CASE REPORT

Bony metaplasia in a caecum adenocarcinoma

S. S. MOGOANTĂ1), C. MEȘINĂ1), LILIANA STREBA2), ANCA PREDESCU2), GAROȘIȚĂ OLIVIA MATEESCU3), GABRIELA MUȚIU3), L. MOGOANTĂ2)

1)Department of Surgery
2)Research Center for Microscopic Morphology and Immunology
University of Medicine and Pharmacy of Craiova
3)Department of Histology,
Faculty of Medicine and Pharmacy, University of Oradea

Abstract

Ectopic bone formation in the digestive tract is a very rare phenomenon in pathology. Most cases of bone metaplasia were found in distal colon tumors, rectum and sigmoid respectively. We present a case of well-differentiated adenocarcinoma of the caecum (the second case of literature) associated with bone metaplasia, which debuted atypical, with symptoms of infectious enterocolitis, in a 72-year-old female patient, with no history of digestive pathology. Highlighting bone metaplasia was achieved by current histological techniques. Patient’s evolution was favorable with surgical treatment and chemotherapy.

Keywords: bony metaplasia, heterotopic ossification, cecal adenocarcinoma.

Introduction

Metaplasia is the replacement process of mature cells or a tissue with another mature well-differentiated cell type, resulting in an ectopic tissue. This happens in response to abnormal stimuli that are subjected to the cells or tissues; stimuli can be represented by chronic irritation, local chemical and physical modifications, chronic inflammatory processes, tumors, etc.

Ectopic bone formation in the gastrointestinal tract is rather rare. In the colon, this process was observed in chronic inflammatory processes [1, 2], benign tumors [3, 4] or malignant [5]. According to some authors [6], the occurrence of heterotopic calcifications in colon tumors is very rare. Same authors mention that in all medical articles published in English language, there are being reported less than 20 cases of heterotopic calcifications in malignant tumors of the large intestine.

Most cases of heterotopic calcifications were reported in malignant tumors of the colon situated in the rectum, sigmoid or descending colon. We report for the first time a case of adenocarcinoma located in the caecum and ascending colon proximal portion, in which we identified heterotopic calcifications.

Patient, Methods and Results

A 72-year-old female patient, with no history of digestive pathology, presented in the Infectious Disease Clinic of Craiova with keen abdominal pain, diarrhea, nausea, vomiting, headaches, dizziness, anxiety, signs of moderate dehydration (dry mucous membranes, persistent skin fold, foul tongue), being diagnosed at admission with infectious enterocolitis. For relieving symptoms, she received hydroelectrolytic rebalancing treatment, antibiotics for intestinal bacteria and anti-diarrhetics, symptoms partially remitting. Abdominal examination evidenced the presence of a 7 cm in diameter tumor in the right lower quadrant, relatively well defined, with limited mobility in lower planes, slightly painful on palpation, without signs of peritoneal irritation, associated with moderate flatulent distension in the mesogastric area. Digital rectal examination revealed an empty rectal ampula, with supple mucosa and painless Douglas bag. Laboratory tests have indicated the existence of a mild anemia (Hb 11 g/dL), with moderate leukocytosis (13 600/mm3), hypokalemia secondary to hydroelectrolytic loss through vomiting and diarrhea, while hepatic and renal tests, glycemia and urine exam were normal. After symptomatic and hydroelectrolytic rebalancing treatment, signs of dehydration disappeared, intestinal transit normalized, general condition improved, but the presence of the tumor in the right iliac fossa persisted. The abdominal ultrasound showed in the right flank and iliac fossa a 6–7 cm round-oval tumor, with parenchymatous appearance, irregular contours, imprecisely defined, heterogeneous echostucture, areas with trans-sonic content and multiple internal septi. There was no evidence of nodular images suspected of liver metastases or in other organs and no lombo-aortic adenopathies. The irigography evidentiated a large area of tight stenosis at cecal level, with eccentric lucarum picture, having irregular contours.

Surgical examination established clinical diagnosis of cecal tumor and decided the transfer in the Surgery Clinic for surgical intervention. After preoperative preparation, surgical intervention was performed by
median laparotomy. Intra-operative exam confirmed the existence of the cecal tumor developing on the posterior wall of the caecum, with organo-axial extension on about 8 cm, hemicircumferential, with predominantly postero-medial development up to the ileocecal valve. Last ileal loops were moderately dilated, with thickened wall looking like “fighting loops”. The tumor was mobile on the posterior plan, so its separation was easily possible. Right hemicolectomy was performed, with ligation at the origin of the ileo-biceco-appendicular trunk, right and medium colic at the origin, followed by termino-lateral ileo-transverse anastomoses.

Macroscopic exam of the excision fragment revealed a vegetant, hemi-circumferential, infiltrative tumor, with low consistency, of 8/6/3 cm, situated on the ceco-ascending colon and invading completely the large intestine wall, including pericolic adipose tissue and infiltrating the ileocecal valve from the lateral. The tumor presented on the surface ulcerated and septic necrosis areas. Fifteen ganglia were identified on the resected mesocolon, three ganglia on the medium colic pedicle, six ganglia on the ileo-biceco-appendicular trunk and other six around the right colic artery, out of which, from the last two vascular trunks, were revealed two ganglia, three ganglia respectively of about 1–1.2 cm in diameter, with confluent tendency.

Patient’s postoperative evolution was good, being discharged after eight days, surgically cured. She was referred to the Oncology Clinic for chemotherapy. Six months and respectively, one-year follow-up revealed absence of any clinical sign of relapse or disease progression, the colonoscopy identifying permeable and functional ileo-transverse-anastomoses, with no evidence of recurrence.

For the histopathological study of the tumor, there were collected fragments from it, the resection edge and from the 15 ganglia macroscopically identified. All collected fragments were included in paraffin and for the study, there were used two stains: Hematoxylin–Eosin (HE) and Goldner–Szeckeli trichromic. Histological analysis revealed the presence of a well-differentiated adenocarcinoma, consisting of glands of various sizes and shapes, unsortedly disposed, with a columnar type epithelium, clear cytoplasm, separated by connective septi, more or less rich in collagen fibers (Figure 1). The neoplastic process totally invaded the large intestine wall, including the perilesional adipose tissue, with intramural focal necrosis areas. It was also noted the perineural invasion and the absence of intratumoral or perilesional inflammatory reaction.

In the tumoral stroma there were isolatedly revealed bone metaplasia islands of various sizes and shapes, from about 50 to 500 μm (Figures 2 and 3). There were well defined, with net shape and numerous peripheral osteoblastic cells (Figure 4). Inside the osseous islands, there were evidenced osteoblasts arranged as osteoplasts. Intercellular matrix appeared homogeneous and acidophilic. In some of the bony parts, we observed spaces similar to Hawers channels (Figure 5). Considering the microscopic appearance, we believe that bony islands occurred through a process of conjunctive ossification and the existence of osteoblastic cells outside it, similar to osteoprogenitor cells of the endostem, ensures bony metaplasia islands growth (Figures 4 and 5). All areas of bony metaplasia had normal aspect, with well-defined trabeculae, tending to organize as Hawersian systems.

Powerful lens study of the tumoral stroma allowed us to observe that in some areas it had the aspect of a young connective tissue with fibroblastic connective cells that had large, hypochrome nuclei with nucleoli and generous cytoplasm. Intercellular matrix was abundant, with thin, unsorted collagen fibers and rare collagen fibers organized as bundles.

Microscopic examination of fragments of biologic material from the surgical resection margins did not reveal presence of tumoral cells or of other pathological changes, which confirmed that resection was performed within oncological limits.

Resection-piece ganglia study showed the existence of tumoral metastases that were infiltrating and partially or totally disorganizing the ganglionic structure in three lymph nodes. If in the primitive tumor the pattern was glandular, in the lymph nodes the tumoral cells disposal was mainly cordonal or insular-like (Figure 6). Among the lymph nodes, there were not identified bony metaplasia islands but were evidenced smaller or larger areas of tumoral necrosis.

Figure 1 – Overview: well-differentiated colon adenocarcinoma (Goldner–Szeckeli trichromic staining, ×100).

Figure 2 – Bony metaplasia island in the tumoral stroma (Goldner–Szeckeli trichromic staining, ×100).
Bony metaplasia in a caecum adenocarcinoma

Figure 3 – Bony metaplasia with multiple well-defined bays (Goldner–Szeckeli trichromic staining, ×100).

Figure 4 – Detail of the previous figure. Areas of osseous metaplasia with osteocytes present in osteoclasts and osteoprogenitor cells at the periphery of these areas (Goldner–Szeckeli trichromic staining, ×200).

Figure 5 – Bony metaplasia island with Hawers channels pattern (HE staining, ×200).

Figure 6 – Lymph node metastatic image (Goldner–Szeckeli trichromic staining, ×200).

Discussion

Heterotopic ossifications in digestive tract tumors were rarely observed. Dukes CE [7] suggests that their overall incidence is only 0.4%. They appear in inflammatory processes, in benign or malignant tumors. Regarding the digestive tract, heterotopic ossifications were more frequently localized in its terminal portion (rectum, sigmoid, transverse colon), but there were also described cases of heterotopic ossification in pre-malignant and malignant lesions of the stomach [9] or liver [10].

Kypson AP et al. [5] found only eight cases of heterotopic ossification when performed a retrospective analysis of patients with rectal adenocarcinoma. Average age of patients with rectal adenocarcinoma associated with bone metaplasia was 55 years, and male/female ratio was about 1/2 [5].

According to some authors [5], the evolution and prognosis of lower digestive tract adenocarcinoma with ossification are no different from an adenocarcinoma without ossification. However, other researchers [6] described a case of rectal adenocarcinoma in which progress was rapid, the patient dying after three months from diagnosis and surgical treatment. Out of the cases of large intestine adenocarcinoma, our case, localized on the caecum, is the second one, after the one described by Papadopoulos MC et al. [11].

Heterotopic bone development was usually observed among tumors that produce abundant mucin [8]; this would be the reason for which some researchers hypothesized that mucus extravasation may have a stimulating role during ossification [12]. Our case was a well-differentiated adenocarcinoma without excessive mucine and with absent inflammatory reaction. Also, heterotopic ossifications appeared, in our case, outside the areas of tumoral necrosis.

Mechanisms leading to heterotopic osteogenesis remain still unknown. Urbanke A [13], when studying heterotopic osseous tissue formation process in a case of rectal carcinoma, revealed in the tumoral stoma all forms of cellular transition starting from inactive fibrocytes (in idle state) to fibroblasts and typical osteoblasts. He concluded that osteoblasts are developing most likely from fibroblasts of stromal connective tissue.

Randall JC et al. [14], when studying a case of transverse colon adenocarcinoma, which developed a
heterotopic ossification in a metastasis from an axillary lymph node, observed through immunohistochemical techniques that osteoblasts-like cells appeared on the surface of mineral deposits. Immunostaining for alkaline phosphatase revealed a significant concentration of the enzyme in these cells and, any less, on the apical membrane of glandular cells neighboring ossification centers of the adenocarcinoma. Same authors have identified proliferative mesenchymal cells in close proximity of osteogenesis areas, which also showed a significant immune reaction to alkaline phosphatase.

Out of this study, we can conclude that ectopic ossification islands development is due to mesenchymal cells that synthesize and excrete alkaline phosphatase, an enzyme that facilitates mineral salts deposit in the cells that synthesize and excrete alkaline phosphatase.

In our case, we found areas of tumoral stroma looking like young connective tissue, with fibroblastic type cells that could differentiate into osteoblasts.

What still remains unknown are the molecular and signaling mechanisms by which fibroblasts differentiate into osteoblasts. Imai N et al. [15] studied the immunohistochemical expression of bone morphogenetic proteins (BMP) in colon carcinomas and observed that BMP-5 and BMP-6 were highly expressed in the cytoplasm of tumoral cells adjacent to ectopic bone tissue islands, but were poorly expressed in osteoblasts. These data indicate that tumoral cells can synthesize biochemical messengers that induce bony metaplasia in the neighboring tumoral stroma.

Conclusions

We reported a very rare case of well-differentiated caecal adenocarcinoma with bony metaplasia, with atypical onset and favorable evolution under surgical treatment and chemotherapy. Cellular and molecular mechanisms of ectopic bone tissue occurrence in digestive tract carcinomas are still insufficiently known.

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References


Corresponding author
Laurențiu Mogoantă, Professor, MD, PhD, Department of Histology, University of Medicine and Pharmacy of Craiova, 2–4 Petru Rareș Street, 200349 Craiova, Romania; Phone +40251–523 654, e-mail: laurentiu_mogoanta@yahoo.com

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