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Axillary node metastatic carcinoma without definitive primary: a case report

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ABSTRACT

Cancer of unknown primary (CUP) is the finding of a metastatic cancerous lesion without an established primary source localized within the body. CUP can be of any cancer cell type, however, adenocarcinoma is most often identified by histology. Up to 5% of all malignant diagnoses are classified as CUP. PET is an imaging modality often utilized to distinguish a primary source in the setting of CUP, yet often a primary is never identified. CUP can be further stratified using specific qualifiers as favorable and unfavorable, indicating the potential therapeutic response to treatment regimens. Treatment approach to CUP relies heavily on the cell type identified by histology, the location of the lesion, and the amount of spread within the body. In the typical setting and presentation, per current literature, CUP arises in the 7th decade of life in patients with multiple comorbidities, and often has a poor prognostic value. This case report identifies an atypical presentation of CUP, a 38-year-old Caucasian female with an axillary mobile mass, and no associated systemic symptoms. Biopsy of the node and immunohistochemical staining showed histology consistent with metastatic carcinoma. Mammography, MRI, and PET scan found no evidence of tumor primary or distant metastasis. Further staining confirmed metastatic carcinoma consistent with breast origin, without an established breast primary. As in this case, CUP may present in an atypical manner, warranting a thorough investigation aiming to identify the tumor primary to aid in identification of a proper treatment regimen and approach.

1. Introduction

This case highlights metastatic carcinoma without a definitive primary source of tumor, better known as cancer of unknown primary (CUP). This is a diverse group of patients with the diagnosis of metastatic malignancy, arising from any potential source in the body. CUP accounts for approximately 3–5% of all malignant diagnoses [1–8]. Of the different types of cancers, adenocarcinoma of various differentiation is the most common histopathological subtype [1,2]. The median age of diagnosis for all CUP, both men and women, ranges from age 60–66 [2,3]. Even with exhaustive work up, often the primary tumor is never found. Occult primary site may remain unidentified in up to 70% of cases even at autopsy [4]. CUP is also most often associated with a poor prognosis [5,6]. Generally, the median survival can range from 11 weeks to 11 months, with a five-year survival rate of approximately 11% [3]. However, CUP can be classified as either favorable, or unfavorable. Both Matias et al. and Ivica et al. report that CUP limited to a lymph node, specifically axillary in women, is a favorable prognostic subset with a survival much greater than those CUPs classified as unfavorable. The current standard of care for isolated axillary nodal metastasis is mastectomy, or irradiation with chemotherapy [2,3].

2. Case

A 38-year-old Caucasian female presents with a 4-day history of a mobile mass in her left axilla. She reports no systemic symptoms of fever, chills, night sweats or weight loss, nor any lumps or masses felt on self-breast examination. Past medical history is negative. Family history is significant for neoplasm of the breast in the maternal grandmother and ovarian cancer in a paternal aunt. Clinically, breasts are small and symmetrical, and a nipple-areolar complex with normal appearance. No palpable mass is assessed in either breast, and no masses noted in the right axilla. A 2.5 cm mobile left axillary node is palpated on examination.

Mammography was negative, and ultrasound showed a solid mass in the left axilla. Excisional biopsy of the $3.5 \times 3.0 \times 2.0$ cm node was performed and histology demonstrated highly pleomorphic, highly atypical cells with large nuclei and prominent nucleoli with increased mitoses as well as necrosis (Figs. 1 and 2). Cells demonstrated strong positivity for cytokeratin 7 and patchy pos-

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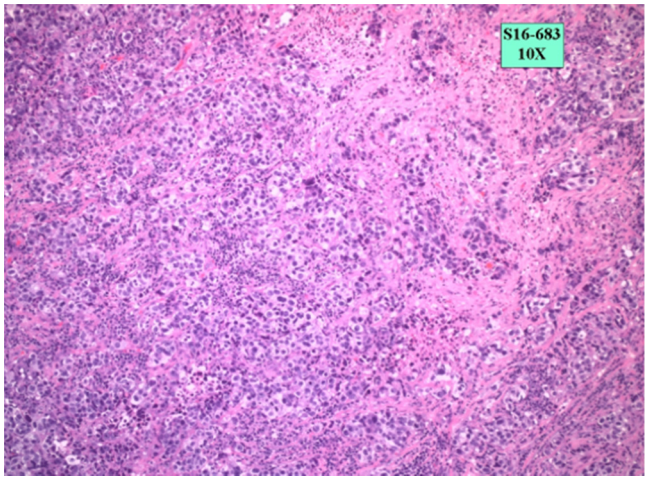

Fig. 1. Axillary node biopsy, magnification 10×.
Courtesy of Dr. Clinton McElroy, Department of Pathology, St. Francis Hospital, Columbus, GA.

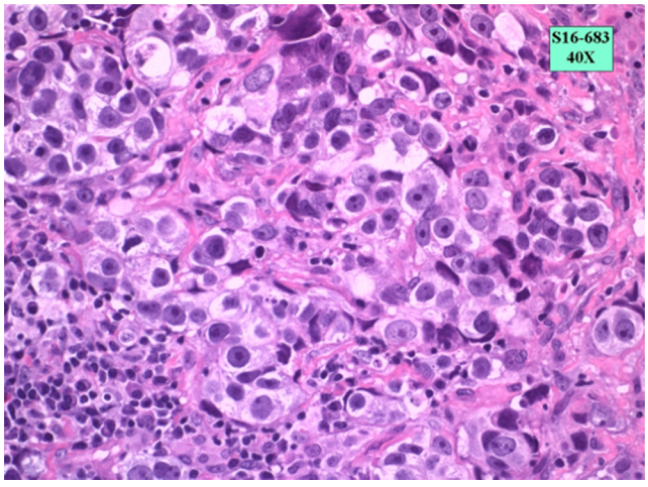

Fig. 2. Axillary node biopsy, magnification 40×. Note the atypical, pleiomorphic cells with large nuclei and nucleoli.

Courtesy of Dr. Clinton McElroy, Department of Pathology, St. Francis Hospital, Columbus, GA.

itivity for cytokeratin 5/6. Faint nuclear ER positivity was shown in approximately 1% of the cells. These findings suggest a probable breast origin. Additional staining for mammaglobin, GCDFP-15, PAX-8, TTF-1, WT-1, S-100, cytokeratin 20, and progesterone receptor all resulted as negative. The tissue was confirmed as metastatic carcinoma consistent with breast primary. MRI findings of the breasts showed no evidence of carcinoma. Other than post-surgical changes in the left axilla, PET scan also showed no definitive evidence of carcinoma or distant metastatic disease.

3. Discussion

CUP is a unique class of metastatic cancer, seemingly operating by its own rules of growth and metastasis. Rather than follow the typical type 1 progression as developing a premalignant lesion transforming to primary malignant lesion and then extension via metastasis, rather, CUP operates as type 2 progression which is metastatic expansion without an established primary [2]. The parallel progression model describes early metastasis in the development of a metastatic process [2,4,6] and predicts greater disparity between metastatic founders and primary tumor cells

Favorable subsets
1. Women with adenocarcinoma involving axillary lymph nodes
2. Women with papillary adenocarcinoma of peritoneal cavity
3. Squamous cell carcinoma involving cervical lymph nodes
4. Poorly differentiated neuroendocrine carcinomas. Merkel cell carcinoma of unknown primary (localized disease)
5. Adenocarcinoma with a colon-profile ($CK20^+$, $CK7^-$, $CDX2^+$)
6. Men with blastic bone metastases and elevated PSA (adenocarcinoma)
7. Isolated inguinal adenopathy (squamous carcinoma)
8. Patients with a single, small, potentially respectable tumor

Unfavorable subsets
1. Adenocarcinoma metastatic to the liver or other organs
2. Poorly differentiated carcinoma
3. Non-papillary malignant ascites (adenocarcinoma)
4. Multiple cerebral metastases (adeno or squamous Ca)
5. Multiple lung/pleural metastases (adenocarcinoma)
6. Multiple metastatic bone disease (adenocarcinoma)
7. Squamous-cell carcinoma of the abdominal cavity

Fig. 3. Favorable and unfavorable subset classification of CUP.
Credit: Pavlidis et al. [2].

than does linear progression [6], which is the development of genetic alterations within a cell, progressing to tumor, and then metastasis in a linear fashion. Vikesa et al. employed an extensive workup investigating genes and transcript coding of CUP, finding homologous repair networks suggesting chromosomal instability (CIN). They conclude that CIN distinguishes CUP from metastases of known origin. This instability of chromosomes renders CUP more lethal and difficult to treat as compared to cancer of known primary.

Diagnosis of CUP and proposed treatment rely heavily on identifying the type of cancer that is present, and also establishing its origin, if possible. With the parallel progression theory in mind, Bakhshayesharam et al. asserts that the primary lesion can be nearly too small to detect on routine imaging, and warrant the use of PET/CT. The advantage of this over anatomical imaging reveals metabolic activity of structures, with whole body imaging as the most useful tool to achieve the highest diagnostic yield [4]. Bakhshayeshkaram et al. utilized PET/CT on 62 patients where CT failed to identify a tumor primary in the setting of CUP. Of those 62 patients, PET/CT only identified a primary in 29 cases (48.8%). As with the specific patient highlighted in this case report, although a very useful imaging modality, PET did fail to identify a tumor primary for our patient. With ill-definitive imaging findings and ambiguous immunohistochemistry (IHC), are there other options to consider for diagnosis? Molecular profiling, also referred to as gene expression profiling (GEP), is a potential alternative. The rationale for studying molecular assays that define the location of origin in CUP is that cancers of different sites have specific genetic expression profiles that match their normal counterpart [5]. Per investigation by Green, the accuracy of GEP was significantly greater for poorly differentiated carcinomas (GEP 91%, IHC 71%, $p = 0.023$), and for cases that required 6 or more IHC stains, or a second requested round of staining [7]. The recommendation is that profiling assays be used in conjunction with IHC assay and clinical presentation [5]. However, Green asserts that even with GEP, up to 40% of CUPs may remain without an identified primary site, and further research on the topic is warranted.

Treatment approach of CUP depends primarily on the type of cancer, location, degree of involvement and spread, and likelihood of therapeutic response. This specific case, showing isolated axillary nodal metastasis, is classified as a favorable outcome subset of CUP (Fig. 3). This classification is generated by oncological stratification based on clinical presentation, host factors, tumor

histology, the amount and location of metastatic sites, and sensitivity to chemoradiation [3]. Per current research, the proposed treatment for isolated axillary metastasis with the best outcome is nodal dissection, mastectomy or breast irradiation and adjuvant chemo/hormonotherapy [2,3]. Survival is said to be longer in patients who received bilateral breast radiotherapy along with adjuvant systemic treatment [2]. Treatment approach selected for this patient is chemotherapy alone, without radiation or mastectomy at this time. This was decided based upon a second PET scan failing to show tumor or metastases, and BRCA testing with a negative result.

Potential and projected outcomes for patients diagnosed with CUP is a very important topic. Schaffer et al. established a retrospective cohort study, utilizing members of the Australian Government Department of Veteran's Affairs. Patients with CUP totaled 252, with a median age of 84 at diagnosis, and 980 patients with cancer of known primary, with median age of 83 at diagnosis. According to Schaffer et al., median survival at two years for CUP was 10%, and 33% for cancer of known primary. It was also established that CUP patients did have more hospitalizations and more comorbidities prior to diagnosis, compared to those patients with cancer of known primary origin [8]. Findings by Schaffer et al. do support the observation that CUP is a more advanced and aggressive metastatic disease at presentation, and with a poorer prognosis and outcome.

4. Conclusion

This case report has identified and presented a 38-year-old Caucasian female patient with an enlarged axillary node found to be metastatic carcinoma of breast origin without an identified breast tumor primary. This patient does not fit the typical profile of CUP, as she is much younger than the median age of diagnosis, and also does not have a history of extensive comorbidities. As previously discussed, given the presentation of isolated axillary node metastasis, this patient has a more favorable prognosis comparatively to those categorized as unfavorable. Treatment for this patient was selected as chemotherapy alone, without mastectomy or combination irradiation and chemotherapy, given the inability to find tumor metastases via PET scanning, and negative BRCA results. It is challenging to predict a prognosis specific to this patient or stratify the risk of relapse as this case is certainly unique compared with current research and presentation. We will continue to follow and monitor this patient.

Conflicts of interest

There are no conflicts of interest.

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Ethical approval

This case report does not require ethics approval.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

Spencer R. Anderson: Responsible for research, organization, and composition of this case report.

Charles S. Scarborough, MD: Responsible for the interview, exam, and management of the patient.

Guarantor

Spencer R. Anderson.

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