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RECTO-SIGMOID SYNCHRONOUS MALIGNANT TUMOR WITH LACK OF MLH1 AND PMS2 EXPRESSION: CASE REPORT AND LITERATURE REVIEW

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ABSTRACT

Background: Synchronous colorectal cancers are defined by the presence of at least two cancers (primary self-standing tumors) in the same time, in the same patient. In these conditions, the tumor with the maximum diameter has nomenclatures such as "primitive", or "index". The preoperative diagnosis of synchronous tumors is very important, as it can turn into metachronous tumors, which require a new surgical intervention.

Case report: In the following, we report a case of a 54 year-old patient without any related oncological family history but with important cardiovascular comorbidities, who has been operated for stenotic synchronous cancer of the recto-sigmoid junction and middle rectum. During the initial work-up, no liver or peritoneal metastases were noted on the CT scan. The surgical intervention opted for was a recto-sigmoid laparoscopic with subtotal mesorectal excision followed by a termino-terminal mechanical stapled colorectal anastomosis. The histopathological examination showed both lesions to be moderately differentiated (G2) adenocarcinomas, with subserosal invasion in 2 of the 12 detected lymph nodes. Immunohistochemistry further revealed microsatellite instability, with MLH1 and PMS2 mutation.

Conclusion: The literature review highlights certain particular aspects regarding the clinical, surgical and morphological management of such cases compared to cases with single tumor. The peculiarity of this case was laposcopic resection of the colon segment, and the microsatellite instability of the specimen, assessed by ancillary studies. Early preoperative diagnosis of synchronous tumors allows the selection of appropriate therapeutic management, depending on their location at the level of the affected colonic segments.

Keywords: adenocarcinoma, synchronous tumor, primary cancer, laparoscopic surgery, microsatellite instability

Background

According to GLOBOCAN 2018 data, colorectal malignancies represents the third cause of mortality and the fourth most frequent lesion among digestive cancers.

In contrast with this, rectal cancer is the eighth most incident, both representing malignant glandular epithelial proliferations, being caused by certain lifestyle habits, diet and genetic factors. Together, colorectal malignant tumors ranks third place in terms of frequency among all types of cancer, globally, which means 11% of them (1-3).

The aim of the article is to present a rare case of double synchronous colorectal malignant tumor, with the same morphological aspect and special immunohistochemical features of microsatellite instability markers, and to present a literature review of this pathology.

Case report

We report a case of a 54-year-old man, with a significant personal pathological cardiovascular history (permanent atrial fibrillation, double mitral and aortic prosthesis, congestive heart failure NYHA II, left branch block), who was

initially examined for the following symptoms: accelerated intestinal transit (multiple diarrheic stools/ 4-5 times per day), accompanied by sporadic minimal rectorrhagia and diffuse colicky abdominal pain. The endoscopic examination revealed a polypoid tumoral mass located at 10 cm above the anal orifice, at the level of the middle rectal segment, and also a sigmoid stenotic mass, located at 18 cm from the anal orifice. Both massed were biopsied. The diagnosis was thus stenotic synchronous neoplasm of the recto-sigmoid junction and middle rectum, without liver or peritoneal metastases on the abdomo-pelvic computed tomography (CT) examination. A left colostomy was performed with subsequent radiotherapy for the rectal mass. Approximately 6 weeks after finishing radiotherapy the patient underwent the radical surgical resection, through a laparoscopic recto-sigmoid resection with subtotal mesorectal excision and mechanical termino-terminal colorectal anastomosis, and a protective ileostomy.

The pacient was prepared for the surgery having a liquids only diet recommendantion for 3 days before the surgery. As well, one day before the surgery we performed a phosphate-containing enema and antibiotic prophylactic dose with ceftriaxone and metronidazole.

We started the laparoscopic rectosigmoid resection by performing the pneumoperitoneum at 12 mmHg pressure by using the Verres needle in the periombilical area and then placed 4 trocars located at 5 mm in the right hypochondrium, 5 mm port in the left flank, 12 mm right iliac fossa and 10 mm port in the hypocondrum and we used a 30 degree telescope.

The procedure started with mobilisation of the left side of colon and splenic flexure. Peritoneum disection included disection of the mesorectal pedicle and ligation of the inferior mezenteric artery. Lymphadenectomy was also performed. We prefered, in this case, to perform the low tie ligation of the inferior mesenteric artery, below the left colic artery origin, with central lymphadenectomy (Figure 1 B).

Our disection was facilitated by use of ultrasonic shears and continued with the mesorectal peritonea reflection that was divided bilaterally with the mobilization of the mesorectal. We performed this by following the holly plane of the mesorectum, along the plane between the mesorectal and presacral fascia. This surgical dissection has the advantage of preserving the sacral vessels and hypogastric nerves, and also is a sphincter-sparing resection, which reduces stoma frequency. This type of disection facilitated us the resection of the entire fatty tissue containing lymph nodes and total mesorectal excision.

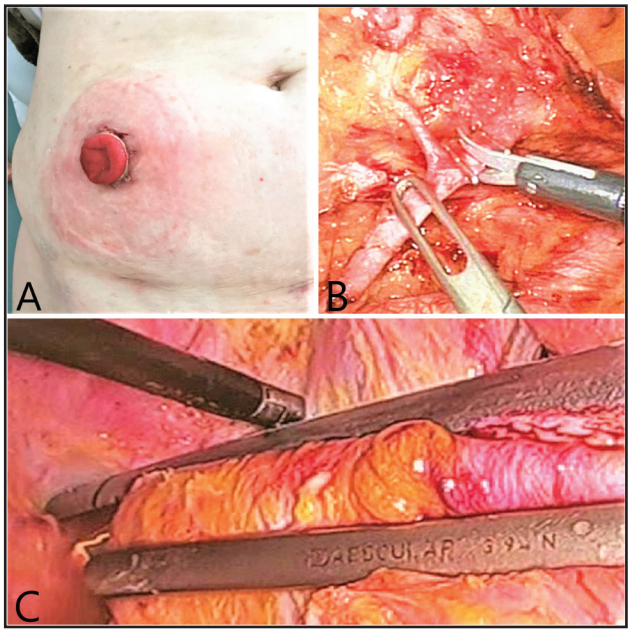

Figure 1. Aspects during laparoscopic and postoperative surgery. A - the postoperative aspects of the surgery at 2 week postop presentantion of the pacient. B - the low tie ligation of the inferior mesenteric artery, below the left colic artery origin, with central lymphadenectomy. C - After the complete mesorectal excision performed, in the distal part of the tumor, we transected the rectum with endoscopic stapler through the hypogastric trocar.

After the complete mesorectal excision performed, in the distal part of the tumor, we transected the rectum with endoscopic stapler through the hypogastric trocar (Figure 1 C). The specimen, including the lymphovascular pedicle, was resected through a mini Pfannenstiel laparotomy, and the anvil of the circular stapler introduced in to the proximal colon, secured after with a 2, polypropylne purse-string suture, the specimen being now extracted, and the anvil of the circular stapler introduced in the segment of proximal colon, secured after with a 2.0 polypropylene purse-string suture, the specimen being now extracted. After positioning back the colon in the abdomen, the laparotomy is closed.

End to end colorectal anastomosis was performed under laparoscopic vision using a circular stapler introducted transannaly. Two pelvic drains were placed in beyond of the anastomosis and procedure was finished by placing a protective ileostomy in the right flanc.

The macroscopic examination of the surgical specimen that includes the initial colostomy shows 5.5 / 3 / 1.2 cm ulcero-infiltrative lesions, and an exophytic mass of 2.3 / 2 / 1.1 cm (Figure 1). The histopathological examination show both lesions to be moderately differentiated adenocarcinomas (Figure 2,3) that invade the wall to the level of the pericolorectal tissues. Out of the 12 lymph nodes examined, two were diagnosed with malignant neoplastic invasion. Prognostic factors, such as the presence of angio-lymphatic and perineural invasion, have been identified. Acute abscessed inflammation and transudative peritonitis lesions were noted. At the level of the initial colostomy, granulomatous inflammation, represented by cholesterol crystals, was highlighted. Surgical excision was complete, with resection margins. The tumors were staged pT3N2ILV1IPN1 G2.

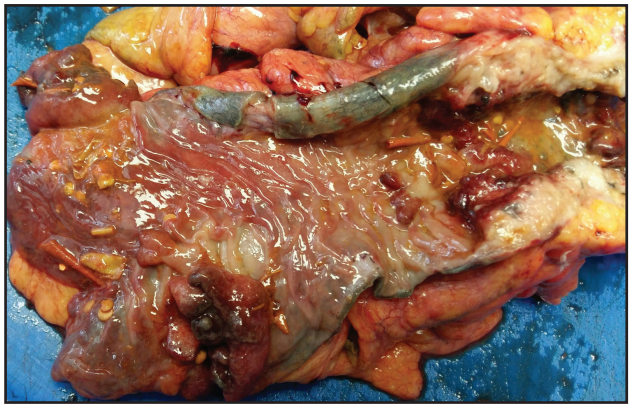

Figure 2. Gross aspects of upper tumor and lower tumor

The immunohistochemical examination was based on the evaluation of markers from the MSI panel, by the MACH 4 Universal HRP method, which represents a polymer detection system for primary antibodies (mouse and rabbit), followed by peroxidase (HRP), which will bind to the sample via the rabbit antibody. Immunohistochemistry assessment for microsatellite instability with MLH1, PMS2, MSH2, MSH6 and Ki67 revealed the MLH1 and PMS2 mutation in neoplastic proliferation (figure 5,6), with a Ki67 nuclear immunoexpression in 80% of neoplastic cells (Figure 3). The postoperative evolution was good, under antibiotic, analgesic, antisecretory and hydro-electrolytic rebalancing treatment, the patient being hemodynamically balanced throughout the hospitalization, with normal intestinal transit on the right ileostomy. Two weeks after discharge, the patient was admitted through the emergency unit for repeated vomiting and diffuse abdominal pain. The diagnosis was: postoperative intestinal occlusion through omento-parietal adhesion and parietal ileostomy stenosis followed by immediate emergency surgery comprising of partial omentectomy. Under complex supportive treatment, the patient develops cardio-respiratory arrest, nonresponsive to resuscitation procedures and declares death of the patient.

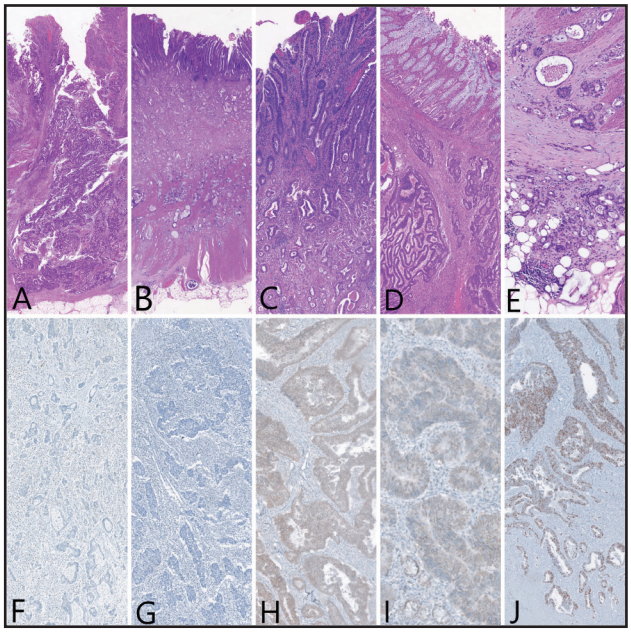

Figure 3. Microscopic and immunohistochemical aspects of both tumors. A- Malignant neoplastic proliferation with glandular architecture, -upper tumor, HEx 40. B Invasion of pericolorectal tissues -upper tumor, HEx 40. C - Microscopic aspects of G2 adenocarcinoma-upper tumor, HEx100. D - Epithelial glandular origin of neoplastic cell proliferation in the lower tumour, HEx100. E - Invasion of subserosal layer of the colon by neoplastic cells, lower tumor, HEx100. F- loss of MLH1 expression in neoplastic cell. G - negative immunoreaction of PMS2 in neoplastic cell proliferation. H - diffuse positivity for MSH2. I - focally positive neoplastic cells to MSH6. J - Ki67 positive in 80% of neoplastic cell proliferation

Discussion

The presence of at least two colorectal neoplastic lesions is defined, according to the time of occurrence, as synchronous or metachronous tumors.

These represent different primary tumors diagnosed simultaneously or at different times, in the same patient. Synchronous colorectal tumors are represented by at least two malignant tumor lesions in the same patient, concurrently, while colonic metachronous cancers are cancers originating in colorectal mucosae, which are form in different times, one after another (4,5).

Among the histopathological forms of adenocarcinoma, it was observed that mucinous adenocarcinoma is more frequently found in cases with synchronous colorectal carcinomas. Also, mucinous component is a morphological aspect of colorectal cancer, that characterizes hereditary nonpolyposis colorectal cancer, which can increase the risk of synchronous or metachronous colorectal carcinoma (6).

The first reported multiple carcinoma of colon in 1880 was by Czerny (7). Specialized articles confirms the existence of primary synchronous malignant tumors (8); malignant synchronous tumors are rarely diagnosed in medical practice, having a frequency between 90,17 and 0,69% in double or triple synchronous lesions, and 0,19 in patients with more than 4 lesions (9).

Since then, the number of cases diagnosed with double synchronous tumors has increased, an aspect encountered in numerous specialized studies (10-19) (Table I), or as single case presentations, being quite rare as a percentage compared to the total number of colorectal cancers, being associated, sometimes, with and familial adenomatous polyposis, inflammatory bowel diseases/ulcerative colitis and microsatellite instability (20-22)

Regarding the patients age upon diagnosis, some studies have shown no differences in age related between solitary and synchronous colorectal cancer.

In terms of gender distribution, men are at greater risk for developing synchronous neoplastic proliferations. The colorectal tumors tumors have a higher frequency in men, and, at the same time, they are approximately four times more frequent in developed countries.

Also, the literature shows that synchronous cancers they have a predilection for the cecum and ascending segment of colon (23). In the case presentation, the tumor lesions are located at the recto-sigmoid level.

Studies show that the diagnosis of malignancy in the large intestine is accompanied by a rate of identification of new cases ranging from 2 to 10%, and a rate of detection of synchronous tubular adenomas up to 50% (24,25).

Specialized research have highlighted that synchronous tumors ranges from 2.4% and 3.9% of all colonic malignant neoplasias (14,26,27).

Approximately two-thirds of colorectal tumors are located proximal from splenic flexure, and approximately 25% of cases are diagnosed in the sigmoid level, 10% of cases are identified in the rectosigmoid segment, and up to 6%, are developing in the descending segment of the colon (28). In day to day practice, a colonoscopy or biopsy report is required in order to complete the diagnosis of double colorectal lesions and to determine the type of surgical intervention.

Regarding surgical treatment, in tumors located in adjacents colonic segments, such as the ascending and transverse colon, one must be performed an extended right hemicolectomy or in the case of the left colon and rectum a left colectomy or anterior excision of the rectum. If the neoplasic tumor is located in segments located at a distance, the performance of Transanal Endoscopic Microsurgical Excisions is required (12).

Regarding the tyreatment of synchronous malignant tumors, total colectomy is sometimes required in the case of those known with predisposing diseases, such as familial adenomatous polyposis or ulcerative colitis. There are clinical contexts in which surgical resection with colonoscopy or clinical follow-up is recommended (29).

In patients with cancers that are overlooked, a double tumor might can progress and became invasive, into a more advanced stage and give metastases.

For tumors of right or transverse segments

of colon, which additionally presents a extraperitoneal rectal malignant tumor, a decrease of laparoscopic and open total colectomy rate was observed (30,31). Regarding postoperative monitoring, the protocols show great variability, with large variation in frequency of postoperative visits, serum CEA level, endoscopy, and thoraco-abdominal radiology (32,33).

Sometimes, the total colonoscopy is not possible, due to the localization of the synchronous tumor above a narrowed area by the ulcero-infiltrative tumor. There are cases in which, even during the performance of a total colonoscopy, the second tumor cannot be identified, due to its very small size or small distance from primary tumor (34).

The study of specialized literature highlights that the basis of the disease's pathogenesis consist in discordant molecular abnormalities (35-39).

The emergence of double primary colorectal malignant tumors is associated with syndromes like hereditary colonic cancer.

However, synchronous malignant tumor of the colon had the highest frequency in patients with hereditary non-polypoid colorectal cancer compared to the general population with colon cancer (40).

Colorectal cancers arise on the base of genetic abnormalities, which consist of oncogenes mutations and also mutations in tumor-suppressor genes. Colorectal malignant tumors can be characterized by one of the two genetic anomalies: chromosomal instability or microsatellite instability.

Microsatellite instability is characterized by the failure of the DNA mismatch repair system to correct errors that are introduced during normal DNA replication, in neoplastic tissues. The lack of PMS2 (IL-PMS2) expression can be caused by PMS2-LS and by MLH1 germline mutation or MLH1 promoter hypermethylation (MLH-PHM). MSH2 and MSH6 proteins are often lost concurrently.. in tumor tissue.

The immunohistochemical tests used in the evaluation of MMR proteins (MLH1, PMS2, MSH2, MSH6) have entered the clinical routine and have an extremely important role in establishing the predictive role of response to oncological treatment as well as in establishing the genetic implications for the patient's family (41-43).

Mismatch repair protein expression is often referred to in medical practice as lack of expression (44), named also „retained''(45,46).

In the study by Hechtman JF et al, it was observed that only approximately 7% of microsatellite instability malignant tumors cases have lack of expression or a different profile of microsatellite instability, so the presence of a high status immunostaining could be omitted with immunohistochemical assessment (47).

Immunohistochemistry identified mutations in MLH1 and PMS2 suggest the possibility of determining somatic mutations, imposing additional testing for Lynch syndrome, that can be an important aspect in defining postoperative treatment.

Immunohistochemical exam for DNA mismatch repair proteins is used, in particular, for screening for Lynch syndrome in malignant intestinal tumors, especially in those with microsatellite instability.

Lynch syndrome represent an autosomal-dominant disease, characterized by a germline mutation in a DNA mismatch repair (MMR) gene or a mutation of EPCAM gene; thus, patients who have an MMR mutation can develop multiorgan cancer, especially large bowel and endometrial carcinomas, but rarely, gastric carcinomas, pancreas, hepatobiliary tract, stomach, small intestines, urothelial, and ovaries.2

Among all mutant immunohistochemical expressions, the most frequent is lack of expression of MLH1 and PMS2. The role of MLH1 and PMS2, along with MSH2, MSH6 and EXO1, is to repair some errors impacting mispaired nucleotides, determined by DNA polymerase during DNA replication (48-50).

A functional defect of MLH1 gene derived from degradation of MLH1 and PMS2 genes, whereas a defect in PMS2 results only in the degradation of PMS2.

Immunohistochemical testing for the DNA MMR proteins, represented by MLH1, PMS2, MSH2 and MSH6 is a usual, highly sensitive test used on a daily basis in screening for Lynch syndrome, with high level concordance with assessment of microsatellite instability (51,52). Despite these results, studies with false-negative results for MLH1 immunohistochemical testing

were mentioned.

Regarding the prognosis of synchronous colon tumors, it is not much different from solitary colon tumors. In this sense, the first prospective study carried out by Nosho et al in 2009 on synchronous tumors, highlighted the fact that they have a worse prognosis, as a result of the higher rate of metastasis and the occurrence of postoperative complications (16).

Some studies stated that the most important genetic foundation was particular to those tumors identified in the same colonic segment, for which factors such as the tumor microenvironment, the local bacterial flora, chemical substances ingested, water content and transit time are blamed for (4,53). In the study of Shia J et al (2014), a patchy, very reduced immunoexpression was described, below 5% of tumor cells for MSH6 in malignant tumors of the colon, especially in cases with neoadjuvant therapy or cases with mismatch repair deficiency. Future studies are needed to confirm the biological potential of the MSH6 mutation among colon cancer vessels with microsatellite instability (54).

Limitations of this study are represented by the small number of cases with synchronous tumors in the south-eastern region of Romania. In the future, a larger study can be carried out on synchronous colorectal tumors, over a longer period, with testing the expression of MMR proteins, both immunohistochemically and molecularly, by PCR. Also, another research directive could be based on the identification of patients with Lynch syndrome and MSI testing on colorectal, endometrial and gastric cancers, in order to establish some correlations.

The strong point of the presented case is represented by the particularity of the immunoexpression of the tumor lesions in a patient with double colorectal cancer, with the implications they represent. In our case, the patient died shortly after the operation, as a result of a complication. In the future, a study can be carried out on cases of double tumors of the large intestines, with following their evolution and the response to oncological treatment and the comparative evaluation of microsatellite instability by molecular testing and immunohistochemistry.

Conclusion

This case highlights the concomitant existence of two malignant tumors at the rectosigmoid level, with similar characteristics, based on: histopathological appearance, degree of invasion in colon and microsatellite instability.

The choice of laparoscopic approach, rectosigmoid resection of both malignant tumors, subtotal excision of the mesorectum and sphincter-sparing surgery in terms of oncological features of prognosis were successfully performed.

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