Multiple Bony Metastatic Lesions and Evaluation of Primary: Case Records of a Cancer Research Centre

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Abstract During 2012–13, we diagnosed 4 patients with extensive skeletal tuberculosis (TB) who were referred to us as cases of bony metastasis with unknown primary. Radiological investigations done outside favoured a diagnosis of disseminated malignancy. Positron emission tomography/computed tomography (PET/CT) scan performed in our institute for localization of primary lesion also suggested metastatic disease. There was no evidence of malignancy on histo-pathological examination (HPE) of the involved sites. The diagnosis of TB was established on characteristics HPE. This article highlights the diagnostic dilemma of PET/CT in cases of TB versus malignancy and the importance of HPE for reaching an accurate diagnosis.

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Introduction

Skeletal TB is a form of extra-pulmonary disease and accounts for 1–20 % of patients with TB. Most common site of involvement is dorso-lumbar spine [1–3]. Simultaneous involvement of multiple bones is uncommonly encountered even in our country which is endemic for TB [4]. Extensive skeletal involvement and vague constitutional symptoms mimics disseminated malignancy on clinical and radiological findings and it becomes difficult to diagnose TB, hence a delay in diagnosis. The availability of Fluoro-deoxy-glucose (FDG)-PET has made it easier to distinguish between benign and malignant lesions. Moreover, FDG-PET is a valuable tool and can localise the primary tumour in patients with cancer of unknown primary (CUP). The integrated PET/CT approach has now virtually replaced the PET alone and is considered as the modality of choice for the detection of unknown primary. The results of a meta-analysis show that FDG-PET/CT can detect primary site in 37 % of patients with CUP, with both sensitivity and specificity of 84 % [5, 6]. However, as FDG is not a cancer specific agent, false positive findings are frequently reported in metabolically active benign lesions associated with infections and inflammations thus creating a diagnostic dilemma [7, 8]. It is necessary to achieve accurate diagnosis by HPE of the involved sites.

Case 1: A 48-year-old male presented to us with complaints of low grade fever and cough of 2 months duration. He also reported severe back ache for the last 1 month. He had been diagnosed and treated as a

Fig. 1 PET image showing FDG avid metabolically active bony lesions mimicking metastatic lesions (*left panel*). Corresponding histo-pathological image of bone biopsy showing granulomatous reaction with epithelioid granulomas (*right panel*)

case of primary central nervous system (CNS) lymphoma 8 years back. Post treatment he was in complete remission and on regular follow up. This time he was initially evaluated outside our institute. A chest X-ray done outside was suggestive of an area of consolidation in the lower lobe of right lung. Magnetic resonance imaging of the spine was reported as areas of altered signal intensity in multiple vertebrae, suggestive of metastasis. He was evaluated further. A PET/CT scan was ordered keeping a suspicion of metastatic lymphoma although uncommon with CNS primary. PET/CT was suggestive of a FDG avid consolidation in right lung middle and lower lobes, standard uptake value (SUV) max 18.17, likely infective; less likely malignant. An FDG avid centrilobular nodular lesion in left lung upper and middle lobe with a maximum SUV of 9.59 was also noted. It was also suggestive of multiple FDG avid sclerotic and lytic lesion involving C6, D3, D8, L3, L4 vertebrae, left iliac crest and sacro-iliac joint region; consistent with metastatic lesions. A biopsy was done from the iliac crest which revealed epithelioid granulomas; acid fast bacilli (AFB) was demonstrated. No evidence of malignancy was found (Fig. 1). Microscopic examination of sputum also revealed AFB. He was started on anti-tubercular therapy (ATT). 2 months later he was further evaluated. His general condition had improved with significant

reduction in pain. A repeat PET/CT done was suggestive of significant decrease in the metabolic activity of the lesions. He was advised to continue ATT.

Case 2: A 45-year old male presented to us with complaints of backache persisting for the last 3 months. He was initially evaluated outside where a magnetic resonance imaging of the spine was performed. It revealed multiple areas of altered signal intensity in multiple vertebrae suggestive of metastasis and thus referred to us for further work up as a case of cancer of unknown primary. General and systemic examination was normal. He was evaluated further. A PET/CT was performed which was suggestive of a metabolically active soft tissue mass lesion in the left lung upper lobe posterior segment abutting the oblique fissure and the pleura with a maximum dimension of 3.3 cm and a maximum SUV of 11.04, likely mitotic in nature. Multiple FDG avid lesions involving sternum, D1, D2, D4, D8, D10, L2 and L4 vertebrae, left acetabulum, left ischium and left iliac crest, likely metastatic in nature were also noted. Biopsy from the iliac crest was taken and it was suggestive of epithelioid granulomas and caseous necrosis (Fig. 2). A repeat biopsy from the involved vertebra was performed which also had the similar findings. Subsequently, biopsy of the lung lesion was performed which also revealed epithelioid granulomas with caseating necrosis. No evidence of

Fig. 2 PET image showing FDG avid metabolically active bony lesions mimicking metastatic lesions (*left panel*). Corresponding histo-pathological image of bone biopsy showing granulomatous reaction with epithelioid granulomas (*right panel*)

Fig. 3 PET image showing FDG avid metabolically active bony lesions mimicking metastatic lesions (*left panel*). Corresponding histo-pathological image of bone biopsy showing granulomatous reaction with epithelioid granulomas (*right panel*)

malignancy was found in any of the biopsies. Serum levels of CEA, CA 19.9, PSA and LDH were within normal limits. Serum and urinary protein electrophoresis (SPE & UPE) were normal. He was started on ATT and was advised to follow up.

Case 3: A 54-year-old male was referred to us for further evaluation as a case of multiple bony metastases with unknown primary. His chief complaints included low grade fever and backache of 4 months duration. 3 years back he had suffered from tubercular lymphadenitis of cervical nodes and taken a complete course of ATT. General physical and systemic examination were unremarkable except multiple areas of bony tenderness in the spine. A CT scan of the thorax done outside was reported as mediastinal lymphadenopathy with sclerotic lesions in multiple ribs and dorsal vertebrae. He was investigated further. A PET-CT scan was ordered for location of the primary lesion. It was suggestive of multiple enlarged discrete and confluent FDG avid lymph nodes at paratracheal, prevascular and subcarinal stations measuring 1.5–3.5 cm and a maximum SUV of 15.47. Multiple FDG avid sclerotic and lytic lesions involving C3, D3, D6, D7, L1 and S1 vertebrae, left scapular, right iliac crest, left anterior superior iliac spine (ASIS) left acetabulum, right 2nd, 6th, and 11th ribs, left 4th and 5th ribs

were noted. Biopsy from the rib lesion was performed and it was suggestive of epithelioid granulomas with areas of caseation. Another biopsy was performed from the left ASIS and it also revealed similar findings on histopathological examination and no evidence of malignancy was seen (Fig. 3). Serum levels of tumor markers (CEA, CA 19.9, PSA and LDH) were in normal range. He was started on a 2nd line ATT regimen and referred to TB centre for evaluation of multi-drug resistance TB.

Case 4: A 37-year-old male was referred to us as a case of bony metastasis with unknown primary. Patient had complaints of fever and backache of 2 months duration. No constitutional symptoms were present. Past history was unremarkable. The diagnosis was made on the basis of an MR imaging of spine which revealed areas of altered signal intensity in multiple vertebrae suggestive of metastatic lesions. He was evaluated further. Tumor markers (PSA, CA 19.9, CEA, LDH), serum and protein electrophoresis were normal. A PETCT scan was done which revealed multiple FDG avid lytic and sclerotic lesions involving D3, D5, D10, D11, D12, L3 and L4 vertebrae consistent with metastases. A CT guided biopsy from vertebral lesion was performed which was suggestive of granulomatous inflammation with caseating epithelioid granulomas (Fig. 4). No

Fig. 4 PET image showing FDG avid metabolically active bony lesions mimicking metastatic lesions (*left panel*). Corresponding histo-pathological image of bone biopsy showing granulomatous reaction with epithelioid granulomas (*right panel*)

Table 1 Clinico-pathological characteristics at presentation

Case	Age (years)	Constitutional symptoms	Prior h/o malignancy	Associated pulmonary lesions	Bony lesions	Tumor markers
1	48	yes	Yes	Yes	Vertebral, pelvic	Normal
2	45	No	No	Yes	Vertebral, pelvic, sternal	Normal
3	54	Yes	No	No	Vertebral, ribs, scapula, pelvis	Normal
4	37	Yes	No	No	Vertebra	Normal

evidence of malignancy was detected. A repeat biopsy from another vertebral lesion was done which revealed similar findings. ATT was started. There was significant reduction in pain intensity with resolution of fever within 3 weeks. He was advised to follow up (Table 1).

Discussion

PET is an established nuclear imaging modality in current oncology practice which provides a metabolic assessment of normal or pathological conditions. PET can be combined with CT. PET images the biological or physiological phenomenon while the anatomical details are provided by the CT. The combined modality is exploited to create an integrated data which improves the diagnostic accuracy [9].

Like any other diagnostic modality, the interpretation of PET/CT scanning is demanding. This is due to several reasons. FDG, the most commonly used tracer in PET imaging shows variable physiological uptake by normal tissues (high in brown fat, heart, brain, kidneys and bladder), unusual tumour sites, infections, granulomatous diseases like tuberculosis, inflammatory conditions and in cases of hyperglycemia [9, 10]. Intense FDG uptake has been demonstrated in the inflammatory cells such as neutrophils and macrophages at the site of infections and this provides the basis for false-positive PET scans [11]. False positive uptake of FDG in TB has been described in many studies. Tian et al. described multi-site abdominal TB in 3 patients mimicking TB on FDG-PET/CT imaging. Go SW et al. described a case of extensive skeletal TB mimicking metastases on PET/CT. The diagnosis of TB was achieved on HPE [12, 13]. The need for an accurate HPE lies in the fact that a patient might have suffered from cancer in the past and this extensive skeletal involvement (which is uncommon in TB) can provide an erroneous label of relapse/recurrent malignant disease. Moreover, both TB and malignancy share the same compendium of vague constitutional symptoms thus making difficult suspecting tuberculosis in a patient of malignancy. TB has a high

prevalence in immune-suppressed states and malignancies create appropriate opportunity. About 50 % of the patients with skeletal TB have negative findings on chest X-ray thus posing a diagnostic difficulty [14, 15]. Extrapulmonary TB is a pauci-bacillary disease in which the bacterial load is low and it is not always possible to demonstrate AFB. Epithelioid granulomas and caseation necrosis serve as excellent diagnostic features and can be demonstrated in 80–90 % of the cases [16–18].

Learning Points

1. PET-CT can produce false-positive results in cases of TB thus creating a diagnostic dilemma.
2. TB should be included in the differential diagnosis of malignant lesions and definite diagnosis is obligatory before starting the definite therapy.
3. TB is a curable disease and hence making an accurate diagnosis of TB by HPE and appropriate treatment can save the lives at the same time allaying the undue anxiety and reduced quality of life.

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