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Multiple primary malignancies. A rare case of five metachronous tumours

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SUMMARY: Multiple primary malignancies. A rare case of five metachronous tumours.

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The Authors report on a patient admitted several times for the occurrence of five multiple metachronous primary malignancies (laryngeal carcinoma, endometrial adenocarcinoma, rectal cancerous polyp, Vater papilla carcinoma and transverse colon cancer). All five carcinomas were independent primary cancers and the lengthy time intervals between the onsets of each individual tumours confirm their independent non-metastatic origin.

Classification, pathogenesis, genetic and environmental interactions of these tumours are discussed; in the case reported a family history of colon cancer was present, while no genetic markers abnormalities or chronic exposure to carcinogens were found.

The case report suggests that an aggressive, appropriate surgical approach together with a through follow-up monitoring offers a chance of long-term survival for patients with metachronous malignant primary tumours.

RIASSUNTO: Le neoplasie maligne primitive multiple. A proposito di un raro caso con cinque tumori metacroni.

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Gli Autori descrivono il caso di una malata trattata chirurgicamente per l'insorgenza successiva di cinque tumori maligni primitivi metacroni (carcinoma epidermoidale del laringe, adenocarcinoma dell'endometrio, polipo cancerizzato del retto, adenocarcinoma della papilla di Vater ed adenocarcinoma del colon trasverso). Il lungo intervallo di tempo tra l'insorgenza dei singoli tumori testimonia la loro origine indipendente e non metastatica.

Vengono discussi gli aspetti classificativi e patogenetici di questi tumori con particolare riferimento al ruolo che possono esplicare, nella loro insorgenza ed evoluzione, le alterazioni genetiche ed i fattori ambientali, anche se nel caso in esame è presente soltanto una familiarità neoplastica per il carcinoma del colon, mentre non sono state evidenziate alterazioni genetiche né esposizione cronica a cancerogeni ambientali.

L'illustrazione del caso dimostra come l'adeguato trattamento chirurgico e l'accurato follow-up offrono buone possibilità di sopravvivenza dei malati con carcinomi primitivi metacroni.

KEY WORDS: Multiple primary malignancies - Metachronous tumours.
Neoplasie maligne primitive multiple - Tumori metacroni.

Introduction

Multiple metachronous primary malignancies (MMPMs) are to be intended as independent primitive malignant tumours arising in different organs at different times. For a long time, MMPMs were considered a scientific curiosity, but a lot of recent studies have suggested that their occurrence is not a rare event and their incidence ranges from 2% to 10% of all malignancies (1).

The purpose of this paper is to report on a patient with five MMPMs: she underwent laryngectomy, hysterectomy, excision of cancerous

rectal polyp, duodenopancreatectomy and transverse colon resection. The case report is very interesting for the number of metachronous cancers and according to our knowledge a patient with a comparable number of MMPMs has never been described before.

Case report

G.C., a 45 years-old woman complaining of menorrhage, was admitted to our Unit for the first time in October 1987. Four years before she underwent partial laryngectomy for a squamous cell carcinoma of the left cord. Moreover, she had had a right hysterectomy six months before because of an ovarian cyst. Family history was positive for malignancies because both her father and uncle on her father's side had died of colon carcinoma, while her only brother had been operated on for the same disease but he is still alive. Endometrial biopsy revealed an adenocarcinoma and the patient underwent total hysterectomy and left salpingo-oophorectomy.

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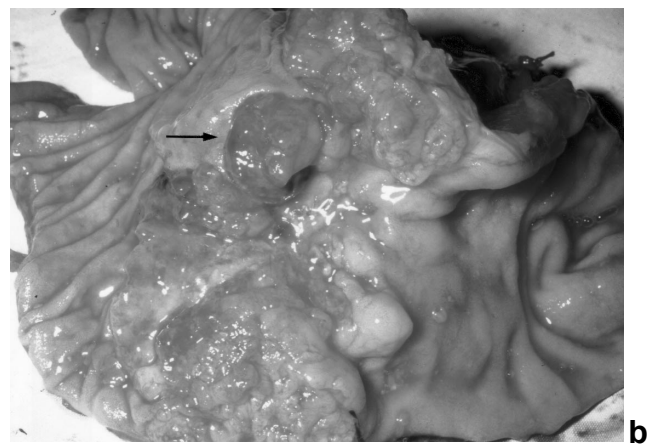
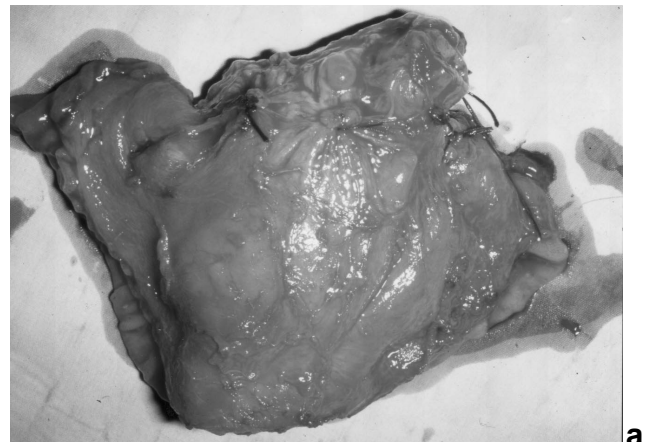


Fig. 1 - Abdomen CT-scan (a) shows a focal vascularized lesion suspicious for metastasis in the second segment of liver. Wedge of liver parenchyma (b) with a cavernous angioma.

Fig. 2 - Pancreaticoduodenectomy: closed (a) and opened (b) surgical specimen; ampullar neoplasm is well seen (arrow).

In October 1994, because of anaemia and hidden fecal blood, a pancolonoscopy detected a sessile, crumbly and easily bleeding polyp, 3.5 cm of a diameter, in the anterior rectal wall and another peduncled polyp, 1 cm of diameter, in the middle part of transverse colon. The patient underwent endoscopic excision of the peduncled polyp (adeno-villous with a moderate grade of dysplasia histologically), while the sessile rectal one was excised through a trans-anal approach. Histologic examination showed an adenomatous tubulo-villous polyp with several cancerous areas. The patient was treated with complementary endocavitary high dose radiotherapy (HDR) on the surgical site.

In February 1995 the patient was admitted again complaining of hematemesis and melena. She was seriously anaemic (Hb 4.8 g/dl). The proctosigmoidoscopy showed soft bloody faeces while the esophago-gastro-duodenoscopy was normal. A restaging with tumoral markers, rhinolaryngo-tracheal endoscopy, chest and brain CT scan, total-body skeletal radioisotopic scan was set and no evidence of recurrent disease was found; whereas an abdomen CT, scan detected a focal lesion located in the second segment of liver, suspicious of metastasis (Fig.1a). She underwent an atypical hepatic resection (Fig. 1b) with the histologic diagnosis of cavernous angioma.

In February 1996 a follow-up colonoscopy detected a little polyp 4-6 mm of diameter in the right part of the transverse; it was endoscopically excised but it was not recovered due its minimal size.

In September 1996 the patient was admitted again complain-

ing of right hypochondrium pain, obstructive jaundice, anaemia (Hb 5.2 g/dl) and weakness. All cholestasis parameters were elevated. An ultrasonography showed normal size and structure of the liver with evidence of surgical treatment outcome. Gallbladder was widely distended with regular walls and biliary sand inside. The main biliary duct was enlarged with an extrinsic compression in its retropancreatic tract, while the pancreas appeared normal. An ERCP showed that the mucosa of the second duodenum was edematous, it had irregularly risen and its lumen was obstructed; it was impossible to thread the papilla. The patient underwent a duodeno-pancreatectomy (Fig. 2) and the histologic diagnosis revealed a moderate-grade adenocarcinoma of the ampullar region infiltrating intestinal wall and pancreatic parenchyma.

The patient was admitted for the last time in February 1998, because a follow-up colonoscopy detected an obstructing adenocarcinoma in the transverse colon. An abdominal CT-scan (Fig. 3) did not detect either lymph node involvement or liver metastasis. The patient underwent segmentary resection of the transverse and the histologic diagnosis revealed a moderately differentiated adenocarcinoma with mucinous aspects (pT3 N0).

Over time, five MMPMs were diagnosed and surgically managed. The patient is thoughtfully followed-up and she is still alive in a good clinical health state fifty-six months after the treatment of the last malignancy.



Fig. 3 - Abdomen CT-scan shows a solid 5 cm of diameter neoplasm in the transverse colon, immediately after the hepatic flexura.

Discussion

Multiple primary malignancies, reported at first by Billroth in 1860, were considered medical curiosities until 1932, when Warren and Gates identified 1259 cases either reported in Literature or found in their own postmortem examinations. They were defined according to the following criteria: a) each tumour had to be malignant histologically; b) it had to be topographically distinct; c) it did not have to be a metastasis. These malignancies were defined synchronous if diagnosed at the same time or within six months of the index tumour, after this period they had to be considered metachronous (MMPMs) (1, 2).

MMPMs are now a well-known nosographic affection and numerous cases variously localized are reported in literature (urinary tract, breast, colon-rectum, respiratory and digestive tract, stomach, testicle, ovary) (2, 26). Their incidence is reported to be 3-4% of all malignancies and they affect males frequently. In most of cases double tumours are observed, triple ones represent 4-5% of all cases, while quadruple and quintuple cases are occasional (1, 27, 28).

MMPMs can be divided in four pathogenetic groups: a) occasional multiple malignancies; b) multiple tumours that form a genetic disease; c) multiple tumours that complicate a genetic disease; d) familial cancerous syndrome (28).

Occasional MMPMs, widely the most frequent, are casual neoplastic associations without relation to any specific genetic disease. They grow because of various factors, including life-style and environmental agents. When malignancies arise in the same organ system, they often result from a process called "field cancerization"; this concept explains the multifocal

growing of independent clones and is thought to be the result of chronic exposure to environmental carcinogens factors (10).

Multiple tumours that form a genetic disease are represented by the following associations: familial retinoblastoma-osteosarcoma, Wilms tumour-hepatoblastoma and medullar thyroid carcinoma-pheochromocytoma in Sipple's syndrome.

Multiple colon tumours arising on familial polyposis (40% of cases) are neoplasms that complicate a genetic disease, while the frequency of multiple tumours of the colon is remarkably lower without this condition (4.5%).

Familial cancerous syndrome is mainly characterized by high incidence of uterus, breast and colon tumours in patients of the same familiar group; the syndrome seems to be, somehow, related to a genetic abnormality, whose nature is still unknown.

The possible occurrence of MMPMs has diagnostic, therapeutic and oncologic follow-up monitoring effects (1).

The diagnostic finding of a metastasis has to lead to its careful histologic definition, because it could be a second primary tumour which must be distinctly staged and treated. The occurrence of an MMPMs needs a definite and appropriate therapeutic strategy, while oncologic follow-up must concern the organ systems more frequently involved in the neoplastic associations, trying to identify MMPMs high-risk groups of patients.

The reported case is very interesting because no other similar cases have been reported in literature. The patient indeed developed five MMPMs in different organ systems: larynx, uterus, rectum, papilla of Vater and transverse colon. The lengthy time interval between the onset of laryngeal and endometrial carcinoma was 47 months, 84 months between the last one and the cancerous rectal polyp, 23 months between rectal tumour and papilla of Vater adenocarcinoma, and 18 months between ampullar neoplasm and transverse colon carcinoma.

The patient also underwent a right salpingo-oophorectomy for an ovarian cyst, several endoscopic polypectomies and an atypical resection of the second hepatic segment for angioma. These procedures were performed for benign disease and are not included among MMPMs surgical provisions. All tumours clearly state their independent non-metastatic origin.

The first malignancy was laryngeal carcinoma which, unlike what occurred to our patient, is usually associated to other tumours of the upper aerodigestive tract (oral cavity, pharynx, esophagus, bronchial tree) caused by chronic exposure of the epithelium to environmental carcinogens factors, mainly cigarette smoke and alcohol; our patient had never been exposed to these factors.

The second tumour was endometrial carcinoma which is frequently associated with colon malignancies in familiar cancerous syndrome (HNPCC syndrome family); our case could be partly related to this syndrome as for the family history of our patient (both her father and uncle on his father's side died from a colon carcinoma and her only brother operated on for the same disease).

Further neoplastic sequence includes cancerous polyp of the rectal ampulla, papilla of the Vater adenocarcinoma and transverse colon carcinoma. The association of the tumour of the Vater's region with other MMPMs observed in our patient has no equals in literature, while the association with intestinal carcinomas has been more frequently observed.

The lengthy time interval between the two large bowel locations is 41 months, therefore they cannot be recognized as synchronous tumours. Actually, it is to be considered an adenomatous polyp-carcinoma sequence as the number of endoscopic polypectomies the patient underwent shows. Furthermore, the second colon site in transverse is above the rectal one, therefore an endocavitary implantation of neoplastic bits detached from the first tumour is not reasonable. Risk factors for multiple tumours of the large bowel are familiar history with three cases of colon cancer, other sites malignancies and colo-rectal polyps.

A careful analysis of all blood values collected during the various hospital stays of the patient shows only a low ferritin and a slightly higher glycaemia, but we do not think that MMPMs could be related to these ordinary blood abnormalities. Moreover, the patient was not exposed to any particular carcinogen environmental factors and her lifestyle was absolutely normal.

The only hypothesis which could explain the sequence of malignancies in our patient regards the alterations of immunity surveillance; according to it, new tumoral cells are continuously produced in the organism, but their growth is hindered by the immu-

nity system, and it is the ones which escape this surveillance that can give lead to a clinically manifest tumour. This loss of function can be due to a failure of the immuno-surveillance mechanism or to an extremely poor antigenic way of the tumoral cells; the cancerous agent, whatever it is, acts on an organism whose antitumoral immunity mechanisms are unsettled (1). In order to verify the validity of this etiopathogenetic hypothesis we evaluated the bio-immoral immunity arrangement of the patient, but we could not find any abnormal changing.

Because of neoplastic familiarity we also informed the patient's sons they could have more probabilities to be taken ill with cancer in comparison with the general population. Therefore, we addressed them, together with their mother, to a research center for a genetic analysis (DNA mismatch repairs genes); the results of this study showed no abnormalities.

Conclusions

The life expectancy of neoplastic patients has been improved by early diagnosis and better therapeutic modalities, so that MMPMs are now diagnosed more frequently than in the past. Therefore, all neoplastic patients who were surgically treated require careful follow-up.

The reported case of five metachronous malignancies is extremely rare and suggests that an appropriate treatment of each tumour and a careful surveillance programme guarantee long-term survival rates.

In our patient familiarity for colon cancer and the polyp-cancer sequence are evident. The association with endometrial adenocarcinoma can suggest a familiar cancerous syndrome (HNPCC); we cannot explain the association with the carcinoma of the ampullar region yet - it being a evidence in literature - and the laryngeal carcinoma, because it lacks the chronic exposure of the patient to risk factors.

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