Microsatellite instability in medullary carcinoma of the colon

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Abstract

Medullary carcinoma (MC) of the large intestine is a relatively new histological type of adenocarcinoma characterized by poor glandular differentiation and an intraepithelial lymphocytic infiltrate. MC can be associated to a defective mechanism for DNA mismatch repair, caused by the so-called microsatellite instability (MSI). We present the case of a 44 years old Caucasian woman, who referred to the Emergency Room with symptoms mimicking an acute appendicitis. Computed tomography and colonoscopy demonstrated an ulcerated and stenotic lesion of the caecum without signs of metastasis and peritoneal carcinoma. Patient underwent a laparoscopic right colectomy. The final pathologic findings provided the diagnosis of medullary carcinoma with MSI. Patient then underwent adjuvant chemotherapy according to the FOLFOX-4 protocol (association of 5-Fluorouracil, Leucovorin, and Oxaliplatin) for twelve cycles. At two-years follow-up, patient is in good health and there is no evidence of metastasis or relapse.

Introduction

Colorectal carcinoma can be characterized by chromosomal instability, accounts for approximately 85% of colorectal carcinomas with defective DNA mismatch repair mechanisms. In case of inability to repair DNA mismatches for the presence of cell-to-cell variability in the length of DNA microsatellites, we can observe a phenomenon known as microsatellite instability (MSI), and tumors with extensive instability are designated as microsatellite instability-high (MSI-H). Approximately 15% of sporadic colorectal carcinomas are MSI-H.

Mucinous carcinoma, signet cell carcinoma, and undifferentiated medullary carcinoma (MC) all are more common in this setting.

Medullary carcinoma, formerly known as large cell adenocarcinoma with minimal differentiation, has been included as a distinct histological type in the World Health Organization (WHO) classification of colorectal epithelial cancers, wherein it is described as being characterized by sheets of malignant cells with vesicular nuclei, and prominent nucleoli, along with prominent intraepithelial lymphocytic infiltrate. Essentially, MCs are a solid variety of adenocarcinoma with very little glandular differentiation; for this reason they are morphologically similar to poorly differentiated adenocarcinoma and undifferentiated adenocarcinoma and histological differential diagnosis can be extremely challenging.1 MC can be represented by a morphological type of minimally differentiated adenocarcinoma (0.03%), poorly differentiated (72%), and undifferentiated (22%);2,3 these tumors are typically more common in older females and tend to have a distinct clinical behavior with less nodal involvement and a better prognosis.4 MC tend to be right-sided (54%) and incidence increase directly with the age (mean age at diagnosis 69.3 years); they are usually diagnosed at an advanced stage but distant metastases are rare at presentation (10%).5

In this paper we report the case of a young Caucasian woman diagnosed with cecal MC with MSI, who was treated with surgery and chemotherapy. The following discussion comprehend a throughout revision of the available literature regarding MC.

Case Report

A 44-year-old Caucasian female referred to the ER with acute abdominal pain. Past medical history revealed no family history of colon cancer and no history of smoke. At the admission, physical examination revealed pain and tenderness in the right lower quadrant with no signs of bowel obstruction, mimicking an acute appendicitis. Laboratory investigation has not shown important pathological signs. Ultrasonography examination of the abdomen showed a contracted gallbladder with normal bile ducts, no pathologies affecting the pancreas and neither free fluid, nor signs of acute appendicitis. In consideration of the clinical status of the patient and the persistent acute abdominal pain even with a negative ultrasound, a CT scan was performed to better comprehend the nature of the underlying pathology. CT scan was performed four hours after the hospital admission, and demonstrated a thickened cecal wall with a small number of pathological nearby lymph nodes, confirming the absence of peritoneal free fluid. Given the absence of radiological signs of GI perforations and of other surgical and medical emergencies, we decided to perform a colonoscopy to better understand the etiology of the underlying pathology. Colonoscopy was performed 24 hours after the hospital admission and after an adequate bowel preparation and revealed a massive, ulcerated, stenotic and necrotic lesion that involved the caecum and the right colon. Biopsies of the lesion were performed and the microscopic examination showed a cell proliferation composed by large, pleomorphic cellular elements with vesicular nuclei, hyperchromatic nucleoli and eosiophilic cytoplasm, mixed with necrotic tissue. These findings were consistent with the diagnosis of poorly differentiated carcinoma (Figure 1).

For these reasons, a laparoscopic right colectomy in an elective setting was performed, together with an accurate lymphadenectomy. Surgical exploration of the abdominal cavity confirmed the absence...
of peritoneal carcinosis and distant metastasis. Pathological examination of the surgical specimen revealed an ulcerated lesion of the right colon with a 6 cm diameter, composed of a whitish and compact tissue, with hard consistency and infiltrative margins that extended to the perivesical adipose tissue. Microscopic examination discovered a poorly differentiated neoplastic epithelial tumor, rich in mitosis, with large-sized cellular elements characterized by vesicular nuclei, occasional nuclear pseudo-inclusions, hyperchromatic nucleoli and eosinophilic cytoplasm and organized in chains and clusters and mixed with necrotic areas. Additionally, an inflammatory component made of lymphocytes, histiocytes and plasma cells with a polytypic expression of Immunoglobulin light chains was present. The neoplastic epithelial tumor showed the following immunohistochemical profile: positive for CK7 (focal), CAM 5.2 (focal), CKA/E1/AE3 (focal), Calretinin (focal), Claudin 4, and negative for CK20, Synaptophysin, Chromogranin, CDX2, TTF-1, P63, CK5-6, CD20, CD3, CD5, CD79, MUM1, S100, ER, MART-1, EBV; proliferation cell index MIB1 was higher than 50% (Figure 2). None of the 35 lymph nodes collected and examined showed presence of malignant cells. The final staging of the disease was B2 according to Astler and Coller, Stage III according to Jass and pT3 N0 Mo for the TNM classification.

The molecular analysis for the MSI has identified a High level of Microsatellite Instability (MSI-H) and was performed with the study of fragments with 3500 Dx Genetic Analyzer - Applied Biosystems.

This particular profile, especially the lack of expression of CDX2 and the positivity for Calretinin, oriented the diagnosis towards a MC rather than to a poorly differentiated carcinoma.

Subsequently, in consideration of different variables, such as the histological characteristics, the poor degree of differentiation, the presence of vascular infiltration, the medullary histological type and the age of the patient, the patient underwent an adjuvant chemotherapy according to the FOLFOX - 4 schedule for 12 cycles (association of 5-Fluorouracil, Leucovorin, and Oxaliplatin).

After 24 months from the index surgery, the patient is disease free and with a good quality of life.

**Discussion**

Medullary carcinoma of the large intestine is a rare tumor characterized by sheets of malignant cells with vesicular nuclei, prominent nucleoli and abundant eosinophilic cytoplasm, and a prominent infiltration of intraepithelial lymphocytes.6

Medullary carcinoma is probably more common compared to what is reported in many previous studies: according to Knox et al., MC accounts for 2.8% of all resected colorectal cancer and for 5% of the lesions of the right colon.7

Male to female ratio is 1:2 and the incidence increases with age and the average age at the diagnosis is 69.3 years. This particular type of cancer usually occurs in the right colon (54%) and only rarely in other sites of the large bowel. These tumors are usually larger in size and have a poorly differentiated or undifferentiated histological appearance.7

Medullary carcinoma typically present a lesser rate of nodal metastasis and a minor tendency toward extramural and invasion, when compared to poorly differentiated adenocarcinoma,4,7 while the lymphovascular invasion can be relatively high (62.9 vs 36.5%).7 In comparison with undifferentiated and poorly-differentiated adenocarcinomas of the large intestine, MC has a better prognosis1 and it improves further in case of MSI - H.8

In 1997, Ruschoff et al. reported a series of poorly differentiated colorectal adenocarcinomas, most of which exhibited an expansive growth pattern and significant peritumoral lymphoid infiltrate; they also noted an high MSI and an overall good prognosis;9 Lanza et al. identified 45 MC among 1265 surgical specimens over a period of 10 years;4 they found that these

![Figure 1. Hematoxylin and Eosin stains of Medullary carcinoma (100x).](image1)

![Figure 2. Medullary carcinoma showing negative staining with MLH-1 (A) and CDX-2 (B). Medullary carcinoma showing positive nuclear and cytoplasmic staining with Calretinin (C). Proliferation index assessed with Ki67/MIB-1 (D) (×200). CK AE1/AE3 was focally positive (E) (×200).](image2)
tumors were typically diploid, p53-negative, with widespread MSI, and had a favorable prognosis in comparison to well differentiated and poorly differentiated adenocarcinomas.

Few other studies are available in literature and confirm the high frequency of MSI, loss of p53 and CDX2 expression and favorable prognosis of MC compared to poorly differentiated colonic adenocarcinomas and neuroendocrine tumors of the colon.8,10,11

Conclusions

Medullary carcinoma with the presence of MSI is a rare tumor of the colon due to a genetic mismatches, that is characterized by a better prognosis when compared to poorly differentiated adenocarcinoma tumors. These two types of colonic tumors, MC and poorly differentiated adenocarcinoma, present a huge difficulty in histological differential diagnosis, but the exact diagnosis is mandatory given the great difference of their prognosis. In the present case, 24 months after surgical treatment, the patient presents a good quality of life, and there is no evidence of metastasis or relapse.

A well-planned surgical approach, associated with chemotherapy is actually considered the best treatment option for these extremely rare tumors, in order to avoid distant metastasis and local recurrence and to provide a good quality of life.

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