Occult Esophageal Squamous Cell Carcinoma Presenting with Multiple Bony Osteolytic Lesions Clinically Mimicking Multiple Myeloma: A Diagnostic Dilemma

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Abstract
Bone metastasis as an initial presentation of esophageal carcinoma is uncommon. In the absence of typical presentations like dysphagia, these cases may lead to diagnostic dilemmas both for the clinicians and pathologists. Here, we report a case of disseminated metastasis of esophageal squamous cell carcinoma to the bone in a 47-year-old female, who presented with multiple osteolytic lesions and clinically mimicking multiple myeloma. A detailed diagnostic work-up established the diagnosis of esophageal squamous cell carcinoma.

Keywords
► esophageal squamous cell carcinoma
► dysphagia
► multiple myeloma

Introduction
Esophageal cancer is one of the fatal cancers worldwide with a 5-year survival rate of 40% for localized tumors and 4% for tumors with advanced distal metastasis.1 Histological types, grade, and stage are important factors in esophageal cancer prognosis. Regional and distant metastases have a profound impact on survival and outcome.1 The most common sites of esophageal cancer metastases are lymph nodes, lung, liver, bones, adrenal glands, and brain.1 Although bone metastasis of esophageal carcinoma is known, metastasis to the bone as an initial presentation is uncommon.2,3 Bone metastasis of esophageal carcinoma presenting with osteolytic lesions may clinically mimic multiple myeloma (MM) leading to delay in diagnosis.3 Here, we present a case of disseminated metastasis of esophageal squamous cell carcinoma (ESCC) to the bone in a 47-year-old female, who presented with multiple osteolytic lesions, clinically mimicking MM.

Case Report
A 47-year-old female was admitted to hospital with an abrupt onset of left forearm pain with limited range of motion in the left hand. She had 6-month history of generalized weakness, decreased appetite, and backache. There was no history of trauma. She had no other significant past history.

On examination, her vitals were stable. She had pronounced lumbar kyphoscoliosis. No other peripheral lymphadenopathy or any organomegaly was detected. The rest of the systemic and general physical examinations were unremarkable.

The patient was found to have anemia with hemoglobin of 7.7 g/dL with normocytic normochromic morphology of the red blood cells, deranged renal parameters with a creatinine of 2.8 mg/dL, and hypercalcemia with a corrected calcium level of 16.8 mg/dL. The parathyroid hormone level was 20.2 pg/mL, which was normal. The Mantoux test was negative. Her skeletal survey revealed a pathological fracture of left humerus with multiple lytic lesions in the skull, dorso-lumbar vertebrae, and iliac bones (►Fig. 1A–C). A provisional diagnosis of MM was maintained after ruling out hyperparathyroidism.

The bone marrow aspirate was diluted; however, it showed an increase in plasma cells. Serum electrophoresis did not reveal any monoclonal peak. Bence Jones protein was not detected in the urine. At this point, the diagnosis of MM was in doubt. Bone marrow biopsy revealed myelofibrosis with infiltration by pleomorphic cells (► Fig. 1D). On immunohistochemistry...
Discussion

ESCC, which is a predominant histologic subtype of esophageal cancer, has an overall 5-year survival rate of 14%. Metastases of ESCC to the bone are uncommon and vary from 1 to 14% in autopsy series. In clinical practice, bone metastases of esophageal cancer occurred infrequently. Radiologically bone metastases in esophageal carcinoma are detected in 1.6% of all cases with distant metastases. The detection rate has improved with positron emission tomography using F-18 FDG (FludeoxyglucoseF18 injection). Micrometastases of esophageal carcinoma to bone marrow are detected in 20.9% of the cases by light microscopic examination and 30.2% of cases by cytokeratin IHC. Usually bone metastases are osteolytic in nature, mixed patterns like osteolytic–osteoblastic and osteolytic–osteosclerotic are also reported.

The various other malignancies, which present with osteolytic metastases, are malignant melanoma, renal cell carcinoma, gastric carcinoma, colorectal carcinoma, hepatocellular carcinoma, thyroid carcinoma, and small cell lung carcinoma. Like other malignancies, spine is the most common site of bone metastases in esophageal carcinoma. In the present case, a panel of IHC markers helped in ruling out other malignancies. The tumor cells in the bone marrow biopsy were negative for HMB45 (ruled out malignant melanoma), CD10 (ruled out renal cell carcinoma), CK20 (ruled out colorectal carcinoma), HepPar1 (ruled out hepatocellular carcinoma), and thyroid transcription factor-1 or TTF1 (ruled out thyroid carcinoma). Negative immunoreactivity for leukocyte common antigen ruled out lymphoma whereas negative immunoreactivity for CD38 and CD138 ruled out plasma cell dyscrasia like MM. Infections like tuberculosis can also present with osteolytic bony lesions. In the present case, tuberculosis was ruled out as there was no fever and the Mantoux test was negative.

The natural course of esophageal carcinoma involves the esophagus primarily with extension to the adjacent structures. So, the symptoms appear when these anatomical structures are involved leading to dysphagia, dysphonia from laryngeal paralysis, weight loss followed by substernal and/or epigastric pain, and regurgitation. Dysphagia is a typical presentation of esophageal carcinoma present in more than 80% of the cases. However, dysphagia occurs only when two-thirds of the esophageal lumen is involved. A deep infiltrating tumor can metastasize to adjacent organs without producing dysphagia. Cases of esophageal carcinoma presenting with bone pain due to bone metastasis and without any complaint of dysphagia are extremely rare. The lack of dysphagia in the present case could be explained by the nonstenotic pattern of the lesion. Comparison of the present case with some of the cases reported in the literature is enumerated in Table 1.

Cases of occult carcinomas presenting with osteolytic bone metastases may clinically mimic MM. The diagnosis of MM requires the presence of ≥10% clonal plasma cells in the bone marrow or biopsy proven plasmacytoma along with evidence of end-organ damage such as hyper
Calcemia, Renal dysfunction, unexplained Anemia, and Bone lytic lesions (CRAB). There are reports of MM presenting with an esophageal ulcer. The present case had features of end-organ damage like hypercalcemia, renal dysfunction, anemia, and bony lytic lesions, which led to the clinical suspicion of MM. Bone marrow biopsy with negative monoclonal peak and urine Bence Jones protein helped in ruling out MM. Upper gastrointestinal endoscopy and biopsy from the esophageal ulcer helped in confirming the diagnosis of ESCC.

Such cases are managed symptomatically as chemotherapy and radiotherapy do not improve survival.

Occult esophageal carcinoma presenting with osteolytic bone metastasis may clinically mimic MM. Typical clinical presentations like dysphagia, dysphonia, substernal and/or epigastric pain, and regurgitation may not be present in these cases leading to diagnostic dilemma both for the clinicians and pathologists.

Conflict of Interest
None declared.

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Table 1
Table showing comparison of the present case with some of the cases reported in the literature

| Authors               | Age (y)/sex | Histological type of esophageal carcinoma | Site(s) of bony metastasis | Nature of bone metastasis |
|-----------------------|-------------|------------------------------------------|----------------------------|---------------------------|
| Alvarez Diaz et al    | 59/M        | Adenocarcinoma                           | Cervical and dorso-lumbar vertebrae, left humerus, ribs and right femoral neck | Osteolytic and osteoblastic |
| Reezae and Bradaran Rahimi | 60/F        | ESCC                                     | Left femur                  | Osteolytic                |
|                       | 42/F        | ESCC                                     | Left tibia                  | Osteolytic                |
|                       | 24/M        | ESCC                                     | Left iliac bone             | Osteolytic                |
|                       | 60/F        | ESCC                                     | Cervical vertebrae          | Osteolytic                |
|                       | 40/M        | ESCC                                     | Ribs                       | Osteolytic-sclerotic      |
| Shewchuk et al        | 59/F        | ESCC                                     | Right femur, left iliac bone, and skull | Osteolytic                |
| Viaro et al           | 58/M        | Epidermoid carcinoma                     | Cervical vertebrae          | Osteolytic                |
| Singh et al           | 37/M        | ESCC (post esophagectomy for ESCC)       | Right calcaneus             | Osteolytic                |
| Sánchez-Jiménez et al | 63/M        | Adenocarcinoma                           | Left maxilla                | Osteolytic                |
| Present case          | 47/F        | ESCC                                     | Skull, dorso-lumbar vertebrae iliac bones, and left humerus | Osteolytic                |

Abbreviation: ESCC, esophageal squamous cell carcinoma.