CASE REPORT

Long-term survival in a patient with advanced gastric cancer and metachronous right-sided colon cancer

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Abstract
Gastrointestinal carcinomas represent the most common cancers worldwide. The coexistence of gastric cancer with metachronous colon cancer represents a rare phenomenon, and the prognosis of the patient is poor. We present here a case of an elderly patient with primary gastric intestinal type well-differentiated adenocarcinoma (pT3N0, stage IIA) who developed a metachronous right-sided colon cancer diagnosed and treated after 11 years from the first surgical intervention. Histopathological and immunohistochemical examination revealed a well-differentiated adenocarcinoma (strongly positive staining for cytokeratin 20 and CDX2), pT3N0 stage IIA. The patient is still alive and active after 16 years from his first surgical intervention, even though no treatment has done after the removal of his second cancer.

In conclusion, in any case of gastric cancer, first the surgeon, and then the general practitioner should be alert to recognize a second primary tumor with different origin and to perform complete postoperative control. The correct diagnosis could lead to the patients’ best prognosis.

Keywords: gastric cancer, metachronous right-sided colon cancer, long-term survival, immunohistochemistry, CDX2.

Introduction
Digestive cancers are a major cause of morbidity and mortality worldwide, including Romania. Of these, gastric cancer (GC), although it appears to have a tendency to decreasing incidence in recent years, especially in Western countries, where the possibilities of diagnosis and treatment have been refined, yet represents the fourth most frequent malignancy and the second most common cause of cancer death [1].

Regarding the colorectal cancer (CRC), its epidemiological trend in Romania is in a continuous increase, being similar with that recorded in Western Europe until 90’s [2, 3]. A recent study also revealed that in recent years the growth trend of CRC in Romania is above the European average [4]. In our country, GC mortality rates decreased, but mortality rates from CRC increased during a recent period of 50 years (1955–2004). The hierarchy of the causes of digestive cancer mortality was dominated by CRC, which recently was revealed to be the first most common carcinoma of the gastrointestinal tract. Gastric cancer appeared to be the second, decreasing after a variable time trend in the same period [5].

The five-year survival rate for GCs is low (10–20%) [6]. Regarding the patients diagnosed with CRC, they also have a low survival, and additionally those with right-sided colon tumor have a worse prognosis than those with left-sided colon cancer [7].

In recent years appeared some reports concerning the synchronous and metachronous development of a second primary cancer in patients with GC, but most of them were from Asian countries where the stomach cancer has a higher incidence [8].

The development of multiple primary malignant neoplasms in the same patient was noted more than a century and a half ago, in 1863, by the founding father of modern abdominal surgery, the Austrian surgeon Christian Albert Theodor Billroth (1829–1894), only based on his surgical intervention and his own microscopic examination [9]. The multiple malignant neoplasms remained unknown until the beginning of the twentieth century, when the interest in this issue raised [10–12].

Anyway, in 1932, Warren & Gates [13] found in literature a number of 1259 patients as having multiple primary malignant tumors (MPMTs) and proposed a set of criteria for their diagnosis: (a) each tumor must have
clear evidence of malignancy on histological examination; (6) each tumor must be distinct and located separate from the others; (c) the possibility of a metastatic lesion having spread from a prior cancer must be excluded.

Swaroop et al. [14] classified multiple primary malignant tumors as synchronous if the different tumors were diagnosed simultaneously or within an interval of six months, and as metachronous when a later tumor was diagnosed more than six months after a preceding tumor. Different authors found out variable percentages of the association between a primary GC and a secondary primary cancer, as ranging between 3.4% and 10.9% [8, 15, 16]. The most frequent detected second primary malignancy in patients with GC was CRC (reported to represent 20% [15] to 37.2% [17] and even 43.8% [18] of all second primary neoplasms), followed by lung, liver, esophagus and breast cancers [8, 16]. The authors who reported series of cases of GC associated with synchronous or metachronous CRC were mainly those from Asia [19]. Until now there were published just over 100 cases of synchronous gastric and colorectal neoplasms [15, 19–26] and no more than 50 metachronous colorectal neoplasms in surgically treated gastric cancer patients [27]. In Romania, there are only three reports about multiple malignancies in the same patient most of them referred to breast cancer associated with synchronous or metachronous cancers of ovary, endometrium, gastric, thyroid, retro- orbital, kidney, colonrectum, skin, stomach and contralateral breast [28]. Irimie et al. [29] reported multiple synchronous and metachronous second primary malignancy associated with genital and breast cancers as primary malignances. One single article published by Pricop et al. [30] highlighted a case of metachronous primary cancers of colon and stomach in a 69-year-old woman. Regarding the second primary tumor after a primary gastric cancer, the Romanian authors reported that breast and ovary tumors were the most frequent, followed by lung, colorectal, and stomach cancer. It was also published a case of prostate adenocarcinoma followed after one year by a gastrointestinal stromal tumor [31].

The aim of this paper was to present a case of an elderly patient with good and long survival after advanced gastric carcinoma and metachronous right-sided colon cancer and to highlight the fact that periodic examination for metachronous cancer should be taken into consideration during the postoperative period, especially when the patient has a good recovery after the first surgical intervention.

Case presentation

In May 23, 2001, a 64-year-old man came in the Emergency Room of “St. Spiridon” Emergency County Hospital of Iasi, Romania, for nausea, vomiting, and hematemesis (500 mL). The esophagogastroscope revealed a bleeding ulcerated lesion, 4×4 cm in diameters, in the posterior wall of the gastric corpus. The patient was admitted in the IIIrd Surgery Clinic of the same Hospital and intravenous proton pump inhibitor (Omeprazole, 40 mg/8 h) was started. Upon evaluation, the patient reported intermittent upper abdominal discomfort in the last year, which was worse without food but was typically relieved with eating. His past medical history was notable for biliary lithiasis and cholecystitis. On examination, the weight was 82 kg, the blood pressure 160/80 mmHg, and the pulse 85 beats/min. There was mild epigastric tenderness without a palpable mass. The ultrasound (US) confirmed biliary lithiasis. Preoperative laboratory findings included mild anemia [hemoglobin (Hb) 10.2 g/dL]. On August 2, 2001, the patient underwent total gastrectomy, D2 lymphadenectomy with the removal of 27 lymph nodes, splenectomy and concomitant cholecystectomy. The surgical specimens were sent to the Laboratory of Pathology for pathological diagnosis.

Macroscopic examination reported the presence of an ulcerative vegetating lesion of 4.5×4 cm in its longest diameters, which was located in posterior gastric wall, infiltrating it.

Histopathological (HP) exam of the ulcerated lesion revealed cohesive tumor cells forming irregular glandular or papillary structures (Figures 1 and 2), with isolated mucinous areas (<10%). The tumor process infiltrated the gastric wall up to the subserosal area (Figures 3 and 4), but no intravascular or perineural invasion was observed. The limits of resection were found to be normal tissue. The 27 removed lymph nodes did not present any metastatic dissemination. The available epiploic specimen was without tumor infiltration. Gastric mucosa from tumor vicinity presented morphological features of chronic gastritis in the active phase, with incomplete intestinal metaplasia (Figure 5). Giemsa staining showed multiple extracellular bacilli floating free in the superficial mucus and adherent to the gastric epithelium surface, suggestive of Helicobacter pylori (Figure 6). The final pathological diagnosis was primary gastric intestinal type well-differentiated adenocarcinoma pT3N0, stage IIA [according to American Joint Committee on Cancer (AJCC) tumor/node/metastasis (TNM) classification and staging system for GC] [32], associated with intestinal metaplasia and chronic gastritis due to H. pylori.

His postoperative course was remarkable for a subdiaphragmatic abscess, treated with antibiotics. He was discharged to home on June 12, 2001, in his postoperative day number 21, in a relative good condition.

The patient received adjuvant chemotherapy with Fluorouracil to a total of six cycles from August 2001 to January 2002. During chemotherapy, a computed tomography (CT) showed no evidence of local or metastatic disease. He then followed a two months treatment with Immunoglobulin injection: 6 g × 2 times/week, for one month, and then 3 g × 2 times/week, for the second month. The patient came to the surgeon for periodic controls for five years. All clinical and the CT investigations made in this period did not showed any relapse of the disease.

In December 4, 2012, the patient was admitted again in the 3rd Surgery Clinic because of the presence of a tumoral formation in the right iliac fossa. He related that this tumor progressed during a period of one year and he could palpated it by himself. He also noticed postprandial pain and diarrhea. On physical examination, a palpable mass in the lower right abdomen was found. Laboratory exam revealed some pathological changes of blood tests: red blood cells (RBC) 3 800 000/mm³, white blood cells (WBC) 11 000/mm³, hemoglobin (Hb) 11.9 g/dL, hematocrit
Long-term survival in a patient with advanced gastric cancer and metachronous right-sided colon cancer

(Hct) 36%, erythrocyte sedimentation rate (ESR) 40 mm/h, serum iron 23 μg/dL (normal values – N: 59–158 μg/dL), folic acid 8.77 ng/mL (N: 3–17 ng/mL), vitamin B12 175 pg/mL (N: 174–878 pg/mL), serum glucose 78 mg/dL (N: 83–110 mg/dL).

The abdominal US revealed an image “in cockade”, with a thickness of 35 mm, located in the right iliac fossa. Preoperative CT scan of the abdomen and pelvis demonstrated a large low-density tumoral mass that narrowed the cecum and ascending colon lumens, without evidence of tumor infiltration of adjacent structures. No metastatic nodules were found. His serum carbohydrate antigen (CA19-9) was only moderate increased – 39 U/mL (N: <27 U/mL).

The patient underwent a radical excision of the tumor and excision of 26 loco-regional lymph nodes and peritoneal peritumoral tissue. The macroscopic examination revealed a right hemicolectomy made up of 20 cm colon, 11 cm ileum, and a 7 cm appendix. The cecum presented a 6.5×6×5.5 cm, circumferential, ulcer-vegetating, brown-gray tumor. A hardened colon serosa surrounded the tumor.

HP examination showed well-formed tumoral glands or simple tubules with variability in their size and configuration (Figures 7 and 8) that invaded the colon wall thickness up to the level of subserosal adipose tissue (Figures 9 and 10). Immunohistochemistry showed cytoplasmatic positivity for cytokeratin (CK) 20 (Figure 11), but cytoplasmatic negativity for CK7 (Figure 12). The tumor cells exhibited a strong nuclear positivity for CDX2 (Figures 13 and 14), suggesting a primary colorectal origin of the tumor. All the 26 removed lymph nodes did not show any metastasis. The available peritoneal peritumor tissue exhibited isolated perivascular lymphoid infiltrates, but no tumoral dissemination. The final pathological diagnosis was metachronous primary well-differentiated colon adenocarcinoma, pT3N0, stage IIA-G1.

The patient was discharged home one week later, in a very good condition. During the period of his follow-up, he showed no symptoms. CT scan of the chest and abdomen made after one year revealed no evidence of metastatic disease. Repeated determination of CA19-9 serum levels decreased to normal over the time. The patient is still alive 16 years after the diagnosis of gastric carcinoma and five years after the diagnosis of right-sided colon carcinoma with no signs of progression despite the fact that no active treatment was given for the last tumor.
Anca Sava et al.

Figure 5 – Adjacent mucosa to gastric adenocarcinoma demonstrated epithelial metaplasia characterized by an incomplete intestinal phenotype with columnar absorptive cells, and goblet cells of intestinal morphology, along with chronic gastritis associated with an inflammatory cellular infiltrate consisting of lymphocyte and plasma cells (HE staining, ×40).

Figure 6 – Stomach mucosa in the vicinity of gastric adenocarcinoma showed isolated colonies of H. pylori floating free in the superficial mucus and adherent to the gastric epithelium surface (Giemsa staining, ×200).

Figure 7 – Metachronous primary well-differentiated adenocarcinoma of right-sided colon: glandular structures with variability in their size and configuration and lined by one or more rows of cancer cells (right). The colon mucosa from tumor vicinity exhibited chronic inflammation (left) (HE staining, ×40).

Figure 8 – Metachronous primary well-differentiated adenocarcinoma of right-sided colon: with a higher magnification, a complicated glandular structures lined by epithelium with nuclear pleomorphism and moderate cellular pleomorphism could be seen (HE staining, ×100).

Figure 9 – Metachronous primary well-differentiated adenocarcinoma of right-sided colon: tumoral invasion into muscularis propria (HE staining, ×100).

Figure 10 – Metachronous primary well-differentiated adenocarcinoma of right-sided colon: tumoral invasion into subserous adipose tissue (HE staining, ×40).
Discussion

Cancer bearing patients who lived long enough are susceptible to an increased risk of developing cancer in other organs [33]. Multiple primary cancers are defined by the International Association of Cancer Registries as the occurrence of two or more primary cancers, where each cancer originates in a separate primary site and there is no extension, and no recurrence or metastasis [34]. Multiple primary cancers are more likely to develop in organs of the same system than in those of different system [35].

In the last two decades, prognosis of patients with advanced GC seemed to be excellent as extraordinary treatment advances have been made, but, in the same time, these patients could develop a second primary cancer. Most CRC, identified after GC surgery, were detected within five years [33, 36]. However, in some studies, about half of the cases of metachronous CRC were identified more than five years after GC surgery [37]. In the case presented in this paper, the right-sided colon adenocarcinoma was diagnosed after a period of 11 years from the first surgical intervention for gastric adenocarcinoma.

The mean age of the patients diagnosed with synchronous and metachronous neoplasms after GC was determined to be about 63.4±11.4 years in the moment of the stomach cancer [38], and this age was similar with our patient’s age who was 64 years-old. The specimen taken at the time of his first surgery was diagnosed with chronic gastritis due to *H. pylori* infection, along with intestinal metaplasia areas and intestinal type well-differentiated adenocarcinoma. All these morphological aspects proved the Correa cascade of multistep gastric carcinogenesis: inflammation–metaplasia–dysplasia–carcinoma sequence [39].

However, the etiology of GC must be sought in multifactorial interaction [40]. This type of cancer is caused by environmental factors and genetic factors. Environmental factors include alcohol consumption, smoking, and dietary factors, such as very high salt diet, low vegetable diet, nitroso-compound content in food, and infectious
factors, such as *H. pylori* and Epstein–Barr virus infections [41]. Many studies have shown that *H. pylori* infection increases the risk of GC significantly, both of the intestinal and diffuse subtypes, and that these bacteria are responsible for approximately 90% of the world’s burden of non-cardia GC [42]. Some Romanian clinical and endoscopic study [43, 44] highlighted the importance of this bacterium in the pathogenesis of chronic gastritis, intestinal metaplasia and GC [44]. Therefore, we can presume the same pathogenesis in the case presented in this paper as *H. pylori* was identified on his histological sections.

Tubular adenocarcinoma is the most common histological type of stomach cancer [45], representing about 85–90% of gastric tumors and carrying a better prognosis [46]. Probably this was one of the factors that had a beneficial effect on our patient’s prognosis.

Our case has really proven that radical total gastrectomy, lymphadenectomy and splenectomy were curative as many studies have reported.

A salutary effect in the good prognosis of the GC probably has had the radical resection of the tumor. Lu *et al.* investigated the clinical and pathological data and postoperative five-year survival rate of 507 patients with GC who underwent radical surgery (R0 resection). The survival rates of patients with pT1, pT2, pT3, and pT4 stage tumors were 89.3%, 72.4%, 36.9% and 23.7%, respectively (p<0.05), and the survival rates of patients with pN0, pN1, pN2, and pN3 stage tumors were 75.2%, 68.8%, 46.7% and 21.3% (p<0.05). Depth of invasion, lymph node metastasis stage, metastatic lymph node ratio (MLR), lymphatic invasion and tumor size were independent predictors of patient prognosis [47].

However, the role of extended lymphadenectomy in the treatment of GC remains controversial. Surgical lymph node levels are usually classified by the Japanese Gastric Cancer Association system and are used to determine the extent of lymphadenectomy needed. Briefly, removal of stations 1 to 6 (perigastric lymph nodes) is considered a D1 dissection, whereas D1 dissection plus removal of stations 8–12 (celiac, common hepatic, and splenic lymph nodes) is considered a D2 dissection [48]. The question of extent of lymphadenectomy in GC has been examined in many studies. Extended lymphadenectomy (≥D2) is helpful for patients with T3N0 disease. Some authors reported radical lymphadenectomy and combined visceral resections could increase the overall five-year survival rate from 34.8% to 59.4% [49].

While accepted as standard in Japan, the role of D2 resection remains controversial in Europe and the United States. However, the Romanian surgeons who realized the total gastrectomy intended also a D2 lymphadenectomy, which proved to be beneficial. The role of splenectomy is also controversial. Some studies made by Asian authors stated that spleen should be preserved for patients with GC at stages I and II, and radical excision combining splenectomy could only be performed at stages III and IV patients with cancer infiltrating body and tail of the pancreas, or lymph nodes metastasis in the splenic hilus [50], or spleen should be preserved in stages I, II, and III patients with curative operation, but for stage IV patients the spleen should be resected [51].

For one century by now, it is known that the limitation of the tumor to the stomach wall in the absence of serosal or local lymph node extension are favorable operative findings [46]. More recently, Liu *et al.* stated that not only the type of resection, but also the status of lymph nodes, metastatic lymph node ratio, and tumor size were independent prognostic factors for patients with T3 GC [52]. Indeed, we can presume that the long survival of our patient was in direct correlation with its limited invasion into the stomach wall, and the absence of lymph node metastasis, along with a radical resection and D2 lymphadenectomy.

Another very well documented article was published by Kooby *et al.* [53] about biological predictors of survival in node-negative GC. These researchers highlighted the fact that in the absence of node invasion there was a greater survival advantage for T3N0 patients (five-year survival was 60%). Also, in these patients should be searched for vascular invasion and neural invasion as these two factors have had independent negative significance for their prognosis.

Raica *et al.* [54] stated that lymphatic microvessel density (LMVD) predicts tumor stage and lymph node metastasis, and podoplanin-positive tumor cells select a subgroup of tumors with high potential of invasion and metastasis. Bilici *et al.* [55] reported that along with pT stage, tumor size, lymph node metastasis, clinical stage, tumor differentiation, Borrmann classification, histological type, lymphatic vessel invasion, and blood vessel invasion, the presence of perineural invasion (PNI) was an independent prognostic factor as the median survival of the PNI-positive patients was significantly worse than that of the PNI-negative patients (28.1 vs. 64.9 months). Jiang *et al.* also reported that PNI may be useful in detecting patients who had poor prognosis after curative resection in GC and it should be incorporated into TNM staging [56].

But we can also hypothesized a beneficial role of preoperative parenteral administration of Omeprazol [57] as the drug probably stopped the tumoral invasion into the serosa or adjacent structures and contributed to the long survival of our patient. Another profitable role could be attributed to postoperative Immunoglobulin (Ig) injection that temporarily boosted the patient’s immunity against disease. Several studies tested the antimitastatic effects of intravenous Ig and found out that this treatment could operate in many different and complex ways, as following: (a) induction of interleukin (IL)-12 secretion, leading to natural killer (NK) cells activation; (b) inhibition of matrix metalloproteinase-9 mRNA expression; (c) suppression of tumor cell growth; (d) hindrance of nuclear factor kappaB (NF-kB) activation and IkappaB degradation; and (e) G1 cell-cycle arrest [58, 59].

Researchers found out that the prognosis of GC patients followed by a second primary cancer was more negatively influenced by the second primary malignancy than by the primary gastric neoplasm [8]. The overall five-year survival rate in synchronous and metachronous cancers in patients with GC is reported to be 69.4% [15]. However, the 10-year survival rate was only 49.7% for the patients with additional malignancies [16]. However, our patient is still alive, in good condition, without any features of metastasis, at 16 years after the primary gastric carcinoma.
and five years after the surgical intervention for colonic carcinoma.

The second primary cancer (be it hepatic cell carcinoma, lung cancer or colorectal cancer) was frequently detected between two and 24 years after gastrectomy [16, 38]. Our patient was admitted in the Surgical Unit for the surgical cure of the second primary tumor after 11 years from the moment of his first intervention, and as such, we classified the colon cancer as a metachronous tumor.

Metachronous dual primary gastric and colorectal cancer tend to occur in patients with early-stage cancer [16, 60], but also with relatively advanced GC [61]. Our patient presented a metachronous right-sided colon adenocarcinoma after a GC pT3N0, stage IIA. Metachronous association between GC and CRC was published by only fewer articles. Euanoraset & Suwanthanan [62] reported two cases of metachronous second primary CRC in patients with GC, but only in one both primary and secondary primary tumors were adenocarcinomas, while the other case was that of a 49-year-old man with a stomach cancer proved to be a signet ring cell carcinoma and a moderately differentiated adenocarcinoma of the upper rectum operated after two years from the first operation. Iioka et al. also reported a case with metachronous triple cancers of the sigmoid colon, stomach and esophagus [63].

Hereditary predisposition may play a role in the coexistence of multiple cancers, which form some rare familial cancer syndromes such as hereditary non-polyposis colorectal cancer (HNPCC) or Li–Fraumeni syndrome. Second primary tumors arise because of either inherited or acquired mutations or deficiencies. Second primary tumors may develop soon or very late after treatment of the first primary tumor and may reflect underlying genetic or immunological defects in the patient, treatment-related damage or environmental exposure to carcinogens. With the increasing success of modern chemotherapy and radiotherapy in achieving long-term remissions in many patients, second primary tumors are a rapidly increasing disease category [64]. Microsatellite instability (MSI) in GC can serve as a molecular marker for the risk-assessment of the development of multiple cancers. The complicated primary tumors in MSI-positive cases arose in colorectum, urogenital tract and ovary, which mimicked the tumor spectrum of hereditary non-polyposis CRC. These observations suggest that MSI test on GC may be considered as a good marker for the assessment of multiple cancer development [65].

Some authors presumed that the high susceptibility of the lower gastrointestinal tract for developing a second neoplasm may be due to: (a) changes in the bacterial intestinal flora in response to modified gastric secretions, (b) overload of this section of intestine, which can occur after gastrectomy, and (c) carcinogenetic processes similar to those active in colon cancer [66].

As both of the tumors expressed by our patient were well-differentiated adenocarcinoma, we should ruled out the idea that the second malignancy could be a intestinal metastasis. However, gut metastases from gastric adenocarcinoma have been rarely reported [67, 68]. Also, this unusual type of metastasis has been associated to Lauren’s diffuse type histology, and peritoneal dissemination [69].

Our case developed a well-differentiated gastric adenocarcinoma, without any node metastasis, or any peritoneal dissemination at the time of the first surgical intervention. Also, secondary primary right-sided colon cancer appeared after 11 years of free period of disease. Moreover, the differentiation of secondary from primary adenocarcinomas of the colorectum could be done by CK7/CK20 staining pattern and CDX2 expression, which are highly specific and sensitive markers of colorectal origin [70]. As our case showed CK7-negativity, and CK20 and CDX2 positivity, we considered the right-sided colon adenocarcinoma to be a primary cancer.

Dual primary gastric and metachronous colon carcinomas (DPGMCCs) had a better prognosis than synchronous DPGMCCs due to the tendency for metachronous DPGMCCs to occur in patients with early-stage cancer [60] and this could be also one of the multiple causes for the long survival of our patient.

As the number of patients with GC increases every year and the survival rate of this disease prolonged, knowledge that a second primary cancer could developed in the cecum and ascending colon is important for the development of effective postoperative follow-up programs of GC patients in order to achieve a possible cure of both of the diseases.

Conclusions

We have reported in this paper a rare combination of metachronous double primary malignancies of stomach and cecum and ascending colon. The present study showed that surgeons should be aware of the occurrence of metachronous CRC in patients with GC in order to detect these lesions as early as possible to prolong their patients’ survival with a good status and a high quality of life. Therefore, a careful periodical postoperative examinations for other primary cancers, especially CRC, should be carried out in these patients. We highlight the fact that with proper clinical, radiological and biological investigations, and with surgical and medical treatment an individual who has suffered for two malignancies could be considered cured as our patient has survived 16 years in good health and full activity and this is the most important thing for every patient with cancer.

Conflict of interests

The authors declare that they have no conflict of interests.

References


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