Case Report

A case of cancer of unknown primary origin without a primary site

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Abstract

About 3% of all patients with cancer have cancer of unknown primary origin (CUP). This study is on a patient who reported for a gynecologic checkup as she was on tamoxifen and noted to have metastatic lesions at multiple sites including pelvis, uterus, tubes, and ovaries. The case presented is interesting as the patient has no primary site of carcinoma of breast, but PET–CT scans and advanced immunohistochemistry techniques used for the metastatic tissue showed strong positivity to breast carcinoma. Various intensive tests were needed to diagnose the primary site without a lesion. Also, the patient received the first-line chemotherapy, multiple transfusions, debulking surgery, and then the second-line chemotherapy. With a poorly differentiated carcinoma spread all over the skeletal system, gut, abdomen, and pelvis, the patient tolerated the second-line chemotherapy also and is still surviving 2 years after the detection of CUP.

KEY WORDS: Carcinoma of unknown primary origin, positron emission tomography, 18 F-fluorodeoxyglucose, immunohistochemistry, debulking surgery

Introduction

About 3% of all cancer patients have cancer of unknown primary origin (CUP). These patients present with widespread metastatic disease for which a primary site cannot be detected at the time of diagnosis despite a good medical history, detailed clinical examination, and extensive investigations. The primary site may either have a slow growth or may possibly become involute and therefore unlikely to manifest itself.

Despite advances in imaging technology and immunohistochemistry (IHC) and the introduction of serum tumor markers in the everyday clinical practice, CUP still imposes a diagnostic and therapeutic dilemma. Advanced investigational procedures and aggressive treatment are needed to treat these patients.[1]

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Case Report

Patient aged 40 years, with intermittent fever, chills, myalgia with headache, giddiness, easy fatigability, and exertional dyspnea for last 1 month, was admitted to a hospital 2 years ago. She had no H/O active bleeding manifestation, dysuria, cough, altered sensorium, or vomiting; no significant menstrual history, past history, family history, or personal history; and no problematic obstetric history—two normal deliveries, breast-fed for 6 and 9 months, respectively.

Patient had severe pallor, no edema, and all other systems normal. She had soft abdomen with no mass

On investigations it was found that she had Hb 4.5 g%, platelet count 23,000 mm^3 and pancytopenia. While the patient received several blood transfusions, antibiotics, antipyretics for the treatment of pancytopenia, a bone marrow biopsy was performed that showed metastatic carcinoma, diagnosed as CUP. The investigations conducted in 2012 are listed with reports in Table 1.

From these investigations, it was evident that the IHC of the tissue showed secondaries in the bones with strong positivity for primary breast carcinoma. Neither mammogram nor FNAC of the breast tissue and supraclavicular nodes showed any evidence of primary malignancy in the breast.

Table 1: Investigations performed in November to December 2012

Bone marrow biopsy	Metastatic carcinoma
IHC	Atypical cells positive for PAN-CK These cells expressed CK-7 positivity Expressed nuclear positivity for ER and PR Her-2 neu showed cytoplasmic staining Tumor cells negative for CK 20 and MPO stains
Bilateral mammogram	ACR BIRADS assessment category 0 No definitive mammographic evidence of malignancy Dense nature of breast parenchyma
FNAC Rt breast lump Rt axillary nodes Rt supraclavicular node	Fibrofatty fragment and small cohesive cluster of ductal epithelial cells; no malignant cells BC—fibrofatty tissue; scattered lymphoid cells No definitive opinion possible
Whole-body PET–CT scan	Bone marrow showed metastatic Ca. ?? primary Low-grade FDG uptake in right axillary nodes No metabolically active lesion seen to suggest a possible primary neoplasm Minimal free fluid seen in POD
Repeat bone marrow biopsy with IHC	Neoplastic cells express CK-7, GCDFP-15, ER, PR, CK 19 Negative to CK-20, CDX -2, CEA, mammoglobin, TTF-1, CA-125, CA-19-9 Impression: metastatic carcinoma, consistent with primary site in breast
Gastro duodenoscopy	Fundic gastritis Duodenal lesion as above GIST??? Lymphoma
Biopsy from duodenal bulb report	Chronic nonspecific duodenitis

Table 2: Post-chemotherapy investigations performed in September 2013

CT scan from vertex to mid-thigh	i. No recurrent breast ca; multiple tiny osteoblastic metastasis throughout vertebral column, pelvic bones, sternum, ribs, proximal femur, and humeri ii. 4.6 × 1 cm mild thickening of post-wall of pylorus iii. Mild diffuse stranding and nodularity in omentum and mesentery
UGI endoscopy	Duodenal bulb deformed with puckered mucosal folds: post-ulcer sequelae
Biopsy from stomach	i. Chr gastritis, with intestinal metaplasia ii. No evidence of malignancy in this biopsy specimen

Table 3: Investigations performed in March 2014

St X-ray chest	Unremarkable radiograph of chest
USG abd and pelvis	Splenomegaly, mild ascites, hemorrhagic cyst of left ovary

She was diagnosed with skeletal and bone marrow metastasis supporting breast carcinoma with no primary site.

She received a total of 18 weeks of chemotherapy with single drug paclitaxel; she also received 40 units of packed cell blood transfusion and two platelet transfusions. Finally, she was placed on tamoxifen 20 mg daily for the past 10 months.

Post-chemotherapy evaluation was carried out as shown in Table 2. Table 3 shows the follow-up investigations performed in March 2014.

In June 2014, a general and gynecological checkup showed pallor++, P/A soft, and non-tender, with no palpable mass. Bimanual examination showed uterus 10-week size, R/V, fixed right forniceal irregular mass, indurated and full posterior fornix. The investigations conducted at that stage are shown in Table 4.

The biopsy tissue from the duodenal nodule and FNAC of the right adnexal mass IHC suggested breast carcinoma metastasis. Following 3 units of packed cells transfusion, laparotomy and panhysterectomy with total omentectomy were performed in July 2014.

Postoperative period was stormy for 5 days, with excessive vomiting, acute renal failure, and paralytic ileus. Hemorrhagic ascitic fluid continued for 15 days through the drain and managed accordingly. She received 2 units more of packed cells postoperatively.

Histopathology of the specimen was as follows: invasive lobular Ca metastasizing to bilateral ovaries, Fallopian tubes, myometrium, cervix, and omentum. Rectal deposit and six lymph nodes showed metastasis.

Postoperative chemotherapy report showed that the patient received three cycles of chemotherapy (Inj.

Table 4: Investigations performed in June 2014

Hb g%	11.6
Platelets, urea, creatinine, LFT	WNL
CA 125	707.3 U/ml
CT scan vertex to mid-thigh	Uterus—unremarkable Multiloculated cystic lesion with septations at right adnexa—10.6 × 7.3 cm Metabolic activity in enhancing nodules Similar left adnexal mass 6.1 × 3.1 cm
PET scan with FDG	No recurrent breast mass Marginal pyloric thickening Moderate ascites Bilateral complex solid cystic masses Tiny osteoblastic metastasis throughout vertebrae, pelvic bones, sternum, ribs, and proximal femur relatively unchanged since prior study
UG endoscopy with biopsy	Dicohesive cells highlighted by ER, CK-7, and patchily GCDFP15 immunomarkers; CK 20 negative Suggestive of breast Ca metastasis
USG guided biopsy of right adnexal mass	Poorly differentiated adenocarcinoma. ? Primary? Secondary
IHC single marker	CK7, GCDFP expressed CA125, E-Cadherin not expressed

Table 5: Follow-up report (October 2014)

CA 125	75
PET–CT scan—no recurrent breast mass	Resolution of moderate ascites and trace pleural effusion
Mild interval regression of pyloric wall thickening	Multiple tiny osteoblastic metastases throughout the vertebral column, pelvic bones, ribs, proximal femora, and humeri relatively unchanged since prior study
Moderate interval regression of stranding and nodularity in mesentery	No new metastasis

gemcitabine + Inj. carboplatin) and showed good response. Follow-up investigations and the reports are shown in Table 5.

Discussion

CUP site is classified into one of five broad categories:

1. Adenocarcinoma: 60% of CUP
2. Poorly differentiated carcinoma: 30% of CUP: about 10% of these turn out to be lymphoma, melanoma, or sarcoma
3. Squamous cell cancer
4. Poorly differentiated malignant neoplasm
5. Neuroendocrine carcinoma: these rare cancers start from cells of the diffuse neuroendocrine system

More intensive testing is needed to classify them better. The various modalities for diagnosing the primary site include the following:

1. X-rays, mammography
2. Scans: CECT, PET scan
3. Biopsy
4. Tumor markers:
   i. CA 15.3: used to find breast and ovarian cancers
   ii. TRU-QUANT and CA 27.29: may mean that breast cancer is present
   iii. CA125: may signal ovarian cancer, ovarian cancer recurrence, and breast cancer recurrence
   iv. CEA (carcinoembryonic antigen): a marker for the presence of colon, lung, and liver cancers. This marker may be used to determine if the breast cancer has traveled to other areas of the body
5. Circulating tumor cells
6. IHC: this has a number of significant inherent advantages over other molecular assay methodologies, including availability, cost, and morphologic confirmation of the tissue assay, turnaround time, and adaptability to most existing pathology practices.[2]
   i. IHC for HER2 testing
   ii. IHC for hormone receptor testing—ER and PR

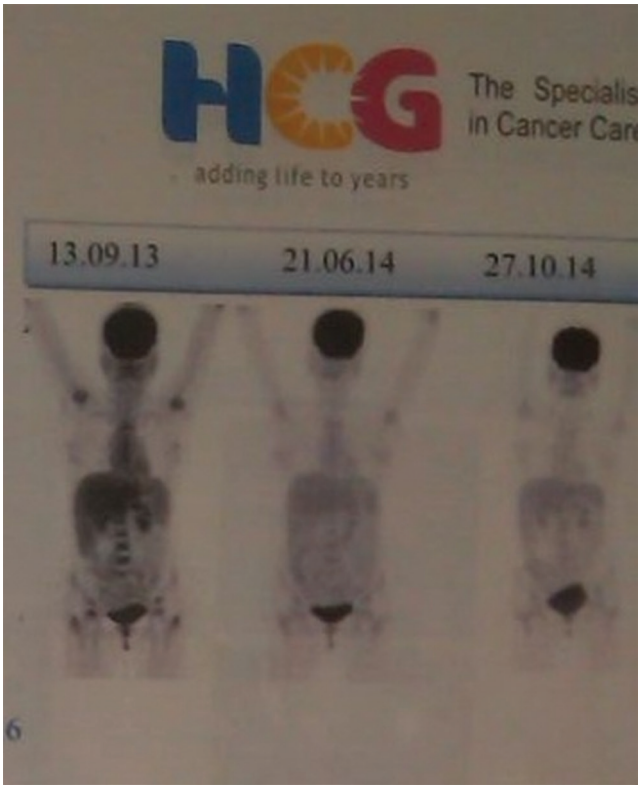

Figure 1: A comparative study of the PET–CT scans of the patient (a) after the first sequence of chemotherapy, (b) before surgery, and (c) after surgery and the second-line chemotherapy.

Table 6: Detail of intraoperative findings

1	2 L of hemorrhagic fluid
2	Whole inner surface of parietal peritoneum covered with fine granular lesions with thickening
3	Whole omentum and appendices epiploiacae were thickened, granular, and firm
4	Uterus 10-week size with bilateral multiloculated hemorrhagic ovarian cysts noted

7. Gene-profiling microarray diagnosis: 21-gene signature (Oncotype DX), 70-Gene signature (Mamma print)
8. Molecular diagnosis shows high sensitivity

The primary site is not detected in most of the instances despite extensive investigations.[3]

In this patient, IHC of CK-7, GCDFP-15, ER, PR, and CK 19 were positive and strongly suggestive of primary site in breast. ER and PR and Her-2 neu were also positive. However, at no point during the last 2 years, the breast tissue tested positive for malignancy. Secondaries were initially found in the brain, skull bones, vertebral column, and other skeletal tissue and bone marrow. Later, even the duodenal growth and bilateral ovarian tumor tissue tested positive for secondary to primary breast carcinoma as diagnosed by IHC. Figure 1 shows the comparison of the PET–CT scans of the patient taken on three occasions.

Metastatic adenocarcinoma is the most common CUP histopathology (80%). CUP patients are divided into subsets of favorable (20%) and unfavorable (80%) prognosis. Favorable subsets are mostly given loco-regional treatment or systemic platinum-based chemotherapy. Responses and survival are similar to those of patients with relevant known primary tumors. Patients in unfavorable subsets are treated with empirical chemotherapy based on combination regimens of platinum or taxane, but responses and survival are generally poor.[4] In the study, the patient belonged to the high-risk category but is responding well to the second-line chemotherapy.

Conclusion

Presented here is a case of a patient with metastatic tissue detected in skeletal system, bone marrow, gut, all over the peritoneal cavity, the uterus, and ovaries. IHC confirmed the markers suggestive of the primary site in the breast, but the breast tissue has not shown any primary site.

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