Dim EM[1,*], Nottidge TE[1], Dim UME[2], Etuk EB[3], Itie JC[4], Uduma F[5], Ita IO[4], David DE[4].

[1]Department of Orthopaedics and Traumatology, Faculty of Clinical Sciences, University of Uyo/ University of Uyo Teaching Hospital, Uyo, Nigeria.

[2]Nursing Services Division, National Orthopaedic Hospital, Lagos, Nigeria.

[3]Department of Surgery, Faculty of Clinical Sciences, University of Uyo/ University of Uyo Teaching Hospital, Uyo, Nigeria.

[4]Department of Orthopaedics and Traumatology, Federal Medical Centre, Ebute Metta, Lagos Nigeria.

[5]Department of Radiology, Faculty of Clinical Sciences, University of Uyo/ University of Uyo Teaching Hospital, Uyo, Nigeria.

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*Corresponding author
Dr. Edwin M. Dim
E-mail:
maduakonamdim@yahoo.com

Adenocarcinoma of the colon presenting as bone metastases of unknown primary- A case report

***Abstract*— The liver and lung are the usual sites of distant metastasis from colorectal tumours. Bone metastasis in patients with colorectal carcinoma is considered extremely rare. It often signifies the terminal phase of colon carcinoma with a median survival of less than ten months. High index of suspicion is required, and the possibility or risk of osseous metastases arising from primary lesion in the colon should be borne in mind when assessing bony lesions that present initially as metastasis of unknown origin. We present a case of adenocarcinoma of the colon which remained undiagnosed until patient reported with a pathological fracture of the humerus and paraparesis.**

***Keywords* — Osseous metastases, unknown primary, adenocarcinoma of the colon.**

1 INTRODUCTION

A predictable pattern of metastasis for colorectal carcinoma (CRC) has been documented by some scholars [1, 2]. In over 70% of patients, the liver is the commonest site of initial metastasis, and in 40-50% of them, other organs are concomitantly involved [1]. 20-30% of all distant metastasis by colorectal carcinoma involves the lung, making it the second commonest site of involvement [2].

Metastasis of colorectal carcinoma to other tissues, including the skeleton, has not been commonly reported [1]. However, available literature suggests that two modes of skeletal involvement by colorectal carcinoma are recognized [1, 3]. There are the more common bony metastases associated with synchronous liver or lung metastases, having an overall incidence of 5-11% [1]. On the other hand, there is also a more uncommon isolated skeletal metastases, occurring at an estimated rate of 1-2% [1, 3].

Skeletal involvement by colorectal carcinoma is rare, irrespective of whether it is an isolated metastasis, or associated with synchronous liver or lung metastasis [1, 3]. It is expected that as more advanced radiological techniques such as positron emission tomography or positron emission tomography/computerized tomography (PET-CT) become available to all centres, especially in resource-constrained settings, skeletal metastases from colorectal carcinomas may be more readily identified.

The aim of this article is to illustrate a case that presented initially as osseous metastases of

unknown primary (in a patient without prior history of primary malignancy), but which was subsequently diagnosed as metastatic adenocarcinoma of the colon.

2 CASE REPORT

A 64- year old hypertensive woman was referred to the Department of Orthopaedics and Traumatology from a peripheral hospital with a nine-month history of pain in the left arm, and a three-week history of bilateral lower limb weakness. Initially, it was a gradual-onset, mild, intermittent, dull and aching pain in the mid portion of the left arm. The pain later became intense, progressive, constant in nature, worse at nights, exacerbated by activities involving the affected limb, and without any known relieving factors. There was no history of preceding trauma.

About four months after onset of pain, she slipped and fell on a staircase at home following which she noticed an aggravation of the left arm pain, with an abnormal mobility and localized swelling over the painful area of the left arm. There was limitation of movement of the affected limb. She sought treatment at the traditional bonesetter's place, where the affected limb was severally manipulated and massaged to no avail. Four months after the domestic fall, she developed bilateral progressive lower limb weakness with inability to walk without support. There was accompanying pelvic and low back pain that radiated to the back of the thighs. There was no history of trauma to the back, pelvis or lower limbs prior to this time.

There was history of malaise, anorexia, progressive weight loss. However, there was no history of cough, haemoptysis, fever, drenching night sweat or contact with persons with chronic cough. There was no history of abdominal pain or swelling, haematochezia, melaena stools, or tenesmus. There was no history of watery or bloody vaginal discharge, tobacco usage, breast surgery, chemotherapy, radiation exposure or use of steroid, including oral contraceptives. Her sister was said to have died from a uterine malignancy.

The patient was referred for Orthopaedic review on account of worsening left upper limb symptoms and progressive weakness of both lower limbs with inability to ambulate.

Physical examination showed a middle-aged lady on a wheelchair and in pain. She was clinically pale, but was afebrile, anicteric, acyanosed, not dehydrated, and without pedal oedema nor peripheral lymphadenopathy. Her anthropometric data was: weight 60kilogram (Kg), height 1.53metres (m) and body mass index (BMI) 25.63Kg/m^2. Head and neck, cardiovascular system, respiratory system, and breasts examination was not remarkable. There were no neck, breast or axillary masses. She had a firm and nodular hepatomegaly, measuring eight centimeters (cm) below the coastal margin at the mid clavicular line. There was no demonstrable ascites. Vaginal and rectal examinations were not remarkable.

Musculoskeletal examination showed no clinical abnormality in the right upper limb. The left upper limb was in flexion at the elbow and suspended on a sling. There was a warm, tender and scarified fusiform mass occupying the distal two-thirds (2/3) of the left arm. The mass was hard in consistency with deep fixity, but not attached to overlying skin. The left elbow range of passive motion was from zero to eighty degrees, and the left shoulder showed no functional limitations. There was wasting of the muscle groups of both the arm and forearm, but no distal neurovascular deficit (Figure 1).

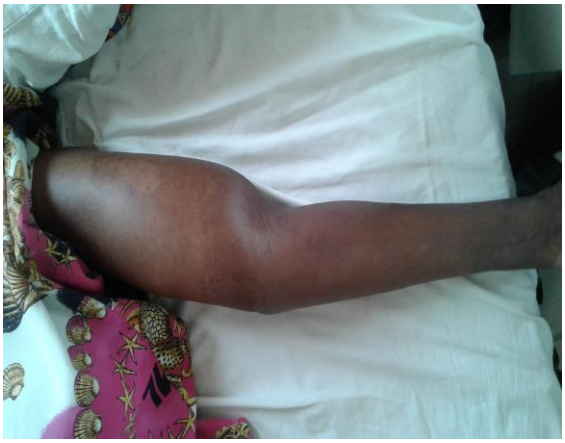

Figure 1: Left upper limb showing fusiform mass distal two-thirds of the left arm.

Both lower limbs showed reduced muscle power of grade 4 in all muscle groups, and hypoaesthesia in the L4 dermatome. The spine showed no deformity, but was tender on palpation at the level of L2-4 lumbar segments.

Plain radiographs of the left arm showed a juxta-articular, expansile, and lytic lesion of the distal humerus, with soap bubble appearance. There was medullary irregularity of the proximal half of the humerus, and a pathological fracture at the mid-shaft. Soft tissue swelling in the arm was also noted (Figure 2).

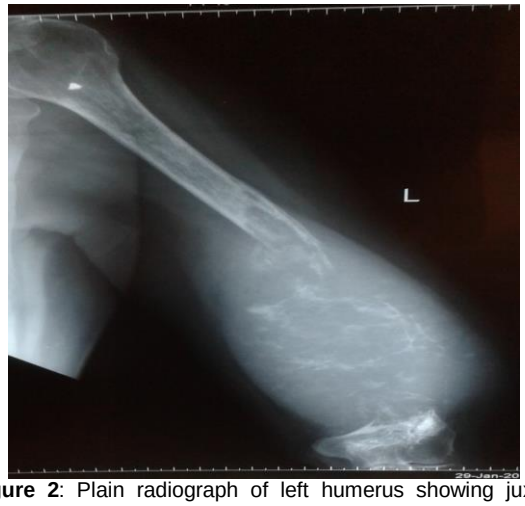

Figure 2: Plain radiograph of left humerus showing juxta-articular, expansile and lytic lesion of the distal humerus with soap bubble appearance.

The plain x-rays of the lumbosacral spine showed a wedge fracture of the L3 vertebral body. The magnetic resonance imaging (MRI) of the left arm showed a large, expansile, and osteolytic lesion with soft tissue component; multiple cystic areas, haemorrhage and heterogenous contrast enhancement in the lower half of the humerus, as well as a pathological fracture. In the lumbosacral spine, MRI showed moderate compression fracture of the L3 vertebra with retropulsed posterior body indenting the thecal sac, and causing spinal canal stenosis and compression of the roots of the Cauda Equina. There was a diffuse posterior annular bulge of the L4/5 intervertebral disc, indenting and compressing the theca, and causing stenosis of the intervertebral neural foramina (Figure 3 a,b,c).

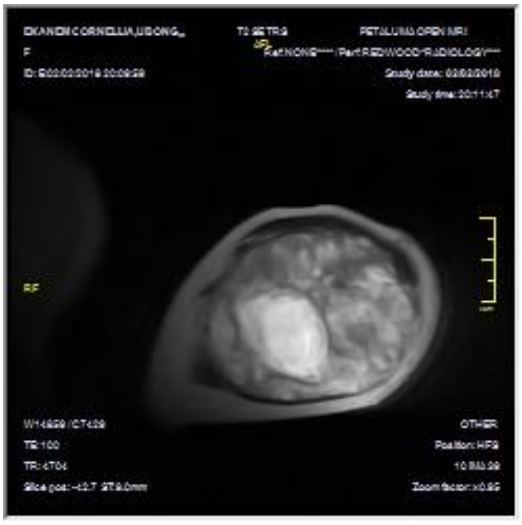

Figure 3a: Axial MRI left arm.

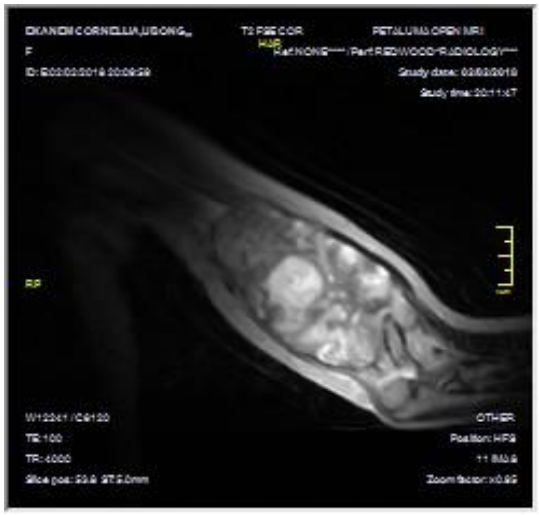

Figure 3b: Coronal view MRI of the left arm.

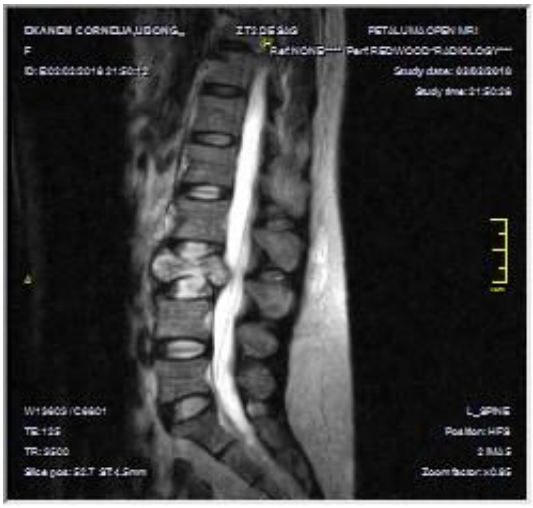

Figure 3c: Sagittal Lumbosacral MRI showing compression fracture of the L3 vertebra and retropulsed posterior body indenting the thecal sac.

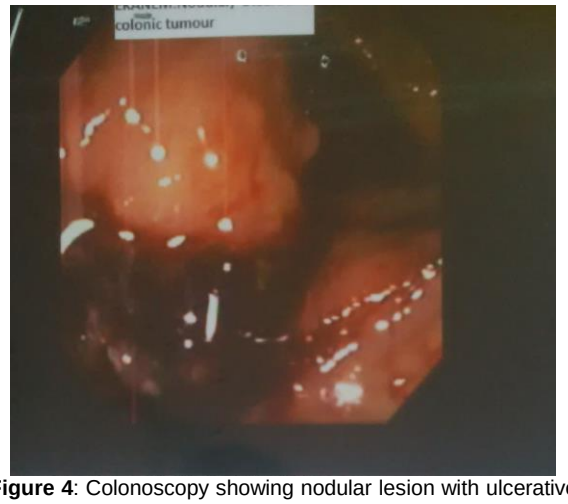

Figure 4: Colonoscopy showing nodular lesion with ulcerative components

Abdominal ultrasound scan showed a liver span of 14.1cm in the cranio-caudal plane, and a fairly homogenous parenchymal echotexture and regular outline. There was a large, well defined, and slightly hyperechoic round mass, measuring 15.6 x 7.8cm within the liver parenchyma, with areas of increased flow on colour doppler interrogation in the left lobe. Computerized tomography (CT scan) of the abdomen and chest was not arranged due to financial constraint.

Remarkable laboratory profiles were Haemoglobin (Hb) 8.2g/dl, erythrocyte sedimentation rate (ESR) 129mm in the 1st hour, carcinoembryonic antigen (CEA) 210ng/ml (0-3), Serum creatinine 91um/L (reference range 40-80), Uric acid 0.62mmol/L (0.18- 0.30), Phosphate 1.46mmol/L (0.96-1.44), Calcium 2.0mmol/l (2.1-2.6), Aspartate Transaminase 17iu/L (0-12), and Alkaline Phosphatase 62iu/L (9-35). Serum protein electrophoresis showed prominent alpha-2 fraction possibly due to an underlying acute/chronic reactive process. Bence Jones protein was absent. Faecal occult blood test was positive (Table 1). Pap smear was negative for intraepithelial lesion or malignancy. Chest X-ray showed no abnormalities.

Based on the clinical, radiologic and laboratory data so far available, patient was diagnosed of metastatic bone disease with unknown primary. Suggested primary pathologies included Primary liver cell carcinoma, adenocarcinoma of the colon, and multiple myeloma. The immediate clinical challenges of the patient were paraparesis and pathological fracture of the distal left humerus. Following appropriate resuscitation with fluid and analgesics, as well as splinting of the fractures with orthotic devices, patient had a core needle biopsy of the left humeral lesion. Histopathological finding showed malignant neoplasm composed of variably sized and shaped glands lined by tall columnar cells with hyperchromatic nuclei and increased nucleo-cytoplasm ratio, suggestive of an adenocarcinoma.

Further review by the General Surgeons was solicited. Patient had a high definition video colonoscopy under conscious sedation, after bowel preparation with oral doses of Dulcolax and 20% Mannitol. This showed a nodular lesion, with ulcerative components, in the hepatic flexure of the right colon. Mucosa around the lesion was friable and exhibited contact bleeding (Figure 4). There were no features of diverticular or inflammatory bowel disease.

Table 1: Laboratory indices

LABORATORY TEST	TEST VALUES	REFERENCE RANGE
BONE PROFILE		
ALP	61.00 IU/L	9.00-35.00 IU/L
Adjusted Calcium	2.00 mmol/L	2.10-2.60 mmol/L
Phosphate	1.46 mmol/L	0.96 -1.44 mmol/L
INFLAMMATORY MARKERS		
CRP	Not available	< 0.76 mg/dL
ESR	129.00 mm 1st hour	0-20 mm 1st hour
TUMOUR MARKERS		
AFP	Not assessed	< 9.00 SI unit
CEA	210 ng/ml	0-3.00 ng/ml
Bence Jones Protein	Negative 0.62mmol/L	0.18-0.30 mmol/L
Uric Acid	Prominent	
Serum protein electrophoresis	alpha-2 fraction	
COMPLETE BLOOD PICTURE		
Haemoglobin	8.60 g/dl	12.00-16.00 g/dL
PCV	29.60%	36-46%
RBC	$2.77x10^{12}$/L	$4.50-5.50x10^{12}$/L
TWBC	$7.97×10^9$/L	$3.0 -13.0×10^9$/L
Platelet	$385×10^9$/L	$100-300×10^9$/L
RENAL, LIVER FUNCTION TESTS		
Creatinine	91.00 µmol/L	40.00-80.00 µmol/L
Urea	3.20 mmol/L	2.70-7.20 mmol/L
Na^+	143 mmol/L	135-145 mmol/L
K^+	3.9 mmol/L	3.2-5.0 mmol/L
Cl^-	97 mmol/L	96-108mmol/L
HCO_3^-	22 mmol/L	22-28 mmol/L
Total protein	56.00g/L	62-82 g/L
Albumin	30.00g/L	36.00-52.00 g/L
Globulin	26.00g/L	18-36 g/L
Total Bilirubin	11.00 µmol/L	2.00-17.00 µmol/L
Conjugated bilirubin	5.9 mmol/L	2-7 mmol/L
ALP	61.00 IU/L	9.00-35.00 IU/L
ALT	5.00 IU/L	0-12 IU/L
AST	17.00 IU/L	0-12 IU/L
GGT	Not assessed	
URINALYSIS		
Appearance	Yellow and clear	
P^H	Acidic 6.0	
SG	1.020	
Protein	Negative	
Glucose	Negative	
Bilirubin	Negative	
Blood	Negative	
Ketone bodies	Negative	
Nitrite	Negative	
Urobilinogen	Normal	
Leucocytes	Negative	

Caecal intubation was achieved. Colonoscopic biopsy of the lesion revealed an adenocarcinoma.

The patient received supportive care, including physiotherapy, opiod analgesics, bisphosphonate (zoledronic acid infusion), erythropoietin, as well as two units of fresh whole

blood to optimize haematological indices prior to chemotherapy and radiation therapy. She could not afford the suggested radiation therapy to the lumbar spine and the left humeral lesions on account of financial constraint and the logistics of being moved to another centre, where radiation therapy was available. However, she received the first course of chemotherapy with the CAPOX regimen, comprising Oxaliplatin 130mg/m^2 in 500mls of 5% Dextrose Water over two hours, and oral Capecitabine 1000mg/m^2 twice daily for 14 days. This regimen was to be repeated every three weeks until eight courses, or until disease regression.

The patient requested to be discharged home, and to come for the subsequent courses of chemotherapy on an outpatient basis. She was not considered fit for bony operative procedures targeted at the bony metastases. She died at home eight weeks after being discharged from the hospital, and twenty one weeks after presentation to the hospital. Clinical autopsy to ascertain the extent of possible distant metastases to the liver and lungs could not be arranged.

3 DISCUSSION

Bone metastasis is frequently seen among patients with breast, prostate and lung cancers. Although the vulnerability of the skeleton to metastatic cancers has been variously mentioned [4, 5], the skeleton remains a rare site for metastatic colorectal carcinomas [1]. Skeletal involvement by colorectal carcinoma is rare, irrespective of whether it is an isolated metastasis, or associated with synchronous liver or lung metastasis [1, 3]. The presence of synchronous or isolated bony metastasis in colorectal carcinomas is often identified by means of advanced imaging techniques employed in the diagnostic workup of these patients. In isolated bony metastatic colorectal carcinoma, the concomitant involvement of the liver and the lungs is absent, and the rate of isolated bony metastasis has been given as 15-30% by some authors following routine imaging techniques [6]. On the other hand, a group of researchers were reported to have conducted a positron emission tomography/computerized tomography (PET-CT) evaluation of colorectal cancer patients in which no patient was found to have an isolated bone metastasis, without liver or lung involvement [6]. For this reason, the authors believed that early metastasis is always present in the lungs and liver before involvement of the bone [6]. The index case presented in this article fits into this category, having been found to have suspicious liver lesions on routine abdominal ultrasound, although a computerized tomographic scan for further evaluation of the liver and lungs could not be arranged.

Not only is bone metastasis uncommon in CRC, early detection is also relatively difficult [7]. The risk factors for bone metastases in patients with colorectal carcinoma have been studied by Li et al [7]. In a comparative analysis of 2790 patients diagnosed with colorectal carcinoma, Li et al categorized the patient population into two groups, namely, bone metastasis and non-bone metastasis groups. They discovered that patients with bone metastases had statistically significant higher concentrations of alkaline phosphatase (ALP), carcinoembryonic antigen (CEA), cancer antigen 199 (CA199), and cancer antigen 125 (CA125) than those without bone metastases. Following binary logistic regression analysis, the authors further identified ALP, CEA, and CA125 as independent risk factors for bone metastasis in colorectal carcinoma [7]. These findings correlate positively with our index case, in whom CEA and ALP were markedly elevated respectively. With respect to predicting the risk of developing bone metastasis in patients with CRC, it has been reported that ALP has the highest diagnostic accuracy, with a sensitivity and specificity rate of 81.1% and 71.5%, respectively [7]. The implication of these is that the finding of elevated levels of these markers in patients diagnosed with CRC would help clinicians to maintain a high index of suspicion for osseous metastases for the purpose of early detection and timely management, aimed at preventing deterioration of patient's condition [7]. Other well established and documented [8] risk factors for bone metastasis in CRC are rectal cancer, lymph node invasion at surgery of primary tumour, and lung metastases at any time. RAS mutation status has also been suggested but results are not conclusive [8]. However, these variables were not applicable to our index case, although a computerized tomography scan for further assessment of her chest was not done. Her plain chest radiograph was not remarkable for pulmonary metastases.

The spine and pelvis have been reported as the most common sites of bone metastasis from CRC, whereas metastasis to the extremities was reported as extremely rare [7, 9]. Our index case had a two-site bony metastasis, involving the spine and the left humerus. Two-site bone

metastasis has been reported to constitute 25.67% of bone metastasis from CRC, and is second to one-site bone metastasis with an incidence of 67.57%. Three or more sites of bone metastases from CRC is said to be rare [7, 9]. The mechanism of metastasis of CRC to the spine has been linked to the vertebral venous plexus of Batson, which communicates the veins of the peritoneal organs and vertebral bodies, thus providing a channel for the migration of tumour cells from the peritoneal cavity to the vertebrae [9, 10]. Haematogenous spread may also have been responsible for a more distant metastasis to the humerus as was seen in our index case.

Bone metastasis often suggests that the disease has reached a late stage, with a poor prognosis [7]. Apart from predicting the risk of bone metastasis from CRC, the tumour markers ALP and CEA are also important in its prognosis. Evidence exists in literature to suggest that elevated levels of ALP and CEA in colorectal carcinoma patients with bone metastasis are associated with poor prognosis [7, 11].

Survival after diagnosis of bone metastasis from CRC depends on cohorts, and has been reported to range from 5 to 21 months [8]. The survival period of 14 months in our index case falls within this range. She presented to us nine months after her first complaints suggestive of bone metastasis and succumbed to the disease five months thereafter. Bone metastasis often suggests that the disease has reached a late stage, with a poor prognosis [7]. At the time we first saw the patient, she was not considered fit for bony operative procedures targeted at the bone metastases. At this time, patient had suffered multiple skeletal related events (specifically pathological fracture, spinal cord compression and hypercalcaemia) and was wheelchair bound.

In general, current guidelines suggest that surgical treatment for bone metastases be considered, when indicated, in patients with life expectancy of more than 3 months. Patients with bone metastasis and having life expectancy of less than 3 months often have poor post-operative rehabilitation potential. The expected life expectancy of the patient will dictate whether surgery is worthwhile as well as the aggressiveness of such surgical intervention. Sometimes, life expectancy may be difficult to predict as patients may suddenly deteriorate. From surgical point of view, life expectancy represents the estimated survival period of the patient after surgical intervention. The estimation of life expectancy is within the domains of the Oncologists using the instrument of the Kaplan-Meier survival curve [12, 13]. Therefore, whenever applicable, systemic treatment should always be considered along with local tumour excision, and a suitable skeletal reconstruction technique. The essence of such surgical intervention is palliative, aimed at maximizing the quality of remaining life [12, 13].

The duration of post-operative survival in metastatic bone disease depends on a number of factors, such as age of the patient, site of primary malignancy, indication for surgery, and the option of surgery [12]. In the study by Dim et al [12], the duration of post-operative survival after surgery for bone metastasis among patients with gastrointestinal/colorectal primary tumours was a range of two to six months.

Other treatment modalities applicable to bone metastases from colorectal carcinoma include bisphosphonate therapy, systemic chemotherapy, radiotherapy, and medical pain relief [8]. The index patient received Bisphosphonate (Zoledronic acid infusion) before she finally succumbed to the disease. Although the level of evidence is not high, studies indicate that bisphosphonate treatment might improve outcome with regard to skeletal-related events (defined as pathologic fracture, spinal cord compression, radiation therapy to bone, change in antineoplastic therapy and surgery to bone), but not overall survival. It is documented that no study has evaluated the role of denosumab in bone metastases from CRC [8]. Systemic chemotherapy may improve survival among bone metastases patients [8], but this effect could not be investigated in our patient because she died after the first course of chemotherapy. She could neither afford to be referred for radiotherapy which was, however, not available in our facility.

4 CONCLUSION

Bone metastases from colorectal carcinoma are relatively uncommon and the literature is sparse on the subject. A number of risk factors and prognostic markers have been mentioned by authors, but investigations into these factors are not conclusive. Survival after diagnosis of bone metastasis from colorectal carcinoma ranges from 5 to 21 months. Palliative surgical intervention, when indicated, reduces associated morbidity, but should be guided by the expected life expectancy of the patient.

5 DISCLOSURES

The authors have no disclosures to make.

6 CONFLICT OF INTERESTS

The authors have no conflict of interest to declare.

7 ETHICAL REVIEW CLEARANCE

This is not applicable to case reports in my institution.

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