

Metastatic breast cancer in a woman with apparent cholangiocarcinoma

Complaints of jaundice and intermittent abdominal pain were the only clues to a primary breast cancer that produced none of the usual symptoms.

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CASE

A 56-year-old white woman in good general health initially presented to the emergency department on July 4, 2000, with jaundice and intermittent abdominal pain that had also occurred on several previous occasions. Her symptoms were consistent with cholelithiasis, and as part of her workup, ultrasound of the right upper quadrant was ordered. Testing confirmed cholelithiasis and revealed suspicious liver lesions. Endoscopic retrograde cholangiopancreatography (ERCP) was ordered, the obstructive stone was removed, and the jaundice resolved.

Two weeks later, the patient underwent laparoscopic cholecystectomy and biopsies of the liver lesions. Liver pathology results confirmed adenocarcinoma. Except for episodic abdominal pain and transient jaundice, the patient was asymptomatic and denied weight loss, change in appetite, or early satiety. Her medical history included a prolapsed uterus for which she underwent a total hysterectomy in 1982 and a clogged breast duct in October 1995. She began menopause in 1998. Her family history was positive for breast cancer in a maternal first cousin. The patient denied using tobacco, alcohol, or illicit drugs.

In August 2000, exploratory laparoscopy of omental and mesenteric nodules determined that the nodules were benign. At this time, the diagnosis was determined to be adenocarcinoma of the liver consistent with either cholangiocarcinoma or metastatic disease of unknown origin. Cholangiocarcinoma was considered the likely diagnosis based on the pathology evaluation as well as the lack of evidence supporting another site as the primary source of the disease. Because of the grim prognosis associated with the diagnosis, the patient was advised to accept her condition and make end-of-life decisions.

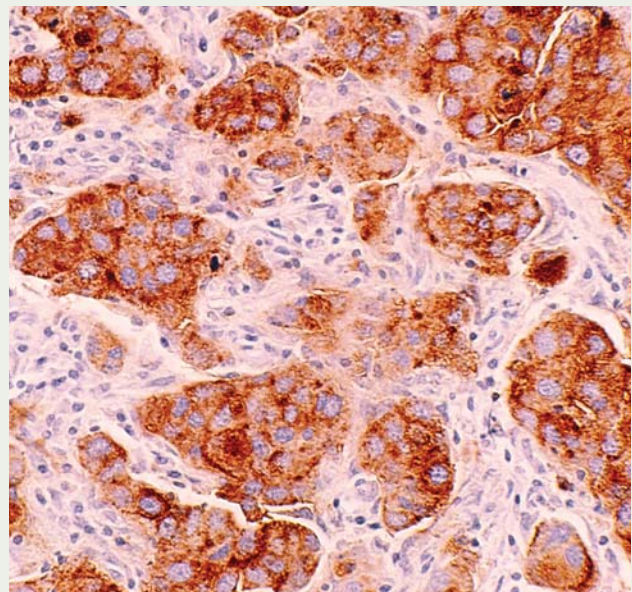
An unexpected twist Fortunately, the woman began researching her disease online and located a specialist at a nearby institution. After evaluation, he initiated chemoembolization of the liver using 50 mg of cisplatin and 10 mg

of mitomycin. As part of his workup, the specialist ordered new scans. On review of the CT, he noticed thickening of the right breast.

Further ultrasound evaluation showed a 1.9 × 2.9 × 2.4-cm lesion. Biopsy of the lesion revealed infiltrating ductal carcinoma; estrogen and progesterone receptors were negative, but *HER2*-receptor status was positive. Comparison of the resected tissue with the previously biopsied liver lesion confirmed metastatic breast cancer.

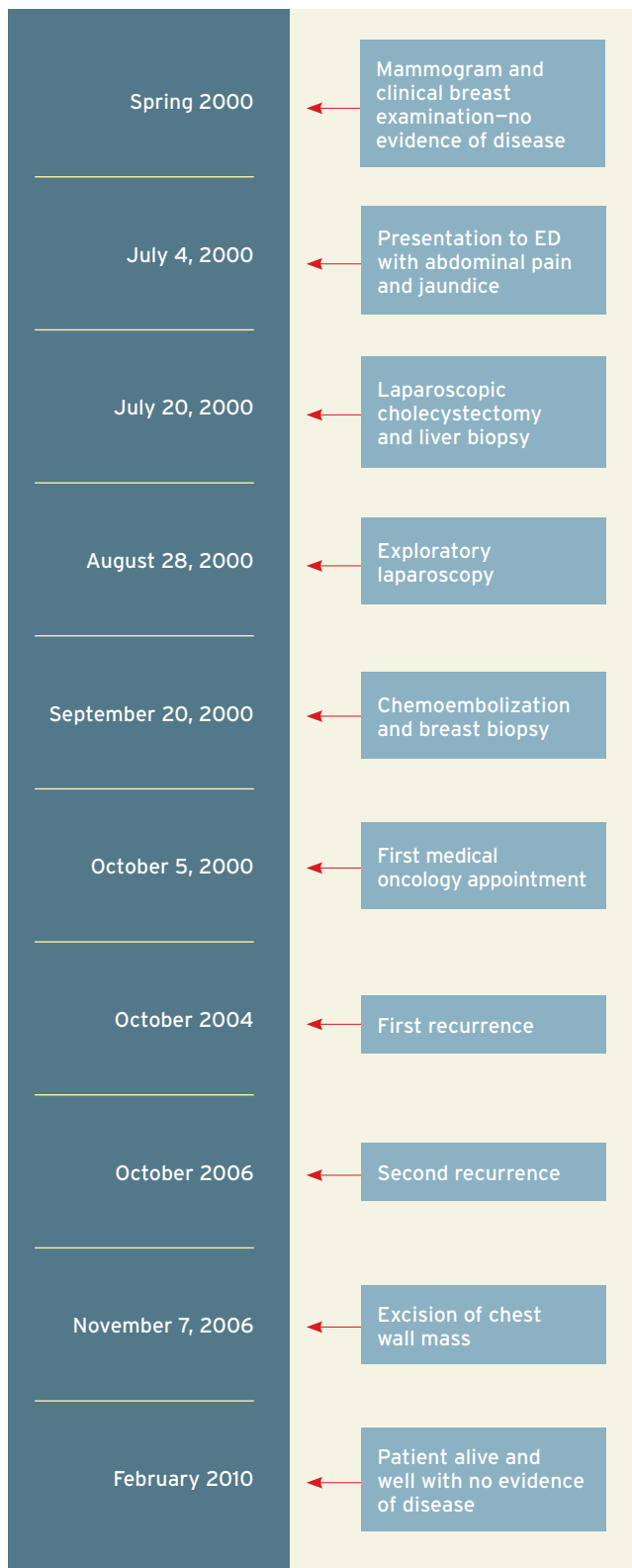
A hard-to-find cancer In retrospect, the patient had had an unremarkable mammogram and clinical breast examination the previous spring. At that time, she was told there was nothing to worry about and she should return for her next routine examination in a year.

A physical examination performed at the patient's initial visit to our medical oncology department on October 5, 2000, revealed a well-developed, well-nourished woman in no distress. She weighed 191 lb and was 5 ft 7 in tall. Her neck was without thyromegaly or jugular venous disten-



Infiltrating ductal carcinoma of the breast

FIGURE 1. Breast cancer diagnosis timeline



tion. The lymphatic system exhibited no adenopathy. At the 9 o'clock position of the right breast was a firm, but not fixed, palpable mass measuring 2.7 × 2.2 cm and a bruise from the recent biopsy. The abdomen showed a well-healed incision from previous gallbladder surgery. The right upper thigh and inguinal area were bruised from recent chemoembolization. The rest of the examination was unremarkable.

The initial diagnostic workup included a bone scan to evaluate for possible metastasis; CT of the chest, pelvis, and abdomen to establish the current status of known metastasis; and a multiple gated acquisition (MUGA) scan to determine baseline heart function prior to administration of chemotherapy. Additionally, several blood tests were ordered, including tumor markers, a complete metabolic panel, and CBC, in order to provide a baseline profile.

The test results were favorable. The bone scan and CT of the chest and pelvis revealed no abnormalities. CT of the abdomen revealed lesions in the liver and the omental fat that suggested metastatic disease, although previous biopsy had indicated otherwise. The MUGA scan showed that the patient had a sufficient ejection fraction to begin chemotherapy. At the time of chemotherapy initiation on October 19, 2000, virtually all laboratory values were normal except for an elevated cancer antigen (CA) 27.29 level.

Treatment was altered in response to the change in diagnosis from cholangiocarcinoma to metastatic breast cancer. Previously, chemoembolization was initiated to treat the presumed cholangiocarcinoma. Now, chemotherapy was chosen to target the primary breast cancer. A regimen of doxorubicin and docetaxel was selected with an anticipated four to six cycles given every 3 weeks. Weekly trastuzumab was also prescribed upon completion of this therapy in order to address the *HER2* status of the cancer. Surgery was not recommended because of the metastatic status of the disease. The patient was successfully treated and remained in remission for several years.

Recurrent breast cancer Then, during a clinical breast examination at a routine visit in October 2004, a lesion was found in the right upper outer quadrant of the patient's breast near the site of the original mass. Biopsy once again demonstrated infiltrating ductal carcinoma of the breast. The patient elected to have a right-sided mastectomy, during which 18 axillary lymph nodes were removed in order to assess the metastatic state of this recurrence. No lymph nodes were found to have disease. This tumor was estrogen receptor-positive, progesterone receptor-negative, and *HER2* receptor-positive. To address the estrogen receptor-positive finding, which was new, daily anastrozole was added to the continued weekly trastuzumab.

The patient's disease responded well to this therapy, but in October 2006, another palpable mass was discovered on the right chest wall. The mass was excised on November 7, 2006, and subsequent pathology confirmed a localized recurrence. The area was treated with radiation. Trastuzumab and anastrozole were discontinued; the anastrozole was replaced by tamoxifen.

The patient recovered well from surgery and was free of disease at all surgical follow-up visits. As of early February 2010, she was alive and well, with no evidence of disease. There has been no recurrence of liver metastasis since the initial chemoembolization. The patient continues follow-up with regular office visits and credits her remission to the care she has received. A timeline of her breast cancer diagnosis appears in Figure 1. In spite of the intricacies of this case, the outcome has been remarkably favorable.

DISCUSSION

Breast cancer typically manifests with breast-related symptoms, including asymmetry, thickening of the skin, lumps, scaling or redness, discharge, or nipple inversion. However, some patients may not have any symptoms in the early stages of the disease, which is why the American Cancer Society still encourages women to have yearly mammograms beginning at age 40 years. Recommendations for screening are presented in Table 1.

Once a diagnosis of breast cancer has been made, the histology has little prognostic value compared with adequate staging of the cancer, and a treatment plan is formulated based on the stage of the disease and the tumor expression.¹ The tumor expression identified from the tissue biopsy is used to determine what hormonal therapy, if any, is required as adjuvant treatment.

Pathology results, therefore, play an important role in the treatment of breast cancer. If the tumor is positive for estrogen or progesterone receptors, the prognosis is more favorable than if receptors are absent.² A positive receptor status indicates that the tumor will likely respond to hormonal therapy. Choice of therapy depends primarily on the menstrual status of the woman at the time treatment is started. In premenopausal women, tamoxifen is used because of its antiestrogen effects. Postmenopausal women are given aromatase inhibitors because these drugs inhibit peripheral conversion of androgens to estrogen.

Another consideration in determining the treatment for women with breast cancer is the *HER2* oncogene. Overexpression or amplification of this gene usually indicates a poorer prognosis because such tumors typically have a less favorable response to hormonal therapy. In patients exhib-

TABLE 1. American Cancer Society recommendations for breast cancer screening

Begin at age 20 years with breast self-examination (BSE).
Have clinical breast examination (CBE) at least every 3 years between ages 20 and 39 years.
Have yearly CBE and mammogram in addition to monthly BSE beginning at age 40 years.

Source: American Cancer Society guidelines for the early detection of cancer. http://www.cancer.org/docroot/PED/content/PED_2_3X_ACS_Cancer_Detection_Guidelines_36.asp?sitearea=PED. Accessed February 19, 2010.

iting this tumor marker, trastuzumab, a monoclonal antibody, is used because of its ability to target the *HER2* oncogene. Additionally, anthracycline-based regimens are recommended because women who exhibit this gene may be resistant to treatment with an alkylating agent-based regimen.³

Monitoring disease progression Some additional tumor markers that may be followed during the course of treatment are CA 27.29 and CA 15-3. These tumor markers are valuable only for monitoring metastatic disease. The increase or decrease in tumor markers can track both the course of the disease and the response of the disease to treatment. While markers are ineffective in diagnosing initial disease because they lack specificity and sensitivity, for a patient in remission, they can serve as an early indicator of disease recurrence. Markers are most effectively used when serial measurements are obtained.⁴

Therapeutic modalities Many women will undergo some form of surgery to excise the cancer. Additional treatment may include chemotherapy or radiation. The more advanced the stage of the cancer, the more likely the patient will receive chemotherapy to prevent metastasis and reduce the risk of recurrence. Radiation therapy is used to reduce the risk of local recurrence especially in those patients with large tumors, lymph-node involvement, or close or positive margins during surgery. Patients presenting with metastatic disease are not candidates for surgery, and neoadjuvant therapy may be necessary before surgery can be considered as an option.

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TEACHING POINTS

- Women may not have the usual symptoms of breast cancer, even in the presence of metastatic disease. This is why mammograms are so important.
- Once breast cancer has been diagnosed, the histology has little prognostic value compared with the adequate staging of the cancer, and a treatment plan is formulated based on the stage of the disease and the tumor expression.
- A positive receptor status indicates that the tumor will likely respond to hormonal therapy. Overexpression or amplification of the *HER2* gene usually indicates a poorer prognosis because such tumors typically have a less favorable response to hormonal therapy.
- The increase or decrease in tumor markers, such as cancer antigen (CA) 27.29 and CA 15-3 can help track both the course of the disease and the response of the disease to treatment.
- The more advanced the stage of the cancer, the more likely the patient will receive chemotherapy to prevent metastasis and reduce the risk of recurrence. Radiation therapy is used to reduce the risk of local recurrence.

CASE REPORT | Breast cancer

The woman in this case did not exhibit any of the classic symptoms of breast cancer. Instead, her disease was discovered only after she became symptomatic secondary to her metastatic disease. Further investigation into her initial symptoms led to the eventual discovery of her primary disease.

Because her disease had already metastasized at presentation, the patient was not initially a candidate for surgical resection. She underwent chemotherapy followed by trastuzumab to address her positive *HER2* status. The primary and metastatic disease was effectively treated, resulting in a disease-free interval. This, along with the lack of evidence of metastasis at the time of her recurrences, allowed her to be restaged and become a candidate for surgical resection. At her first recurrence, the tumor was estrogen receptor-positive, and anastrozole was prescribed in consideration of the patient's postmenopausal state. At the time of her second recurrence, she was switched to tamoxifen because of cardiotoxic effects she experienced while taking anastrozole. Trastuzumab was also abandoned, as it was clearly ineffective in preventing recurrences.

Even though this woman followed established screening guidelines, her breast cancer went undetected by conventional methods and presented in an advanced stage. Had she heeded the advice of her oncologist, she would not be here today. In this case, the accurate diagnosis came only after one of the basic principles of medicine was considered. Had the specialist

physician responsible for administering her chemoembolization not done a complete physical examination and reviewed her studies in detail, he likely would have continued treating her for the incorrect diagnosis of primary cholangiocarcinoma. Fortunately for the patient, the combination of diligence in searching for a treatment, her resiliency to the disease with which she was faced, and the excellent professionals she encountered through her own research resulted in an outcome that has surpassed everyone's expectations. **JAAPA**

Holly Johnson practices in thoracic surgery at The Arthur G. James Cancer Hospital, Ohio State University Medical Center, Columbus. She has indicated no relationships to disclose relating to the content of this article.

DRUGS MENTIONED

Anastrozole (Arimidex)	Mitomycin (Mutamycin, generics)
Cisplatin (Platinol-AQ, generics)	Tamoxifen (Nolvadex, Soltamox, generics)
Docetaxel (Taxotere)	Trastuzumab (Herceptin)
Doxorubicin (Adriamycin, Doxil, Rubex, generics)	

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