The role of immunohistochemistry in diagnosing a synchronous colon tumor

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Abstract
Simultaneous presence of an epithelial and lymphoid tumor of the digestive tract is quite rarely met in literature. In this paper, we describe a case which presented such an association. Diagnosis was established by histological study, followed by immunohistochemistry. It is a synchronous colon tumor, associating a non-Hodgkin’s lymphoma to a colon adenocarcinoma. The 57-year-old male patient has been clinically diagnosed with a tumor of the left abdominal quadrant and paraclinically (imaging and endoscopic) with colon neoplasm. Exploratory laparotomy revealed two tumors: one tumor of five centimeters in the sigmoid, with firm consistency, mobile on lower plans and the second tumor in the ceco-ascending colon, measuring about 7 cm, irregular, with firm consistency, mobile on lower plans, with lymph nodes extending to retroperitoneal space. The urinary bladder, kidneys, liver and stomach were of normal aspect. Subtotal colectomy was performed with latero-lateral ileo-sigmoid anastomosis. Microscopic examination revealed sigmoid tumor as G1 adenocarcinoma and cecal tumor as B-cell type lymphoma. Immunohistochemistry established the final diagnosis of cecal localization being a diffuse immunoblastic large B-cell non-Hodgkin’s malignant lymphoma. The final diagnosis of this patient was actually a synchronous manifestation of a colon adenocarcinoma and non-Hodgkin’s lymphoma. This association puts into question synchronous tumors etiopathogeny matter.

Keywords: synchronous tumor, colon, lymphoma.

Introduction
Synchronous tumors represent the coexistence of two adjacent malignant neoplasms developed in the same organ, but histologically different and without interpenetration of cell population.

Histogenesis of these two types of tumors is different, as well as their tumorigenesis. Collision tumors synchronously occur in the same organ but are independent and morphologically different. Their clinical manifestations are nonspecific, being difficult to preoperatively diagnose. Etiologic diagnosis is based on histopathological examination, often helped by immunohistochemistry [1, 2].

From the clinical point of view, lymphomas starting within the gastrointestinal tract have no systemic symptoms [1]. These lymphomas are mainly found in the stomach and small intestine, colorectal localization is much less common – 5–10% according to some authors [3] or 1–4% by other authors [4]. Therefore, any synchronous development at the colorectal level of a lymphoma and another type of cancer is a very rare feature in medical practice, estimated by some authors to 0.0002% [5]. Both types of tumors could develop in separate segments or in the same segment as collision tumors.

In terms of histopathology, diffuse non-Hodgkin’s large B-type cell lymphoma is the most common subtype in the gastrointestinal tract [1] having in general an aggressive development. Consequently, synchronism achieved by malignant B-type lymph proliferation present a significant incidence of colorectal carcinoma [6]. It is difficult to predict the factors responsible for the predominance of one type of proliferation in regard to others. There is no documented scientific information about a possible common etiologic mechanism of the two tumor types; however, the existence of genetic defects responsible for triggering an adenoma-adenocarcinoma sequence are usually suspected. These epidemiological conditions favor sometimes the development of a B-type lymphoma and an adenocarcinoma with the same colorectal location.

Patient, Methods and Results
In this paper, we present the case of a 57-year-old man who was admitted through the Emergency Room with non-specific symptoms: abdominal pain, intestinal motility disorders, fatigue.

Clinical and laboratory data
The clinical examination revealed an abdominal tumor, in his left abdominal quadrant, of about 10 cm in diameter,
firm consistency, irregular surface, painful and mobile. Laboratory examinations revealed an anemic syndrome with hemoglobin of 8 g/dL, hematocrit of 25%, thrombocyte count $344 \times 10^3$/mmc and white blood cells count of $12 \times 10^3$/mmc and glucose (68 mg/dL) and urea (46 mg/dL), creatinine (0.92 mg/dL) and were within the normal range. Other laboratory values were consistently within normal ranges, with the exception of a hypokalemia on presentation (serum potassium 3 mEq/L, normal 3.5–5.5 mEq/L).

**Imaging tests**

We performed lower gastrointestinal endoscopy and identified a circumferential, ulcer-vegetant tumor of 5 to 6 cm in the sigmoid, at 40 cm from external anal orifice. Also, in the ceco-ascending colon, another hemi-circumferential ulcer-vegetant tumor, at 90 cm from external anal orifice was identified.

Native and post-contrast CT examination revealed confluent lymph nodes with a maximum diameter of 7 to 8 cm, located in the mesenteric, celiac, hepatic, interaortocaval and lumbo-aortic region, with minimum peritoneal fluid, nodular peritoneal thickening having peritoneal metastases appearance, without liver metastases.

**Surgical intervention**

During surgical intervention, we found a tumoral block comprising the ceco-ascending colon and exceeding the serous membrane, lymph nodes organized as tumoral blocks around the entire mesentery and tumoral blocks comprising the right half of the retroperitoneum. In the sigmoid there was evidenced a 3/4 cm stenosing area.

Subtotal colectomy with latero-lateral ileo-sigmoid anastomosis was performed. Mesenteric lymph nodes were excised, but adenopathic blocks from the mesentery root or the retroperitoneum could not be removed because of the vascular risk. The postoperative evolution was favorable.

**Pathology – macroscopic aspect**

Macroscopic examination of the 1.5 m long intestinal fragment showed the first tumor in the immediate vicinity of the ileocecal valve, on the side of the colonic segment and with upward extension. It had approximately 16 cm in the long axis, yellow-gray color and relatively low consistency. This voluminous tumor infiltrated the full thickness of the intestinal wall, encompassing the cecal appendix. At a distance from the first tumor, the second developed in the sigmoid and had approximately 2.5 cm in the long axis, ulcerative aspect and a white-gray color.

**Microscopy and immunohistochemistry**

Microscopic examination of the first tumor highlighted a diffuse proliferation of malignant lymphoid cells, mainly medium and large lymphocytes with marked pleomorphism, vesicular nuclei, 1–4 nucleoli, frequent mitoses, as well as atypical immunoblasts. Diffuse infiltrative-proliferation invaded the intestinal wall and the cecum (Figures 1 and 2) as well as the wall of the cecal appendix (Figure 3), (including the mesoappendix). The 37 loco-regional lymph nodes showed the removal of architectural sections revealing the existence of the same type of malignant lymphoproliferation (Figures 4 and 5). Immunohistochemical profile of this first tumor proliferation, situated at the cecal level, showed an intense and diffuse immunopositivity for CD20 (B-lymphocytes) (Figure 6), the absence of CD30 in tumor immunostaining (for activated lymphocytes and Reed–Sternberg cells) and the absence of CD3 (T-lymphocytes) positivity. These observations suggested diagnosis of large diffuse B-cell immunoblastic non-Hodgkin’s malignant lymphoma.

In the same context, CD5 (both T-lymphocytes and in a variety of B-type malignant lymphoproliferation) showed a weak positive immunofixation, (Figure 7), and proliferation index expressed a high value, above 50% (Figure 8). The existence of a Ki-67 index showed the aggressive nature of the B-cell lymphoma.

Microscopic examination of the second tumor revealed the existence of cecal synchronously with the formation of a well-differentiated adenocarcinoma, G1. From the time of diagnosis, it already fully invaded the intestinal wall to the entire subserosa (Figures 9 and 10).

Histopathological examination of the two tumors revealed well-differentiated G1 adenocarcinoma for the sigmoid tumor, its staging being $T_3N_0M_x$ and the cecal tumor was found as being a high-grade malignant B-cell lymphoma, invading completely the cecal and appendicular wall, with 37 locoregional lymph nodes. According to the TNM classification, we treated it as stage 3 $T_3N_0M_x$.

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**Figure 1 – Intestinal malignant lymphoma. Hematoxylin–Eosin (HE) staining, 40×.**

**Figure 2 – Infiltrating malignant lymphoma within the muscular tunic. Detail. HE staining, 80×.**
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Figure 3 – Infiltrative malignant intestinal lymphoma of the appendix wall. HE staining, 20×.

Figure 4 – Intestinal malignant lymphoma, locoregional lymph node. HE staining, 20×.

Figure 5 – Intestinal malignant lymphoma, locoregional lymph node. Detail. HE staining, 80×.

Figure 6 – Intestinal malignant lymphoma, intense positive CD20 immunostaining and diffuse within the tumor proliferation. Anti-CD20 immunostaining, 40×.

Figure 7 – Weak positive focal immunostaining for CD5 within the tumor proliferation. Anti-CD5 immunostaining, 40×.

Figure 8 – Positive Ki-67 immunostaining in over 50% of tumor cells. Anti Ki-67 immunostaining, 40×.
Discussion

Synchronous tumors’ reporting was relatively rare in the literature. These may occur in the digestive tract as: colon adenoma and carcinoid, colon adenocarcinoma and transitional cell carcinoma of the bladder, colon adenocarcinoma and non-Hodgkin’s lymphoma, adenocarcinoma of the colon and peritoneal metastases of a hepatoid variant of yolk sac tumor. Lymphomas are a group of hematological malignancies that only rarely affect the colorectum. Literature mentions a percentage of 0.16% of malignant tumors in this location [7]. Also, a synchronous development of lymphoma in the same patient and an adenocarcinoma of the colon is even more unlikely.

The case of synchronous tumors presented in our study, that of a man aged 50 years, is in full agreement with epidemiological data from the literature that states there is a higher incidence of synchronous colorectal tumors in males [8] and senior persons [1].

Highlighting these tumors is important on one hand because it raises treatment problems specific to each histological type and secondly, because they influence the evolution and prognosis of the patient.

Associations of non-Hodgkin’s type lymphoma and mucinous adenocarcinoma of the colon are rare. Diagnosis problems occurred when determining the type of adenocarcinoma. Resection pieces macroscopic examination revealed two tumors developed each in the sigmoidum and cecum. Paraffin blocks were made and sections were conventionally prepared and stained with Hematoxylin–Eosin (HE).

There are various theoretical assumptions and studies that have attempted to explain the mechanisms that enable the emergence of synchronisms of colorectal tumors. Some theories [9] theorized the existence of a single stem cell common to different gastrointestinal malignancies. Other studies state the possible involvement of genetic and immunological abnormalities in patients, as well as the importance of environmental factors [7].

Diagnosis of cases published in the literature of patients with synchronous colorectal cancers, one of which being represented by a malignant lymphoma, was performed either by imaging or by histopathological examination [10]. In our case, endoscopic examination of the lower gastrointestinal tract revealed the existence of two tumors located in different segments of the colon or rectum, without ruling out a possible invasion from one of the locations to the other. There are studies demonstrating that 30% of cases are diagnosed by colonoscopy prior to surgery [11]. Pathological examination specified in our case the existence of a synchronous tumor.

The patient in our study was diagnosed with a large B-cell malignant lymphoma in the cecal region, this location is in close agreement with data from the literature that states the existence of most colorectal lymphomas proximally to the hepatic flexure of the colon [1]. However, this type of intestinal lymphoma is the most common subtype of non-Hodgkin’s lymphoma with intestinal histopathology. The aggressive prognosis was demonstrated in our study by a high rate of proliferation.

Although non-specific symptoms of patients diagnosed with intestinal lymphoma are most commonly manifested as abdominal pain and weight loss, with less frequency were recorded lower gastrointestinal bleeding, even intestinal perforation [1]. In our case, abdominal pain was present, accompanied by asthenia and bowel disorders.

Sigmoid adenocarcinoma development, the second tumor belonging to our case, had a less frequent location between colorectal segments. Most studies indicate the right colon as the most frequent location of adenocarcinomas [12, 13].

This tumoral association has a poor prognosis [14], in our case the patient presenting with end-stage peritoneal metastases, having very limited therapeutic possibilities. Aggressivity of the tumor combination presented in our study is motivated by high proliferation index (Ki-67 index above 50%) and the particularly high number of loco-regional lymph nodes (37 lymph nodes) having modified architecture of the same type as the malignant lymphoproliferation.

Both components invade colonic wall going beyond the serous membrane and raiding into the mesentery. The bladder was not reached.

Conclusions

This tumor association restricts survival chances due to tumor aggressiveness. The diagnosis of synchronous
neoplasia (benign or malignant) with colorectal location is most often the result of a sequence of clinical findings and laboratory tests. Preoperative diagnostic of the histological type is hard to establish. This association usually develops in immunosuppressed patients, with many comorbidities. Therapeutic approach is not easy due to difficulties in choosing the right cytostatic drugs combination, prognosis being unfavorable firstly due to the aggressive nature of the intestinal lymphoma.

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Author contribution

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References


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