The Utility of Ultrasound-guided Tru-cut Biopsy in the Diagnosis of Occult Breast Carcinoma Presenting as Ovarian Malignancy with Multiple Metastases: A Case of Unknown Primary

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ABSTRACT

This paper documents the utility of ultrasound-guided tru-cut biopsy in the diagnosis and subsequent management of a case of occult breast carcinoma presenting with multiple distant metastases in the absence of a primary breast lesion. She was initially diagnosed as primary ovarian malignancy with metastatic disease and subsequently underwent transvaginal ultrasound-guided tru-cut biopsy of the right ovarian mass. Histologic and immunohistochemical studies were consistent with a metastatic adenocarcinoma of breast origin. The patient underwent chemotherapy for primary breast carcinoma and has responded well.

Keywords: carcinoma of unknown primary, occult breast cancer, ovarian metastases, tru-cut biopsy, ultrasound

INTRODUCTION

Carcinoma of unknown primary (CUP) refers to a heterogeneous group of metastatic cancers with no identifiable primary tumor at initial presentation following a standard clinical and radiological evaluation.[1] It accounts for 3-5% of all cancer cases presenting most commonly as metastases to the lymph nodes, lung, liver and bone. Majority (75-85%) present as disseminated metastases whereas 15-25% present as solitary metastasis.[2] Because of its predilection for early and aggressive metastasis, establishing a definitive histopathologic diagnosis of the primary site of tumor is crucial in determining the most appropriate management.

Tru-cut, also known as core needle biopsy, is a minimally invasive technique for acquiring tissue samples for histopathologic diagnosis. It was first used by Mellinger and Blackhard in 1967 for obtaining prostate biopsies.[3] Since then, tru-cut biopsy has been commonly used in the diagnosis of different types of tumors including breast, liver and kidneys. Its use in gynecology, however, has been limited by the accessibility of most pelvic tumors which are located deep within the pelvis. With the advent of ultrasound-guidance, tru-cut biopsy has become an emerging diagnostic tool in gynecologic oncology. To the best of our knowledge, the first case of transvaginal ultrasound-guided tru-cut biopsy in the Philippines was performed in our institution in August of 2019.

The most common indication for tru-cut biopsy is a primary inoperable or suboptimally operable advanced tumor.

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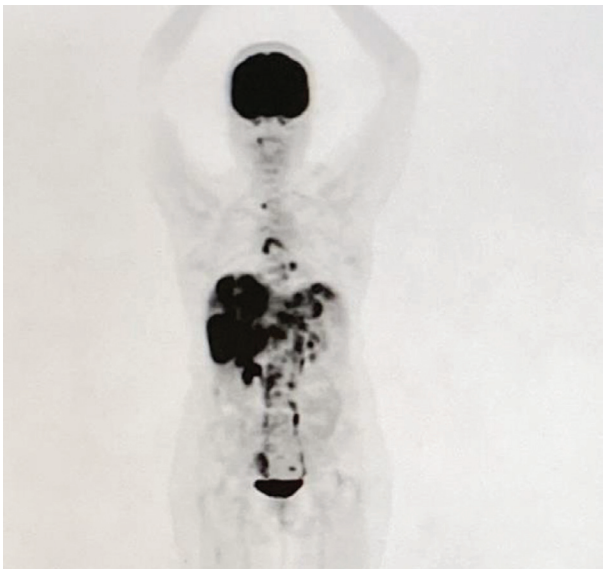

Figure 1. ^{18}F-fluorodeoxyglucose PET-CT showing hypermetabolic areas with intense FDG uptake in the liver, right adnexal region and multiple lymph nodes in the mediastinum and abdomen.

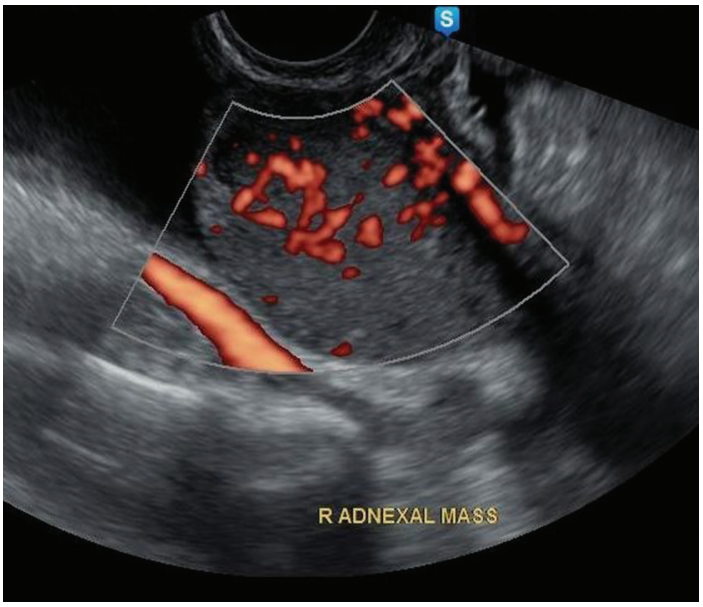

Figure 2. Transvaginal ultrasound showing a solid ovarian mass with abundant central and peripheral branching vascularity (Color Score – 4).

It may also be done when there is diagnostic uncertainty of tumor recurrence from either a known gynecologic or non-gynecologic tumor, suspicious pelvic metastases in a patient with a known non-gynecologic tumor, or tumors suspected to be of non-gynecologic origin. Patients who are not good candidates for surgery due to comorbidities may also undergo the procedure.[4,5]

This paper highlights the role of ultrasound-guided tru-cut biopsy in the diagnosis and subsequent management of a case of carcinoma of unknown primary from an occult breast cancer, presenting initially as ovarian malignancy with multiple metastases.

CASE REPORT

A 49-year-old G2P2 (2002) presented with a two-month history of right upper quadrant pain with anorexia and weight loss. The bilateral breasts were symmetrical with no palpable mass. On pelvic examination, there was a right adnexal solid mass measuring 3 x 3 cm, movable and nontender.

An abdominal CT scan showed a solid right ovarian mass measuring 3 x 2.4 x 3.6 cm. There were multiple hepatic masses with the largest measuring 7.4 x 6.1 x 6.7 cm and multiple lymph nodes in the pelvis, abdomen and retroperitoneum.

PET-CT demonstrated hypermetabolic areas in the right adnexal region, liver, abdominal and mediastinal lymph nodes and suspicious foci on the 3rd right rib, T6 and right posterolateral abdominal wall (Figure 1). There was no suspicious mass on both breasts and axillae. The primary impression was a right ovarian mass, likely to be the primary malignancy, with metastatic disease. Serum CA-125 (>5,000 U/mL), CEA (>1,000 ng/mL) and CA 15-3 (>300 U/mL) were markedly elevated. Serum HE4, CA 19-9 and AFP were normal.

The patient was referred to an interventional radiologist for ultrasound- guided fine needle aspiration biopsy (FNAB) of the hepatic mass which showed adenocarcinoma. The samples, however, were insufficient for further testing including immunohistochemistry. She was subsequently referred to our institution for ultrasound-guided tru-cut biopsy of the right ovarian mass. On transvaginal scan, there was a solid right ovarian mass measuring 4.9 x 3.2 x 3.2 cm with abundant central and peripheral branching vascularity, Color score – 4 (Figure 2). There were tumor implants in the pelvic peritoneum with sizes up to 1.4 x 2.2 x 0.9 cm and moderate ascites. On transabdominal scan, there were hyperechogenic masses with hypoechogenic halo ("bull's eye" or "target" sign) within the liver, with the largest measuring 6.2 x 5.2 x 5.1 cm (Figure 3), with enhanced peripheral vascularity. The sonologic impression was a right ovarian new growth, malignant by subjective assessment with hepatic metastases and peritoneal carcinomatosis.

Since the ovarian mass was more accessible at the cul-de-sac, transvaginal ultrasound-guided tru-cut biopsy was performed with a Bard Magnum biopsy device which is fully automated with a spring-activated mechanism (Figure 4). It has a selectable penetration depth of 15 mm and 22 mm allowing the operator to preset the depth of needle throw depending on the size of the lesion. A gauge-18 tru-cut needle was loaded to the device and inserted through the needle guide attached to the transvaginal probe. The needle was then directed to well-vascularized, viable areas within

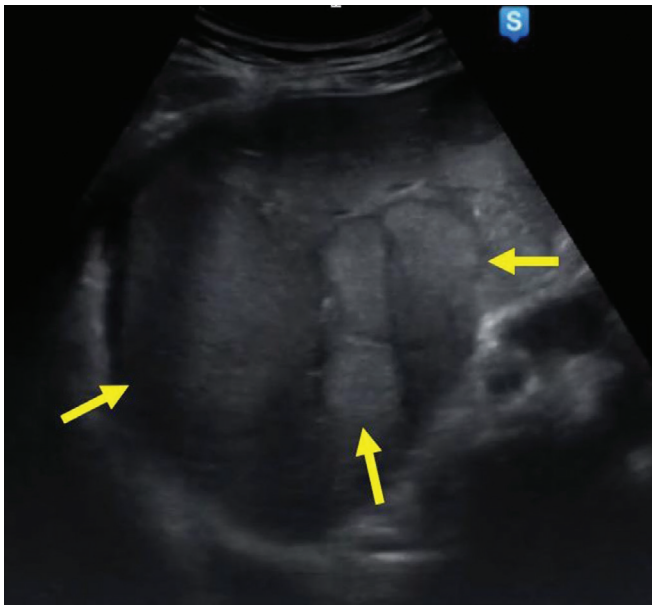

Figure 3. Transabdominal scan showing multiple hyperechogenic hepatic masses with hypoechogenic halo *("bull's eye" or "target" sign, yellow arrows)*, suggestive of hepatic metastases.

the tumor to avoid sampling necrotic tissues. Six cylinders of compact tissues measuring 10-20 mm long and 1.4-2 mm wide were obtained from multiple sites and fixed in 10% formaldehyde solution (Figure 5).

Histopathologic examination showed a poorly differentiated adenocarcinoma. The specimen was subsequently sent for immunohistochemistry (IHC) which turned positive for CK7, GATA-3, mammaglobin, MOC31 and HepPar1 and negative for CK20, PAX8, CDX2 and estrogen receptor. The case was signed out as a metastatic adenocarcinoma of breast origin. The patient was subsequently started on chemotherapy and has responded well.

DISCUSSION

Occult breast carcinoma (OBC) refers to a histologically confirmed metastatic breast cancer in the absence of a primary breast tumor. It accounts for 0.3–1% of all breast cancers, most commonly presenting as metastasis to the axillary lymph nodes.[6] OBC is thought to be secondary to microinvasive breast cancer.[7] Due to its rarity, the mechanism by which metastatic disease occurs in the absence of a primary breast lesion remains unclear. It is suggested that spread to distant organs is due to the inherent metastatic aggressiveness of cancer cells.

Primary breast carcinoma was not entertained in this patient due to the absence of a breast mass on physical examination and imaging studies. Both PET-CT and ultrasound favored the diagnosis of a primary ovarian malignancy with multiple metastases. Results of the tumor markers, however, were equivocal with markedly elevated serum CA-125, CEA and CA 15-3. Increased CEA levels may be seen in colorectal, gastric, pancreatic, breast and

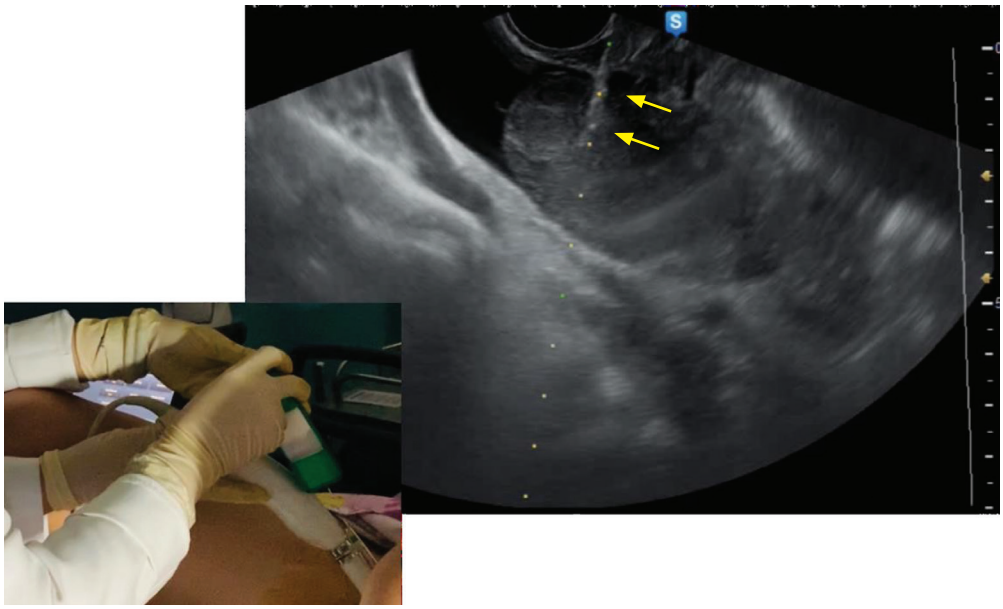

Figure 4. Tru-cut biopsy of the right ovarian mass done under transvaginal ultrasound guidance. The tru-cut needle is inserted through the needle guide attached to the transvaginal probe. After securing placement of the needle within the tumor, the biopsy gun is fired. The biopsy needle *(yellow arrows)* is shown penetrating into the lesion. The dotted line represents the track of the needle.

Figure 5. Tissue specimen obtained from tru-cut biopsy fixed in 10% formaldehyde solution.

lung cancers while CA 15-3 is used as marker for advanced breast cancer.

Distinguishing primary ovarian cancer from secondary ovarian metastasis is important since management is different. For primary ovarian cancer, the main goal is primary cytoreductive surgery whereas treatment approach varies for metastatic ovarian cancer. Most ovarian metastases are derived from the gastrointestinal tract , followed by breast and gynecologic organs.[8] Majority present as predominantly or purely solid ovarian masses and bilateral in about 69% of cases. They are generally smaller than primary ovarian carcinomas, usually less than 10 cm in diameter. Metastases from breast cancer are usually smaller than those from the gastrointestinal tract. Testa, et al.[9] described ovarian metastases from breast as predominantly solid and smaller in size with mean diameter of 5.5 cm compared to colorectal metastases which were larger with mean diameter of 11.3 cm and predominantly multilocular-solid. The presence of a 'lead vessel" defined as a major vessel exhibiting a 'tree-shaped' morphology, penetrating from the periphery into the center of an ovarian tumor, has been introduced by Testa, et al.[10] as a sonographic feature of ovarian metastasis. It has been found in 35% of metastatic ovarian tumors and in 0.01% of primary ovarian tumors. This patient presented with a 4.9 cm solid ovarian mass with abundant central and peripheral branching vascularity. The lead vessel was not described but as seen in the power Doppler image (Figure 2), there's note of abundant branching vascularity from the periphery and central part of the lesion.

The most common sites of metastasis for breast cancer are bone (65.1%), lung (31.4%), liver (26%) and brain (8.8%).[11] As seen on imaging, the patient had multiple metastases in the liver, lymph nodes and bone. Hepatic metastases usually present as multiple solid lesions in 77% of cases and as a solitary mass in 10%.[12] On ultrasound, they appear as round hypoechoic or hyperechoic lesions with irregular borders and may exhibit peripheral hypoechoic rim or halo as seen in this case. This hypoechoic halo corresponds histologically to an intratumoral rim of proliferating tumor cells surrounding a central hyperechoic or isoechoic area with coagulation necrosis, resembling a "bull's eye" or "target" sign appearance.[13]

Doppler sonography often demonstrates peripheral vascularity in the hypoechoic zone containing viable tissues.

The evaluation of CUP is aimed at determining the primary site of origin in order to institute the most appropriate management. Histopathologic examination remains to be the gold standard. There are different methods to obtain tissue biopsy which include FNAB, tru-cut biopsy, diagnostic laparoscopy and mini- laparotomy. The most ideal method should be minimally invasive, can be done in an outpatient setting, does not require general anesthesia and should not cause any complications. Among these techniques, only FNAB and tru-cut biopsy satisfy these criteria, being the least invasive. Although FNAB provided the initial diagnosis of adenocarcinoma in this case, the sample was not sufficient for IHC. Tru-cut biopsy provided adequate samples which helped in establishing the definitive diagnosis. The main limiting factor of FNAB is the small sample size which only provides isolated cells or cluster of cells suitable only for cytologic evaluation, resulting to high false negative results. The tissue architecture is also disrupted and provides insufficient sample for IHC. In contrast, tru-cut biopsy provides compact tissue with preserved architecture suitable for complete histopathologic evaluation including IHC. At least 3 tissue core samples are adequate enough to establish a definitive diagnosis.

Several studies have shown ultrasound-guided tru-cut biopsy to have high diagnostic accuracy in the diagnosis of abdominopelvic tumors, ranging from 93-98% and high adequacy rates ranging from 93-100%.[5,6,14] Compared to FNAB, tru- cut biopsy has been shown to provide higher tissue adequacy for histopathologic examination (93-100% versus 73.5-92.8%) and IHC tumor subtyping (92.9% versus 75%). In addition, tru-cut biopsy has demonstrated higher concordance with the final histopathologic diagnosis compared to FNAB (93.3% versus 39.4%).[15]

Ultrasound-guided tru-cut biopsy can be done transvaginally, transabdominally and transrectally. The transvaginal is generally more favored over the transabdominal approach due to the proximity of the probe to the deeply located pelvic tumors. It provides a better sonographic window and shorter biopsy distance, resulting in higher diagnostic yield and safer tissue sampling. The transrectal approach, on the other hand, is preferred in patients with no history of coitus, with radiation-induced vaginal stenosis, or with post-surgical or postmenopausal vaginal shortening. In this patient, the biopsy was done under transvaginal ultrasound guidance since the mass was more accessible at the cul-de-sac. Since post-procedural bleeding is a major concern in any patient undergoing biopsy, bleeding parameters are checked prior to the procedure to exclude patients who are at higher risk for bleeding. Platelet counts of >100,000/uL and an International Normalized Ratio (INR) <1.4 are required. The reported complication rates are low ranging from 0-1.2%.[4,5,14-17]

IHC is recommended to identify specific protein markers which can help in establishing the specific tumor subtype and site of origin in cases of CUP. Since most ovarian metastases originate from the gastrointestinal tract and breast, the specimen in this case was tested for different IHC stains that would establish the primary site of origin. A metastatic adenocarcinoma of breast origin was favored since the tumor stained positive for mammaglobin and GATA-3 which are known markers for breast carcinoma. CK7 is expressed in various ductal and glandular epithelia including lung, breast, ovary and endometrium. CK20 and CDX2, on the other hand, are primarily found in the gastrointestinal epithelium. The combined expression patterns of CK7 and CK20 have been extensively used to differentiate adenocarcinomas arising from the female genital tract from those arising from other

organs. This patient stained positive for CK7 and negative for CK20 which further strengthened the diagnosis of a metastatic breast carcinoma. Metastatic colorectal cancer was not favored due to negative staining with CDX2 and CK20. A primary ovarian cancer was ruled out since the patient stained negative for PAX-8 which is a known marker for primary ovarian carcinomas. Primary hepatocellular carcinoma was excluded due to immunoreactivity to MOC-31 which is a marker for metastatic adenocarcinoma. The weak staining with Hep-Par1 was thought to be an aberrant expression of the tumor rather than evidence of hepatocellular origin.[18]

CONCLUSION

Identifying the primary site of tumor in patients presenting with metastatic cancer without a known primary tumor takes precedence since this will dictate the management, outcomes and overall prognosis. As highlighted in this case, ultrasound-guided tru-cut biopsy proves to be a safe and viable diagnostic procedure, being minimally invasive with high adequacy and diagnostic accuracy rates.

Statement of Authorship

Both authors contributed in the conceptualization of work, acquisition and analysis of data, drafting and revising, and final approval of the version to be published.

Author Disclosure

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