Synchronous carcinoma of the ascending colon and caecum

CORINA GRUIA1), CAMELIA FOARFA2), LILIANA STREBA3),
P. MĂNESCU4)

1)Department of Pathology,
Emergency County Hospital, Craiova
2)Department of Pathology
3)Department of Histology
4)Department of Surgery
University of Medicine and Pharmacy of Craiova

Abstract
The caecum and the ascending colon are the colon segments most frequently affected by tumoral synchronism. Synchronous colorectal carcinoma etiopathogenesis is complex and most likely by malignancy of preexisting adenomas (adenoma–adenocarcinoma sequence). The following tumoral synchronism clinical case’s particularity is represented by the simultaneous diagnosis of a flat-type adenocarcinoma of the caecum (less common histopathological type) and of a mucinous adenocarcinoma on the ascending colon. Tumor profiles of both carcinomas were examined histologically and immunohistochemically, emphasizing: (1) tumor proliferation different histological type; (2) residual adenomas in the periphery of the flat-type adenocarcinoma; (3) hardly microscopic detectable invasive character of the flat-type carcinoma; (4) mucinous carcinoma’s infiltrating character and its immunohistochemical phenotype; (5) both tumor aggressiveness.

Keywords: synchronous colorectal carcinoma, etiopathogenesis, flat-type adenocarcinoma, mucinous adenocarcinoma, histopathology.

Introduction
Patients diagnosed with two or more cancers simultaneously developed in the same organ or different organs represent a distinct clinical and pathologic entity. According to literature, in order to define the concept of synchronous neoplasia, Billroth’s criteria (1879) is being used [1]: (1) tumors should have different histologic appearance; (2) to have the point of start in different epithelia of that organ; (3) each tumor to generate their own metastases. The phenomenon of multiple primary malignancies was described later by Warren S and Gates O, who brought some changes in Billroth’s too strict criteria [2, 3].

The colon is the most damaged organ by multiple tumor types [4–8]. According to one study, 32% of cases of multiple tumors are localized in the large intestine [9]. Other organs with a large proportion of damage through synchronous cancers are: the liver, the lungs, the female and male genitalia [10]. Also, synchronous colorectal cancer patients are more likely to develop carcinomas in other organs too [11].

The etiopathogenesis of synchronous malignancies of the digestive tract is difficult to establish because there is a wide variety of histopathological synchronous neoplasms, both of those limited to the gastrointestinal tract and those with simultaneous location in different organs. This prevents from an eventual systematization of synchronous tumors [12]. It is assumed that these synchronous tumors would develop from similar embryological origin tissues, simultaneously being under the action of carcinogenic agents [13]. Colorectal multiple carcinomas occur more frequently in patients with polyposis syndromes or in those with idiopathic colonic inflammatory diseases, as ulcero-hemorrhagic rectocolitis or Crohn’s disease [11]. Adenoma–adenocarcinoma sequence is most likely the main etiopathic mechanism of colorectal carcinoma development, both single or multiple, therefore clinical and pathological aspects of the two groups do not differ [14, 15]. Approximately 75% of patients diagnosed with synchronous colorectal carcinoma also present associated adenoma [16]. Proximal colon is the intestine segment with a growing predilection for synchronous carcinomas and adenomas in people over 65-year-old. The five-year survival rate for patients with synchronous carcinoma of the colon is estimated to 53%, similar to patients with solitary colorectal carcinoma [17].

Unlike pedunculated adenoma, flat adenoma (both single and multiple) represents a special subset of adenomas, with great potential for malignant transformation and favorite development in the proximal colon [18]. Colorectal carcinoma developed from a flat adenoma was first described in Japan, being rarer in Europe and North America [19]. Ganglionic metastases to regional lymph nodes, even when there is evidence of only submucosal invasion is an important argument of the particularly aggressive potential of flat colon carcinoma, so that these cancers have a poor prognosis.

Colon mucinous tumors represent 10–15% out of all adenocarcinomas [20, 21]. Mucinous type carcinomas
are clinically and histopathologically different of an ordinary adenocarcinoma by having the capacity to easily invade adjacent viscera and determine extensive lymph node metastases of the pericolic ganglia, which confers a very bad prognosis to this type of carcinoma [22].

**Materials and Methods**

We report a case of synchronous tumor in the proximal colon of a 73-year-old male patient admitted to the IIIrd Surgery Department of the Emergency County Hospital of Craiova. Clinical examination on admission revealed the existence of a palpable mass in the right iliac fossa. The fragment obtained following bowel resection surgery (right hemicolectomy with latero-lateral ileotransverse anastomosis) emphasized the existence of two distinct tumors. Fragments collected from the two tumors were processed by paraffin inclusion technique and Hematoxylin–Eosin staining with further immunohistochemical viewing using En Vision™ G/2 Doublestain Rabbit/Mouse System (DAB+/Permanent Red). Histopathological diagnosis was developed in accordance with WHO criteria (2000) regarding the colon and rectum tumor classification. We used PAS histochemical staining technique to confirm one of the tumors mucinous aspect. The list of immunohistochemical antibodies that were used consisted of: AE1/AE3 (clone AE1/AE3, isotype IgG1 kappa), CK20 (clone KS 20.8, isotype IgG2a kappa), CK7 (clone OV / TL 12/30 IgG1 kappa isotype), COX2 (clone CX-294, isotype IgG1, kappa), CDX2 (clone DAK-CDX2, isotype IgG1 kappa), MUC2 (clone NCL, isotype IgG1 kappa). Afterwards, visualization was performed using DAKO LSAB+/HRP and DAKO En Vision+/HRP and DAB chromogen.

**Results**

We present the case of patient U.V., who referred to the hospital for intestinal transit disorders, vomiting, flatulence and abdominal pain. The ultrasound examination performed on admission revealed pathological changes of the caecum and middle part of the ascending colon: irregular thickening of the intestinal wall for a distance of about 7 cm with stenosis at this level and relaxed ileal loop. The ultrasound aspect suggested an atypical caecum and ascending colon stenosing and infiltrative process (Figure 1).

**Figure 1 – (A–D) Ultrasound revealed the atypical caecum and ascending colon stenosing and infiltrative process.**

Tumoral surgical excision was performed by resecting the loop fragment that includes the last 20 cm of ileum, the caecum with the caecal appendix, the ascending colon, half of the transverse colon, mezoco-lon and the great epiploon.

The macroscopic examination of the longitudinally sectioned piece identified in the immediate vicinity of the ileocaecal valve the first tumor which caused only a slight elevation of the intestinal mucosa, on an area of about 4 cm; cross-sections performed at this level showed predominantly surface development of the tumor. At about 3 cm of the first tumor was identified another one of about 6 cm on the ascending colon, with vegetant aspect, circumferential and with marginal ulceration. By sectioning the second tumor, we established its low consistency, grey-rose color, invading the whole thickness of the wall, sometimes with papillary appearance. There were also taken...
samples of 19 lymph nodes from peritumoral adipose tissue for microscopic examination.

Microscopic examination of the first tumor, from the caecum, revealed the existence of a well-differentiated adenocarcinoma, with malignant glandular proliferation not exceeding 2× normal thickness of adjacent mucosa (Figure 2) and simultaneous presence of numerous follicular lymphocytic aggregates at the bottom of glandular crypts (Figure 3). These aspects have allowed enframing in a G1 well-differentiated adenocarcinoma, flat-type. The examination of numerous fragments collected at this level could reveal the presence of invasion in an intramural ganglion (Figure 4), establishing the invasive nature of the tumor. Simultaneously, on the caecum we could observe the coexistence of multiple adenomas, some of them exhibiting simple dysplasia changes at the apical pole (Figure 5).

The second tumor, located in the ascending colon, microscopically evidenced the existence of a mucinous G3 type adenocarcinoma, infiltrating the full thickness of the intestinal wall, including peritumoral adipose tissue (Figure 6), with over 50% mucus secretion. Using PAS staining, we highlighted the presence of mucinous secretion with net aggressive nature, dissociating the adenocarcinoma’s tissue layers and other issues related to the aggressive potential evidenced by detecting sanguine and lymphatic tumor emboli (Figures 7–9).

Immunohistochemical profile of mucinous tumor of the ascending colon was evaluated using several markers. There was a diffuse immunofixation of the cytokeratin cocktail of AE1/AE3 (Figure 10) and cytokeratin 20 (Figure 11), as well as an absent expression of cytokeratin 7 (Figure 12).

The presence in a large proportion of the second proliferation of the goblet cells was evidenced by immunofixation with MUC2 (Figure 13), which showed an intense and diffuse positivity. The differentiation rate and risk of metastases of this ascending colon tumor has been investigated with COX2 and CDX2. In our case, COX2 expression was weak and focal, unlike CDX2 that was intense and diffusely expressed (Figures 14 and 15).

Figure 2 – Well-differentiated flat-type adenocarcinoma (HE stain, ob. 40×).

Figure 3 – Lymphoid follicle at the basis of epithelial proliferation (HE stain, ob. 40×).

Figure 4 – Metastasis in an intramural ganglia (HE stain, ob. 40×).

Figure 5 – Adenomatous polyp with dysplasia (HE stain, ob. 40×).
Figure 6 – Invasive mucinous adenocarcinoma (HE stain, ob. 40×).

Figure 7 – Lymphatic tumor embolus (PAS stain, ob. 10×).

Figure 8 – Tumor blood embolus in an artery (HE stain, ob. 10×).

Figure 9 – Extracellular mucus in a mucinous adenocarcinoma (HE stain, ob. 40×).

Figure 10 – Positively and diffuse intensely positive AE1/AE3 (ob. 10×).

Figure 11 – Immunofixation. Diffuse positive CK20 (ob. 10×).
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Figure 12 – Negative CD7 fixation (ob. 10×).

Figure 13 – Positive MUC2 immunofixation (ob. 10×).

Figure 14 – Positive CDX2 immunofixation (ob. 40×).

Figure 15 – Weakly positive COX immunofixation (ob. 10×).

Discussion

The case presented is of an over 60-year-old male patient; these epidemiological factors being overlapped with literature data that range colorectal synchronous carcinoma compared to the solitary with a higher incidence in old age and in males. The risk of synchronous cancers more common in old aged people is related to many factors: decreased resistance to carcinogenic agents, environmental factors (persistent exposure to pollutants), immunological changes occurring with age or combinations of these [23–26].

Proximal colon appears to be, with predilection, the frequently affected bowel segment by tumoral synchronism with the two tumors tending to develop with a short distance from one another. In the case of patient U.V., after measurements of all macroscopic tumoral parameters, there was also registered the existence of a small segment of a normal colonic mucosa between the two neoplasms (about 3 cm).

More than 80% of colon polyps have the histological structure of an adenoma and at some point it may become malignant through the adenoma–adenocarcinoma sequence. The very careful examination of the caecum mucosa, both at the edges of the first tumor, as well as the “apparently” healthy mucosa between the two tumors, revealed the existence of multiple adenomas, some of them being dysplastic. Identifying the simultaneous existence of malignant tumors, as well as of adenomas, represent very important arguments for this histogenetic theory.

Flat type adenocarcinoma, by its location, in this case – the proximal colon, coincides with the statistical data which mainly lies this type of tumor in the caecum and the ascending colon [27], remaining a much more rare form in our casuistry, but more common in Japanese. Flat neoplastic lesions were situated by Japanese gastroenterologists as type II adenocarcinoma, with three subtypes: Ila “en plateau”, IIb completely flat, and IIC depressed “en plateau” [28]. Microscopically, flat type adenocarcinoma is characterized by a glandular proliferation composed of unequal glands wallpapered by a largely flattened epithelium. Glandular proliferation sometimes achieves a tubulovillous pattern, with a height not exceeding twice the around normal mucosal thickness. Glandular epithelium asserts by a not too large number of atypical mitoses and a less marked
cellular pleomorphism, these cytological features framing the tumor in a well-differentiated G1 adenocarcinoma. The presence of numerous lymphoid aggregates at the base of the proliferation creates an apparently discontinuous aspect of the muscular mucosa and muscular tunic, making it difficult to assess the invasion degree of the flat adenocarcinoma. Flat lesions, despite their small size and less aggressive cytological features, have a poor prognosis [29], with rapid penetration of the colonic wall. In this case, careful examination revealed the existence of tumoral invasion in an intramural lymph node.

However, it is known that mucinous type adenocarcinoma is a histopathological form with a poor prognosis, with tissue plans infiltration, reduced desmoplastic reaction around and direct extension to the serous membrane, by lymphatic and blood tumoral emboli and perineural invasion. In our case, the microscopic examination of the second tumor reveals the existence of a proliferation type different from the first tumor, that of a mucinous adenocarcinoma, thus making possible the inclusion in a form of tumoral synchronism. Microscopically there can be noticed numerous extracellular mucus ponds containing malignant tumor cell groups with sporadic acinar placement or scattered, surrounded by stroma with reduced desmoplastic reaction and concurrently certain tumor infiltrative aspect and direct expansion to the serous membrane. Examination of dissemination via the lymphatic and blood vessels using current staining (Hematoxylin–Eosin) and PAS staining reveals a quite important number of blood and lymphatic tumor emboli. Literature data also confirm vascular dissemination as a general pathway that can early occur in the development of colorectal cancer [30]. Immunohistochemical profile of the second tumor, due to diffuse immunofixation of the AE1/AE3 cytokeratins cocktail and cytokeratin 20, expresses the proliferation’s epithelial character and frames it in the general profile of colorectal carcinomas. According to literature, the cellular phenotype of colorectal carcinomas is achieved by 85–100% immunofixation of cytokeratin 20 and by the absence of cytokeratin 7 immunofixation in 50% of cases. In our patients’ case, cytokeratin 7 was not expressed. It is remarkable that the cytokeratin 20 immunofixation intensity was not diminished by the mucinous carcinoma’s aggressive character. Highlighting proliferated cell type was performed by using MUC2, which revealed a diffuse immunopositivity of goblet tumoral cells. MUC2 positive phenotype is associated with poorly differentiated tumors and with advanced disease, which is a corresponding aspect of the histopathological of the examined tumor. In the same context, that of highlighting mucinous carcinoma’s bad prognosis, there was used COX2 immunolabeling. By its weakly positive fixation, could not be consistent with literature data indicating an increased expression of COX2 for poor prognosis carcinomas.

The tumoral synchronism does not worsen the prognosis compared with single tumor situation. Thus, tumoral multiplicity is not itself a prognosis indicator. We can note the extension of the “synchronous neoplasia” concept, introduced by Billroth, to that of “tumoral associations” [31].

**Conclusions**

In recent years, there is an increased incidence of synchronous cancers of the gastrointestinal tract following the progress of imaging techniques, screening policies and the deepening of the genetic mechanisms responsible for the neoplastic disease appearance. The initial detection of a single colonic tumor demands careful examination of the entire digestive tract in order to exclude an eventual tumoral synchronism.

**References**

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Corresponding author
Camelia Foarfă, Assistant Professor, MD, PhD, Department of Pathology, University of Medicine and Pharmacy of Craiova, 66 1 May Avenue, 200628 Craiova, Romania; Phone/Fax +40251–599 228, e-mail: csimionescu2004@yahoo.com

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