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Case 30-2008: A 47-Year-Old Woman with a Mass in the Breast and a Solitary Lesion in the Spine

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Helen Anne D'Alessandro, M.D., and Kristina Braaten, M.D.

PRESENTATION OF CASE

From the Department of Medicine, Northwestern University, and the Feinberg School of Medicine (W.J.G.) — both in Chicago; and the Department of Radiation Oncology, Brigham and Women's Hospital, and the Dana-Farber Cancer Institute (J.R.B.); the Departments of Surgical Oncology (M.A.G.), Radiology (H.A.D.), and Pathology (K.B.), Massachusetts General Hospital; and the Departments of Radiation Oncology (J.R.B.), Surgery (M.A.G.), Radiology (H.A.D.), and Pathology (K.B.), Harvard Medical School — all in Boston.

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Dr. Barbara L. Smith (Surgical Oncology): A 47-year-old premenopausal woman came to this hospital for treatment of breast cancer.

The patient had been well until 8 months earlier, when she felt a lump in the upper outer quadrant of her left breast, near the 2 o'clock position. A diagnostic mammogram obtained at another hospital revealed two nodular densities in the left upper portion of the breast, close to the palpable abnormality. The same day, an ultrasonographic examination showed a cluster of cysts between the 12 o'clock position and the 1 o'clock position and a thick-walled cyst, 1.8 cm in diameter, between the 11 o'clock position and the 12 o'clock position, from which greenish black fluid was aspirated; the fluid was not submitted for microscopical examination. The patient did not return for the scheduled follow-up visit. Five months before the current evaluation, she returned to her primary care physician, who referred her to a surgeon. Approximately 2 months before the current evaluation, she saw the surgeon, who ordered a repeated ultrasonographic study. The study, which was performed 5 weeks later (3 weeks before the current evaluation), showed a suspicious solid mass. An ultrasound-guided core needle biopsy performed the same day showed invasive ductal carcinoma, grade 2, in four of four cores. Tumor cells expressed estrogen and progesterone receptors and did not overexpress HER2/neu. The patient was referred to a surgeon at this hospital.

The patient was nulliparous. Menarche had occurred at the age of 13 years. She had been exposed to diethylstilbestrol in utero, had never taken oral contraceptives or other hormones, and had undergone routine gynecologic screening. Pathological examination of a specimen from a vaginal biopsy, performed 23 years earlier, was reported to show adenosis with no evidence of cancer. The patient was allergic to stinging insects, had no other medical illnesses, and was taking no medications. She was living with a partner, drank fewer than five alcoholic beverages per week, and was a nonsmoker. There was no family history of breast or ovarian cancer.

On examination, the vital signs were normal. The breasts were symmetric, with no skin changes, nipple discharge, or erosions. A flat mass, 5.0 cm by 5.0 cm, was palpated in the upper outer quadrant of the left breast. It was mobile and not at-

Figure 1. Breast Imaging Studies.

Craniocaudal mammographic view of the left breast (Panel A) reveals an ill-defined mass (arrow) in the lateral left breast in the area of concern, indicated by a metallic spherical marker. An ultrasonographic image of the left breast (Panel B) reveals a lobulated, hypoechoic, solid mass at the 2 o'clock position, measuring 3.5 cm by 2.7 cm by 2.0 cm. A bilateral breast MRI (Panel C) reveals a lobulated enhancing mass (arrow) in the upper outer quadrant of the left breast, measuring 2.9 cm by 2.7 cm by 2.5 cm.

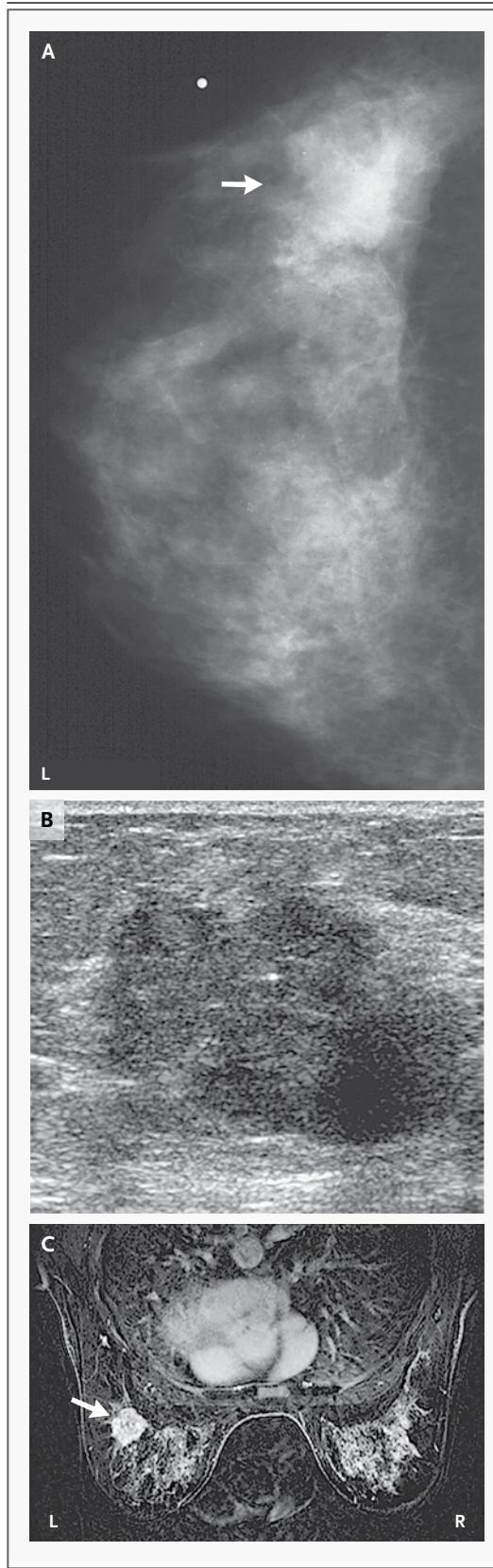
tached to overlying skin. There was no lymphadenopathy, and there was no mass in the right breast; the remainder of the examination was normal.

A radiograph of the chest obtained the same day showed no abnormalities. A radionuclide bone scan obtained the next day showed a focus of increased uptake in the right aspect of the T6 vertebral body, which suggested the possibility of a metastasis. Mammography revealed an ill-defined mass in the upper outer quadrant of the left breast. A targeted ultrasonographic examination of the left breast revealed an ill-defined, hypoechoic, lobulated mass, 3.5 cm by 2.7 cm by 2.0 cm, at the 2 o'clock position. Magnetic resonance imaging (MRI) of the breasts the next day revealed an ill-defined, lobulated, enhancing mass, 2.9 cm by 2.7 cm by 2.5 cm, in the upper outer quadrant of the left breast, corresponding to the mammographic and ultrasonographic findings. The next day, a clip was placed in the abnormal area of the breast under ultrasonographic guidance. Computed tomography (CT) of the thoracic spine, performed 2 days later, revealed a lytic destructive lesion, 1.8 cm by 1.6 cm by 1.5 cm, in the right side of the T6 vertebral body. A small, soft-tissue component extended into the right anterior lateral epidural space, without central canal stenosis.

Five days later, the patient was seen by a medical oncologist at this hospital. Twelve days after the visit to the oncologist, needle biopsy of the T6 vertebral lesion was performed under CT guidance, and pathological examination showed metastatic carcinoma. A management decision was made.

DIFFERENTIAL DIAGNOSIS

Dr. Helen Anne D'Alessandro: Mammographic views of the left breast (Fig. 1A) showed an irregular



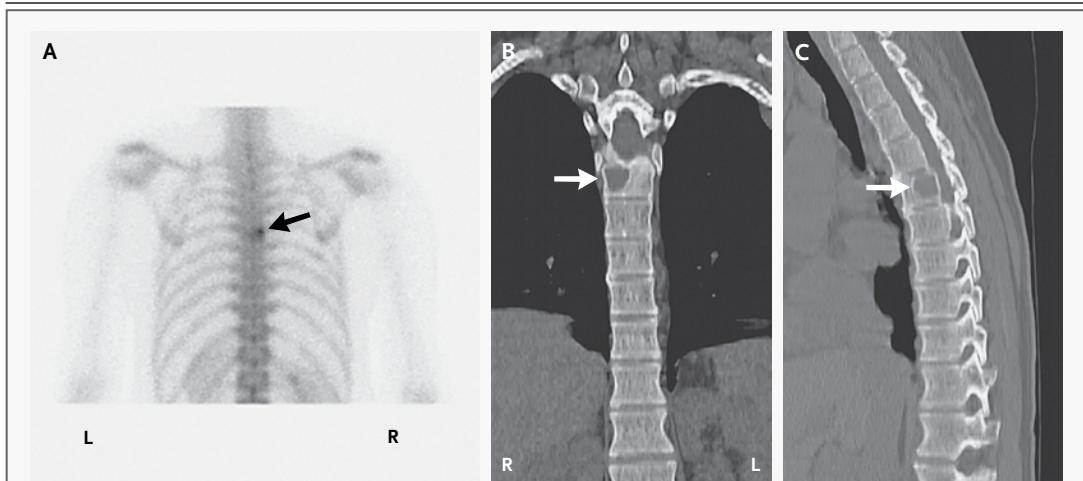


Figure 2. Spine Lesion Imaging Study.

Images of the thoracic spine (posterior view) from a bone scan (Panel A) reveal a focus of increased tracer activity (arrow) in the right aspect of the T6 vertebral body. Coronal (Panel B) and sagittal (Panel C) views of the thoracic spine from reconstructed CT images show the lytic lesion in the T6 vertebral body (arrows).

mass in the upper outer quadrant. A targeted ultrasonographic examination of the left breast (Fig. 1B) revealed a lobulated, hypoechoic, solid mass at the 2 o'clock position, which corresponded to the palpable abnormality. MRI of the breast (Fig. 1C) revealed a corresponding lobulated, enhancing mass in the upper outer quadrant of the left breast.

A bone scan (Fig. 2A) revealed a focus of increased tracer uptake in the right aspect of the T6 vertebral body. CT scans of the thoracic spine (Fig. 2B and 2C) revealed a lytic destructive lesion in the right aspect of the T6 vertebral body, with destruction of the posterior cortex and superior end plate. The findings are consistent with the presence of an invasive cancer of the left breast, with metastasis to the T6 vertebral body.

PATHOLOGICAL DISCUSSION

Dr. Kristina Braaten: All four tissue cores had involvement by both infiltrating ductal carcinoma (Fig. 3A) and ductal carcinoma in situ (Fig. 3B), with focally abundant extracellular mucin (Fig. 3C). Carcinomas that are entirely of the mucinous type are associated with a very good prognosis, but when conventional infiltrating ductal carcinoma is also present, as in this case, the

mucinous component is not clinically significant.¹ Several prognostic and predictive features were reported, including histologic grade, hormone-receptor status, and HER2/neu expression. Prognostic features reflect the projected clinical outcome on the basis of the biologic features of the tumor, whereas predictive markers reflect the likelihood of a response to a particular treatment.

The histologic grade of the tumor has prognostic significance for both disease recurrence and overall survival.² According to the modified Bloom–Richardson grading system, this tumor is grade 2 of 3 (Fig. 3A). Lymphatic invasion, which is a negative prognostic marker in patients with early-stage disease,³ was not seen.

Immunohistochemical staining of the tumor cells showed the expression of both estrogen (Fig. 3D) and progesterone receptors (Fig. 3E). Estrogen receptor is a very strong predictive factor for response to hormonal therapy.³ There is no lower limit for reporting a positive result, since even the presence of a small percentage of weakly positive cells has some positive predictive value.⁴ The concomitant presence of progesterone receptors is an independent predictive marker for a response to hormone therapy, probably because its presence reflects a fully functional estrogen-receptor pathway.⁵

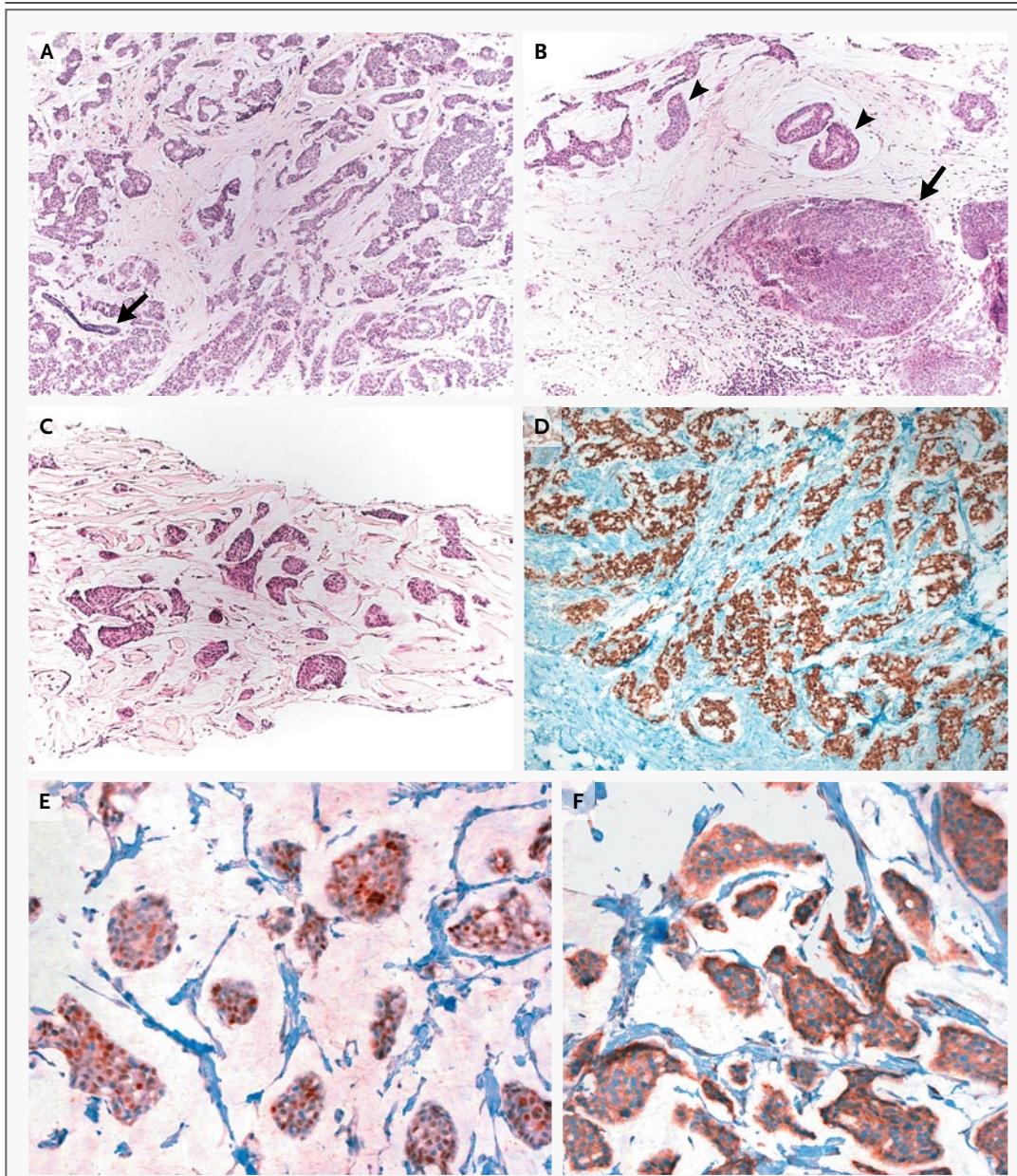


Figure 3. Biopsy Specimens of the Breast.

A histologic section of the specimen of the breast obtained by means of core needle biopsy (Panel A, low magnification) shows infiltrating ductal carcinoma. A benign duct (arrow) is surrounded by the invasive tumor. According to the modified Bloom–Richardson grading criteria, based on three histologic features (tubule formation, nuclear pleomorphism, and mitotic count), the tumor was assigned a score of 3 for lack of tubule formation, 2 for moderate nuclear pleomorphism, and 1 for a low mitotic count, for an overall score of 6, which corresponds to grade 2 of 3. A component of ductal carcinoma in situ (Panel B, arrow) is present adjacent to the invasive ductal carcinoma (arrowheads). Areas of the infiltrating carcinoma were associated with abundant extracellular mucin in the stroma (Panel C). Immunohistochemical staining for estrogen receptor (Panel D) and progesterone receptor (Panel E) shows positive nuclear staining of the infiltrating ductal carcinoma cells. An indeterminate degree of cell-membrane staining for HER2/neu protein (2+ of 3) is shown in Panel F.

The tumor was also evaluated for the status of HER2/neu, a transmembrane growth factor receptor,⁶ because of its importance both as a negative prognostic marker⁷ and as a predictor of response to trastuzumab therapy.⁷ In the case under discussion, immunohistochemical staining to detect HER2/neu protein on the tumor-cell membrane was scored as 2+ of 3 (Fig. 3F), an indeterminate pattern, which is not reliably predictive of *HER2/neu* gene amplification. In such cases, reflexive fluorescence in situ hybridization (FISH) is performed to assess the status of the gene; in this case, FISH did not reveal amplification of the *HER2/neu* gene.

Specimens of the T6 vertebral-body lesion obtained by means of fine-needle aspiration (Fig. 4A and 4B) and core needle biopsy (Fig. 4C) contained metastatic adenocarcinoma with morphologic features similar to those seen in the breast-biopsy specimen; the lesion was positive for estrogen and progesterone receptors and negative for HER2/neu overexpression.

DISCUSSION OF MANAGEMENT

Dr. William J. Gradishar: This asymptomatic, 47-year-old premenopausal woman has hormone-receptor-positive, HER2/neu-negative primary breast cancer, with a single, confirmed distant site of metastatic disease at the time of initial presentation — a clinical scenario known as an intact primary tumor with oligometastatic disease. Metastatic disease is found in 3 to 4% of women at the time of the diagnosis of breast cancer.⁸⁻¹⁰ We do not know whether oligometastatic disease, as seen in this patient, represents a distinct biologic entity with a different prognosis from that of cases with more widespread metastases.^{11,12} The key management question is whether this patient should be treated differently from any other patient with metastatic breast cancer.

SYSTEMIC THERAPY FOR METASTATIC BREAST CANCER

If we consider that oligometastatic disease is not different from widely metastatic breast cancer, then the primary focus should be on selecting optimal systemic therapy with minimal side effects. Evidence-based practice guidelines, such as those of the National Comprehensive Cancer Network¹³ (www.nccn.org/professionals/physician_gls/PDF/breast.pdf), suggest that a patient with estrogen-receptor-positive metastatic breast cancer could

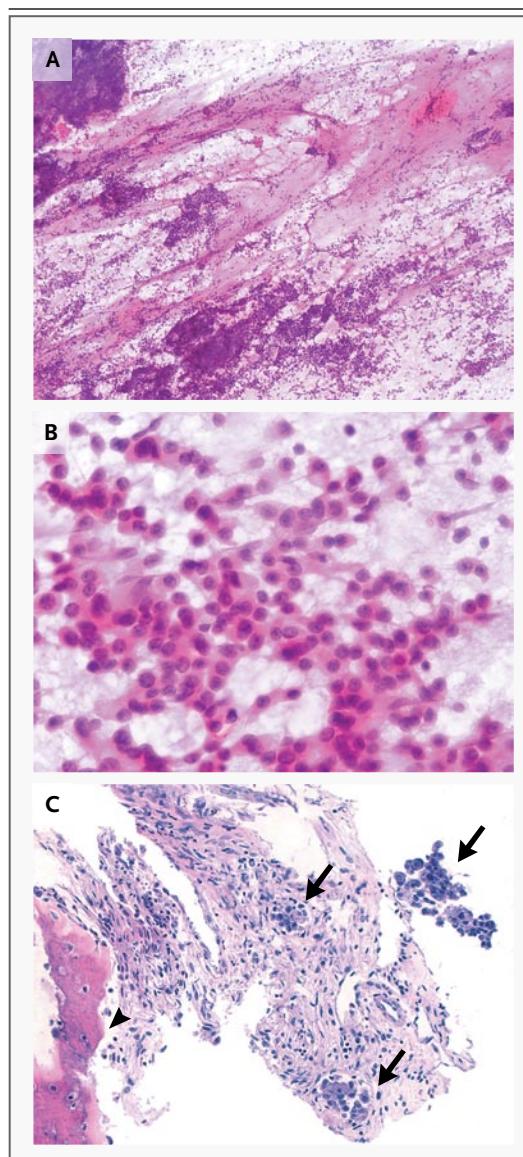


Figure 4. Specimens of the T6 Vertebral-Body Lesion Obtained by Means of Fine-Needle Aspiration and Core Needle Biopsy (Hematoxylin and Eosin).

Aspirate (Panel A) shows a densely cellular smear with a background of mucin. At high magnification (Panel B), there is a monomorphic population of epithelial cells in a mucinous background, a finding that is consistent with metastatic adenocarcinoma. The core-biopsy specimen (Panel C) shows clusters of carcinoma cells (arrows) adjacent to a trabecula of bone (arrowhead).

reasonably be treated with endocrine therapy as a first choice. Chemotherapy could be considered as a first option but has more side effects. If a patient benefits from one endocrine agent, an alternative endocrine agent is tried at the time of disease progression, and this strategy of sequenc-

ing endocrine agents is continued until the disease becomes refractory to endocrine manipulation or until the tempo or volume of disease necessitates chemotherapy.

In this premenopausal woman, the options for endocrine therapy are more limited than those in a postmenopausal woman. Aromatase inhibitors, which inhibit conversion of adrenal steroids (i.e., androstenedione) to estrogen by inhibiting aromatase activity in extraovarian sites, would not be effective in this patient, since the ovaries are her main source of estrogen. The antiestrogen agent tamoxifen would be the standard of care for this patient, since its antitumor effect is similar across age groups, with objective tumor responses in about 30% of premenopausal patients.¹⁴⁻¹⁶ Luteinizing hormone-releasing hormone analogues, such as leuprolide, buserelin, or goserelin, which inhibit the hypothalamic-pituitary-ovarian axis and result in reversible medical castration, could also be considered for her; when used as single agents in premenopausal women with metastatic breast cancer, they result in response rates of approximately 40%.¹⁷⁻¹⁹ I would also consider using both tamoxifen and a luteinizing hormone-releasing hormone agonist, since in some premenopausal patients, tamoxifen therapy is associated with elevated plasma estradiol levels,²⁰ and in one randomized trial,²¹ combined treatment with buserelin and tamoxifen was superior to treatment with either agent alone. Permanent ovarian suppression can also be achieved by means of oophorectomy, but this is less commonly performed today than in the past.

For systemic therapy in this patient, I would recommend tamoxifen, possibly with the addition of a luteinizing hormone-releasing hormone analogue. In addition to systemic therapy directed to the tumor, intravenous bisphosphonate therapy is generally recommended for any patient who has breast cancer with bone metastases,¹³ since fractures are common in such patients and can be prevented with bisphosphonate therapy.²² I would thus recommend zoledronic acid for this patient.

LOCAL THERAPY FOR THE PRIMARY BREAST CANCER

An alternative approach for this patient would be to assume that this oligometastatic breast cancer is biologically different from one with widespread metastases, so that a treatment approach aimed at long-term, disease-free survival should

be used, including local as well as systemic therapy. The rationale for a more aggressive approach is based on two retrospective observations from single institutions. First, among patients treated with anthracycline-based chemotherapy, those who were younger and had minimal organ involvement tended to have a better outcome than those who were older and had more widespread disease. Second, in some patients with metastatic disease, all clinical evidence of disease resolved after treatment. These patients had long-term survival and possibly were cured of their disease.^{23,24-30}

If a more aggressive approach is considered for this patient, several management questions follow. Should the patient undergo a lumpectomy, with or without radiation therapy? If so, when? Should the axilla be assessed? Should the solitary site of metastasis be treated definitively with either surgery or radiation therapy? A key issue is the optimal timing of excision of the primary breast lesion. Should it be left intact temporarily as an indicator of the antitumor activity of systemic therapy? Or should it be excised as soon as possible to eliminate a potential source of tumor stem cells that might be resistant to systemic therapy or that might result in additional metastases?

In this young patient with limited metastatic disease, an excellent performance status, and an absence of symptoms related to the disease, I would recommend surgical excision of the primary tumor and radiation to the spinal lesion. Endocrine therapy would be the foundation of systemic treatment, but I would also discuss the possibility of anthracycline-based chemotherapy. Once this patient has been treated, regular follow-up should consist of assessment for symptoms, physical examination, and standard imaging. The usefulness of the assessment of serum levels of tumor markers or of circulating tumor cells has not been validated for such patients.

Surgical Management

Dr. Michele A. Gadd: There are several issues for the surgeon to address in this case. Should the primary tumor be excised? If so, how comprehensive should the excision be, and what is the optimal timing of surgery? Hesitation to intervene surgically in a patient with metastatic cancer stems from the opinion that, since we cannot successfully eradicate metastatic disease, addressing the primary tumor is unnecessary. De-

spite evidence that an increasing proportion of patients with metastatic breast cancer have prolonged survival, the presence of local disease in the breast is largely ignored. Today, more than 50% of patients with limited or oligometastatic disease in whom multiple treatment approaches are used remain alive at 2 years^{8,10,24,28}; 30% remain alive at 5 years, and some survive for more than 10 years.³⁰⁻³³ As a consequence of improved systemic therapies, some patients live long enough that local problems related to their primary tumor develop, and it has been suggested that the unresected primary sites of disease may become a source of tumor reseeding. During the past decade, published data have shown that in patients with metastatic breast cancer, resection of the primary tumor with negative margins is associated with improved survival rates at 3 and 5 years, as compared with the rates among patients who undergo resection with positive margins or those who do not undergo resection.^{8,10} Little is known about how the axillary nodes were handled in most of these cases or about the effect of axillary dissection on survival.

For this patient, I would recommend an aggressive approach with the goal of eradicating all known disease. I would begin with a course of systemic therapy, followed by restaging to determine the response to treatment and to look for new sites of metastasis. The primary goal of systemic therapy is to control the metastatic focus within the spine and eradicate occult, microscopic disease. However, since the primary breast cancer is too large for breast-conserving surgery, a secondary goal is to reduce the size of the breast tumor. If restaging indicates no new sites of distant disease and suggests that the patient would have a response to systemic therapy, I would recommend surgical removal of the primary tumor and an axillary-node evaluation. A breast-conserving approach might be feasible if the tumor is sufficiently reduced in size, but mastectomy might be preferred, since the goal should include achieving negative margins. I would also recommend a sentinel-node biopsy at the time of the breast procedure, and if the sentinel node is positive for tumor cells, a dissection of the axillary lymph nodes, in order to prevent a relapse of cancer within the axilla. The multidisciplinary team should periodically reassess the treatment goals according to responses to the treatment.

Radiation Therapy

Dr. Jennifer R. Bellon: There are two issues for the radiation oncologist to consider in this case: treatment of the primary tumor in the breast, and treatment of the spinal metastasis. If the tumor in the breast is excised, should radiation therapy be considered to address residual microscopic disease? The effect of such treatment on the survival of patients with localized breast cancer has been the subject of debate,³⁴ but a recent meta-analysis of 78 randomized clinical trials³⁵ showed that improvements in locoregional control with radiation therapy after either breast-conserving therapy or mastectomy translate into a significant benefit in long-term overall survival. It is less clear whether locoregional control would affect survival in this patient, who has minimal metastatic disease. Although three retrospective studies^{8,10,28} that addressed this question showed a benefit of surgical resection, the validity of these findings is limited by selection bias. Although we do not know whether radiation therapy would add to any possible benefit of resection in this patient, in view of its benefit in the adjuvant setting, it is conceivable that radiation therapy might also provide a survival benefit for the patient. It would have few side effects and might prevent symptomatic local recurrence. Therefore, if breast-conserving surgery is performed, I would recommend postoperative radiation to the breast with standard fractionation.

MANAGEMENT OF THE METASTASIS

There are two goals in the treatment of the metastasis: the first and most important is the prevention of fracture and neurologic complications, and the second is the prevention of additional metastases emanating from this site. I would obtain an MRI scan for more detailed evaluation of the spinal cord; if evidence of cord compression is present, I would consult a surgeon, since a combination of surgery and radiation therapy results in better function than radiation therapy alone.³⁶ If there is no cord compression, I would recommend radiation to the vertebral body, with the goal of preventing neurologic compromise and pain.

Would it be appropriate to treat this asymptomatic site of distant disease aggressively, with the goal of prolonging survival? Radiation to metastatic sites is typically given at relatively low

doses, with the goals of palliation or prevention of symptoms and avoidance of complications of radiation. However, in addition to nonrandomized series suggesting that resection of solitary visceral metastases may lead to extended disease-free survival,³⁷⁻⁴² two studies showed that higher doses of radiation led to better local control and overall survival in patients with oligometastatic disease to the spine⁴³ or brain.⁴⁴ Although it is possible that in all these cases the improved survival resulted from improved functional status because of better local control, rather than from prevention of additional metastatic disease, the results encourage us to think about aggressive treatment of the metastasis in this case. Thus, I would irradiate the T6 lesion at the highest dose that the spinal cord can tolerate. Stereotactic radiation, in which very high doses of radiation can safely be given to a small focus of tumor, sparing normal tissue, is used in the treatment of spinal metastases⁴⁵ and could be considered in this case. As systemic therapy becomes more effective in eradicating microscopic metastatic foci, treatment of larger metastatic foci with ablative radiation may assume greater importance in the management of metastatic disease in a patient such as this one.

Dr. Nancy Lee Harris (Pathology): Dr. Smith, will you tell us how you managed this patient's disease and how she is now?

Dr. Smith: This patient initially presented before the publication of the recent studies on the effect of local control on survival. We selected her case for presentation because it illustrated many of the clinical decisions that have to be made and that we have discussed. She was initially treated with radiation to the spine (4000 cGy in 20 fractions), hormonal therapy with tamoxifen and leuprolide, and bisphosphonate therapy with zoledronic acid. After approximately 3 months of hormonal therapy, the breast mass had not decreased in size, and the patient was disconcerted by its palpable presence. On restaging, no new metastatic foci had developed and the bone lesion was unchanged or smaller. Approximately 6 months after her initial presentation, I excised the breast tumor during an outpatient procedure; there was an infiltrating ductal carcinoma measuring approximately 3.5 cm in diameter and lobular carcinoma in situ. The tumor remained positive for estrogen receptor and pro-

gesterone receptor, and negative for HER2/neu. The surgical clearance was less than 2 mm in diameter, but the margins were free of cancer. We did not perform a reexcision or sentinel-node biopsy, and she did not receive radiation therapy.

The patient remained asymptomatic until approximately 1 year later, 18 months after her initial presentation, when CT scans showed enlarging axillary nodes that grew rapidly over a period of several weeks, from approximately 2 cm to 5 cm in diameter, causing discomfort. At that time, we performed an axillary dissection. Five of 11 axillary lymph nodes contained cancer cells, with areas of necrosis, that were positive for estrogen and progesterone receptors and negative for HER2/neu. The bone lesion remained stable, and there were no new metastases. We discontinued tamoxifen therapy and began treatment with anastrozole, continuing the treatment with leuprolide and zoledronic acid.

Thirty-seven months after her initial presentation, a new cancer was found in the opposite breast: a grade 3 infiltrating ductal carcinoma, 1.1 cm in diameter, that was negative for both estrogen receptor and progesterone receptor; the expression of HER2/neu was 3+. We elected to perform a lumpectomy with a sentinel-lymph-node biopsy, since this cancer would not be responsive to hormonal therapy. The margins were clear, and the sentinel node did not contain tumor cells. After extensive discussion, the patient received radiation treatment to the right breast. She remains asymptomatic, with no progression of the disease in the bone.

A Physician: In a patient with known breast cancer, why was it necessary to perform a biopsy of the spinal lesion?

Dr. Bellon: It is important to establish that the lesion is indeed cancer and that it shares the same hormonal and HER2/neu status as the primary tumor, in order to determine the best therapy.

Dr. Braaten: We have all seen cases in which lesions of the spine in patients with known cancers prove to be either a second tumor, such as a plasmacytoma, or a benign lesion, such as a hemangioma.

A Physician: My training would have led me to make a histologic assessment of the axilla earlier than was done in this case. Would you comment?

Dr. Smith: For many years, we thought that the

presence of metastatic disease determined the outcome, and we often would not treat patients until they became symptomatic. As this case illustrates, with improved early detection of metastases and with improved systemic therapy, we now have patients whose distant disease is not going to be a problem for a long time. As we saw in this case, if you try watching and waiting with the local disease, sooner or later it will require your attention. If I saw this patient for the first time today, I would treat the local disease more as though it were a localized rather than a metastatic cancer. With the new cancer in the opposite breast, we have given standard local therapy.

Dr. Harris: Despite the fact that this patient did not receive aggressive local therapy early, new

sites of metastatic disease still have not developed. Her tumor was clearly not releasing cells capable of rapidly establishing distant metastatic lesions, at least in the presence of hormonal therapy.

ANATOMICAL DIAGNOSIS

Breast cancer with minimal metastatic disease.

Dr. Gradishar reports receiving consulting fees from or serving on the paid advisory boards of Genentech, GlaxoSmithKline, Novartis, Abraxis Bioscience, and Bristol-Myers Squibb Oncology and receiving grant support for clinical trials from Genentech, GlaxoSmithKline, Abraxis Bioscience, Bristol-Myers Squibb, and Imclone. No other potential conflict of interest relevant to this article was reported.

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