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Case Study

Multiple malignant tumors – a clinical case

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Abstract. Objective**:** We present a clinical case of an old woman who suffered at different ages surgical excisions for three different primary malignant tumors. The patient is now 86 years old. She was diagnosed at the age of 35 with a malignant tumor of the corpus uteri, and then when she was 78 with a basocellular carcinoma of the nose skin and at 81 she was diagnosed with an ascendant large bowel adenocarcinoma. Despite the occurrence of three different tumors she is alive five years later and cancer-free, but suffering because of other medical diseases including diabetes, hypertension, myocardial ischemia and migraines. Conclusion: a patient diagnosed with a cancer and who survive from it must be submitted to periodically medical controls because of the possibility to develop several other cancers. With an increasing survival in patients after malignant tumors therapy, there is an increased risk to develop other cancers as the patients are getting older.

Key Words: multiple primary malignant tumors, age.

Rezumat. Obiectiv: Prezentăm cazul clinic al unei paciente vârstnice, care a suferit rezecţii chirurgicale la vârste diferite pentru trei tumori maligne primitive. Pacienta are acum 86 ani şi a fost diagnosticată la vârsta de 35 ani cu o tumoră malignă a corpului uterin, apoi la 78 ani cu un carcinom bazocelular al piramidei nazale şi la 81 ani cu un adenocarcinom de colon ascendent. Rezultate: În ciuda apariţiei a trei tumori diferite, pacienta este în viaţă cinci ani mai târziu, fără semne de recidivă tumorală, dar suferind datorită altor afecţiuni medicale inclusiv diabet, hipertensiune arterială, ischemie miocardică şi migrene. Concluzii: un pacient diagnosticat cu un cancer şi care supravieţuieşte acestuia trebuie urmărit periodic datorită posibilităţii de dezvoltare a altor tumori maligne. Crescând supravieţuirea după tratamentul tumorilor maligne, creşte riscul de dezvoltare a altor cancere pe măsură ce pacienţii îmbătrânesc.

Cuvinte cheie: tumori multiple maligne primitive, vârstă.

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Introduction

In high-income countries cardiovascular disease is the leading cause of death. In United States the second cause of death is cancer. Nowadays survivors of all cancers are living for longer periods, due to a more frequent use of chemotherapy and radiotherapy, so there is an increased chance to develop subsequent malignant tumors after a first treated one. Ulterior primary cancers became an increasingly important concern in oncology during the last two decades, as they comprise the sixth most common group of malignancies after skin, prostate, breast, lung, and colorectal cancers (Rheingold *et al* 2003; Fratila *et al* 2010; Jalba *et al* 2010).

Case presentation

We analyzed the clinical case of M.V., an 86 years old woman, diagnosed at the age of 35 (1960) with an adenocarcinoma of the uterine body. She was submitted to surgery, a total hysterectomy with bilateral adnexectomy, not followed by irradiation or chemotherapy. The patient had no family history of malignant tumors. Later, at the age of 78 she was diagnosed with a skin tumor with macroscopical appearance of a basal cell carcinoma localized on the nose. The tumor has been excised and the histopathology revealed the type supposed preoperatively. After surgery there was a local recurrence 2 years later and after a new excision she underwent local radiotherapy and there was no recurrence. At the age of 81, in 2006, she had several biliary colic pains, being diagnosed ultrasonographical with gall bladder lithiasis. At the time of the surgery she had also a severe anemia (Hb=4.7 g dL-1), hipoproteinaemia (5.1 g L-1), diabetes mellitus controlled by oral medication with diabetic retinopathy and nephropathy, arterial hypertension, aortic valve stenosis, mitral insufficiency, heart failure NYHA class III, angor pectoris, median subumbilical hernia subsequent to laparotomy for uterine tumor. Because of many other symptoms that she had, including anorexia, digestive intolerance, weight loss and pallor, combined with anemia, we used a barium enema, because she refused colonoscopy. The large intestine was opacified only through the middle transverse colon, showing sigmoidal diverticulosis. She was operated by classical retrograde cholecystectomy by median laparotomy. At the inspection of the peritoneal cavity we discovered a tumoral mass on the ascendant colon, near the right hepatic angle, along with an adherential syndrome after hysterectomy. There were no distant

macroscopic metastases found. Because of an uninformed patient, we did not remove the large bowel tumor at that time. After 2 months we performed a right hemicolectomy with termino-terminal ileo-transverse anastomosis and drainage of the peritoneal cavity after 2 months. The histopathological examination revealed a G2 mucinous adenocarcinoma (B2 Astler-Coller) of the ascendant colon (the tumor had 6.5 cm in length infiltrating all layers of the bowel and the adipous tissue around it), with no tumoral adenopathy. Six months later the patient underwent another laparotomy for mechanical ileus due to adhesions. A segmentary enterectomy (ileum) with end-to-end entero-enterostomy was necessary. The evolution after surgery was uneventful. Now, after 5 years she is free of neoplastic disease, under medical treatment for the medical associated diseases, almost blind and deaf. The postoperative controls, including CT scans, revealed no other neoplasia.

Discussion

In recent years many advances were made in diagnosis methods and cancer therapy so patients can have a greater life expectancy. However, with an increased longevity the risk of developing other cancers at multiple sites also increases.

Of twenty patients who attend hospital because of a malignant tumor, one will later develop another primary malignant tumor (La Ferla *et al* 1984). That is why the follow-up is very important and we need to investigate all the new symptoms because they may demonstrate further tumors. Is is also important to avoid attributing symptoms that can appear, to metastases from the previous malignant tumor and not to a new primary cancer that can benefit from surgery. One of the organs that are often affected in patients with multiple primary cancers is the large bowel.

Approximately 5-10% of all cancers are hereditary, which means that changes (or mutations) in specific genes are passed from one blood relative to another. Individuals who inherit one of these gene changes will have a higher likelihood of developing cancer within their lifetime. Currently, we have an understanding about mutations in several genes that increase the risk for developing several types of cancer; however, we have not yet identified genetic causes for all types of cancer.

In 1932, Warren and Gates defined the three criteria for the diagnosis of the 'syndrome' of multiple tumors either simultaneously or sequentially: the tumor has to be malignant, distinct and not the result of metastases. By 1961 there were more than 10000 cases reported with multiple primary malignant tumors and this probably reflected the general improved survival rate after treatment of cancer in that the increased period of survival has permitted more patients to live enough for a second primary lesion to develop (Moertel *et al* 1961). In 1966, the same authors showed that the risk of developing new malignancies increases with each successive cancer and, in 1969, Schottenfield, Berg and Vitsky sustained that the patients with colo-rectal cancer have a threefold increase in the incidence of metachronous primary cancers of other organs (Schottenfeld *et al* 1969).

Patients with multiple tumors are uncommon, the reported incidence in cancer patients being 3% clinically detected and 7-8% in post mortem studies (Polk *et al* 1965). patients with more than five distinct tumors are rare. Many tumors had a gastrointestinal origin.

Billroth described for the first time multiple malignancies in a single patient in 1879. In different reports, the incidence of primary malignant tumors in different tissues varies between 2.8-6.7% (Varty *et al* 1994). In the series reported by this author it was found an incidence of 5.8% of previous extracolonic cancers in patients with primary colonic cancer, and it was considered that the explanation could be given by increased awareness, better recording of data or improved survival after successful treatment of previous cancer. It was said that the patients with multiple primary malignant tumors have the first primary cancer at an early age (Cleary *et al* 1975; Shah *et al* 1984; Swaroop *et al* 1987), existing an interval of several years before the second tumor appears, this being also the case of our patient. In many reports was found a preponderance of breast, female genital, gastric, urological, skin and lung primary malignant tumors (Cleary *et al* 1975; Shah *et al* 1984; Swaroop *et al* 1987; Varty *et al* 1994). The survival in patients with multiple primary cancers may be better in Lynch syndromes compared with patients with a single colonic cancer. Survival of patients with primary rectocolonic and extracolonic tumors was similar with the survival of patients with multiple rectocolic cancers (Lee *et al* 1982), this being supported also by other earlier reports.

Multiple primary cancers are defined as two or more abnormal growths of tissue occurring simultaneously or abnormal growths of tissues that follow a previous malignant neoplasm but are not metastases of the latter in the same individual. Survival from cancer is spectacular improved as a result of recent advances in the treatment of cancer and its detection at an early stage. In the U.S., 5-year relative survival rates for all cancers combined increased steadily, from 50% in 1975-1979 to 66% in 1996-2002 among adults, and from 61% to 79% among children (Ries *et al* 2006). Many studies showed an incidence of multiple primary cancers of 2-6 %. A study performed in almost 12 years revealed a 1.95% of all malignancies of patients with multiple primary cancers (207 patients), with a male to female ratio of 1.84, with a median age first cancer diagnosis of 67 years old in males and 57 in females; with an incidence of synchronous cancers higher than metachronous (108 vs. 99) and the median time to additional cancers in metachronous group was 35 months. The most frequent cancers were gastrointestinal cancers in both sex synchronously and metachronously. In males, colorectal cancer followed by methachronous gastric cancer (9.1%) and synchronous genitourinary cancer with another genitourinary cancer (12.7%) were frequently observed. In females, breast cancer followed by metachronous colorectal cancer (6.8%) and gastric cancer with colorectal cancer (6.9%) were frequently observed. The median survival duration was 14.4 months totally from the index diagnosis of the second cancer. Synchronous cancers showed lower survival duration than metachronous cancers (Lee *et al* 2007).

The risk of subsequent primary cancers evaluated in more than 115,000 women diagnosed with cancer of the uterine corpus or ovary between 1973 and 2000 was significantly increased outside

the female genital tract among survivors of ovarian (31%) but not of uterine corpus (Freedman *et al* 2006). It was found that an excess of new malignancies of the colon, rectum, urinary bladder, and breast associated with both gynecologic cancer sites, being implied hormonal and dietary factors, as well as genetic predisposition, contributing to the elevated risks of cancers of the breast and colon. The uterine corpus and ovarian cancers are associated with hereditary nonpolyposis colorectal cancer, which could be an explanation of the excess of colorectal cancer among younger gynecologic patients and also account for some of the excess cancers of the small intestine, renal pelvis, and biliary tract among ovarian cancer patients. Radiotherapy is considered to be a factor that contributed to the excess of certain solid tumors following uterine corpus and ovarian cancers, particularly sarcomas, and cancers of the urinary bladder and colon, as well as rectal cancer following uterine corpus cancer. Uterine corpus cancer is the fourth most common cancer among U.S. women, accounting for about 6% of incident cancers and 2.7% of cancer deaths with a relative survival rate of 87.0% at 5 years (83.0% at 10 years) among white females but only 64.7% at 5 years among black females, reflecting racial disparities in the stage of disease at the time of diagnosis. Most women (91%) are surgically treated (Rose 1996) with removal of the uterus, cervix, ovaries, and fallopian tubes, that is why few remain at risk to develop subsequent cancers of the female genital tract. Adjuvant radiotherapy to the pelvis is given to 35% of patients, while primary radiotherapy is administered to a much smaller percentage of cases, usually those considered at high risk of surgical complications (Jemal *et al* 2005). There are some established risk factors for uterine corpus cancer: sustained estrogen stimulation of the endometrium, estrogen replacement therapy, nulliparity, late menopause, and obesity (Freedman *et al* 1997; Brinton & Hoover 2000). It was stated that hormone replacement therapy increases the risk of breast cancer and of uterine corpus cancer, but it appears to lower the risk of colon cancer. Some studies have reported a positive relation to socioeconomic status, diabetes, and hypertension, and an inverse relation to cigarette smoking (Freedman *et al* 1997; Brinton & Hoover 2000). The risk for developing uterine corpus cancer, colon cancer and postmenopausal breast cancer seems to be increased by obesity and physical inactivity; Brinton & Hoover 2000). The increased risk for subsequent primary colon cancer may also reflect shared risk factors with ovarian cancer, including nutritional, hormonal, and genetic influences (Weinberg *et al* 1999). The study revealed an elevated risk for subsequent cancers of the colon, urinary bladder, breast and leukemia.

A study performed on 25,000 women with cancer of the genital organs diagnosed between 1935 and 1982 in Connecticut showed a significant additional of subsequent cancers following the cervix (35%), uterine corpus (16%) and ovary (58%). Among women with either cancer of the cervix or uterine corpus, the risk of developing a second cancer rose with increasing duration of follow-up, after 20 years reaching an overflow of 61 and 34%, respectively (Freedman *et al* 1985). When observed and expected second cancers of the female genital tract were excluded, these overabundances became 40%, 30%, and 59% after cervix, uterine corpus, and ovary, respectively. In contrast, among patients with ovarian cancer, the second cancer risk decreased over time to 41% after 10 years. Cancers related to smoking, i.e., oral cavity and pharynx, esophagus, and respiratory system, were notably increased among cervical cancer patients. An increased incidence of second cancer of the abdominal organs (colon, rectum, kidney, bladder, ovaries) was generally observed for each gynecologic site, but only rectal cancer was linked with radiation treatment for the first primary cancer. Leukemia occurred supernumerary after cancers of the uterine corpus and ovary, but not after cervical cancer. Cancers of the breast and colon were increased following uterine corpus and ovarian cancer and vice versa, which supports the notion that these sites share a common etiology, perhaps related to dietary or hormonal factors.

A Portuguese study of 10,746 women with gynecological cancer found that 0.8% of them (91) had a second primitive malignant neoplasia, 64% (58 cases) located at a gynecological site and in 31% (28 cases) a non-gynecological cancer, the most common location being the colon and rectum. The most frequent associations were endometrium/breast (13 cases), bilateral breast (12 cases) and ovary/endometrium (11 cases) (Nunes *et al* 1997).

About 70 patients (5.8%) of 1198 patients presented for a colo-rectal cancer between 1971 and 1990 had a previous extracolonic primary malignancies with a preponderance of breast, female genital, gastric, urological, lung and skin cancers. The median time to develop a colorectal primary tumor was 7 years. The patients with colorectal cancer and a history of previous extracolonic tumors have similar clinicopathological features as the general colorectal cancer population, but have a better survival (Varty *et al* 1994).

Basal cell carcinomas and squamous cell carcinomas have the tendency to occur in the same individuals (Berwick 1999), these persons being affected by the sun exposure which is a shared risk factor. This is the reason for which the persons who have non-melanotic skin malignant tumors should avoid sun exposure and undergo regular surveillance for appearing of new skin tumors.

The risk for a secondary cancer following a colorectal one is elevated for other colorectal cancers, breast, uterus and ovarian cancer (Weinberg *et al* 1999). Survivors of endometrial cancers have an elevated risk to develop subsequent ovarian, colorectal and breast cancers (Travis *et al* 1996; Weinberg *et al* 1999).

It was said that patients with a colorectal cancer associated with a previous extracolonic cancer survive as well as or perhaps better than patients with a single colorectal cancer (Varty *et al* 1994), this being important because as a result of improvements in cancer therapies and greater longevity more patients will develop multiple cancers. In our case we had a genital cancer followed after many years by a skin malignant tumor and, very soon after the second tumor occurred, a large bowel cancer. The patient, despite many other diseases, is still alive and well, with no sign of recurrence.

Some of the multiple cancers may be multicentric or multifocal tumors arising in the same site or organ. In the SEER series multicentric tumors that occurred in the same site or organ as

the first primary cancer accounted for 13.2% of the 185,407 subsequent cancers, with new tumors in the female breast (7.2%), colon (2.0%), lung (1.8%), and melanoma of the skin (0.9%). While multicentric tumors are likely to reflect shared exposures and/or genetic predisposition, it is possible that heightened medical surveillance and mistaken diagnoses of cancer recurrence may play a role in some cases.

PET/CT with 18F-FDG has proven to be effective in detecting and assessing various types of cancers. A yearly PET/CT may be helpful in surveillance of patients with cancer, because multiple synchronous or metachronous cancers (at least 10.6%) are present in a significant number of patients undergoing PET/CT scanning (Krumrey *et al* 2007).

The studies reported a modest (twofold) increase in risk for colorectal cancer in first-degree relatives of patients with common colorectal cancer (Woolf 1958; Macklin 1960; Lovett 1976; Bonelli *et al* 1988; Fisher & Armstrong 1989; Kune *et al* 1989; Sondergaard *et al* 1991; St. John *et al* 1993). The odds ratio reported for colorectal cancer was 1.8 for patients having one affected relative and 5.7 for patients having two affected relatives, results that support the view that the risk is higher in the latter situation (Rozen *et al* 1987).

Conclusions

It is important the follow-up of the patients with a primary tumor, being alert to every new symptom that appears because it may be the sign of a new malignancy not necessarily of a metastases of the previous tumor.

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