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Carcinoma of unknown primary radiologically presenting as myeloma

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Abstract
An elderly male patient presented with complaints of bone pain with lower backache and on initial investigation was found to be mildly anaemic with raised erythrocyte sedimentation rate, C reactive protein, mild hypercalcemia and mildly raised serum creatinine levels. On imaging studies multiple bony lytic lesions were seen predominantly in axial skeleton. A provisional diagnosis of multiple myeloma was made and he was further investigated for M proteins and bone marrow abnormalities. Serum and Urine examination were negative for paraproteins but bone marrow showed clusters of atypical epithelial cells pointing towards metastatic carcinoma, primary site/origin of which remain unknown despite using immunohistochemical markers along with PET (Positron Emission Tomography) scan favoring a diagnosis of Carcinoma of Unknown Primary (CUP). This report suggest that Carcinoma of unknown primary must be considered as a differential diagnosis in elderly patient with multiple skeletal lesions and equivocal findings of hypercalcemia, abnormal renal function, anaemia and bone lesions and avoid the diagnostic pitfall of labeling these patients as of Multiple Myeloma.

Keywords: Carcinoma of Unknown Primary (CUP), myeloma, metastatic disease

Introduction
Carcinoma of Unknown Primary (CUP) is a metastatic malignant disease where a primary site cannot be ascertained even after thorough clinical examination supplemented by radiology, biochemistry and immunohistochemistry [1]. In carcinoma of unknown primary (CUP), a malignant lesion is confirmed on biopsy but its origin cannot be ascertained even after thorough clinical examination, immunohistochemical markers for origin and advanced radiological techniques including Magnetic resonance Imaging (MRI) and Positron emission tomography (PET) scan [2]. The advantage of PET scan being that whole body can be assessed in a single setting thereby making it the investigation of choice whereas MRI can be used to find extent of soft tissue involvement thereby helping in clinical staging [3, 4]. CUP is the sixth to eighth most common malignancy, accounting for 2.3 to 5% of new cancer diagnosis and third to fourth most common cause of cancer related death [1].
Multiple myeloma is malignant neoplasm of monoclonal plasma cells that accumulate in the bone marrow and produce M-protein. Patients with multiple myeloma usually have hypercalcemia due to increase bone breakdown, renal failure due to excess immunoglobulin formation, anaemia due to overgrowth of plasma cells in bone marrow which crowd out normal blood forming cells, or osteolytic bone lesions due to increased osteoclasts destruction and decreased activity of osteoblasts [15]. Diagnostic investigations for myeloma include serum protein electrophoresis and the serum free light chain assays and urine protein electrophoresis. Bone marrow studies are done for exact identification and percentage of bone marrow involvement by myeloma cells whereas radiological investigations such as Computed Tomography (CT) and PET scan are done to detect extent of involvement by osteolytic bony lesions and subsequent clinical staging [4, 5].
So the presenting sign and symptoms can be common to both multiple myeloma and carcinoma of unknown primary [2, 5]. Similarly, lytic lesion are common in bone metastasis from carcinoma lung, thyroid, kidney and prostate and are another differential diagnoses in such clinical presentations [6]. Bone metastases can cause pain, make the bone more susceptible to fractures and can increase the level of calcium in blood and they generally occur in the central part of the skeleton [6, 7].

Case Presentation
A 85 year presented with complaints of generalized diffuse bone pain and lower backache

from past 2 years along with history of loss of appetite and significant weight loss over past 3 months. He had a history of shortness of breath on exertion from past 15 days. There was no history of any trauma or fall. The patient was controlled hypertensive, non- diabetic, non-smoker. He was consulting some local practitioners for his ailments but was getting temporary relief from his pain for short duration of time.

Investigations

Hemogram shows mild anemia (Hb – 9.8 gm/dl) Normocytic normochromic type. Renal function test were within normal range and serum calcium level was 12.4 gm/dl. Erythrocyte sedimentation rate (ESR) was 110mm/1hr. C reactive protein was also raised. No abnormality detected in routine urine examination. Computed Tomography scan reveals widespread multiple bony lytic lesion of left scapula, ribs, sternum, sacrum, pelvis, left femur and multiple vertebrae. Magnetic resonance imaging (MRI) shows paraortic lymph nodes and mild pleural effusion.

These initial investigation leads to a provisional diagnosis of Plasma cell neoplasm (most likely myeloma) and further workup was initiated.

On Pleural fluid cytology straw color fluid with predominantly lymphocytes and few mesothelial cells without malignant cell was reported. Serum electrophoresis done which revealed absence of M –protein however Bone marrow aspiration showed few atypical appearing cell cluster which was reported as suspicious for malignancy. Bone marrow biopsy also showed clusters of atypical appearing epithelial cells which were pleomorphic, having high nucleo-cytoplasmic ratio, hyperchromatic nuclei and prominent nucleoli (Fig 1A). On further immunohistochemistry working these atypical cells stained positive for PAN-CK (Fig 1B) CEA (Fig 1C), and weakly for CD 138 while negative for CD45, Melan A leading to diagnosis of metastatic carcinoma (most likely adenocarcinoma).

Additional immune marker were applied to search for primary sites like TTF1 for lung and thyroid cancer, PAX8 for thyroid cancer, P63 for pancreatic cancer, Synaptophysin for neuroendocrine carcinoma, S100 for melanoma, SALL4 for germ cell tumor, Glypican3 for liver cancer, CK7, CK20 for epithelial carcinoma which all turned out to be negative. Other tumor markers in serum like PSA, CEA and AFP level were within normal limits. Subsequently CT-Positron emission tomography (PET) scan was done which confirms multiple metabolic active lytic-sclerotic lesions in scapula, ribs, sternum, sacrum, pelvis left femur and no localization of primary site (Fig 2).

Outcome and follow up

Patient was lost to follow up

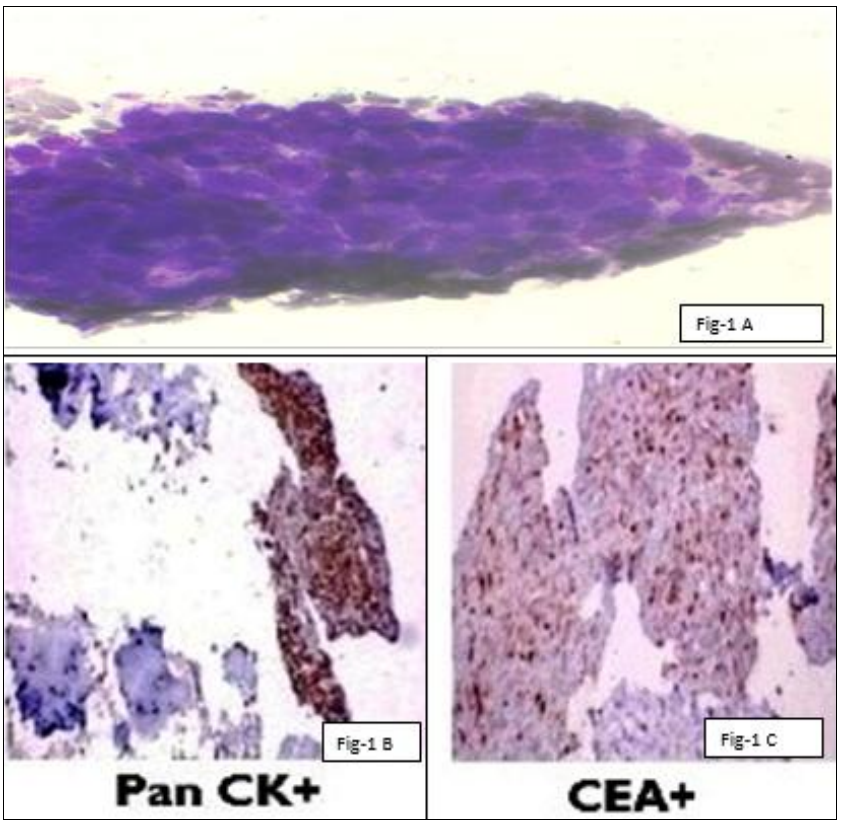

Fig 1: 1A: Fragment of atypical appearing epithelial cells. (Hematoxylin & Eosin x 400); 1B: PAN-Cytokeratin-Diffuse strong positive x 100; 1C: Carcinoembryonic antigen-weak to moderate diffuse positive x 400

FIGURE2: CT-PET scan showing multiple metabolic active lytic-sclerotic lesions in scapula, ribs, sternum, sacrum, pelvis, left femur and no localization of primary site.

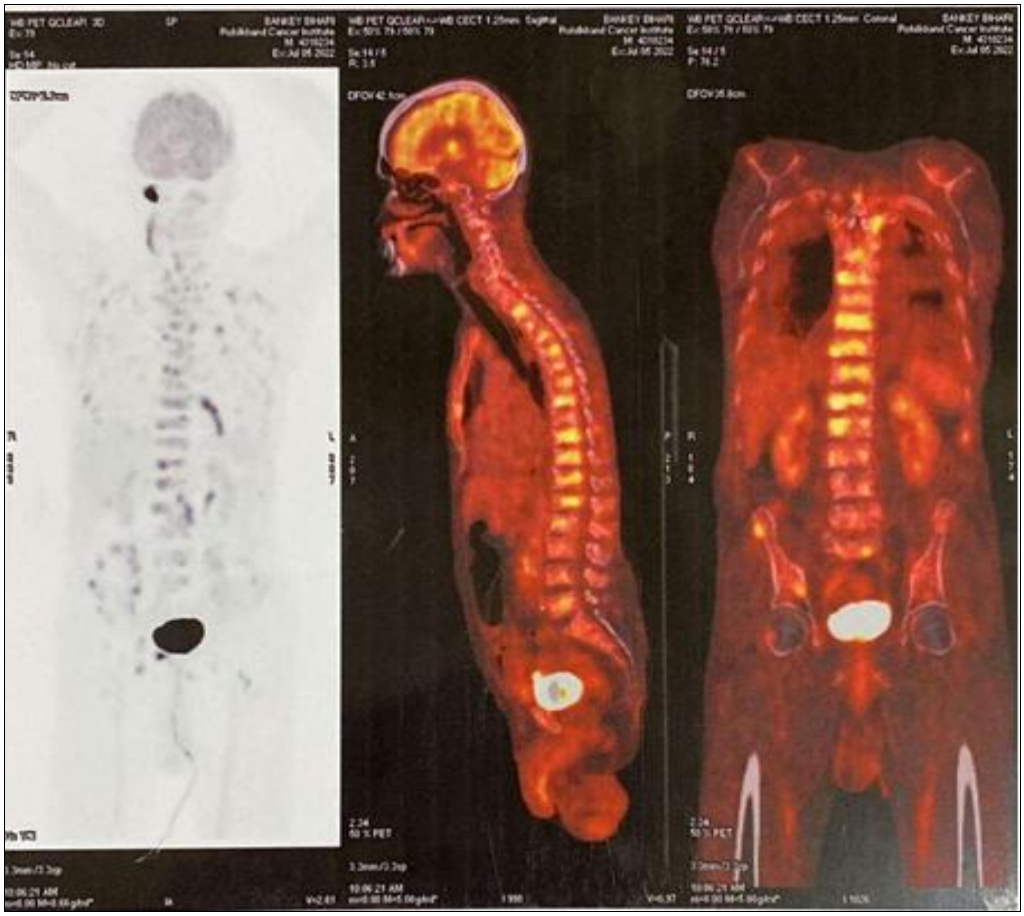

Fig 2: Showing PET- CT scan with multiple sclerotic- lytic lesions

Discussion

Carcinoma of unknown primary (CUP) represents a heterogenous group of tumor with histologically confirmed diagnosis of cancer, which originates as metastatic disease where primary tumor is undetectable with standardized diagnostic approach that includes clinical history, physical examination and routine laboratory test [8]. There is no gender difference and the average age of presentation is 60(1, 8). The clinical findings as well as radiological investigations are similar to other pathological conditions most important differentials being identifiable metastasis from a known primary and multiple myeloma. In our case, multiple myeloma was the primary differential as no primary tumor was identifiable elsewhere with associated CRAB (Hypercalcaemia, Renal abnormality, Anaemia, Bony lytic lesion) symptoms classically associated with myeloma. However on applying the revised criteria for diagnosis of myeloma [9], clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma, free light chains and end organ damage attributable to plasma cell proliferation were not present. However on bone marrow studies, a cluster of atypical appearing epithelial cells was seen on biopsy which led to provisional diagnoses of metatstatic carcinoma which was positive for PAN-CK, CEA and CD138 whereas markers for localization of primary were negative. The patient was subjected to whole body PET/CT scan, the investigation of choice for CUP having specificity, sensitivity, and accuracy of 95%, 79%, and 87%, respectively in CUP patients [10] which identified similar metabolically active lesions at various bony locations few with soft tissue involvement and few groups of lymph node but no metabolically active tracer could be attributed to a possible site of origin. So we subjected the patient to extensive clinical examination along with biochemical, radiological and immunohistochemistry on biopsy to localize the primary site or site of origin. An extensive list of immunohistochemistry markers were applied and radiological assessment could not confirm any primary site and the diagnosis of carcinoma of unknown primary was made.

Bone is one of the common sites for metastasis from adenocarcinoma and is the first presentation of carcinoma in 23% of 429 previously undiagnosed patient [2]. Diagnosis of CUP is made when there is evidence of metastasis confirmed by histology and even after extensive clinical, biochemical and radiological investigations including PET-CT, primary cannot be localized. [2, 3]. However immunohistochemistry can be used for determining the origin of metastatic lesion which may be epithelial, hematolymphoid, melanocytic or neuroendocrine, subsequently organ specific markers to determine the exact site of origin like PSA, CDX2, TTF1 for prostatic, colonic, thyroid, or lung primary along with neuroendocrine markers respectively [11]. Immuno histochemistry in our case was positive for PAN-CK, CEA rendering a diagnosis of metastatic adenocarcinoma and all other markers were negative so no localization to any primary site was possible.

Reasons for the difficulty in determining the primary site of tumor were studied by Alaa T *et al*, where they concluded that if the size of primary tumor is very small or the tumor growth is slow or the immune system of the body has killed the primary cancer or the primary tumor has been removed during surgery without knowing we cannot find the primary tumor [12]. But identifying the site of primary tumor will

improve the customization of therapy resulting in improvement of patient survival rate.

Conclusion

Carcinoma of unknown primary must be kept as differential diagnosis especially in lesions of bone as it can present as multiple myeloma and metastatic lesions clinically and radiologically. Both radiology including PET/CT scan and Immunohistochemistry must be used to confirm the diagnosis of CUP, in addition to clinical findings and routine investigations because most patients are asymptomatic, present late leading to poor prognosis, apart from lack of definitive therapy.

Take home message

- In elderly patients Carcinoma of unknown primary can masquerade Multiple myeloma as
- Presenting signs and symptoms can be similar.
- CUP presents late owing to the difficulty in diagnosis and treatment.
- An extensive workup including PET scan and immunohistochemistry must be done to before a diagnosis of CUP is given.

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Conflict of Interest

Not available

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Not available

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