Ultra-late recurrences of gastro-intestinal carcinoma after primary resection : the mechanism of dormancy

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Abstract

Curative resection of limited gastro-intestinal carcinoma does not always mean curation with tumor-free long-term survival. We present two cases of ultra-late recurrence 14 years after initial treatment. In the first case a 50-year-old male underwent in 1997 a subtotal esophagectomy with tubulation of the stomach for a localized Barrett carcinoma. Postoperative staging showed a poorly differentiated adenocarcinoma, pT1N1 (stage IIB). In May 2011, 14 years after the initial resection, multiple bone metastases were diagnosed and a biopsy confirmed the poorly differentiated carcinoma with the same characteristics as the primary tumor. Investigations showed no evidence for a new primary tumor.

The second case is a 52-year old man who underwent a low anterior resection for a small rectal cancer in 1997, histologically a well differentiated adenocarcinoma, stage IB (pT2N0). In December 2011 multiple metastases were diagnosed and a biopsy showed a metastasis from a mucinous carcinoma, suggestive for a colorectal carcinoma. There was also no evidence for a new primary tumor.

Although the prognosis of limited esophageal and colorectal cancer is good, recurrence is always possible and an ultra-late recurrence may exceptionally occur. The mechanism of tumor dormancy is described. (Acta gastroenterol. belg., **2013**, 76, **251-254**).

Key words : ultra-late recurrence, esophageal cancer, rectal cancer, tumor dormancy.

Introduction

Long-term recurrences have been described for tumors of various histological origins, most frequently however in breast cancer, renal cell carcinoma and malignant melanoma (1,2,3,4,5). Although very rare, it can also occur in tumors of gastro-intestinal origin (6,7,8,9,10, 11,12,13,14,15,16,17). We describe here two patients with an ultra-late recurrence, one with an esophageal and one with a rectal cancer, who presented initially with a localised tumor with a fairly good postoperative staging and prognosis.

Case report

A 50-year-old man, with no remarkable history except chronic heartburn, underwent an esophagogastroscopy and a Barrett esophagus with an ulcer was diagnosed. Biopsies showed moderately differentiated adenocarcinoma with partial mucinous differentiation. There was no evidence for metastases.

A subtotal esophagectomy with gastric tubulation was performed. Histological examination of the resected specimen revealed moderate to poorly differentiated adenocarcinoma. The depth of the tumor invasion was confirmed as submucosal, but with vascular and lymphatic invasion ; with no perineural invasion. There was one lymph node, near the left gastric artery, with microscopic tumor invasion (pT1N1).

Fourteen years after initial surgery, the patient presented with pain and sensatory changes in the saddle area, and less muscle power in the lower limbs. An osteolytic sacral tumoral process was diagnosed and further investigations with bone scintigraphy and PET-CT showed multiple bone metastases (Fig. 1 ; Fig. 2). There was no evidence for other metastases, apart from the bones (liver, lung, lymph nodes). A neurosurgical decompression was done and a biopsy confirmed poorly differentiated adenocarcinoma, with partial mucinous differentiation. Immunohistochemical staining was CK7 positive, CK20 negative,TTF-1 negative and CDX-2 focal slightly positive. These findings were compatible with a metastasis of a gastro-esophageal carcinoma.

Further investigations with esophagogastroduodenoscopy, total colonoscopy, CT Thorax, CT Abdomen and PET-CT showed no evidence for a new primary tumor. Tumor markers were normal (CEA : 2,3 μG/l ; PSA : 1,5 μg/l).

After local radiotherapy S1-S2 (20 Gy), palliative chemotherapy with Cisplatin-Capecitabine was started.

The second patient was a 52-year-old man when in 1997 a low anterior resection was performed because of a midrectal cancer. The anatomopathological examination showed a good differentiated adenocarcinoma with partial mucinous differentiation, invasive in the muscular layer (pT2N0).

A CT-scan of the abdomen, done in 2009 because of renal colic, showed, with the exception of ureterolithiasis, no other lesions.

In December 2011 he presented with ischialgic pain in the left leg. A CT of the lumbosacral spine showed an extensive osteolytic mass in the sacrum (Fig. 3). A biopsy demonstrated a metastasis of a mucinous adenocarcinoma, suggestive for metastasis of colorectal adenocarcinoma, and this was confirmed by immunohistochemistry

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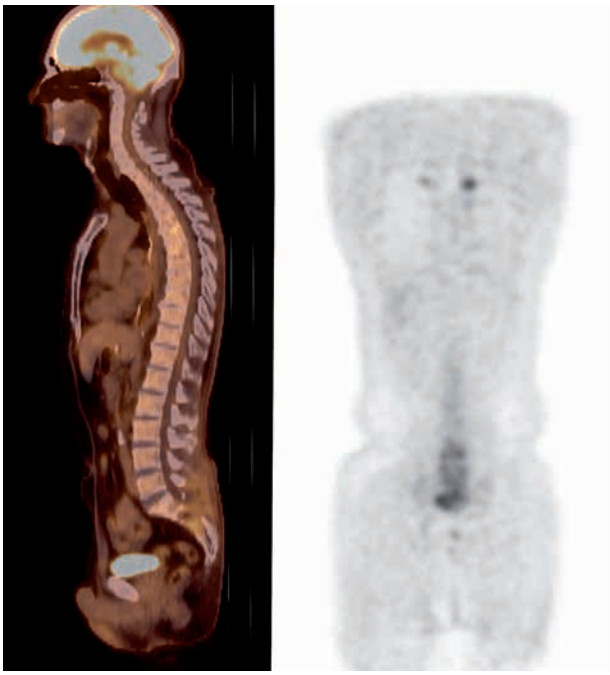

Fig. 1. — Pet-CT revealed osteolytic bone metastases, mainly sacral.

(CDX 2 positive, Villin : positive, CK 20 positive, CK 7 : negative). Further investigation showed also bilateral small lung metastases, and multiple abdominal and mediastinal adenopathies on PET-CT. There was no evidence for a new primary tumor. A colonoscopy and gastroduodenoscopy was normal. CEA was moderately elevated (14 μg/l) and PSA was normal (0,45 μg/l).

Antalgic radiotherapy on the sacrum was started (33 Gy), and palliative chemotherapy for the metastatic rectal cancer is planned.

Discussion

Metastasis is a complex, multistage process in which malignant tumor cells spread from the primary tumor to secondary organs. Tumor cells acquire an invasive phenotype to invade the stromal tissue and disrupt the vascular endothelium (intravasation). Once in the blood the disseminated tumor cells (DTC) must survive in the circulating environment and escape physical damage and attack by the immune system. After the tumor cells arrest or adhere to vessel wall, they invade through the capillary wall (extravasation). Finally, DTCs must adapt to the new microenvironment of the secondary site and start to form micrometastasis or reprogram into a quiescent state, which can last for years (5).

Although treatment of a cancer can be apparently successful, tumor may recur either locally, or as distant metastasis, years or even decades later. Tumor late recurrences and the long periods of minimal residual disease are clearly associated with tumor dormancy. Tumor dormancy can occur in primary, as well as in secondary tumors. While dormancy in primary tumors is best defined as the time between the carcinogenic transformation event and the onset of inexorable progressive growth, it can also occur as minimal residual or occult disease from treated tumors or as micrometastases. It can occur in any patient, with or without identifiable risk factors (19, 20).

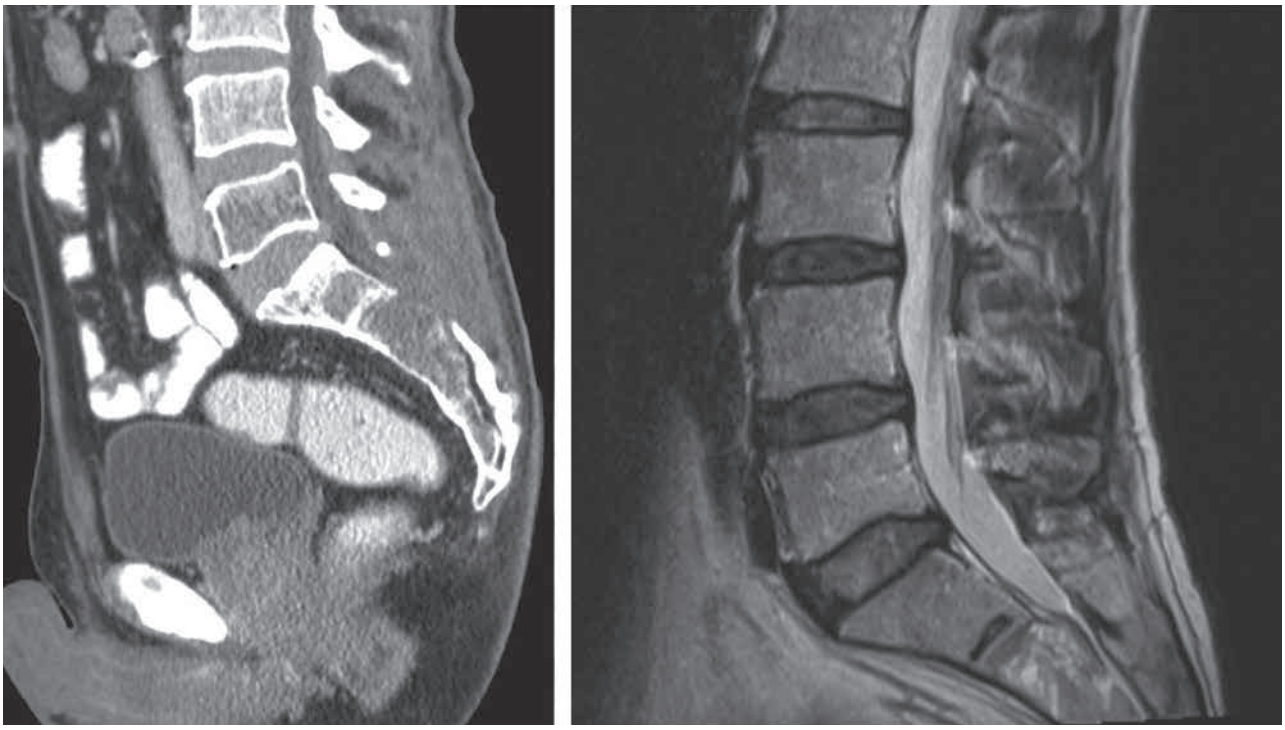

Fig. 2. — CT and MRI with the tumoral mass of S2-S3, spreading to sacral neuroforamina

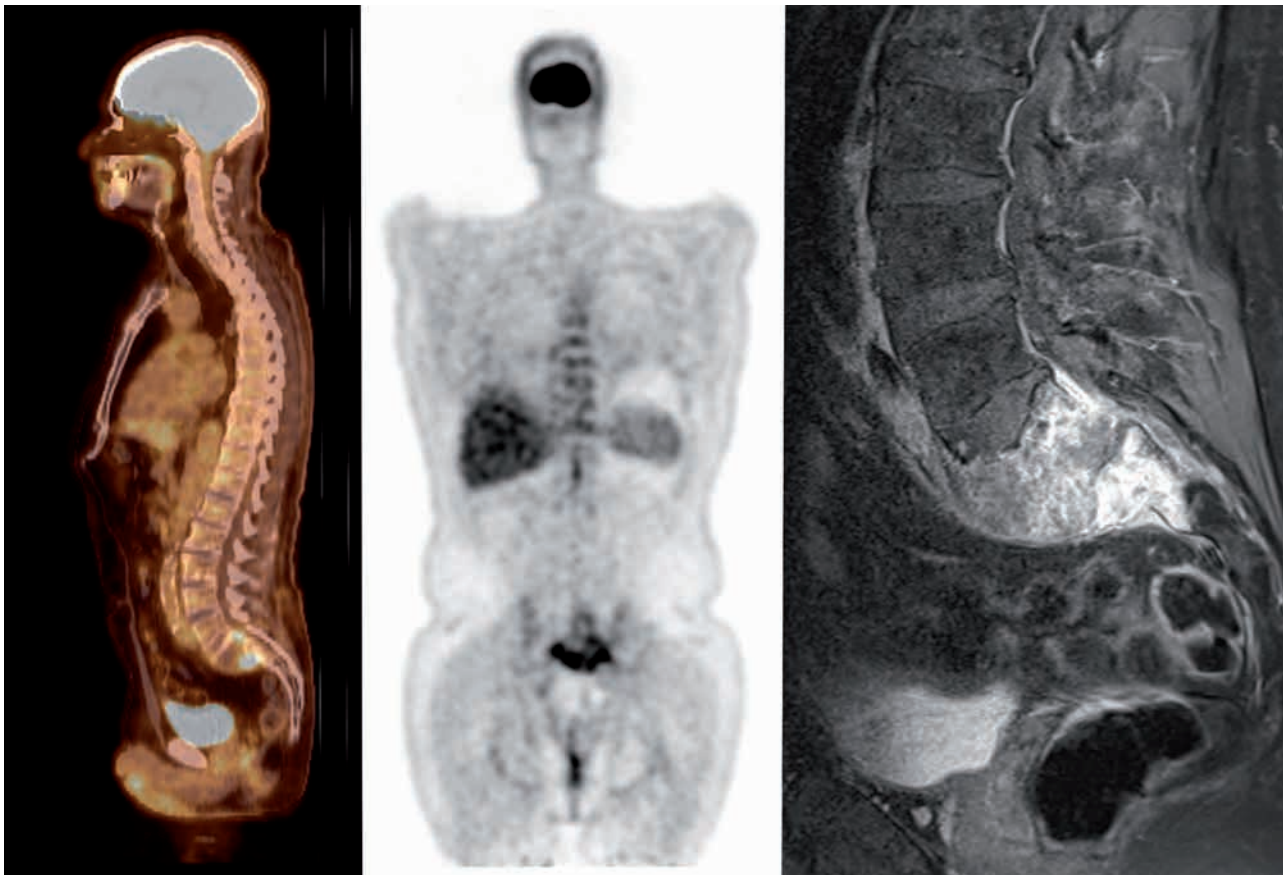

Fig. 3. — Pet-CT and MRI showing the tumoral bone lesion S1-S2, with perisacral extension

Autopsy studies of non-cancer-related deaths indicate that the majority of individuals harbour dormant cancers that do not expand and are too small to be detected by conventional diagnostic methods. Only a few of the microscopic cancers may progress or expand to a detectable size (19).

Of clinical importance is the fact that dormant tumors are highly prevalent in the general population and that dormant tumor cells left after primary tumor removal or treatment are commonly refractory to chemotherapy. Dormant cells are often only a few millimetres in diameter, but the concern lies in the fact they can switch to fast-growing, clinically apparent and potential lethal cancers. Both clinical and experimental data suggest that dissemination can occur at very early stages and that disseminated cells can remain dormant rather than grow progressively. The presence of particular genetic abnormalities acquired by dormant cells may explain the early dissemination of tumor cells, the latency state, and the resistance to the conventional therapeutics used in the treatment of cancer that target actively dividing cells. There is growing evidence that several metastasis suppressor genes that respond to microenvironmental stress may regulate this dormancy state (22).

In spite of the development of high-resolution imaging approaches and sensitive assays for detection of disseminated and circulating tumor cells, detecting clinically occult primary tumors or micro-metastases still remain a major challenge.

Tumor dormancy is a phenomenon whereby cancer cells persist below the threshold of diagnostic detection for months or decades. This condition may arise due to either cell cycle arrest or a dynamic equilibrium state in which cell proliferation is in balance with cells undergoing apoptosis.

Different mechanisms that operate alone or in combination may induce static or dynamic equilibrium conditions. Possible mechanisms include cell cycle withdrawal and differentiation, suppression of angiogenesis, and immune surveillance. The escape from tumor cell dormancy into a growing metastasis is influenced by a shift in the angiogenic and immune factors resulting in an increased rate of proliferation. The transition from a predominantly anti-angiogenic factor environment and dormant cell state to a predominantly proangiogenic factor environment and progressive outgrowth of the tumor is known as the angiogenic switch. A better understanding of the angiogenesis switch will aid in the design of therapies to

either induce or maintain tumor dormancy, or, conversely, to induce cell death in residual dormant cells (5,17,18, 19,20,21,22).

Immunosurveillance is an additional mechanism whereby equilibrium between the host's immune response and dormant tumor cells could be established. The genetic disparity of primary tumors and DTCs forces the immune system to respond flexibly and continuously to emerging variant cancer cells. Dormant tumor cells in equilibrium with the immune system may escape and be responsible for cancer recurrence. Additionally, the antitumor adaptive immune response could select tumor subclones that are resistant to apoptosis, resulting in more aggressive tumors. The identification of such mechanisms would offer new possibilities to favor the immune balance and thus eradicate minimal residual disease (5,19).

Currently it's not possible to predict which dormant tumors will eventually grow, and when, and which will remain dormant and will never switch to the lethal phenotype. Neither the triggers of this switch nor the changes in molecular signature as dormant tumors transition to progressive disease have been fully elucidated (20).

The existence of dormant tumors has important implications for the early detection and treatment of cancer. Elucidating the regulatory machinery of the dormancy phenomenon, including both tumor and host genetic alterations would permit to identify novel early cancer biomarkers and could provide a rationale for the development of dormancy-promoting therapies (5,23).

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