Ossification of a rectal tumor : an uncommon finding

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Abstract

The authors report the case of a 29-year-old woman with partially calcified stage cT4N2M0 mucoid adenocarcinoma of the mid-rectum. Concomitant neoadjuvant chemoradiotherapy was administered. Preoperative CT scan and MRI demonstrated stable disease with a marked increase of its mineralized component. Histology confirmed a mucoid adenocarcinoma with ossified matrix. Osteocytes were identified in the tumor. TNM (5th edition) staging was ypT3N2M1.

This case illustrates heterotopic ossification of a rectal tumor, a fairly uncommon finding. The mechanism of heterotopic bone formation within gastrointestinal adenocarcinoma has not been fully elucidated. The impact of this particular feature on patient outcome is unknown. (Acta gastroenterol. belg., **2015**, 78, **431-435**).

Key words : heterotopic ossification, colorectal cancer, imaging, CT.

Introduction

Despite the high incidence of colorectal cancer, heterotopic bone formation in the primary tumor is rare with only 15 to 20 cases reported in the literature. We present the case of a young female patient with rectal cancer, who developed tumor ossification wich increased after chemoradiotherapy and review the literature in an attempt to explain this phenomenon.

Case History

A 29-year-old woman consulted in October 2011 for severe and persistent constipation that had deteriorated over the last 3 months. She complained of sporadic abdominal pain and mucus loss with the stool, without blood.

Rectoscopy showed a very large rectal tumor preventing passage of the endoscope. CT and MRI demonstrated a very large mass invading the middle and lower rectum (Fig. 1). The lower pole of the tumor was situated 7 cm from the anal margin. Endoscopic ultrasound was poorly contributive due to the large solid and calcified component of the tumor. At the CT, thin rows of calcic density were observed (Fig. 1).

Histological examination of a biopsy demonstrated a moderately differentiated adenocarcinoma. The staging was cT4N2M0. Carcinoembryonic antigen (CEA) was 7.8 ng/ml (normal < 5 ng/ml).

There was no sign of microsatellite instability based on the immuno-histochemical analysis (MLH1, MSH2, MSH6 et PMS2).

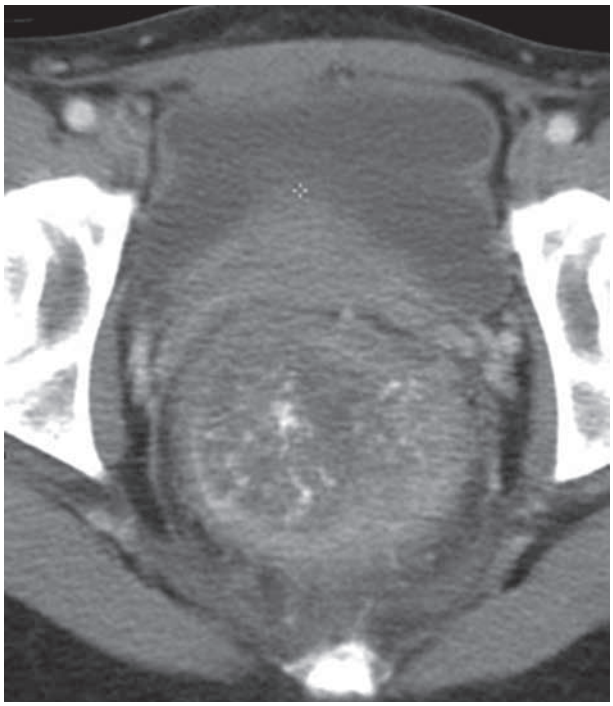

Fig. 1. — Axial contrast enhanced CT image (L : -10 HU ; W : 386 HU) demonstrates a voluminous mass invading the middle and inferior rectum. Thin rows of calcic density are observed. Biopsy reveals the histological nature of the tumor : a moderately differentiated adenocarcinoma.

The patient rapidly developed bowel obstruction and diversion surgery was performed. Neoadjuvant chemoradiotherapy was administered in another institution. Three cycles of chemotherapy (FOLFOX6 regimen) were initiated in December 2011 followed by combination chemotherapy (Xeloda®-capecitabine)-radiotherapy (45 Gy) from January to February 2012.

Surgical resection of the rectal tumor was planned, as the patient had a good performance status (ECOG : 0, BMI : 19,3 kg/m2).

In April 2012, preoperative CT scan and MRI demonstrated global stability of the mass with a marked increase

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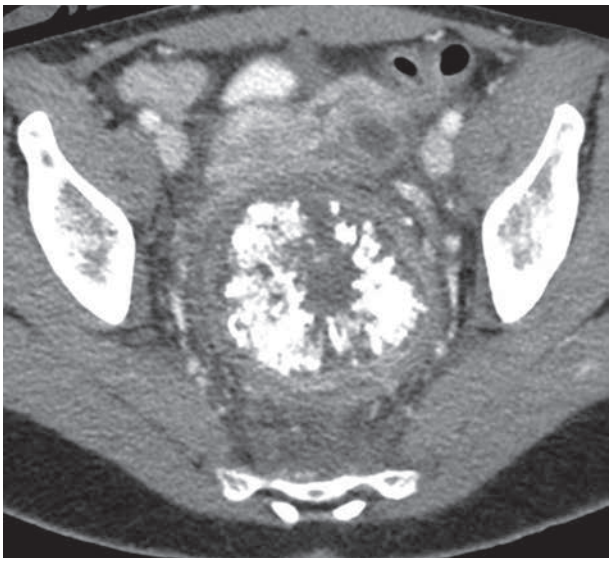

Fig. 2. — Axial contrast enhanced CT image (L : -10 HU ; W : 386 HU) five months later after neoadjuvant chemo-radiotherapy. Note the global stability of the mass but an important increase in its mineralized component.

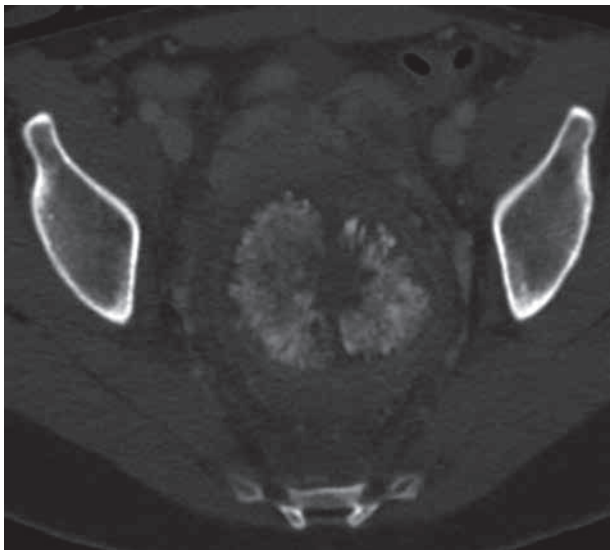

Fig. 3. — Axial contrast enhanced CT image (L : 800 HU ; W : 2000 HU) shows the calcified component of the rectal mass. Note the radial and organised disposition suggesting osseous matrix.

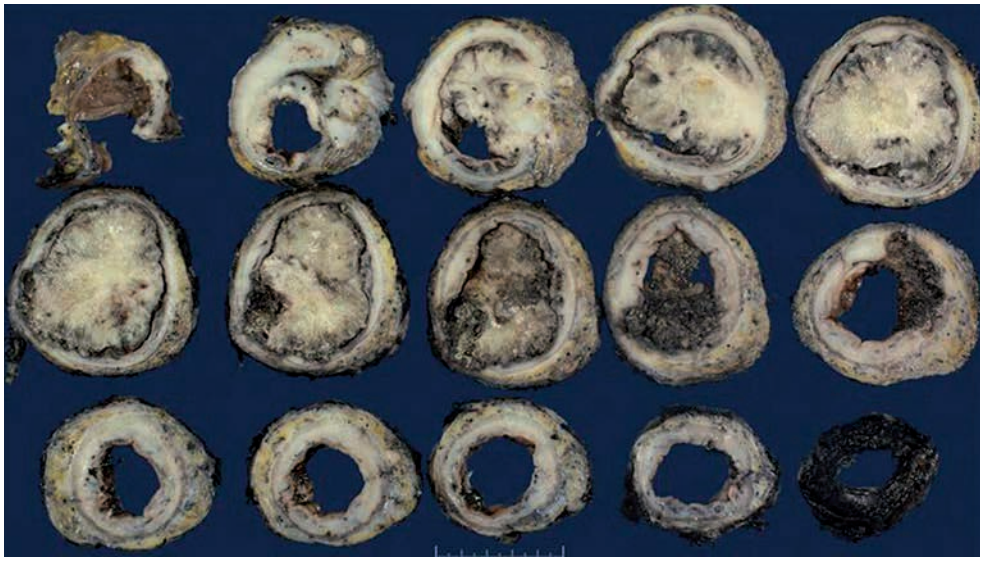

Fig. 4. — Photograph of macroscopic slides of the resected rectal mass. Slicing of the mass was possible only after 10 days in decalcifying solution. Tumor grows through the muscularis propria and into the mesorectum : T3. Seven metastasis sites are found with two interaortocaval lymph nodes : N2M1.

of its mineralized component (Fig. 2-3). New peritoneal nodules were also observed. The staging became ycT-3N2M1.

Beginning of May 2012, complete excision of the tumor was performed in combination with hyperthermic intraperitoneal chemotherapy (HIPEC).

Histological examination of the mass confirmed a mucoid adenocarcinoma (by definition grade 3 or poorly differentiated) with ossified matrix (Fig. 4). Osteocytes were identified in the ossified trabeculae (Fig. 5-6). There was no sign of osteosarcomatous degeneration. TNM classification (5th edition) was ypT3N2M1. Expression in the tumor cell nucleus of hMLH1, hMSH2, hMSH6 and PMS2 was maintained, arguing against a hereditary non-polyposis colorectal cancer. Peritoneal metastases did not contain any ossification or calcification. Detection of osteopontin or BMP proteins could unfortunately not be realised because specific antibodies were not available.

Given the peritoneal metastases adjuvant chemotherapy (Folfox and Bevacizumab) was administered until October 2012. Work-up showed progressive disease. Despite the administration of chemotherapy (Folfiri and Bevacizumab) and stereotaxic radiotherapy, the patient developed a local and metastatic recurrence and passed away in December 2013.

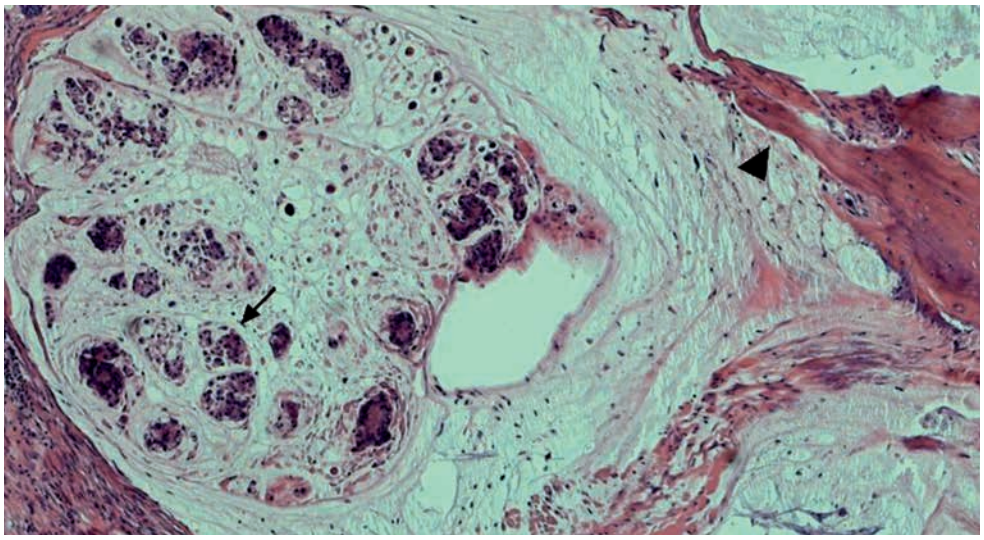

Fig. 5. — Photomicrograph (original magnification, ×5 ; hematoxylin-eosin [H-E] stain) shows osseous trabeculae (arrowheads), glandular cells (arrows) and stromal tissue. Adjacent to the tumoral cells ossified matrix is found. Immunohistochemical tests performed for hMLH1, hMSH2, hMSH6 and PMS2 don't show loss of expression.

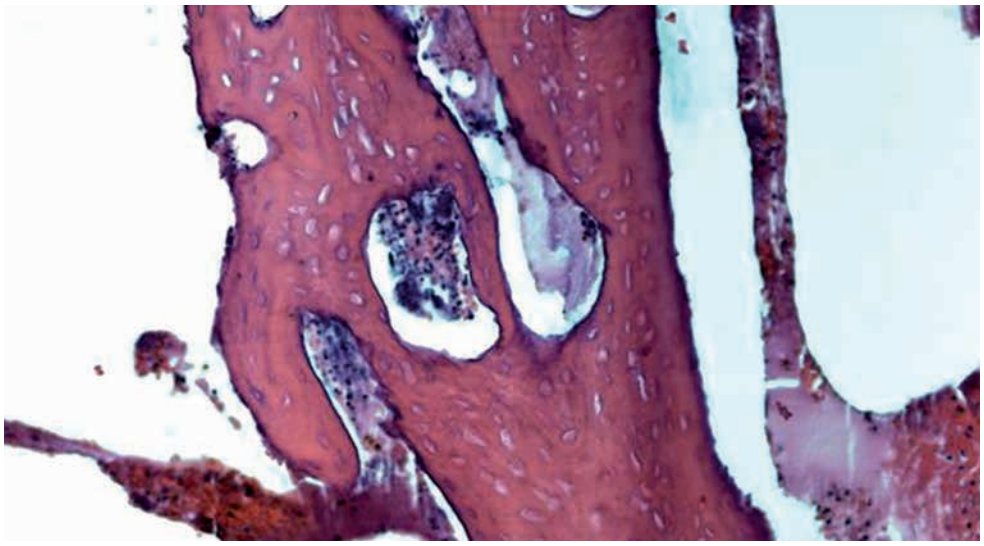

Fig. 6. — Photomicrograph (original magnification, ×10 ; hematoxylin-eosin [H-E] stain) shows osseous matrix. Osteocytes are identified within the ossified trabeculae. There is no evidence of osteosarcomatous degeneration.

Discussion

Rectal cancer is one of the most common cancers, but intra-tumoral heterotopic bone, unlike calcification, is rarely observed. Heterotopic bone formation has been reported in malignancies involving the kidney, liver, breast, and skin (1-3) and has to be distinguished from the much more frequent intra-tumoral calcification. Indeed, ossification is a process of laying down new bone material. Conversely, calcification is a process in which calcium salts build up in soft tissue causing it to harden.

Less than 25 cases of heterotopic bone tissue in rectal cancer have been reported in the literature. The first cases have been reported by Hasegawa (4) in 1923 and Dukes in 1939 (5). Beauchamp (6), in 1997, described the first case of CT demonstration of the ossified component.

The causes of heterotopic bone formation in colorectal cancer have not been clearly established. The general process leading to heterotopic ossification frequently involves soft tissues, wether malignant or not. These lesions have been first described as "para-osteoarthropathy" by Dejenre and Ceillier (20). The postulated

process responsible for this condition depends on three entities : an osteogenic precursor cell, inducing agents and a permissive environment.

Two hypothetical mechanisms have been reported in the literature to explain presence of bone tissue in colorectal cancer : tumor cells undergo osseous metaplasia or tumor cells secrete substances that induce metaplasia in connective tissue, such as bone morphogenetic proteins (BMP) or other diffusible factors (released from rapidly dividing epithelial cells). Binding of these substances to the appropriate receptors induces stimulation of mesenchymal cell differentiation into osteoblasts, which then manufacture bone.

Kypson (7) was the first to demonstrate overexpression of BMP-2 in rectal adenocarcinoma cells. This implies that an osteogenic signal is present within tumor cells, which may be the mechanism responsible for initiating induction of osteoblasts, ultimately leading to the presence of heterotopic bone. In contrast, Imani (8) found strong expression of BMP-5 and -6 in tumor cells with weak expression of BMP-2. In our case, detection of BMP proteins could unfortunately not be realised because specific antibodies were not available.

Randall (9) found alkaline phosphatase activity in osteoblasts, in proliferating mesenchymal cells surrounding osseous foci, and on the apical membranes of colonic adenocarcinoma cells. These investigators concluded that colonic carcinomas ''can promote heterotopic ossification, and that alkaline phosphatase is intimately associated with bone formation''.

In support of the second theory, some authors have reported that heterotopic bone is more likely to be found in necrotic tumors (5), containing mucin pools (10), and tumor stroma (11).

In this case, histological type was mucoid adenocarcinoma and foci of necrosis were present . We observed a marked increase of the intra-tumoral mineralization process during neoadjuvant chemo-radiotherapy. The link between the increase of the ossification process within the tumor and the neoadjuvant therapy is unclear.

No case of heterotopic bone formation related to the administration of Folfox or capecitabine are described in the literature. Folfox is a chemotherapy regimen for treatment of colorectal cancer made up of folinic acid, 5 fluoro-uracil (5-FU) and oxaliplatin. Capecitabine is a 5-FU pro-drug metabolised in liver and tumour by carboxylesterases and cytidine deaminase to 5'-deoxy-5-fluorocytidine (5'DFCR) and 5'- deoxy-5-fluorouracil (5'DFUR) respectively. The final step of the activation of capecitabine, conversion of 5'-DFUR to cytotoxic 5-fluorouracil (5-FU) is mediated by thymidine phophorylase. Otherwise, 5-FU and oxaliplatin counteract the Hedgehog pathway (20-21). Hedgehog pathway plays a role in bone formation as it allows the differentiation of osteoblast cells from mesenchymal progenitor cells (22). Interestingly, National Institutes of Health investigators (USA) have discovered that administration of an antagonist of a Hedgehog pathway can result in amelioration of heterotopic ossification symptoms, as well as those of vascular calcification (22). This element argues against a positive role of the neoadjuvant therapy in the ossification process of the tumor.

The possible role of radiotherapy is also unclear, especially as radiotherapy (dose of 30 Gy) has been used for prophylaxis and treatment of soft tissue ossifications (23) and inhibits differentiation of osteoprogenitor cells, which are radiosensitive only in the early phase. Neuhauser *et al*. documented the impact of radiation on the growing vertebrae of children and found that doses higher than 20 Gy caused inhibition of bone growth (24). It is interesting to note that heterotopic calcification is a rare but well- known late complication of irradiation (25).

Eventually, in our case, there was no sign of osteosarcomatous degeneration in the osseous component of the tumor. Extraskeletal primary osteosarcoma is rare and commonly arises in the retroperitoneum, limbs, head and neck (26).

Conclusion

Heterotopic ossification of a colorectal tumor is rare. The mechanism of heterotopic bone formation in gastrointestinal adenocarcinoma has not been clearly elucidated, but promoting factors have been described in tumor cells. In our case, the mineralization process of the tumor increased after neoadjuvant chemo-radiotherapy. Nevertheless the role of chemo-radiotherapy in this process is still unclear.

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