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Case Report

Case Report

Metastatic osseous disease of unknown primary origin: a case report and review of literature

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Abstract

Cancer of unknown primary (CUP) is a heterogeneous group of metastatic tumors in the absence of a clinically identifiable site. We describe the case of a 66-year-old female with an extensive history of non-specific imaging concerning for malignancy who did not undergo further workup and in whom a diagnosis of CUP was made. The patient initially presented to her specialist with concern of right leg pain. Imaging at that time was concerning for a progressive malignant process. Given this, the patient was referred urgently for surgery. Final surgical pathology and breast prognostic panel were consistent with metastatic breast carcinoma at that time. Follow-up imaging performed 1-week postoperatively did not show suspicious findings in either breast, further supporting a diagnosis of CUP. To this end, we highlight the importance of follow-up imaging but recognize the challenges facing healthcare professionals in navigating the ethical principles of nonmalificience and beneficence in diagnostic workup.

Keywords: Cancer of unknown primary; metastatic breast carcinoma; breast carcinoma; breast cancer; female cancer

Introduction

Cancer of unknown primary (CUP), which accounts for 3–5% of diagnosed malignancies worldwide, is a heterogeneous group of metastatic tumors in the absence of a clinically identifiable site [1]. Two theories exist regarding the etiology of this disease process including distant metastasis of early tumor cells and spontaneous malignancy with no true primary source [1]. We describe the case of a 66-year-old female who presented with a 7-year history of imaging findings showing diffuse osteoblastic lesions concerning for malignancy.

Case report

A 66-year-old female with past medical history of right total knee arthroplasty and left knee hemiarthroplasty presented to her orthopedic surgeon with complaints of worsening right leg pain. On physical exam, the pain was localized to the patient's right distal femur. Full range of motion was demonstrated on flexion and extension of the right knee. Good joint stability was appreciated. There was no obvious evidence of a definite soft tissue mass, knee joint effusion, or synovitis of the right knee. She had no tenderness to palpation of the left knee. Imaging at that time showed "permeative radiolucent and destructive changes at the right distal femoral diaphysis" and "focal cortical destruction at the lateral cortex", which were new findings compared to prior imaging. With a high risk for pathologic fracture and findings concerning for a progressive malignant process, the patient was referred for urgent surgical consultation and further evaluation.

After thorough counseling and consultation, the decision was made for emergency department admission with plans for urgent open surgical biopsy and prophylactic internal fixation of the right distal femur. On admission, the surgery was performed without complications. The patient's final surgical pathology report was consistent with metastatic breast carcinoma. Subsequent breast prognostic panel demonstrated weak ER (75%)/PR (25%) positivity, HER-2 negativity on fluorescence in situ hybridization, a Ki-67 of 35%, and GATA3 positivity (3+). Follow-up tumor marker evaluation was strongly positive for Cancer Antigen 15–3, further supporting a diagnosis of metastatic breast carcinoma.

Additional medical history included an extensive record of skeletal abnormalities found on imaging. In late 2015, the patient underwent evaluation for symptoms consistent with urinary incontinence. Imaging at that time showed no evidence of underlying abnormalities but did note "numerous sclerotic lesions throughout the visualized thoracic and lumbar vertebral bodies". The patient elected to undergo follow-up imaging in January 2016 which noted a "stable, nonspecific focus of asymmetric increased uptake in the left iliac bone". In April 2017, the patient was seen in the emergency department for evaluation of symptoms consistent with pyelonephritis. Computed tomography (CT) scans showed "diffuse sclerotic lesions throughout the visualized axial and appendicular skeleton consistent with osseous metastatic

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disease until proven otherwise". In August 2019, the patient underwent evaluation for symptoms concerning for pulmonary embolism. Imaging at that time showed no evidence of pulmonary embolism but did note "diffuse osteoblastic metastatic disease throughout the axial and appendicular skeleton." Total-body bone scan performed at that time noted diffuse uptake in the sternum. Follow-up sternal biopsy showed "atypical cells highly suspect for metastatic carcinoma." Through shared decision making, the patient elected not to undergo further evaluation.

The patient denied a personal history of breast carcinoma and underwent annual screening mammography for the past 25 years without abnormalities. She endorsed undergoing one fine needle aspiration for a right breast cyst that was later proven benign, but she denied any additional history of breast abnormalities. Age of menarche was 13 years old. She had her first live birth at age 23 and breastfed her second child for approximately 5 weeks. Menopause occurred naturally at age 45. She underwent a partial hysterectomy in 1984 and used hormone replacement therapy (estrogen only) until her breast cancer diagnosis in 2022. She denied a history of tobacco or alcohol use. She denied a family history of breast carcinoma specifically, but endorsed a history of leukemia in her mother, colon cancer and lymphoma in her father, and cancer in her maternal grandmother but could not recall the type.

A PET CT performed approximately 1-week post-operative in July 2022 showed no abnormal uptake in either breast. Follow-up breast magnetic resonance imaging (MRI) performed August 2022 showed no suspicious findings within either breast but did note an area of "ill-defined and irregular enhancement" measuring ~3 cm in the right axilla. This did not demonstrate abnormal activity on the previous PET CT. Additionally, no pathologically enlarged lymph nodes were noted. The patient was given a BI-RADS Category 1.

After thorough counseling and consultation, the patient elected to undergo eleven treatments of radiation therapy to the femur (September 2022) and tolerated the intervention well. Today, the patient continues active surveillance every 3 months. She is currently on antiestrogen therapy (Letrozole 2.5 mg qd), targeted therapy (Palbociclib 125 mg qd), and zoledronic acid infusion (q 3 mos).

Discussion

CUP is a heterogeneous group of metastatic tumors defined by the absence of a clinically identifiable primary site. It accounts for 3–5% of newly diagnosed malignancies worldwide, ranking among the ten most common causes of cancer-related deaths. The median age at diagnosis is 65 and is slightly more common in men [1, 2]. Though little is understood of its biology, two predominant theories exist. The parallel progression model posits CUP tumors are metastatic tumors that have arisen from early, disseminated primary tumor cells, where subsequent genetic evolution of the metastasis occurs independent from the primary lesion. The second theory posits CUP tumors are single entities that occur in the absence of a primary tumor altogether. In this scenario, the tumor microenvironment favors the evolution of tumor cells at the metastatic site, while simultaneously arresting tumor cell growth at the primary site [1, 2]. The clinical presentation of patients with CUP is variable, with signs and symptoms related to the metastatic site. Frequently, radiological examination supports clinical presentation. Unexpected radiological evidence of metastasis at the lymph nodes, bone, liver, and lung is most common [3].

A thorough history and comprehensive physical examination is essential in the primary clinical workup of CUP. Attention to medical, surgical, and family history proves especially useful. Initial laboratory testing includes complete blood count, liver and kidney function tests, and electrolytes [4, 5]. Beyond this, radiological examination including CT with intravenous (IV) contrast, or MRI of the neck, thorax, abdomen, and pelvis is also recommended. In the cases of female patients, mammography should also be performed [4, 5]. Besides basic laboratory testing and radiological examination, tissue biopsy is essential, as histopathological classifies tumor type, gene expression profile, and immunophenotype. Adenocarcinomas (60%) and poorly differentiated carcinomas (30%) are among the most common histological subtypes of CUP [2, 5].

Patients with confirmed CUP may be sub-classified into favorable (~20%) and unfavorable (80%) sub-groups. Favorable risk CUP subsets (F-CUP) seemingly retain tumor equivalents in histopathological features, gene expression profiling, and immunophenotyping of known primary cancers. Favorable risk subsets include adenocarcinomas with isolated axillary adenopathy, papillary adenocarcinoma of the peritoneal cavity, and adenocarcinoma with a single metastatic lesion, among others [5, 6]. Unfavorable risk CUP (U-CUP) subsets, conversely, often have greater visceral metastatic involvement and higher tumor burden. Unfavorable risk CUP subsets include poorly differentiated carcinomas and poorly differentiated neuroendocrine carcinomas [4, 6].

The sub-classification of CUP is the cornerstone of subsequent management. Patients of F-CUP subsets are managed according to the presumed primary cancer. With a presumed diagnosis of ER/PR-positive, HER2-negative metastatic breast carcinoma, our patient received treatment according to primary breast cancer protocols, including CDK4/6 inhibition in combination with endocrine therapy and radiation therapy due to risk of residual disease [4]. A recent meta-analysis showed statistically significant improvement in progression free survival and overall survival (OS) in breast cancer patients treated with CDK4/6 inhibitors in combination with endocrine therapy [7]. Our patient, in accordance with ESMO clinical guideline recommendations, follows up at 3-month intervals. Though the prognosis of CUP, overall (~1 year), is dismal, Kodaira *et al*. demonstrated favorable outcomes and improved OS in CUP patients treated for presumed breast carcinoma versus CUP patients in whom the primary site could not be identified (OS 50.0 months and OS 16.9 months, respectively) [8].

Patients of U-CUP subsets, on the other hand, are treated with platinum-based regimens with the aims of prolonged survival and improved quality of life. Newer agents such as gemcitabine and irinotecan have also been incorporated following objective responses in smaller studies [1]. Despite modest response to the above, overall median survival remains poor at 6–8 months. Fortunately, accumulating evidence suggests individualized targeting of genomic alterations may prove useful in improving clinical outcomes in patients of U-CUP subsets [9, 10]. Interestingly, in a study of 300 patients, Kato *et al*. demonstrated most individuals (97%) of U-CUP subsets had at least one genomic alteration that could be impacted by an FDA-approved agent. Though novel, this presents a promising improvement in treatment of CUP, especially in those with an unfavorable subset.

To this end, we highlight the importance of follow-up imaging but recognize the challenges facing healthcare professionals in navigating the ethical principles of nonmalificience and beneficence in diagnostic workup. This patient showed evidence

of malignant metastasis for years before her official diagnosis. With advancing treatment for metastatic breast carcinoma, early diagnosis is crucial. Follow-up on incidental imaging findings is important, while also seeking to avoid unnecessary medical tests and supporting patient autonomy.

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Conflict of interest statement

None declared.

Data availability

Not applicable.

Ethical statement

The patient in this paper provided fully informed written consent to be the subject of this report. Written informed consent has been obtained from our patient to report all findings. Ethical review and approval were waived as this is a single subject case report, in accordance with IRB policy.

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