CASE REPORT

Lung Adenocarcinoma with Miliary Metastases and Left Femur Pathologic Fracture: an Unusual Case Mimicking Disseminated Tuberculosis

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Introduction

Lung adenocarcinoma can have a varied appearance at presentation. Solid, ground-glass, or part-solid and part-ground-glass nodules are commonly seen [1]. Multifocal areas of consolidation that are peribronchovascular and contain air bronchograms may also be identified [3]. Multiple discrete nodules, or the so-called miliary pattern, are rare, with few cases reported in the literature [3, 10, 12, 14]. This pattern is more commonly reported as multifocal or diffuse adenocarcinoma, and detailed data regarding the incidence has not yet been studied in depth. However, in one case report of 73 patients with adenocarcinoma, 14 presented with multifocal disease, though only one had innumerable discrete nodules [19, 22]. In another study examining 548 patients with non-small cell lung cancer, 504 patients presented with a dominant lesion (stage I disease) and 44 with multifocal disease. Of the 44 patients, 18 had multifocal adenocarcinoma [2]. Some have suggested that the miliary pattern of adenocarcinoma may be produced by bone or liver metastases

that continually seed the lung, though this has yet to be verified [10]. Because the miliary pattern is much less common, it may be confused for other entities, such as tuberculosis.

Non-small cell lung cancer metastasizes to the bone in approximately 15–40% of cases, mostly involving the axial skeleton [11, 16]. Appendicular metastases are more common proximal to the knee and elbow, though more distal involvement is reported [5, 9, 11, 15, 18, 20, 21]. Extremity metastases are often initially misdiagnosed as benign entities such as infection due to presenting symptoms of local redness, pain, and swelling. Generally, a bony metastasis on radiograph appears as a lytic lesion and may be centered in the cortex (cookie-bite lesion). There may or may not be a demonstrable soft tissue mass [7].

Tuberculous and malignant involvement of the bone is often indistinguishable on imaging, particularly in the spine, where MRI findings can be similar [4, 13, 17, 23]. Diagnosis of tuberculous spread to the bone in general is often difficult, with an average delay in diagnosis of 16–19 months [4]. The musculoskeletal system is involved in 1–3% of cases of tuberculosis. The femur, tibia, and small bones of the hands and feet are often affected [6]. Typically, the metaphyses are involved, with radiographic features that include osteopenia and poorly defined lytic lesions with minimal surrounding sclerosis [4].

Our goal is to highlight the importance of maintaining a broad differential when evaluating a patient with confounding risk factors and imaging findings. Premature diagnoses may lead to delays in appropriate management [13]. Ultimately, tissue sampling may be necessary in providing a definitive, timely diagnosis.

Case Report

A 51-year-old Vietnamese man presented to an outside urgent care facility with a 2-week history of palpitations, night sweats, nausea, and intermittent chest pain with

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Fig. 1. Posteroanterior chest radiograph demonstrates diffuse nodular opacities bilaterally.

shortness of breath. The patient also reported a sensation of left thigh “firmness” for the past 3 months, which had

become increasingly painful over the preceding 2 weeks. He also noted a 20-lb unintentional weight loss over the past 6 months. His medical history was significant for chronic hepatitis B, type 2 diabetes, and latent tuberculosis that was treated 30 years ago. Relevant social history included a 27-pack-year history of smoking and recent travel to Vietnam.

On initial exam in the urgent care, the patient was found to be tachycardic and in mild distress. A basic medical work-up was initiated, but the patient was referred to the ER at our institution for further care.

A chest x-ray was obtained in the ER which showed diffuse (miliary) nodular opacities bilaterally (Fig. 1). The patient was placed on airborne precautions. A subsequent CT of the chest demonstrated extensive, bilateral, randomly distributed pulmonary nodules without a dominant mass and associated enlarged mediastinal lymph nodes, many of which appeared to have central low attenuation (Fig. 2). The CT was interpreted as diffuse pulmonary infection, with tuberculosis being the chief differential consideration. The CT scanner was shut down and cleaned before scanning the next patient.

Fig. 2. Axial CT images through the level of the left pulmonary artery in lung (a) and soft tissue (b) windows demonstrates extensive, bilateral, small, randomly distributed (miliary) pulmonary nodules with associated enlarged mediastinal lymph nodes, some of which appeared to have central low attenuation (arrow). No dominant lung mass was present.

Fig. 3. Anteroposterior radiograph of the left femur demonstrates a displaced left mid-shaft femur fracture with central permeative lucent areas within the bone and extensive aggressive periosteal reaction, consistent with a pathologic fracture.

Due to the patient's history of left thigh pain, a radiograph of the left femur was also obtained, which demonstrated a displaced left mid-shaft femur fracture with central

permeative lucent areas within the bone and extensive periosteal reaction, concerning for a possible pathologic fracture (Fig. 3). Given the patient's history and chest CT findings, the primary clinical consideration was tuberculosis with dissemination to the bone. Other etiologies, including malignancy, remained on the differential, but were felt to be less likely. The patient was admitted to internal medicine for further work-up.

Orthopedics was consulted and an MRI of the left femur was ordered. Images showed the oblique pathologic fracture through the femoral diaphysis and an associated, predominantly extramedullary, soft tissue mass adjacent to the fracture site (Figs. 4 and 5, Table 1). Additional nonspecific lesions were seen in the pelvic bones. The lesion was biopsied under ultrasound-guidance on the same day as the MRI using a 4-MHz curvilinear transducer and 14-gauge coaxial biopsy system (Fig. 6). A total of six core biopsy specimens were obtained: three samples were placed in formalin (standard protocol) and three samples were placed in sterile water (to help preserve any organism should infection be present).

While awaiting biopsy results from the left femur biopsy, the patient underwent bronchoscopy with bronchoalveolar lavage and fine-needle aspiration of mediastinal lymph nodes using endobronchial ultrasound guidance.

In the interim, Infectious Disease was also consulted. Recommendations were made to start the patient on rifampin, isoniazid, pyrazinamide, and ethambutol (RIPE) for presumed tuberculosis. A less likely differential consideration was melioidosis (infection with the gram-negative bacterium *Burkholderia pseudomallei*, also sometimes called “Vietnamese tuberculosis”) given the patient's recent travel to Vietnam, and therefore, recommendations were also made to start the patient on ceftazidime.

Fig. 4. Coronal T1 (a) and STIR (b) and sagittal STIR (c) images of the left femur demonstrate a pathologic fracture (arrows) with an associated, predominantly extramedullary, soft tissue mass adjacent to the fracture site, which measured $5.4 \times 3.7 \times 16.9$ cm (arrowheads). Extensive increased STIR signal in the thigh musculature likely reflects peritumoral edema.

Fig. 5. Axial T1 fat-saturated post-contrast image (**a**) through the level of the fracture demonstrates the intramedullary portion of the soft tissue mass as it extends outward into the soft tissues. Transverse gray scale ultrasound image (**b**) through the same level as (**a**) similarly demonstrates the soft tissue component arising from within the bone. Axial T1 fat-saturated pre-contrast (**c**), T1 fat-saturated post-contrast (**d**), and STIR (**e**) images slightly more inferiorly further characterizes the lesion, with areas of T1 hyperintensity (possibly hemorrhage), heterogeneous enhancement, and marked adjacent reactive edema in the thigh musculature.

Over the course of his hospital stay, the patient became increasingly short of breath and required transfer to the medical intensive care unit. Microbiologic studies, including three sputum acid-fast bacilli stains and cultures, two mycobacterium tuberculosis polymerase chain reaction (MTB-PCR) studies, and all blood and urine cultures were negative for growth of any organism. RIPE therapy and ceftazidime, however, were continued due to high clinical suspicion for infection.

One week following admission, biopsy results of the left femur mass and mediastinal lymph nodes became available, demonstrating metastatic moderately differentiated adenocarcinoma, with an immunohistochemical profile consistent with a lung primary, including thyroid transcription factor-1 (TTF1) and cytokeratin 7 (CK7) positive (Fig. 7).

RIPE therapy and ceftazidime were discontinued. Oncology and palliative care were consulted, with subsequent recommendations to start chemotherapy as an outpatient.

Unfortunately, over the ensuing few days, the patient became progressively more short of breath and ultimately went into asystole and passed away.

Discussion

To our knowledge, a case of lung adenocarcinoma presenting with miliary nodules and metastases to the bone with pathologic fracture has not yet been described. This case is important as it highlights the significant overlap that may be seen in infectious and malignant processes. Patients commonly present with histories and imaging findings that do not simply fit into one category of pathology, and this sometimes leads to early misdiagnoses and delays in treatment.

In our case, the clinical team had a high degree of suspicion for tuberculosis and empirically started the patient on RIPE and antibiotics; however, the differential

Table 1 MRI pulse sequence parameters

MR pulse sequence	Flip angle (°)	Repetition time (TR) (msec)	Echo time (TE) (msec)	Display field of view (DFOV) (cm)
Coronal T1	90	516.7	20.6	44 × 49.7
Coronal STIR	90	4766.7	44.6	44 × 49.7
Sagittal STIR	90	3000	46.7	44 × 49.7
Axial T1 fat-saturated pre-contrast	90	566.7	20.7	20 × 22.6
Axial T1 fat-saturated post-contrast	90	566.7	20.7	20 × 22.6
Axial STIR	90	3250	46.6	20 × 22.6

Fig. 6. Single intra-procedural transverse grayscale ultrasound image demonstrates the biopsy needle within the soft tissue mass adjacent to the femur prior to needle firing.

diagnosis for a miliary pattern of lung nodules includes other infections (e.g., fungal and viral pneumonias), metastatic disease (most highly associated with thyroid and renal cancer, but can be seen with a range of other primaries), sarcoidosis, pneumoconiosis, and hypersensitivity pneumonitis [8]. The presence of a pathologic fracture of the femur narrowed this differential diagnosis to tuberculous or fungal infection versus metastatic disease. Highlighting the overlapping imaging features that may be seen in tuberculous and malignant involvement of the bone, a case recently reported in the literature describes a patient with eccentric cortical lesions of the

proximal left femur with a pathologic fracture and adjacent soft tissue hemorrhage and edema. The patient was found to have disseminated tuberculosis [17].

Because a broad differential diagnosis was considered, the work-up remained thorough for our patient. Radiologists in particular played a critical role in this patient's timely management with early tissue sampling.

At the time of interpretation of the MRI, infection and malignancy were both included on the differential by the radiologists. To this end, at the time of biopsy, core specimens were placed in formalin (as standard protocol, to provide sufficient tissue for immunohistochemical staining) as well as in sterile saline for culturing (as formalin may have a bactericidal effect). This allowed pathologists to conduct a more comprehensive range of tests on our specimens to arrive at the most appropriate diagnosis.

Ultimately, a number of factors ensured a timely and accurate diagnosis in this case despite a challenging initial clinical presentation. From the start, a broad differential diagnosis was maintained. This concept was applied to the patient's treatment, where he was empirically started on RIPE therapy while awaiting biopsy results, and in the diagnostic work-up, where the radiologists provided specimens that could be analyzed by pathology for infection and malignancy. Perhaps most importantly, direct communication and collaboration between the clinicians, radiologists, and pathologists was maintained throughout the course of this patient's care. In this way, open discussions could be had regarding the most appropriate course of action for this patient. In

Fig. 7. Pathology slides from left femur soft tissue mass core biopsy specimens. Hematoxylin and eosin (H&E) stain (a) demonstrates hyperchromatic, pleomorphic cells with increased nuclear to cytoplasm ratio forming glands. CK7 (b) and TTF1 (c) stains demonstrate positivity. The overall immunohistochemical profile is consistent with moderately differentiated lung adenocarcinoma.

some hospital settings, this may be facilitated further via a formal tumor board.

Compliance with Ethical Standards

Conflict of Interest: Nasim Khadem, MD; Cristina Costales, MD; Eric A. White, MD; Dakshesh B. Patel, MD; Anderanik Tomasian, MD; and George R. Matcuk, Jr., MD, have declared that they have no conflict of interest.

Human/Animal Rights: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5).

Informed Consent: N/A

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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