Surgical treatment of isolated lung and adrenal metastasis from colorectal cancer.
Case report

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INTRODUCTION: *Up to 30% of stage I and II colorectal cancers (CRCs) treated with surgical resection alone show disease recurrence, indicating that lymph node (LN) involvement was probably underestimated. Lung is a common site of CRC metastasis, whereas adrenal glands are rarely involved.*
CASE REPORT: *On July 2004 a 56-year old woman underwent left hemicolectomy for a stage I sigmoid cancer. Four years later a lobectomy was performed for an isolated lung metastasis; thirteen months thereafter she underwent left adrenalectomy for adrenal metastasis. No lymph node involvement has ever been demonstrated either histopathologically or radiologically. At present, the patient is alive and apparently disease-free.*
DISCUSSION: *The presence of LN occult metastasis, that might explain recurrence in stage I and II CRCs, has recently been investigated by means of immunohistochemistry and polymerase chain reaction; evidence of LN metastasis obtained with the latter technique is associated to a worse outcome. There have been very few cases that resemble our patient's neoplastic progression and they were either stage III neoplasms or rectal cancers. Our patient's primitive localization in the sigmoid colon makes it difficult to imagine why the liver has not been a site of metastasis. Finally, surgery has an important role in treating isolated metastasis in both lungs and adrenal glands.*

KEY WORDS: Colorectal cancer, Lung metastasis, Solitary adrenal metastasis

Introduction

Colorectal cancer (CRC) is one of the most common malignancies worldwide, with more than 1 million cases diagnosed and about 600.000 deaths caused annually [1].
The wide diffusion of endoscopy and the technical advances of the last years, along with the implementation of cancer screening programmes, have increased the number of cases of early-stage detection and reduced the need for surgery.
The complete endoscopic removal of intramucosal carcinoma is considered curative, as there is virtually no risk for lymph node (LN) involvement [2,3], whereas submucosal invasive carcinoma metastasize to LN in 6-12% of cases [4-7]. Negative prognostic factors, requiring surgical resection and LN harvesting, are: 1) cancer invading resection edges, 2) massive submucosal invasion, 3) poorly differentiated histology, 4) vascular infiltration [8-11].
The pathological evaluation of resected lymph nodes plays a major role in the determination of CRC outcome, as N0 cancers usually do not require adjuvant chemotherapy. Nonetheless, up to 30% of CCR initially classified as stage I or II and treated with surgical

resection alone show a recurrence, suggesting that lymph node involvement was probably underestimated [12].

When the disease spreads to other organs, the most common sites of metastasis are the liver and the lung. Metastasis to the adrenal glands are relatively rare, but are described in up to 17.4% of CRC cases in autopsy series [13-20].

Overall 5-years survival of untreated stage IV CRC is about 11,3%, while resection of isolated lung metastasis can increase this figure up to 50% [21,22]. Surgical approach has been proposed also for isolated adrenal metastasis, although the rarity of their occurrence makes difficult to estimate its efficacy.

Case report

On July 2004 a 56-year-old female underwent total colonoscopy for rectal bleeding, recent changes in bowel habits (constipation), tenesmus and family history of colorectal cancer (her brother died of the disease at age 41). Colonoscopy showed a 3 cm sessile polypoid lesion in the sigmoid colon, which was endoscopically resected en bloc 11 days later. The histological examination revealed an adenocarcinoma on tubular-villous adenoma, but it did not describe the grading of the neoplasm, the depth of invasion, the status of lymphatic/hematic vessels nor the status of the resection edge.

Abdominal CT scan did not show lymph node involvement or any other significant finding; nonetheless on September 2004 the patient underwent laparoscopic left hemicolectomy. Histology showed no residual disease (R0 resection) and no lymph node metastasis (N0). Adjuvant chemotherapy was judged unnecessary. On January 2008,

a total body CT scan showed a 4 cm spiculated mass in the posterior-basal segment of the left lung's lower lobe (Fig. 1) and a subcentimetric isolated lymph node near the left adrenal gland. The patient underwent left lower lobectomy and hilar lymphadenectomy, along with the removal of other mediastinic lymph nodes. Histological assessment showed pulmonary localization of well-differentiated mucinous adenocarcinoma (G1), morphologically similar to colonic adenocarcinoma, marked positively for colonic tissue and negatively for pulmonary tissue (CDX2+, TTF1-), thus suggesting a metastatic origin. Peribronchial lymph nodes and nodes from stations 9 and 11 were free of metastatic localization.

A colonoscopy performed on April 2008 showed no metachronous cancer and a CT scan was negative for abdominal masses or lymph node enlargement. The patient underwent adjuvant chemotherapy (FOLFOX: fluorouracil, leucoverin and oxaliplatin).

On December 2008 an abdominal CT scan showed a voluminous mass (7x5,5 cm) in the left adrenal gland, contiguous to the spleen and to the posterior gastric wall (Fig. 2). On February 2009, a left surrenalectomy and a spleenectomy were performed. Histopathology of the adrenal gland revealed a metastasis from adenocarcinoma of probable intestinal origin (CK20+, CDX2+, CK7, TTF1-).

In 2009 and 2010 two endoscopic controls showed no metachronous lesions of the colon.

At present, patient is asymptomatic and apparently disease-free.

The histological preparation of the colonic polyp was recently revised by an independent pathologist, who described small areas of poorly differentiated cells (G3) in the context of a well differentiated adenocarcinoma
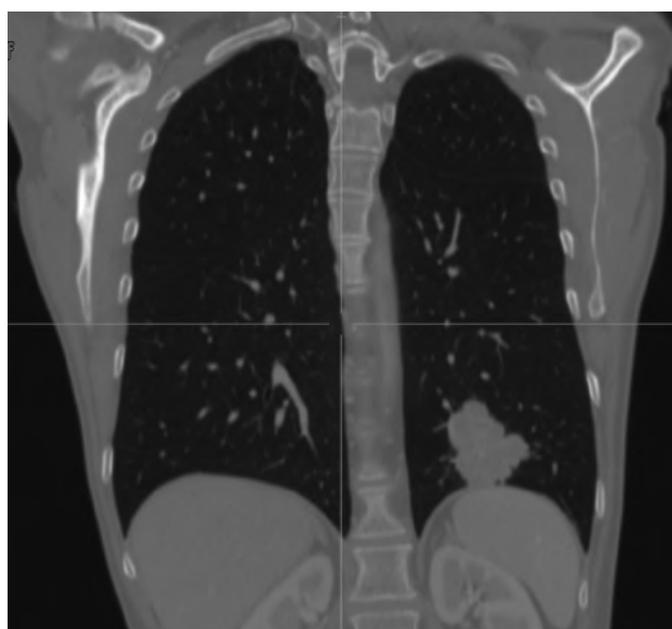

Fig. 1: Total body CT scan (January 2008): spiculated mass in the posterior-basal segment of the left lung's lower lobe.

Fig. 2: Abdominal CT scan (December 2008): voluminous mass (7x5,5 cm) in the left adrenal gland.

Fig. 3: Total body CT scan (January 2008): left adrenal gland slightly increased in volume and inhomogeneous, showing a microcalcification.

(G1), invading the submucosa, with a distance from the resection edge of at least 3 mm, but with features of hematic vascular invasion.

Discussion

Among other prognostic factors for CRC outcome, lymph node involvement has been widely considered outstanding. Five-years survival rates drop from 80% for patients with stage II disease (no lymph node involvement) to 45-50% for patients with stage III cancer (lymph node metastasis) [23].
Nonetheless, about 20-30% of patients initially classified as pN0 develops recurrent disease [12].

The reliability of the N assessment undoubtedly depends on the number of harvested LN as well as on the thoroughness of the pathologist; moreover in the last years there has been a growing interest about the presence of CRC nodal occult metastasis.
Micrometastasis are defined as cluster of tumor cells measuring >0.2 mm but <2.0 mm in diameter, whereas for single cells or for cell cluster measuring <0,2 mm the term "isolated tumor cells" (ITCs) has been established [24].
The presence of LN occult metastastatic disease and its clinical relevance has been investigated by means of immunohistochemistry (IHC) [25-37] and carcinoembryonic antigen (CEA)-specific reverse-transcriptase polymerase chain reaction (RT-PCR) [37-42]; LN occult metastasis have been found in pN0 patients in 5-76% of cases using IHC and in 29,7-54% of cases using RT-PCR. The wide variability of the IHC studies can be mostly explained by the use of different types of antibodies to detect neoplastic cells. The IHC studies overall do not demonstrate a significant trend towards a decrease of survival in the upstaged patients; conversely the fewer studies performed by means of RT-PCR show that occult metastasis identified with this technique are significantly associated to a worse clinical outcome, suggesting the need for randomized trial of adjuvant chemotherapy in pN0/RT-PCR positive patients.
We found this new investigation field of great interest especially for stage I cases, like the one we presented, with vascular invasion and poorly differentiated histology at the pathological analysis of the endoscopically removed polyp, but for which adjuvant chemotherapy is currently not recommended.
Some attention has to be paid to the peculiar metastatic spread of our patient's cancer.
CRC shows an elevated tendency to dissemination to distant organs, and about 19% of CRC are diagnosed as a stage IV disease [1].
The specific metastatic pattern is mainly mediated by molecular interactions between circulating cancer cells and the vessel wall of potential target organs, whose environment facilitates cell adhesion, as demonstrated by Schlüter et al. [43]. The liver is the preferred organ, being involved in about 70% of metastatic diseases. The second most important target is the lung, which is involved in 20-30% of stage IV cases. Other organs, such as adrenal glands, central nervous system, spleen or bone are infrequent metastatic sites and overall account for less than 10% of CRC metastasis [44,45].
Isolated lung metastasis, as in our patient's case, are diagnosed in 5-10% of cases.
A quite recent systematic review by Pfannschmidt et al. confirms that in an highly selected group of patients pulmonary metastasectomy can be performed safely and can lead to a 5-years survival of about 50%. Selection criteria are an adequate cardiopulmonary reserve and the chance for a R0 resection, defined as the absence of

extrapulmonary disease or as a distant disease that is considered resectable [21].

On the other hand, adrenal metastasis from CRC are quite rare and usually indicate a disseminated disease. In reviewed autopsy series the prevalence of adrenal metastasis from CRC ranged from 1.9% to 17.4%, the vast majority of them being associated with several other metastasis [13-20].

In vivo reports of isolated adrenal metastasis are sporadic, but their surgical treatment seem associated with a better prognosis, although given the small number of cases no randomized controlled trial of surgical vs non surgical treatment can be designed to confirm this observation.

There have been a few cases with a history that closely resemble our patient's progression, all reported in the Japanese literature.

The first one has been described by Fujita et al. in 1988 [46]: a woman was operated for pulmonary metastasis four years after a radical resection of the rectum, and four years thereafter a solitary metastasis to the left adrenal was found. Adrenalectomy was performed and two years later the patient had no further evidence of disease.

The last one has been reported by Katayama et al. in 2000 [47]: seven years after anterior rectal resection for rectal cancer, lobar pneumonectomy was performed for a metastatic lung tumor; more than two years later, left adrenalectomy was performed for solitary adrenal metastasis. The patient remained disease-free for 10 months postoperatively, then multiple lung metastasis appeared. Nonetheless, three and a half years after adrenalectomy the patient was alive and under mild oral chemotherapy.

In both these cases, the cancer was localized in the rectum, invaded the muscle layer or the subserosa and had shown metastasis to the regional lymph nodes, therefore the pTNM at diagnosis indicated a stage III neoplasm. The only other stage I CRC case with a similar neoplastic history has been described by Sakagawa et al. in 1995 [48]: two years after the diagnosis and rectal resection, lung metastasis appeared; almost three years after lung resection, left adrenalectomy was performed. A year later bilateral lung metastasis recurred, but there was no further follow up.

From the review of these cases and of other cases without lung involvement Katayama et al. suggest the possibility of an hematogenous route for the diffusion of CRC to the adrenal gland via the lung [47].

At the best of our knowledge, our patient's case is the second stage I CRC case, and the first one described in Italy, to show such a progression, which is even more surprising considering that no lymph node involvement in the abdomen or chest has ever been demonstrated either histopathologically or by imaging techniques. Moreover, our patient had a primitive localization in the sigmoid colon, which makes it difficult to imagine why the liver has not been a site of metastasis.

The rapid growth of the left adrenal metastasis, even comparing to the most similar cases, made us question the CT scan made in January 2008. We asked a dedicated radiologist to review the images and she confirmed the presence of a subcentimetric lymph node near the left adrenal gland, whereas the adrenal gland retrospectively appeared slightly augmented in volume and inhomogeneous, with the presence of a microcalcification (Fig. 3).

Our patient is alive and well 6 and a half years after sigmoidectomy, 3 years after pulmonary lobectomy and 2 years after left adrenalectomy; her story offers the chance for a few considerations.

First of all, it should be underlined the delay in our patient's access to colonoscopy: her family history should have prompted the beginning of the CRC screening at least 20 years earlier, whereas she was referred for colonoscopy only when symptomatic.

Secondly, it might be necessary to study other parameters, besides the ones contained in the TNM classification, for the improvement of the prognostic evaluation. Thirdly, the possibility of adrenal metastasis, although infrequent, must be kept in mind during follow up, expecially since they can reach large dimensions being completely asymptomatic.

Finally, we found confirmation of the central role of surgery in isolated metastasis from CRC.

Riassunto

Viene descritto il caso clinico di una donna di 56 anni che nel luglio 2004 dopo elettroresezione elettronica, è stata sottoposta ad un'emicolectomia sinistra in laparoscopia. L'istologia non ha mostrato alcuna malattia residua (R0 resezione) e nessuna metastasi linfonodale (N0). La chemioterapia adiuvante è stata considerata non necessaria. Nel Gennaio 2008 la paziente è stata sottoposta ad una lobectomia inferiore sinistra e linfoadenectomia ilare per un adenocarcinoma mucinoso ben differenziato (G1)(TAC diagnosticato) suggerendo così un'origine metastatoco- I linfonodi peribronchiale i linfonodi dealle stazioni 9 e 11 erano liberi di localizzazione metastatica.

La colonscopia eseguita ad Aprile 2008 non mostrava nessun cancro metacrono e una TC è risultata anch'essa negativa per masse addominali o infossamento linfonodale. La paziente ha subìto la chemioterapia adiuvante (schema FOLFOX).

Nel febbraio del 2009 viene sottoposta ad una surrenalectomia sinistra e alla splectomia. L'istologia della ghiandola surrenale ha rivelato una metastasi da adenocarcinoma di probabile origine intestinale (CK20+, CDX2+, TTF1-). Anche in questo caso la colonscopia è stata del tutto negativa.

Attualmente la paziente è asintomatica e apparentemente libera da malattia.

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