence of systemic disease (1). ADT consists of gonadotropin-releasing hormone (GnRH) agonist administration (typically, intramuscular leuprolide or subcutaneous implanted goserelin) with or without an antiandrogen (bicalutamide, flutamide, or nilutamide) or, less commonly, bilateral orchiectomy (2, 3). All current forms of androgen deprivation function by reducing the ability of androgen to activate the androgen receptor, whether through lowering levels of androgen or by blocking androgen-androgen receptor binding.

Without a detailed patient history, we initially postulated that the interval improvement of metastatic skeletal disease in the upper thoracic spine and upper ribs bilaterally in contrast to significant interval progression in the lower thoracic spine, lumbar spine, pelvis, and right femur could represent radiation therapy (port) to the upper chest. Upon confirmation, the patient had not received radiation therapy, but only LHRH/antiandrogen treatment since the pretherapy bone scan. We did confirm that the patient had a long sports career as a baseball pitcher and still actively pitches. With androgen receptor function shown to be essential for androgen effects on the male skeleton in murine models and humans (4, 5), we hypothesize that the patient's increased repetitive use of the upper extremities during his pitching career has possibly increased vascularity to the upper thorax and allowed for better delivery of antiandrogen agent to the upper thoracic skeleton relative to the rest of the body. This might explain the contradictory improvement of metastatic disease in the upper thorax versus progression of metastatic disease elsewhere in the body.

Alternative explanations for the discrepant response to therapy seen in this patient may be the transformation of certain regions of disease to an androgen-independent/hormone-refractory tumor that no longer responds to standard hormone deprivation therapy, or preferential healing of certain metastatic sites for other unexplained reasons. If indeed this patient's paradoxical response to therapy represented transformation to androgen-independent prostate cancer, alternative treatments including docetaxel may be indicated; however, the reason for such geographic transformation of tumor must be further investigated (6). In addition, it has been recognized that a bone scan to determine treatment efficacy in patients with prostate cancer and bone metastases should be performed after a minimum of three months (7). Because bone scans assess changes in the bone itself and not the tumor directly, it is possible that an apparent false pattern of worsening (flare phenomenon) may reflect healing response of bone and not true progression of disease. In our patient, the post-therapy bone scan was obtained at six months, making flareup less likely.

To our knowledge, this is the first study to report such significant contradictory change of prostate cancer bone metastases on bone scan following hormone deprivation therapy. Further understanding of the mechanism of geographic responses to hormone deprivation therapy may have implications in targeting specific regions of disease for treatment in the future. Perhaps tagging a monoclonal antibody (such as that used in ProstaScint imaging) with a radioactive isotope such as Yttrium-90 or Iodine-131 (similar to the concept of Bexxar and Zevalin) may be helpful in treating patients who do not respond to ADT. The delivery of antiangiogenesis agents via a similar method may also be more effective in treating metastatic disease that does not respond to initial hormone deprivation therapy.

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