Case Report

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Pathology Section

Heterotopic Ossification (HO) in Caecal Adenocarcinoma: A Case Report

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ABSTRACT

The Heterotopic Ossification (HO) or Osseous Metaplasia (OM), is a rare condition that presents as benign bone formation at non-skeletal locations, often incidentally identified during histopathological evaluation but not typically radiologically detected. HO within colorectal adenocarcinoma occurs rarely; only a few cases have been reported in the literature, which demonstrate how unique cases expand our knowledge of this unusual entity and its diagnostic implications. Author presents a case of a 47-year-old female patient who had a history of three months of abdominal pain with a 5 kg weight loss over the past month. She was found to have a 3×3 cm hard immobile mass in the right iliac fossa on physical examination, which CT imaging showed to be an irregular circumferential thickening with a malignant-appearance involving the caecum, terminal ileum, lower ascending colon and proximal appendix. Interestingly, there was no sign of ossification on CT scan. A right hemicolectomy was done and the resected specimen was sent for histopathological examination. Histology confirmed an infiltrative malignant neoplasm consistent with a moderately differentiated adenocarcinoma. Importantly, benign bone tissue was seen within the fibrous stroma of the tumour. In this case, we emphasise the significance of histopathological evaluation for correct diagnosis when primary ossifying soft-tissue neoplasms or carcinosarcomas are suspected because these have a worse prognosis than HO. Although HO in colorectal carcinoma is rare, it does not appear to directly affect the patient's prognosis; however, further study of this entity is crucial as cases continue to increase.

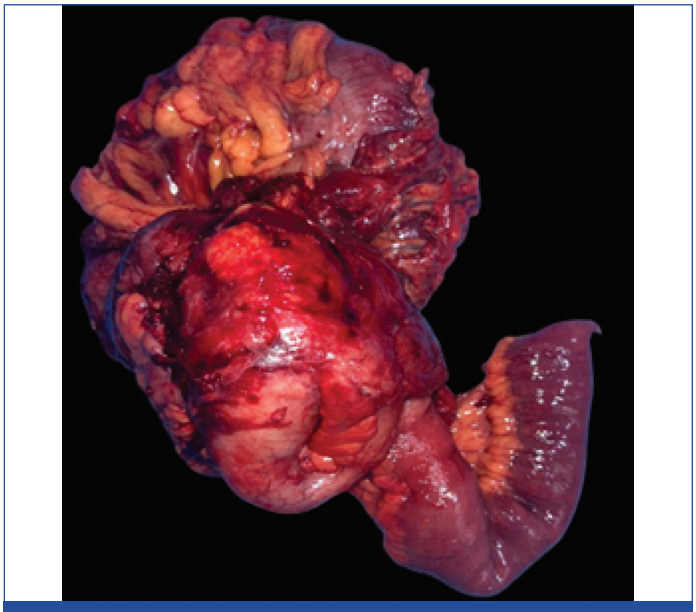
Keywords: Colorectal carcinoma, Histopathology, Malignancy, Osseous metaplasia, Tumour

CASE REPORT

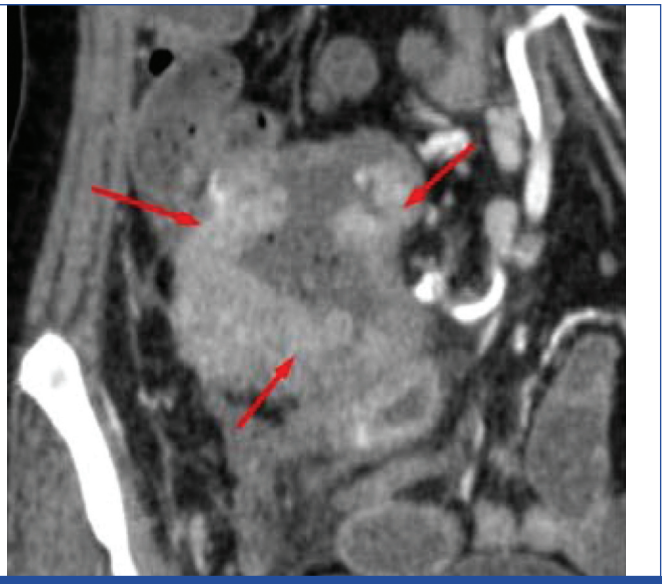
A 47-year-old woman had complaints of persistent abdominal pain for about three months, along with loss of 5 kg in the previous month. Patient was a known diabetic on medications for past five months. She attained menopause two years back. No significant traumatic history was present. The patient had no evidence of abnormal general condition upon physical inspection, but palpation revealed a 3×3 cm, smooth-surfaced, firm mass in the right iliac fossa that was fixed. Baseline investigations revealed haemoglobin of 11.7 g/dL, total leukocyte count of 12,980 cells/mm^3, and platelet count of 3.47 lakh/mm^3. Liver Function Tests (LFTs), Renal Function Tests (RFTs), and coagulation profile were within normal limits. The Carcinoembryonic Antigen (CEA) level was slightly elevated at 4.91 ng/mL.

Further radiological examination by CT scan [Table/Fig-1,2] revealed ill-defined, circumferential wall thickening with a malignant appearance in several anatomical structures: caecum, terminal ileum, lower ascending colon and the proximal aspect of the appendix with the provisional radiological diagnosis of neoplastic etiology of caecum. There was no evidence of ossification within the lesion, which may be why the subsequent histopathological diagnosis of HO was incidental. Histopathological evaluation of colonic biopsy revealed a diagnosis of moderately differentiated adenocarcinoma. Radiological diagnosis was suggestive of a neoplastic etiology involving the caecum. Carcinoma caecum was confirmed by correlation between radiology and histopathology report of colonoscopy biopsy.

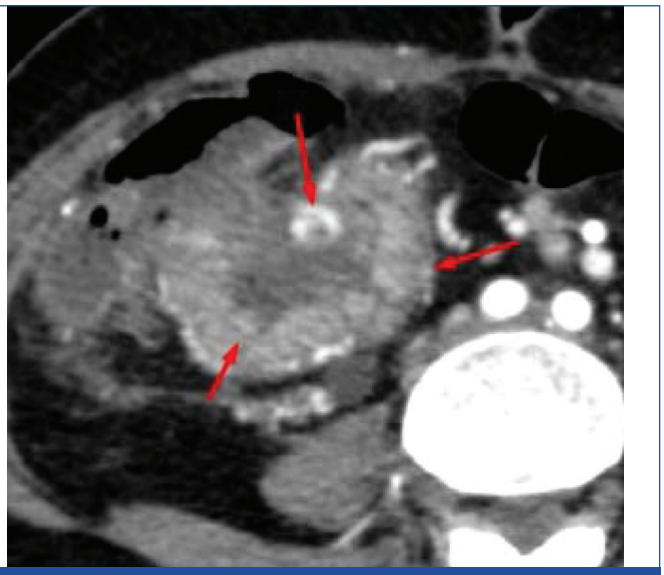
After the diagnostic workup, a right hemicolectomy was performed on the patient, and the resected specimen [Table/Fig-3] was sent to histopathology for full examination. Definitive diagnostic information was obtained through microscopic examination of the resected tissue, which showed infiltrative malignant neoplasm of the colonic mucosa in which the tumour cells were largely arranged in back-to-back glands but demonstrated cribriforming patterns in some areas. The neoplastic cells were oval with scant to moderate cytoplasm and a high nuclear-cytoplasmic ratio, large pleomorphic nuclei with prominent nucleoli in many of the cells [Table/Fig-4a]. But incidentally, numerous areas of benign bone tissue were seen within the fibrous stroma of the tumour well as areas of dystrophic calcification [Table/Fig-4b]. Final diagnosis was given as pT3pN0, moderately differentiated adenocarcinoma. For prognosis, immunohistochemistry for the Microsatellite Instability (MSI) panel (MLH1, MSH2, MSH6, PMS2) was done which showed intact nuclear expression (MMR-proficient). Since no nodal metastasis was present, the patient was kept on annual clinical and radiological follow-up.



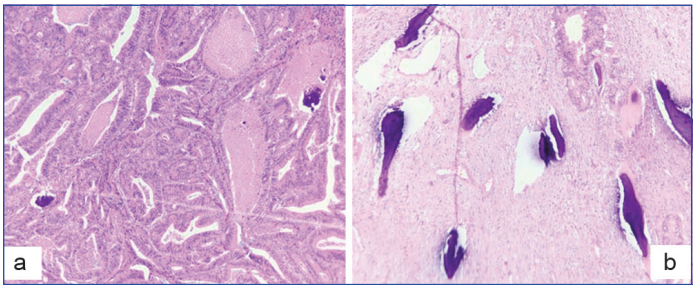
[Table/Fig-1]: The resected right hemicolectomy specimen showing a caecal mass.



[Table/Fig-2]: Coronal section of computed tomography scan showing irregular circumferential asymmetrical enhancing wall thickening involving the ileocaecal junction, caecum and proximal ascending colon without any sign of calcification or ossification.



[Table/Fig-3]: A transverse section of the computed tomography scan showing irregular circumferential asymmetrical enhancing wall thickening involving the ileocecal junction, caecum and proximal ascending colon without any sign of calcification or ossification.



[Table/Fig-4]: a) Haematoxylin and Eosin stain, Section of tumour comprising of moderately differentiated adenocarcinoma (100x); b) Haematoxylin and Eosin stain, shows areas of adenocarcinoma with stroma showing benign mature bony trabeculae (200x).

DISCUSSION

The HO, also known as OM, is a rare process that involves the benign formation of bone tissue in an anatomical location where bone is not normally present. Hasegawa initially described stromal ossification in gastrointestinal malignancies, but it was Dukes who coined the term ossification for colorectal adenocarcinoma in 1939 [1]. According to Dukes, the estimated frequency of HO in rectal cancer is less than 0.4%. OM within a colorectal carcinoma is rare and most often reported to occur more frequently in rectal tumors than those arising on the right or left colon, or the appendix [1].

The occurrence of HO associated with caecal adenocarcinoma is extremely uncommon; only three other published cases could be identified from the medical literature prior to this case. Further data on these reported cases are presented in [Table/Fig-5] that allows for a direct structured comparison of patient demographics, diagnosis, presence of metastasis, treatment modalities and the specific site of HO [2-4].

The precise pathogenesis of HO in colorectal carcinoma remains largely unknown, although several hypotheses have been proposed. A widely accepted framework, as suggested by Vos AM et al., postulates that three fundamental conditions are necessary for heterotopic bone formation to occur: 1) the presence of osteoinductive factors; 2) the availability of osteogenic precursor cells, and 3) an osteoinductive matrix [5].

The most commonly implicated osteoinductive factors are the Bone Morphogenetic Proteins (BMPs), glycoproteins that are involved in early differentiation of mesenchymal stem cells and in osteoblastic differentiation via the Transforming Growth Factor-beta (TGF-β) signalling pathway [6]. BMPs work through the BMP-Smad pathway, which is essential for promoting mesenchymal stem cell differentiation and the expression of osteogenic markers in the surrounding stroma, such as RUNX2 and SP7 [7]. Researches have recently identified several specific lineage cells that contribute to HO like Gli2 and α-SMA in the microenvironment which is additional evidence for the role of TGF-β pathway in HO [8].

In terms of osteogenic precursor cells, it has been proposed that these may be mesenchymal stem cells or fibroblasts that have undergone metaplasia into osteoblasts under conditions within the tumour environment. The osteoinductive matrix provided by the tumour microenvironment itself is also important, and it has been hypothesised that surrounding areas of inflammation, necrosis, calcification, and mucin production all play inductive roles in HO [5]. The sites in Gastrointestinal Tract (GIT) in which HO are commonly noted are rectum, colon, carcinoids of the stomach and mucoceles of the appendix while other sites are sporadically in the neoplasm of organs such as the lung, kidney and breast.

The HO has important diagnostic implications; it can be mistaken for other primary ossifying soft tissue neoplasms or even more critically for carcinosarcomas, which have a much worse prognosis than typical adenocarcinomas or adenocarcinomas with benign metaplasia. The carcinosarcomas are tumours which have both carcinomatous and sarcomatous differentiation (osteosarcomatous, chondrosarcomatous or liposarcomatous differentiation) but OM presents only with benign bone formation [9].

The correlation between HO and the epithelial/endothelial-mesenchymal transition (EMT/EndMT) is another prognostic factor.

S. No.	Reference	Year	Patient details	Diagnosis	Metastasis	Treatment	Site of HO
1.	Papadopoulos MC et al., [2]	1998	47/F	Moderately differentiated adenocarcinoma	Liver	Right hemicolectomy en bloc	Primary site
2.	Itoh H et al., [3]	2002	75/F	Well differentiated adenocarcinoma	-	right hemicolectomy with a D3 lymphadenectomy	Primary site
3.	Omori A et al., [4]	2018	45/M	Moderately differentiated adenocarcinoma	Lymph node	Right hemicolectomy with a regional lymphadenopathy	Primary site
4.	Present case	2025	47/F	Moderately differentiated adenocarcinoma	-	Right hemicolectomy	Primary site

[Table/Fig-5]: Similar case reports of Heterotopic Ossification (HO) in caecal adenocarcinoma [2-4].

Bei M et al., examined the mechanisms behind HO and found that EndMT is an important source of mesenchymal stem-like cells in the formation of pathological bone [8]. They also found that important signalling pathways {Vascular Endothelial Growth Factor (VEGF), TGF-β, and neurotrophins} are directly linked to the onset and possible recurrence of HO. Because mesenchymal progenitors remain in the affected tissue after surgical excision, there is a higher chance of local recurrence in cases of high EMT/EndMT activity in HO.

There have been several suggested modalities to treat HO, but none have become the gold standard. Although surgical excision is still the only effective treatment, there are debates about it because it can result in HO recurrence [8]. In the current case, the absence of ossification on radiological imaging in contrast to its presence on histopathology highlights the diagnostic challenge and the importance of microscopic examination.

CONCLUSION(S)

This case report of HO in caecal adenocarcinoma underscores the importance of thorough histopathological evaluation to diagnose unusual findings in malignant neoplasms, as benign bone tissue was discovered inside the tumour by chance that could not be detected on radiological imaging. It also emphasises the need for accurate pathological characterisation of HO to differentiate it from other primary ossifying soft-tissue neoplasms or carcinosarcomas, which have a worse prognosis. Although the development of HO in colorectal carcinoma is a very uncommon pathological finding that does not directly impact prognosis, further studies on cases that report HO in colon cancer are warranted so that we can better understand the underlying aetiology and pathophysiological factors involved to fully characterise its biological significance and clinical implications.

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