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Carcinoma of Unknown Primary: A Case Report

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Abstract Cancer of unknown primary (CUP), is a rare malignancy with unknown site of origin. The disease accounting for 2%-3% of all fatal malignancies, have variable histologic tumour types and clinical presentations. The present study discusses a case of CUP in a 68-year-old male subject, presenting with a 6-month history of abdominal pain in the upper abdomen. The patient was a chronic smoker and had the presence of bilateral testicular swelling for the past 15 years. The clinical examination of the patient revealed bilateral inguinal lymphadenopathy. The findings of the abdominal CT scan and the bone biopsy of the patient suggested metastatic carcinoma. 18F-fluorodeoxyglucose PET CT scan showed lytic lesions. The study recommends the need for a focused search, comprising of robust immunohistochemical profiling, for locating the primary tumors in CUP.

Keywords: *cancer of unknown primary (CUP), tumor, malignancies, metastatic carcinoma, biopsy, immunohistochemical profiling*

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1. Introduction

Cancer of unknown primary (CUP) is a rare heterogeneous group of cancers, for which the site of origin remains unknown, despite following a standard diagnostic approach. [1] CUP poses major diagnostic and therapeutic challenges to the oncologists. [2] The disease, which has been reported to be frequently originating from the lungs and the upper abdominal organs accounts for 2%-3% of all fatal malignancies. [3] Increased incidence of CUP has been noted in elderly, females and individuals belonging to less affluent or less educated localities. [4,5] According to the 2012-14 report, 6 out of 10 individuals belonging to the ≥75 year age group were diagnosed with CUP per year in the UK [6,7].

The etiology and pathogenesis of CUP is poorly comprehended. [8] The signs and symptoms of the disease, which may vary depending on the site of metastasis, are usually caused by other conditions or by CUP. [9] Patients with CUP have variable histologic tumor types and clinical presentations. [10] Smoking accounts for 19% of the cases with CUP. [11] The present study discusses an interesting case of CUP in an elderly subject.

2. Case Presentation

A 68-year-old male patient was admitted to the hospital with a 6-month history of abdominal pain in the upper abdomen, which did not relieve with analgesic administrations. The pain was continuous, insidious in onset, and vague aching type with moderate to severe intensity, which aggravated with forward bending. However, the patient did not have nausea, vomiting, melena, hematochezia or bleeding per rectum.

The patient history revealed the presence of bilateral testicular swelling for the past 15 years with more enlargements in the right side. The swelling was not associated with pain and the etiology was undiagnosed. The patient had loss of appetite for the past three months, but no weight loss. He had no history of fever, abdominal distension, chest pain, palpitation or syncope.

The patient was diagnosed with chronic obstructive pulmonary disease around one month back. Further investigations ruled out the presence of diabetes mellitus, hypertension and ischemic heart disease. The patient was a chronic smoker for the past 50 years, with an average consumption of 10 beedis/day. He did not have any other addictive habits.

3. Investigations

The patient was moderately built and nourished, conscious and oriented. The clinical examination of the patient revealed: normal pulse and oral temperature; 100/60 mmHg blood pressure; bilateral inguinal lymphadenopathy with firm and non-tender lymph nodes of 2-4 cm in size; and absence of pallor, icterus, clubbing, cyanosis or pedal edema. His skin examination revealed absence of periorbital edema, purpura, petechiae or ecchymoses. The patient had normal jugular venous pressure. Examination of his abdomen showed mild tenderness in the epigastric region, but there was no organomegaly or free fluid. Local examination of the external genitalia revealed non-tender bilateral scrotal swelling, predominantly on the right side, but the trans-illumination test was negative. Examination of the spine revealed tenderness at the D8 vertebral region. The clinical examination of the cardiovascular, respiratory, nervous systems was normal. The results of the laboratory investigations conducted are provided in Table 1.

Peripheral smear showed normocytic normochromic anemia of mild degree. The chest X-ray findings of the patient was normal. Esophagogastroduodenoscopy showed Los Angeles grade A oesophagitis and pangastritis. Ileocolonoscopy was indicative of grade II internal hemorrhoids.

The CT scan of the abdomen showed large right sided epididymal cyst with left moderate hydrocele; and lytic lesions in the pedicle lamina and transverse process of D8 vertebra and intertrochanteric region of left femur, possibly suggestive of metastasis. It also revealed minimal circumferential enhancing wall thickening (5mm) in the lower rectum. Inflammatory and emphysematous changes were also noted in the bilateral lung field of the patient.

18F-fluorodeoxyglucose (FDG) PET CT scan showed FDG lytic lesions in left transverse process of T5 vertebra; body, left transverse process and spine of T8 vertebra with soft tissue component (Max SUV 10.1) with lysis of adjacent left 8th rib and intra-spinal extension with mild cord compression; T9 vertebra; Spine of L2 and L3 vertebra (Max SUV 10); Sacrum (Max SUV 10.2 in left ala); Proximal shaft of left femur. There was no abnormal enhancing or FDG avid lesions in the brain, lungs, liver or adrenals.

Table 1. Results of the laboratory investigations

Parameters evaluated	Results
HB (g/dl)	12.9
Total leukocyte count (cells/mm^3)	9,400
Red blood cell count (cells/mm^3)	4,36,000
Packed cell volume (%)	38.7
Mean corpuscular volume (fL)	88.8
Mean corpuscular hemoglobin (pg)	29.6
Mean corpuscular hemoglobin concentration (%)	**33.3**
Platelet count (cells/mm^3)	136,000
Blood urea (mg/dl)	38
Serum creatinine (mg/dl)	0.67
Serum sodium (mEq/L)	135.9
Serum potassium (mEq/L)	4.42
Serum calcium (mEq/L)	8.5
Total prostate specific antigen (ng/dl)	0.58
Free prostate specific antigen (ng/dl)	0.11
Free prostate specific antigen (%)	18.97
Serum alkaline phosphatase (mg/dl)	34
Random blood sugar (mg/dl)	108
Prothrombin time (s)	13.5
Activated partial thromboplastin time (s)	26.6
INR	1.20
HIV-ELISA	Non-reactive
HCV-ELISA	Non-reactive
HBsAg-ELISA	Non-reactive

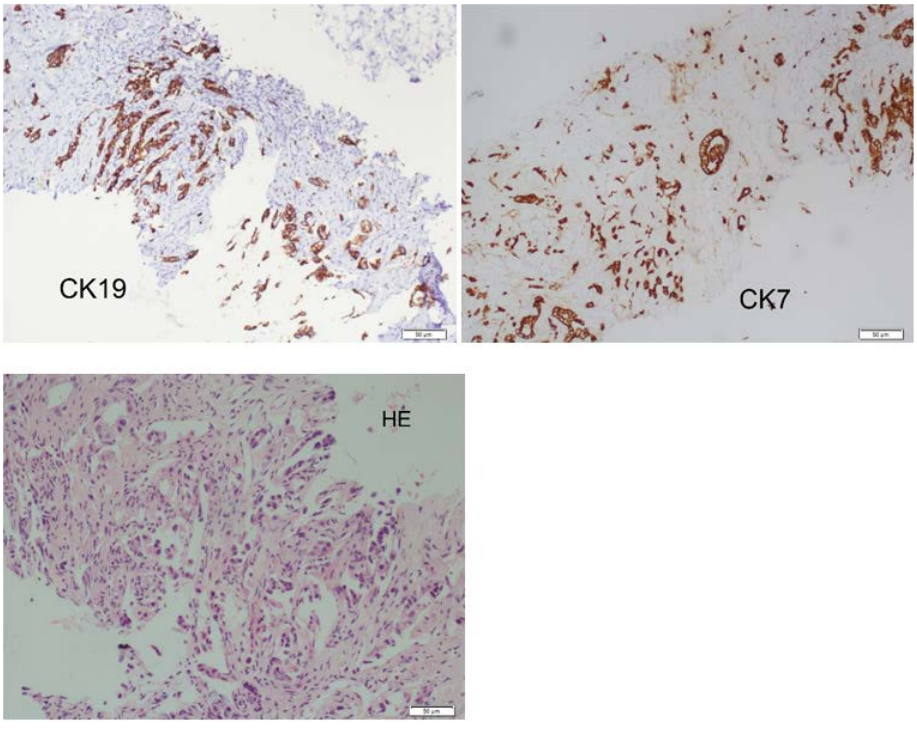

Figure 1. Immunohistochemical findings showing positive for CK 19 and CK 7

The bone biopsy of the patient revealed metastatic carcinoma. The immunohistochemistry (IHC) profile of the patient suggested a possibility primary site being upper gastrointestinal tract or pancreato-biliary tract. The microscopic examination of the specimen showed fibro-collagenous tissue with the presence of tumor cells scattered singly, cords and occasionally forming glandular structures. On IHC, the cells were found to be positive for CK7, CK19, CA19.9 and negative for CD20, PSA, TTF1, CDX2, WT1 and CD56 (Figure l).

4. Treatment

Based on the clinical investigation, the diagnosis was concluded as CUP. The patient was advised to undergo 6 cycles of paclitaxel and carboplatin (Taxol/Carbo) chemotherapy.

5. Discussion

The inability to identify the primary origin poses a major challenge in the management of CUP. Diverse range of symptoms, varying from lymphadenopathy to bone pain, has been reported in ~10% of the patients diagnosed with cancer secondary to metastasis. [12] Majority of the bone metastasis has been speculated to arise from lungs, breast, prostate and the kidney. [12] Spine is the most common site of bony metastasis of unknown origin followed by lungs and bones. [13] Lung cancer, which has been identified as main causative occult primary for bone metastases, is associated with poor prognosis and average survival rate of 4-8 months. [13] In the present case, the immunohistochemistry findings were suggestive of metastasis from upper gastrointestinal tract or pancreato-biliary tract.

Briasoulis and Pavlidis have reported that, despite the significant advances in imaging technology and immunohistochemistry, and the introduction of serum tumour markers, CUP poses a major diagnostic and therapeutic challenge to practicing oncologists. [14] Though several studies have explored the roles of chromosomal and molecular abnormalities in CUP, there is no data associating unique CUP characteristics with metastases from known primary tumors. [15] Locating the primary site is imperative to decide the treatment strategy and for early disease management. [16] A through diagnostic evaluation of CUP should include: complete physical examination, detailed medical history, complete medical count, standard biochemistry evaluation, urinalysis and stool occult blood testing, histopathological analysis using immunohistochemistry, computed tomography (CT) of the abdomen and pelvis, chest radiography, and mammography in certain patients [17].

In patients with CUP, CT scan focusing on the chest, abdomen and the pelvis has been found to be beneficial in evaluating the extend of disease, determining the most appropriate site for biopsy and searching the primary site of tumor. [8] In the present case, the CT scan of the abdomen was suggestive of metastasis. The effectiveness of FDG-PET scanning in locating the site of primary tumor in patients with CUP has been well documented. [8] In the present case, FDG-PET revealed metastasis involving the spine and left femur with no obvious primary source. The tumour detection rates reported by several meta-analyses upon using stand-alone FDG PET in patients with CUP, were 41%, 24.5%, and 43% [18].

IHC has contributed to significant improvement in the diagnosis of the CUP. [12] IHC has been reported to be effective in predicting the primary site in nearly 35%-40% of the patients with early metastatic cancer. [14] Tumor biomarkers such as carcinoembryonic antigen (CEA), cancer antigen (CA)-125, β-human chorionic gonadotropin (β-hCG), prostate-specific antigen (PSA) and CA-19.9 are commonly studied to identify the primary site of cancer, in patients with CUP. [19] Varadhachary *et al*. and Greco *et al*. have concluded that IHC profiling could be beneficial in deciding the treatment in patients with CUP. [10,20] Dennis *et al*. have reported that upon using a diagnostic panel containing 10 markers, the IHC classified 88% of the cases with metastatic adenocarcinoma. [21] In the present case, the IHC was found to be positive for CK7, CK19 and CA19.9 biomarkers.

Eri *et al*. have reported a case of CUP, which was positive for cytokeratin 7 (CK7) and CK19, and negative for CK 20 IHC biomarker. Though the findings of ERCP were negative for cholangiocarcinoma, the autopsy results indicated that the patient had cholangiocarcinoma. The study has highlighted the role of IHC and exploratory laparoscopy in detecting the primary lesion [22].

6. Conclusion

The present study underscores the need of conducting a focused search, comprising of a robust immunohistochemical profiling, for locating the primary tumors in carcinoma of unknown primary.

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