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Anatomical Pathology

Heterotopic Ossification in Colorectal Adenocarcinoma: Pathological Insights from a Rare Case

Wafae El Aftassi[1]*, Amine Essaoudi[1], Mohamed Allaoui[1], Mohamed Reda El Ochi[1], Abderrahim El Ktaibi[1], Amal Damiri[1], Hafsa Chahdi[1], Mohamed Oukabli[1]

[1]Service d'Anatomie Pathologique, Hôpital Militaire d'Instruction Mohammed V, BP 1018, Rabat, Maroc

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***Corresponding author:** Wafae El Aftassi
Department of Anatomical Pathology, Mohammed V Military Teaching Hospital, P.O. Box 1018, Rabat, Morocco

Abstract | **Original Research Article**

Purpose: Heterotopic ossification (HO) within colorectal adenocarcinoma is an exceptionally rare pathological finding. We report a case of colonic adenocarcinoma with mature heterotopic bone formation and summarize plausible pathogenetic mechanisms with emphasis on the bone morphogenetic protein (BMP) pathway and tumor–stroma interaction. ***Methods:*** Clinical data, preoperative imaging, endoscopic biopsy findings, and resection pathology were reviewed. Histological assessment focused on the interface between neoplastic glands, desmoplastic stroma, and osseous foci. ***Results:*** The colectomy specimen showed a well-differentiated infiltrating adenocarcinoma invading into pericolic fat, associated with fibro-inflammatory stroma and multinucleated giant cells. Multiple foci of mature lamellar bone with osteocytes were present in the tumor stroma, without malignant osteoid or sarcomatoid differentiation; lymph nodes were negative for metastasis. ***Conclusion:*** HO in colorectal adenocarcinoma likely reflects a locally orchestrated osteogenic program within a permissive stromal microenvironment, potentially driven by BMP signaling. Recognizing this phenomenon is important to avoid diagnostic pitfalls; its prognostic significance remains to be clarified.

Keywords: Colorectal adenocarcinoma; Heterotopic ossification; Osseous metaplasia; Bone morphogenetic protein; Tumor stroma.

INTRODUCTION

Heterotopic ossification is defined as the formation of mature bone tissue in non-skeletal sites. In colorectal adenocarcinoma, this phenomenon is exceedingly rare, with most data derived from isolated case reports and small series. Initially described by Hasegawa and later by Dukes, heterotopic ossification was long regarded as a morphological curiosity. Recent pathological and molecular studies, however, suggest that this phenomenon may represent a specific biological process related to tumor–stroma interactions and osteogenic signaling pathways [2,4,6].

METHODS

A 57-year-old patient with no significant past medical history presented with progressive abdominal pain, intermittent constipation, and altered bowel habits evolving over several months. Physical examination was unremarkable. Laboratory investigations, including carcinoembryonic antigen (CEA), were within normal limits. Abdominopelvic computed tomography demonstrated a circumferential mass at the right colonic angle, measuring approximately 6 cm, with irregular mural thickening and infiltration of the pericolic fat. No distant metastases were identified. Colonoscopy revealed an ulcerated, stenosing lesion in the right colon; multiple biopsies showed a well-differentiated infiltrating adenocarcinoma composed of irregular glands lined by atypical epithelial cells. The patient underwent right hemicolectomy with regional lymphadenectomy.

RESULTS

Gross examination showed an ulceroinfiltrative tumor measuring 6.0 × 5.0 cm, with firm whitish cut surface and focal gritty areas. Proximal and distal margins were free of tumor. Microscopically, the resection specimen confirmed a well-differentiated adenocarcinoma forming irregular, occasionally fused glands invading through the muscularis propria into pericolic adipose tissue (pT3). The stroma was markedly fibro-inflammatory with macrophages and multinucleated giant cells. Multiple foci of heterotopic ossification were present in the stroma, composed of

mature lamellar trabeculae containing osteocytes, without malignant osteoid, osteoblastic atypia, or sarcomatous differentiation. Lymphovascular invasion was not identified and all examined lymph nodes were negative (pN0). The postoperative course was uneventful.

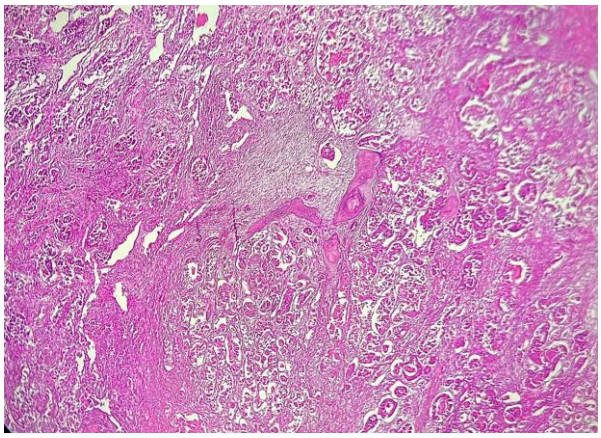

Figure 1. Low-power view (H&E stain, ×20) showing infiltrating colorectal adenocarcinoma associated with stromal heterotopic ossification. Multiple foci of mature lamellar bone are embedded within a desmoplastic fibro-inflammatory stroma adjacent to neoplastic glandular structures

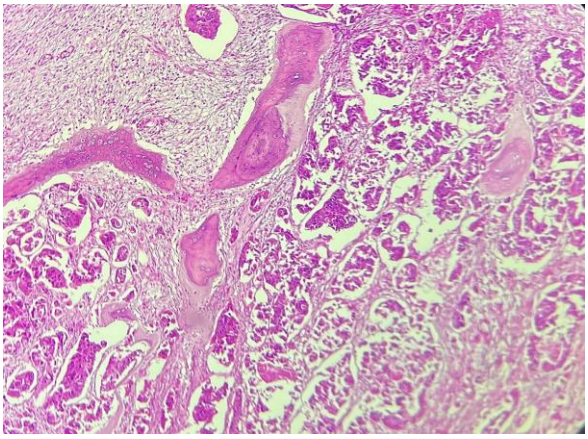

Figure 2. Intermediate magnification (H&E stain, ×40) highlighting several trabeculae of mature heterotopic bone within the tumor stroma. The osseous structures show regular contours and are surrounded by fibro-inflammatory tissue without sarcomatous features

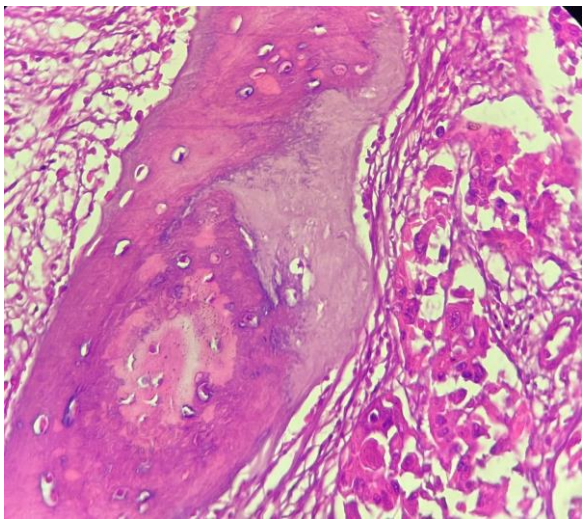

Figure 3. High-power view (H&E stain, ×100) demonstrating mature lamellar bone with osteocytes within lacunae. No osteoblastic atypia, malignant osteoid, or sarcomatoid differentiation is identified.

DISCUSSION

Heterotopic ossification in colorectal adenocarcinoma represents true osteogenic differentiation and should be distinguished from dystrophic calcifications. Pathologically, it is characterized by mature bone formation within the tumor stroma, often in association with fibrosis, chronic inflammation, mucin deposition, and calcifications [3,5]. Recent large-scale pathological analysis by Vos *et al.,* demonstrated that colorectal carcinomas with heterotopic ossification frequently display a stroma-rich phenotype, often corresponding to the CMS4 molecular subtype. Immunohistochemical evaluation showed localized overexpression of BMP2 and SMAD4 in tumor and stromal cells adjacent to bone, with consistent stromal expression of Osterix, a key transcription factor for osteoblastic differentiation [6]. These findings support a locally orchestrated osteogenic process within the tumor microenvironment. Earlier immunohistochemical evidence by Kypson *et al.,* showed cytoplasmic expression of BMP-2 in tumor cells from rectal adenocarcinomas with heterotopic ossification, providing proof that epithelial tumor cells may act as a primary source of osteoinductive signals [2]. This concept was further expanded by Noh *et al.,* who reported overexpression of BMP9, osteocalcin, and osteopontin in tumor cells, together with nuclear β-catenin accumulation, suggesting partial osteoblast-like transformation and involvement of epithelial–mesenchymal transition-related pathways [4]. Collectively, these observations support a model in which heterotopic ossification arises from complex tumor–stroma interactions: osteoinductive signals produced by tumor cells activate BMP/TGFβ pathways, leading to differentiation of stromal mesenchymal cells into osteoblasts. The presence of heterotopic ossification thus reflects stromal and epithelial plasticity rather than a degenerative process. Current data do not support a clearly adverse prognostic impact; however, its association with stroma-rich tumor biology warrants further investigation [3,5,6].

The features observed in our case, including extensive fibro-inflammatory stroma and benign mature bone formation, are fully consistent with these pathogenetic hypotheses. From a practical pathological perspective, the identification of heterotopic bone requires careful exclusion of biphasic malignancies, particularly carcinosarcoma and primary or secondary osteogenic sarcomas. In colorectal adenocarcinoma-associated heterotopic ossification, the osseous component consistently shows benign morphology, with mature lamellar trabeculae and osteocytes, lacking malignant osteoid or cytological atypia. Adequate sampling of the tumor–bone interface is essential to document the absence of sarcomatous transformation. In cases with prominent spindle-cell stromal proliferation, immunohistochemistry may support a reactive stromal process, as epithelial markers remain confined to the glandular component [1,5].

CONCLUSION

Heterotopic ossification in colorectal adenocarcinoma is a rare but biologically meaningful pathological finding. It reflects activation of osteogenic signaling pathways within a permissive stromal microenvironment. Recognition of this phenomenon is important for accurate pathological interpretation, while its prognostic significance remains to be clarified.

Statements and Declarations

Ethics approval: Not applicable.

Consent to participate: Written informed consent was obtained from the patient for publication of anonymized clinical data and images.

Consent for publication: Obtained.

Competing interests: The authors declare no competing interests.

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Data availability: Data supporting the findings of this study are available from the corresponding author upon reasonable request.

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