An elusive tumor in a man who has evidence of prostate cancer metastasis

Conventional imaging studies failed to locate the metastasis in a patient with a rising PSA level. A tumor in the lung was found using scintigraphy with capromab pendetide.

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CASE

A 65-year-old man presented for consultation because his prostate-specific antigen (PSA) level was elevated. The patient's medical history is significant for a radical retropubic prostatectomy 11 years ago. Before the surgery, the patient's serum PSA level was 3.0 ng/mL. Adenocarcinoma of the prostate was diagnosed by biopsy. The pelvic lymph nodes were negative at the time of the surgery; therefore, the disease was determined to be confined to the prostate. Pathology confirmed stage II adenocarcinoma with a Gleason score of 3+3. The patient's serum PSA was subsequently undetectable; he was lost to follow-up for several years. When the patient returned in 2002, his PSA level was 0.2 ng/mL. The following year, it had increased to 0.3 ng/mL, and in 2005, it was 1.9 ng/mL. One month before this consultation, the patient's PSA level was 9.4 ng/mL. At this visit, the PSA level was 10.56 ng/mL. The patient had no symptoms other than erectile dysfunction, a common side effect of prostatectomy. He had no new areas of bone pain and no new respiratory, GI, genitourinary, or neurologic complaints.

CT with contrast of the pelvis and abdomen showed no obvious evidence of metastatic disease. A whole-body bone scan displayed some osteoarthritic changes but no definitive evidence of metastasis. Immunoscintigraphy with capromab pendetide (ProstaScint), a murine monoclonal antibody that reacts with prostate-specific membrane antigen (PSMA), was ordered. A low level of reactivity was seen in the prostatic fossa, but it was less intense than would be seen in recurrent disease. No reactive adenopathy or evidence of bony metastatic disease was apparent. However, focal radiotracer reactivity appeared in the upper lobe of the left lung (**Figure 1**). Chest CT revealed a spiculated lesion measuring 2.8 cm in diameter. The nodular density resembled a primary lung carcinoma; however, the lesion's location correlated with the area of reactivity seen on the scintigram (**Figure 2**). Biopsy confirmed that the tumor was a prostate cancer metastasis, which was surgically removed in October 2006. The margins of the excision were negative, but vascular channel invasion by carcinoma existed. Treatment with leuprolide (Lupron) injections for systemic metastasis of prostate cancer was initiated.

One month after resection of the lung tumor, the patient's PSA level was 2.06 ng/mL, and it continued to decrease. Follow-up serum PSA levels were 0.07 ng/mL in March 2007 and 0.16 ng/mL in June 2007. At this time, the patient chose to proceed with pulse hormonal therapy. In September 2007, the patient's PSA level had increased to 2.19 ng/mL. He continued to experience erectile dysfunction and noted having hot flashes, both of which were attributed to the hormone treatment. He had no other symptoms of metastatic disease.

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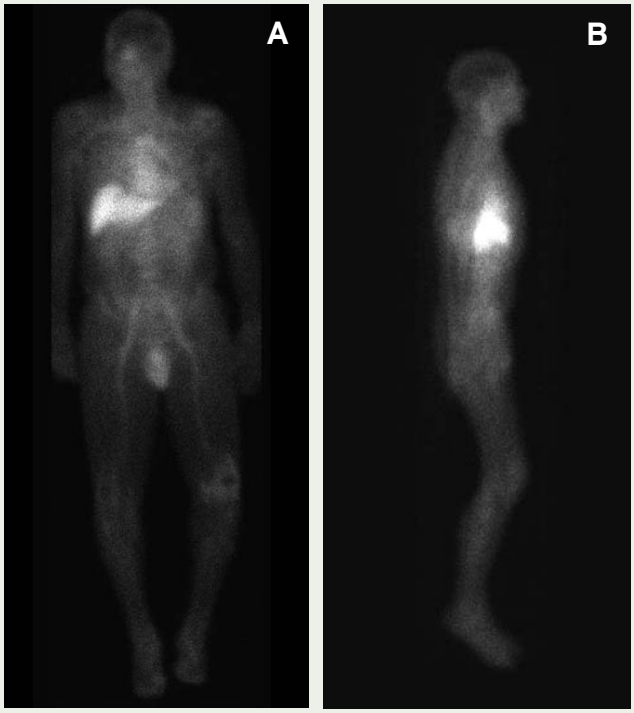

FIGURE 1. Varying levels of reactivity appear on immunoscintigraphy. Here, a low level is seen in the prostatic fossa but focal reactivity is seen in the upper lobe of the left lung (A, frontal view; B, lateral view).

"Radical prostatectomy is intended to be curative; in theory, PSA levels should decrease after surgery and remain undetectable."

DISCUSSION

Prostate cancer is the most prevalent cancer in men, with an estimated 186,320 new cases and an estimated 28,660 deaths in 2008.[1] Cancer deaths as a result of prostate cancer are second only to deaths resulting from lung malignancies. The lifetime risk of developing prostate cancer is more than 16%.[1] Radical prostatectomy, a common procedure for cases of localized prostate cancer, includes removal of the nearby lymph nodes as well as the prostate. The procedure is intended to be curative; in theory, PSA levels should decrease after surgery and remain undetectable. Unfortunately, a significant number of men have measurable serum PSA levels after primary treatment, a situation known as *biochemical recurrence*. Furthermore, clinical evidence of distant metastases develops within 10 years after radical prostatectomy in 15% of patients.[2]

An elevated PSA level after treatment is caused by local disease recurrence in the prostatic fossa or a distant metastasis. Locating the cancerous tissue is essential to determine whether treatment should be localized or systemic; however, tracking the source of an elevated PSA level can be a difficult task. Prostate cancer most often metastasizes to bone and pelvic lymph nodes. As such, CT of the pelvis/abdomen and radionuclide bone scan are commonly used modalities to find metastases, but these scans have limited usefulness.[3] Metastatic disease can occur in any tissue; therefore, it may not be found with these modalities. An autopsy study found evidence of metastasis to the lung in 46% of men with prostate cancer.[4] However, lung metastasis with no known bone or lymph node involvement is extremely rare and has been described in only a handful of case reports. Therefore, imaging studies of the lungs are usually not warranted when the findings on pelvic/abdominal CT and bone scan are negative and the patient has no respiratory symptoms.

PSMA is a protein expressed by both normal and malignant prostate epithelial cells. Imaging with capromab pendetide is indicated for biopsy-proven prostate cancer tumors that are thought to be clinically localized after standard radiographic evaluation (chest radiography, bone scan, CT, or MRI) and are at high risk of metastasizing to the pelvic lymph nodes. The imaging study is also indicated when PSA levels are elevated postprostatectomy, standard metastatic evaluation results are negative or equivocal, and occult metastatic disease is strongly suspected.[5]

Clinical trials of capromab pendetide assessed the performance of the imaging agent in two populations. The first study population was composed of patients with a new diagnosis of prostate cancer who had tissue confirmation and were considered to be at high risk for metastasis to the lymph nodes. These patients underwent immunoscintigraphy with capromab pendetide before staging via pelvic lymphadenectomy. Sensitivity was 62% and specificity was 72%.[5] In addition, positive predictive value (PPV) was 62%, negative predictive value (NPV) was 72%, and overall accuracy relative to histologic results was 68%.[5] The second study population included patients with high clinical suspicion of occult recurrent or residual disease after radical prostatectomy. Admission criteria included PSA level higher than 1.0 ng/mL, negative findings on bone scan within 8 weeks before the study, and a prostatic fossa biopsy scheduled for 8 weeks or less after administration of the monoclonal antibody. Patients with a PSA of 1.0 ng/mL or lower were included only if they had a history of increasing PSA level and suspicion of recurrent disease on digital rectal examination.[6] Using tissue confirmation from the prostatic fossa as the standard for comparison, yields for capromab pendetide were sensitivity, 49%; specificity, 71%; PPV, 50%; NPV, 70%; and overall accuracy, 63%.[5,6]

Other clinical studies of posttreatment populations reported various sensitivity, specificity, and accuracy results. A number of factors may be responsible for the different results among the studies, the lack of a perfect standard being foremost. Whereas histologic confirmation via biopsy offers high

TEACHING POINTS

- Radical prostatectomy, a common procedure for cases of localized prostate cancer, includes removal of the nearby lymph nodes as well as the prostate. The procedure is intended to be curative; in theory, prostate-specific antigen (PSA) levels should decrease after surgery and remain undetectable. Unfortunately, a significant number of men have measurable serum PSA levels after primary treatment.
- Prostate cancer most often metastasizes to bone and pelvic lymph nodes. CT of the pelvis/abdomen and radionuclide bone scan are commonly used modalities to find metastases but have limited effectiveness. Metastatic disease can occur in any tissue; therefore, it may not be found with these modalities. Lung metastasis with no known bone or lymph node involvement is extremely rare.
- The most common reactions to capromab pendetide included hypotension, hypertension, elevated bilirubin, and elevated liver enzymes. Less common effects included itching, stinging at the infusion site, fever, chills, headache, myalgia, chest pain, and shortness of breath. No deaths have been attributed to capromab pendetide administration. However, the monoclonal antibody is developed from mice; therefore, it is a foreign-body protein and patients may produce human antimouse antibodies. Although uncommon, this response can change the efficacy of future murine-based diagnostic and therapeutic procedures as well as increase the risk of adverse reactions.

specificity, sensitivity is limited by sampling error. In addition, scintigrams can be difficult to interpret and readings vary by radiologist.[7] Furthermore, PSMA expression has been seen in a variety of tissue samples, including normal tissue from the prostate, bladder, kidney, testis, ovary, fallopian tube, breast, adrenal gland, liver, esophagus, stomach, small intestine, and colon; and cancerous tissue from the bladder, kidney, testis, esophagus, stomach, small intestine, colon, adrenal gland, and lung.[8] Expression of PSMA in other tissues can decrease specificity. Conversely, some lines of prostate cancer do not express PSMA, potentially decreasing sensitivity.[9]

Despite the inconsistent results, immunoscintigraphy with capromab pendetide does offer clinicians an additional tool for planning treatment of prostate cancer. However, as with any medical test, the potential benefit must be weighed against the negative effects and financial cost. Adverse effects were reported in 4% of patients.[5] The most common reactions included hypotension, hypertension, elevated bilirubin levels, and elevated liver enzymes. Less common effects included itching, stinging at the infusion site, fever, chills, headache, myalgia, chest pain, and shortness of breath. No deaths have been attributed to capromab pendetide administration. However, the monoclonal antibody is developed from mice; therefore, it is a foreign-body protein and patients may produce human antimouse antibodies. Although uncommon, this response can change the efficacy of future murine-based diagnostic and therapeutic procedures as well as increase the risk of adverse reactions.[5,7] Although relatively safe, the cost of the scan is an estimated $2,500, and thus it may not be a cost-effective option for all patients.[7]

The role of immunoscintigraphy with capromab pendetide in the postprostatectomy population is to aid in finding the cause of an elevated PSA level. Bone scans are more sensitive for evaluating skeletal metastases; therefore, immunoscintigraphy with this agent should not replace bone scans in the evaluation of such lesions. Imaging with capromab pendetide is also not indicated for screening or assessment of response to treatment. Whereas immunoscintigraphy with capromab pendetide seems to be more effective at detecting residual or recurrent disease than CT, MRI, or positron emission tomography, direct comparisons of these more conventional imaging studies to immunoscintigraphy with capromab pendetide, using biopsy confirmation as the standard of comparison, are lacking. Current efficacy data do not provide convincing evidence for clinicians to comfortably trust this modality's findings.

> "Immunoscintigraphy with capromab pendetide is useful when no evidence of disease can be found with conventional imaging."

Given the metastatic patterns of prostate cancer, immunoscintigraphy with capromab pendetide should be considered only after bone scan and CT of the pelvis/abdomen are ineffective. No studies indicate that treatment plans should be based solely on capromab pendetide scan findings, therefore, use of conventional imaging studies first is the more cost-effective approach. However, as in the case of our patient, immunoscintigraphy with capromab pendetide can be invaluable when no evidence of disease can be found with conventional imaging studies. JAAPA

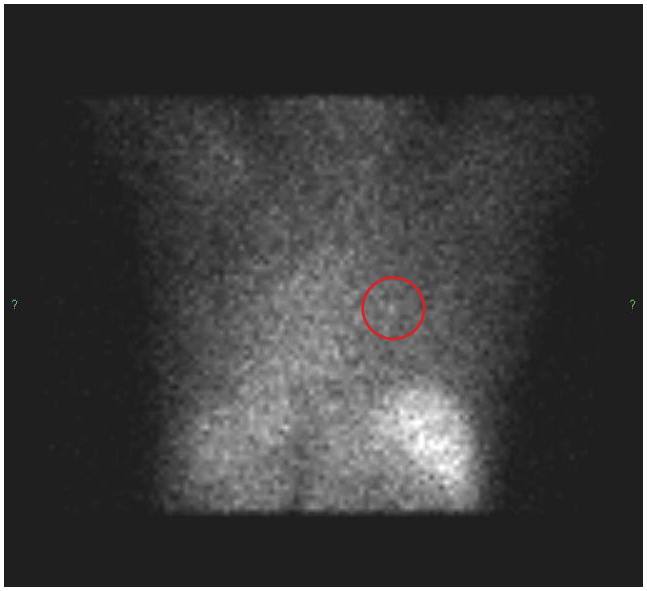

FIGURE 2. Immunoscintigraphy with capromab pendetide locates a metastatic lesion (red circle) in the left chest.

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REFERENCES

1. American Cancer Society. *Cancer Facts and Figures 2008.* Atlanta, GA: American Cancer Society; 2008.
2. Bill-Axelson A, Holmberg L, Ruutu M, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med.* 2005;352(19):1977-1984.
3. Kane CJ, Amling CL, Johnstone PA, et al. Limited value of bone scintigraphy and computed tomography in assessing biochemical failure after radical prostatectomy. *Urology.* 2003;61(3):607-611.
4. Bubendorf L, Schöpfer A, Wagner U, et al. Metastatic patterns of prostate cancer: an autopsy study of 1,589 patients. *Hum Pathol.* 2000;31(5):578-583.
5. ProstaScint Kit [package insert]. Princeton, NJ: Cytogen Corporation; 1997. http://www.prostascintimaging.com/assets/pdf/ProstaScintPI.pdf. Accessed July 13, 2009.
6. Kahn D, Williams RD, Manyak MJ, et al; The ProstaScint Study Group. ^{111}Indium-capromab pendetide in the evaluation of patients with residual or recurrent prostate cancer after radical prostatectomy. *J Urol.* 1998;159(6):2041-2046; discussion 6-7.
7. Howell T, Hailey D. *Use of In-111 Capromab Pendetide in Detecting Metastatic Prostate Cancer.* Edmonton, AB: Alberta Heritage Foundation for Medical Research; 1999. http://www.ihe.ca/publications/library/2005-and-earlier/use-of-in-111-capromab-pendetide-in-detecting-metastatic-prostate-cancer. Accessed July 14, 2009
8. Kinoshita Y, Kuratsukuri K, Landas S, et al. Expression of prostate-specific membrane antigen in normal and malignant human tissues. *World J Surg.* 2006;30(4):628-636.
9. Israeli RS, Powell CT, Corr JG, et al. Expression of the prostate-specific membrane antigen. *Cancer Res.* 1994;54(7):1807-1811.