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General

Distal Fibular Metastasis of Colorectal Carcinoma: A Case Report

Lauren Luther, Patrick J. McGlone, Kyle D. Hardacker, Daniel Alsoof[a], Roman A. Hayda, Richard M. Terek

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Case

A 62-year-old woman presenting with ankle pain was initially treated for a non-displaced fracture. Persistent pain despite months of conservative management for her presumed injury prompted repeat radiographs which demonstrated the progression of a lytic lesion and led to an orthopedic oncology referral. Following a complete work-up, including biopsy and staging, she was diagnosed with colorectal carcinoma metastatic to the distal fibula.

Conclusion

Secondary tumors of the fibula are uncommon but an important diagnosis to consider for intractable lower extremity pain especially in patients with history of malignancy or lack of age-appropriate cancer screening.

INTRODUCTION

We discuss the case of a patient presenting with lateral leg pain initially managed as an ankle fracture who was ultimately found to have colorectal carcinoma (CRC) metastatic to the distal fibula. The differential diagnosis for ankle pain is broad and includes lateral ankle sprain and fibula fracture, two of the most common orthopedic injuries in urgent care settings.[1-4] In contrast, both primary and secondary tumors rarely occur near the ankle. Only 2.5% of all primary bone tumors are found in the fibula.[5] Metastatic tumors are similarly uncommon in this region; lesions distal to the elbow and knee represent an estimated 0.1% of all bone metastases.[6] Initial radiographs need to be carefully reviewed for lesions and in cases of persistent lateral ankle pain or delayed fracture healing despite appropriate management, a fibular tumor should be considered, especially in patients with previous malignancy, prodromal pain, smoking history, or constitutional symptoms.[7,8]

CRC is the third most common malignancy in the United States and a leading cause of cancer-related mortality worldwide.[9,10] A minority (3-7%) of patients with CRC experience skeletal manifestations of the disease.[11-14] The spine followed by the pelvis are the most commonly affected skeletal regions and, to our knowledge, only one report of a fibular metastasis of CRC exists in the literature.[15,16] However, as advances in medical and surgical management of CRC lead to increased survival, the incidence of bone metastases at previously uncommon sites is increasing.[17,18] Therefore, it will be important for providers to consider the potential for metastatic disease in the appropriate clinical setting, as misdiagnosis of these lesions delays local control and treatment of the primary cancer.[19]

The patient's power of attorney was informed the data concerning the case would be submitted for publication and she provided consent.

CASE PRESENTATION

A 62-year-old female presented to an outside urgent care facility with a chief complaint of left ankle pain. The pain began ten days prior to presentation after a fall while performing yard work. She underwent radiographic evaluation of the left ankle (Figure 1) on which a subtle lucency was noted and interpreted as suspicious of a non-displaced fibula fracture. She was made weight-bearing as tolerated in a walking boot and provided with an appointment at an orthopedic clinic. The orthopedic surgeon at her follow-up appointment reviewed the original radiographs, concurred with the radiologist's findings, and continued non-opera-

a **Corresponding Author:**
Daniel Alsoof
Department of Orthopaedic Surgery
Brown University, Warren Alpert School of Medicine
1 Kettle Point Avenue
Providence, RI 02906
Email: daniel_alsoof@brown.edu

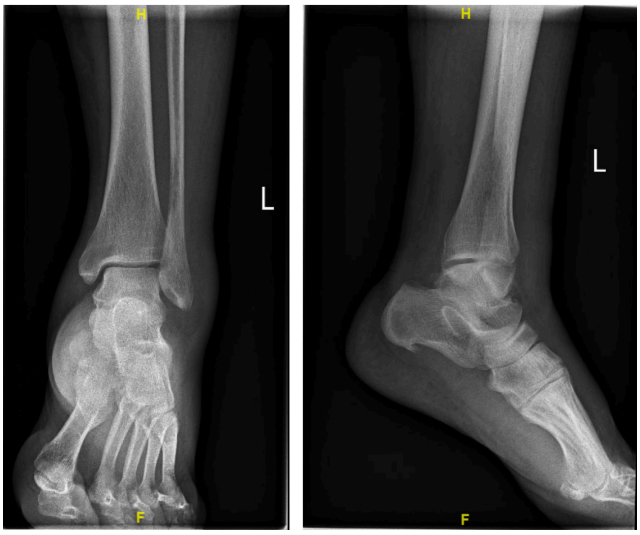

Figure 1. AP and lateral radiographs at patient's initial presentation demonstrate a lytic meta-diaphyseal lesion with erosion of the posterior cortex.

tive management of a presumed ankle fracture. One month later, repeat radiographs of the left ankle were interpreted as a distal fibular fracture with evidence of interval healing. The following month, 12 weeks after her initial injury, she experienced a second fall. Radiographs following the re-injury (Figure 2) were interpreted as a comminuted spiral fracture of the distal fibula and the decision was made to continue with non-operative management. However, subsequent imaging (Figure 3) demonstrated extensive bone erosion of the distal fibula and extension into the surrounding soft tissues, prompting referral to orthopedic oncology.

The patient was seen one week later at our outpatient orthopedic oncology clinic. A history obtained from the patient's sister revealed months of cognitive deterioration along with progressive urinary and bowel incontinence. Over the same period, the patient had developed significant low back pain and now required a wheelchair to mobilize. Her past medical history was significant for 20 pack years of smoking but otherwise largely unknown due to a long-term lack of primary medical care. Physical exam was significant for altered mental status, a lateral ankle mass, and lower extremity weakness. Review of outside imaging revealed findings suspicious of malignancy on her initial radiographs.

The patient was referred to the emergency department, where initial workup found hypercalcemia, acute kidney injury, hypovolemia, and metabolic acidosis treated with zoledronate & fluids with resolution (Tables 1-2). Chest X-ray demonstrated innumerable nodular opacities consistent with metastatic disease. CT scan of the abdomen and pelvis was significant for a circumferential soft tissue mass of the rectum as well as destruction of the sacrum and coccyx, multiple hypoattenuating lesions in the liver, and adenopathy in the thorax, abdomen, and pelvis (Figures 4-6).

The patient was admitted to the intensive care unit for management of her electrolyte and metabolic abnormalities as well as further investigation of her widespread

Figure 2. Radiographs after re-injury 12-weeks following initial presentation reveal a new pathologic fracture and progression of the fibular lesion.

Figure 3. Radiographs demonstrate extensive bone destruction of the distal fibula, an associated soft tissue mass, and diffuse osteopenia.

metastatic disease. Her cauda equina syndrome was treated with corticosteroids and one session of radiation therapy. Needle biopsy of the sacral mass revealed poorly differentiated adenocarcinoma expressing tumor markers consistent with adenocarcinoma of the colon (Fig 7, Table 3). The patient and her family in light of the advanced nature of

Table 1. Labs on initial presentation to the Emergency Room after referral from the outpatient Orthopaedic oncologist's office. Abnormal values in bold

Lab	Value	Ref Range & Units
WBC	**19.4**	3.5-11 x10^9/L
Hgb	9.3	11.0-15.0 G/DL
Platelets	202	150-400 x10^0/L
Na	**134**	135-145 mEq/L
K	4.5	3.6-5.1 mEq/L
Cl	105	98-110 mEq/L
CO2	**14**	22-32 mEq/L
BUN	**63**	6-24 mg/DL
Cr	**2.02**	0.44-1.03 mg/DL
Ca	**14.1**	8.5-10.5 mg/DL
iCa	**6.9**	4.2-5.2 mg/DL
Mg	1.7	1.3-1.9 mEq/L
Phos	4.1	2.4-4.8 mg/DL
Alb	4.4	3.5-5.0 g/DL
Alk Phos	**140**	34-104
ALT	9	6-45 IU/L
AST	38	10-42 IU/L
Bilirubin, Total	0.4	0.2-1.3 mg/DL
PT	12.6	10.0-13.0 sec
PTT	27	24.0-37.0 sec
INR	1.1	0.8-1.2 sec
Lactate (VBG)	1.8	0.2-1.9 mEq/L
pH (VBG)	**7.24**	7.32-7.42
ESR	**52**	0-30 mm/h
CRP	**63.92**	0.00-10.00 mg/L

Table 2. SPEP. All within normal limits. SPEP interpretation – No monoclonal gamma paraprotein is detected in this pattern. Immunofixation Electrophoresis for the serum and the urine were negative for monoclonal paraprotein.

Component	Value	Ref Range & Units
Total Protein	6.8	6.0-8.0 G/DL
Albumin SPE	4.08	3.54-5.04 G/DL
Alpha 1	0.23	0.10-0.25 G/DL
Alpha 2	0.78	0.57-1.04 G/DL
Beta	0.78	0.61-1.17 G/DL
Gamma	0.92	0.50-1.50 G/DL

her disease elected to transition to home hospice instead of pursuing further treatment.

Treatment would have consisted of palliative radiation to her pelvic masses and steroids for neurologic symptoms. Given her overall health and limited ambulatory status since her injury, there was no plan to offer any reconstructive surgery of the ankle. Due to the duration of her cauda equina symptoms & extremely unlikely recovery of function, she was not offered decompression of her sacral nerve roots.

DISCUSSION

Colorectal cancer (CRC) rarely presents as a skeletal metastasis and even more uncommonly as a metastasis in a distal extremity.[20-23] We present a case of CRC metastatic to the distal fibula. Only one similar case has been reported in the literature as part of a retrospective analysis of patients with disseminated CRC treated at Memorial Sloan Kettering over a 10 year period.[16] Metastases distal to the knee or elbow

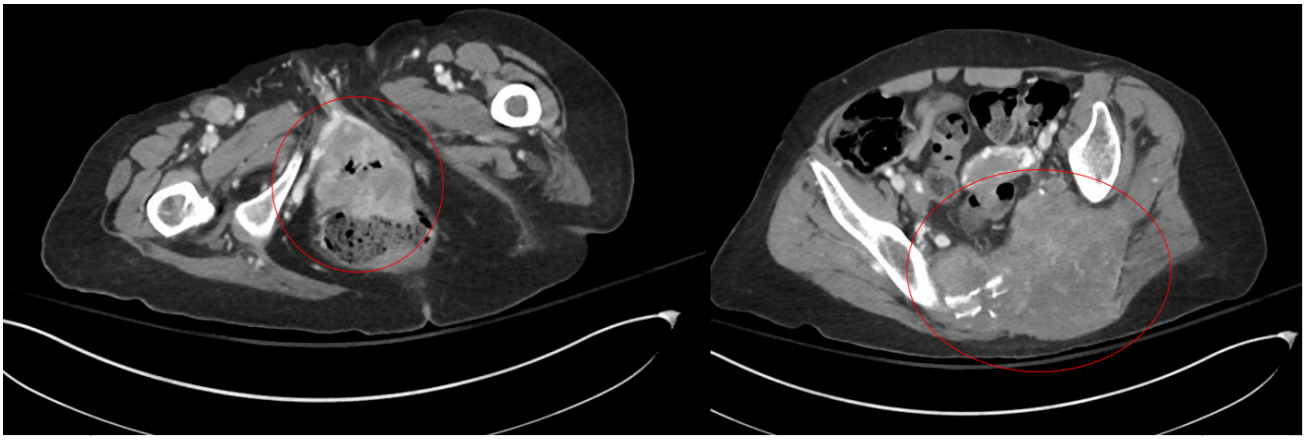

Figure 4. CT chest/abdomen/pelvis with and without contrast. Axial plane images with a red circle showing large circumferential soft tissue mass extending to perineal soft tissues, vaginal cuff, and left gluteal fold (left panel). Large destructive soft tissue mass with significant osseous destruction of the sacrum and coccyx (right panel).

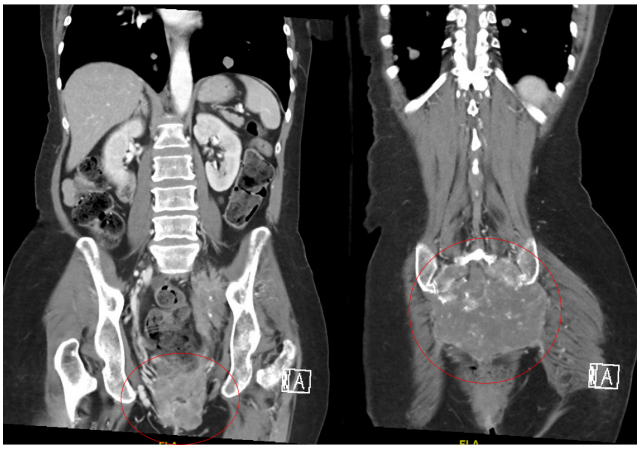

Figure 5. CT chest/abdomen/pelvis with and without contrast. Coronal plane images with a red circle showing large circumferential soft tissue mass extending to perineal soft tissues, vaginal cuff, and left gluteal fold (left panel). Large destructive soft tissue mass with significant osseous destruction of the sacrum and coccyx (right panel).

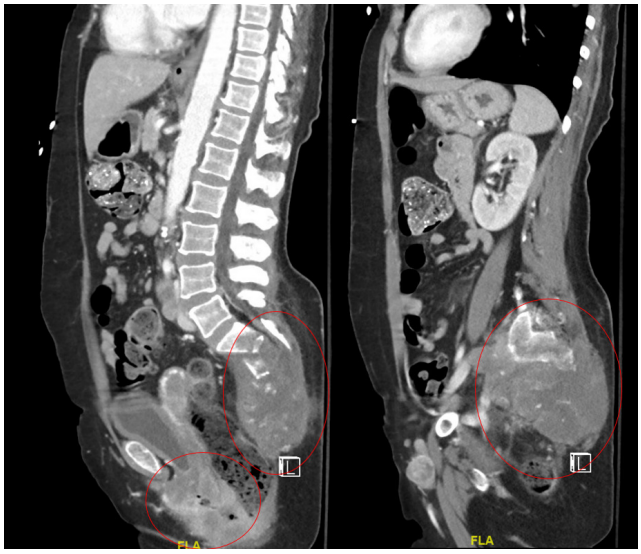

Figure 6. CT chest/abdomen/pelvis with and without contrast. Sagittal slices with a red circle showing large circumferential soft tissue mass extending to perineal soft tissues, vaginal cuff, and left gluteal fold. Large destructive soft tissue mass with significant osseous destruction of the sacrum and coccyx.

are uncommon and when they occur are most commonly lung and renal cell carcinoma.[6,24-28]

In an analysis of 2429 cases of bone metastases from carcinomas, only 3.5% of cases were distal to the elbow or knee whereas 43% were in the axial skeleton.[29] In a review of 539 patients diagnosed with bone metastases, Tani et al found a similarly low frequency of distal extremity metastases, 2.4%.[24] Proposed explanations for the non-random pattern of bone metastasis include peculiarities of the microenvironment such as the higher proportion of red marrow in the axial skeleton as well as the ability for cancer cells to gain access to the spine in the setting of retrograde flow through the valveless veins in Batson's plexus.[30-32]

Distal metastases are often indicative of widespread metastatic disease and are associated with a poor prognosis.[18,19] As a result, except in rare cases of oligometastasis, treatment of fibular metastases focuses on palliative therapy.[33-35] Non-surgical options for bone metastases include radiotherapy, bisphosphonates, and chemotherapy.[36] Surgical intervention may be considered based on the size and location of the metastasis, the risk of pathologic fracture, presence of other metastatic disease, and the patient's pain and performance status.[35,36] The primary cancer may also influence treatment decisions. Renal cell carcinoma, for example, has a poor response to radiation and wide surgical resection of an isolated metastasis is associated with increased survival.[37,38] Bone metastasis in CRC, conversely, is associated with a poor prognosis and, with or without surgical intervention for the skeletal disease, has a median life expectancy of less than 10 months.[14,39]

When operative intervention is determined appropriate, multiple options exist for treating lesions in the distal

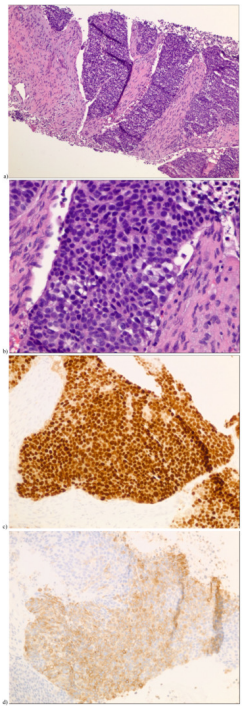

Figure 7. Biopsy pathology with hematoxylin & eosin staining under low (a) & high power (b) showing sheets of cells without glandular formation. Cdx2 immunohistochemistry stain (c) and ck20 immunohistochemistry stain (d) consistent with adenocarcinoma of the colon.

fibula. Methods for reconstruction of the lateral malleolus include transfer of the fibular head, allograft, or iliac crest bone graft.[40-42] Alternatively, the lateral ankle ligamentous complex can be reconstructed with the peroneus brevis or mesh.[43,44] Resection followed by arthrodesis is another option to address stability, although it sacrifices mobility.[45, 46] The current literature on surgical intervention for distal fibular metastases is limited to case reports and small case series, many of which combine primary and secondary tumors.[47-50] Further research is needed to determine if any of the described techniques produces superior outcomes.

Although rare, the prevalence of CRC metastatic to bone may be increasing. The incidence of osseous metastases aggregated across primary gastrointestinal tumors is estimated at 5.6-7.9% and even lower in CRC, ranging from 3-7% in several retrospective studies.[11-13,16,51] CRC metastases most commonly present as osteolytic lesions although mixed lytic/blastic lesions have been reported.[16] Unknown CRC presenting as a secondary tumor will likely remain uncommon given the effectiveness of colonoscopy screening in detecting early-stage disease.[35] However, the incidence of bone metastasis may increase as patients with a history of CRC live longer secondary to improving pharmacologic and targeted therapies for CRC treatment.[20] In a recent retrospective review of patients with metastatic CRC, Sundermeyer et al found a 10.4% incidence of bone metastases, higher than historically reported in the literature, as well as a significant association between bone metastases and the number of systemic chemotherapy agents a patient received.[18]

Our patient's experience illustrates several types of cognitive biases that may contribute to delays in diagnosis for patients with rare pathology. First, physicians are susceptible to an availability bias, a cognitive distortion that leads to under-diagnosis of disease processes uncommonly encountered.[52] Because orthopedic surgeons frequently encounter fibula fractures presenting as lateral ankle pain after a fall, this diagnosis comes to mind more readily, and the ease of arriving at fibula fracture is misinterpreted as an indication the diagnosis is correct. After the initial misdi-

Table 3. Left sacrum needle biopsy pathology immunohistochemistry staining, consistent with colorectal origin

Antibody	Result
Cytokeratin 7	Negative
Thyroid Transcription Factor	Negative
CDX2	Positive
Pax-9	Negative
Gata-3	Negative
P40	Negative
Chromogranin A	Negative
Synaptophysin	Negative
Cytokeratin 5/6	Focally positive
Cytokeratin 20	Positive
CD56	Focally positive
Melan-A	Negative
MLH-1	No loss of nuclear expression
MSH-2	No loss of nuclear expression
MSH-6	No loss of nuclear expression
PMS-2	No loss of nuclear expression

agnosis, the provider may also have experienced an anchoring bias, or failure to adjust an initial impression based on information presented later, such as a lack of clinical improvement and progressively abnormal radiographs, as was seen in this case.[52]

As the incidence of skeletal metastases increases, orthopedic surgeons are more likely to encounter a patient with a secondary tumor in a historically uncommon location. Therefore, it is critical to include metastatic disease in the differential diagnosis for distal extremity pain, especially in patients with a history of malignancy or lack of age-appropriate cancer screening.

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