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CASE REPORT

Collision Metastases of Breast and Rectal Carcinoma – A Possible Role for Chemokines Receptors Expression

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Introduction

Collision metastases are a very rare finding, classically described in lymph nodes, in two settings: two carcinomas metastasizing to the same lymph node or a carcinoma metastasizing to a lymph node already harboring a malignant lymphoma [1, 2]. The occurrence of collision tumours, whether they are primary or metastatic, seems to be strongly related to the anatomical context. The majority of reported cases refers to neoplasms arising in anatomically close organs sharing the same routes for lymphatic or venous drainage. On the contrary, the occurrence of collision metastases of primary distant tumours, draining to distinct lymph nodes groups, becomes a more complex matter. The mechanisms underlying metastatic spread and metastases survival are still a subject of active research and it has been recently proposed that specific molecules may be related to the metastatic destination of malignant cells. Some of them belong to the chemokines family.

Chemokines are a group of low molecular weight proteins, which play a crucial role in the regulation of hematopoiesis, leukocyte maturation, cellular trafficking, angiogenesis and cell homing. Based on the positioning of the conserved two N-terminal cysteine residues (C), chemokines are classified into four groups, namely CXC, CC, CX3C and C. Their respective receptors are similarly named: CXCR, CCR, CX3CR and CR [3]. Several studies proposed that the selective expression of chemokines in certain tissues may promote the development of metastases by attracting specific cytokine receptors-expressing cells. They seem to be involved in the establishment of metastatic patterns for breast, cervical, esophageal, colorectal and lung carcinomas, among others [3–9]. In breast carcinoma, for instance, lymph nodes and bone marrow metastases seem to be strongly related to CCR7 and CXCR4 expression patterns [4] which also play a role in the prediction of the site of relapse [6], and are a predictor of worse outcome [7].

Herein, we report the first known case of collision metastases of invasive ductal carcinoma of the breast and neuroendocrine carcinoma of the rectum, in liver and in lymph nodes. We also discuss the expression pattern of chemokines receptors that might provide a basis for the understanding of such a rare phenomenon.

Case-Report

A 55-year-old female underwent a modified radical mastectomy for an invasive ductal carcinoma, staged as T2N1a, and began adjuvant chemotherapy. Due to tenesmus and rectal bleeding, a rectal biopsy followed by an anterior low rectum resection disclosed a neuroendocrine carcinoma, with a high mitotic index and vascular invasion. Two years later, on a control computerized tomography scan, multiple hepatic nodules and a pelvic solid mass were simultaneously found. A liver biopsy revealed a hepatic metastasis of invasive ductal carcinoma, of primary breast origin. A endoscopic ultrasound-guided fine needle aspiration cytology of the pelvic mass was also performed and yielded a neuroendocrine carcinoma. The patient was started on chemotherapy with paclitaxel. During the treatment, she developed sudden severe dyspnoea with hypoxemia and

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hypotension, which progressed to refractory severe respiratory acidosis and shock. The patient died some hours after the onset of symptoms and an autopsy was performed.

The cause of death was a pulmonary thromboembolism, due to a thrombus located at the pulmonary right artery. Additional findings included enlarged lung hilar lymph nodes, a solid mass located at Douglas' pouch and a markedly enlarged liver, containing multiple white solid nodules with central umbilication.

In the hilar lymph nodes and liver samples, two different morphological patterns suggestive of a neuroendocrine carcinoma and a ductal carcinoma were evident. Immunohistochemistry with synaptophysin, chromogranin and gross cystic disease fluid protein-15 (GCDFP-15) confirmed the distinct nature of the neoplastic cells. They were collision metastases of two different and not related neoplasias, both in liver and hilar lymph nodes (Fig. 1).

In order to better understand this unusual biological behaviour, we studied the expression pattern of chemokines receptors CCR6 and CCR7, in sections of the liver and the hilar nodules (material and methods described in appendix 1). In both neoplasias and in both locations, over 90% of neoplastic cells were strongly positive for both receptors. The obtained staining was predominantly cytoplasmic and focal membranous; no nuclear staining was observed. These multiorgan collision metastases expressed identical chemokine receptors profile in both tumours (Fig. 2). We also tested sections from the primary neuroendocrine carcinoma, which disclosed the same pattern. Material from primary breast carcinoma was not available for testing.

Discussion

The rare occurrence of the collision metastases phenomenon, described in the late 50s, refers to the simultaneous presence of two distinct tumours which originate from topographically different organs, secondarily settled in the same organ. They are exceedingly rare, with only 10 cases, exclusively concerning carcinomas, described in the literature [1, 2]. To our knowledge, this is the first reported case of collision metastases of breast and colorectal carcinoma.

The majority of reported cases (7/10 cases) refer to prostate adenocarcinoma metastasizing to the same lymph node as adenocarcinoma of colon (two cases), rectum (one case), stomach (one case) and bladder or urothelial carcinoma (three cases). All cases were seen in pelvic lymph nodes, except for the case of gastric adenocarcinoma, in which the affected lymph node was para-aortic. The cases involving colorectal carcinoma only displayed glandular differentiation; neuroendocrine carcinoma has not been yet described in this setting, until our case.

Two of the remaining cases refer to collision metastases of squamous cell carcinoma and papillary thyroid carcinoma, both in cervical lymph nodes. The last case describes a collision metastasis from breast and ovarian adenocarcinoma in an axillary lymph node. This is the only previous reported case, in English literature, of collision metastases of breast carcinoma with another carcinoma, besides our own. We couldn't find any report of collision metastasis settled in liver.

The rarity of this metastatic pattern led us to reason that both tumors must share some similarity between them to account for the similar metastatic destinations. Chemokine receptors profiles could be one possible explanation (or at least a contributing factor). Breast carcinoma is already known to be related to specific chemokine receptors expression (eg, CXCR4, CCR7), while chemokine expression by neuroendocrine neoplasms is less well understood.

Depending on the cellular type and context, chemokine receptor activation triggers several effector pathways

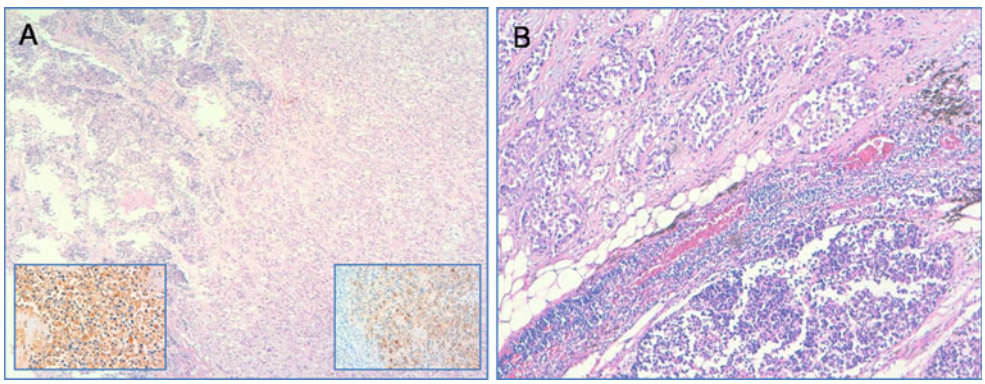

Fig. 1 Collision metastases of breast carcinoma and neuroendocrine rectal carcinoma. **a**- Hematoxylin-eosin stained hepatic nodules. Two different morphologic patterns were evident. Immunohistochemistry with anti-synaptophysin (*left* insert) was positive in one morphologic pattern, while immunohistochemistry with anti-GCDFP15 (*right* insert) was positive in the other nodules. **b**- The same patterns were obvious in lung hilar lymph nodes

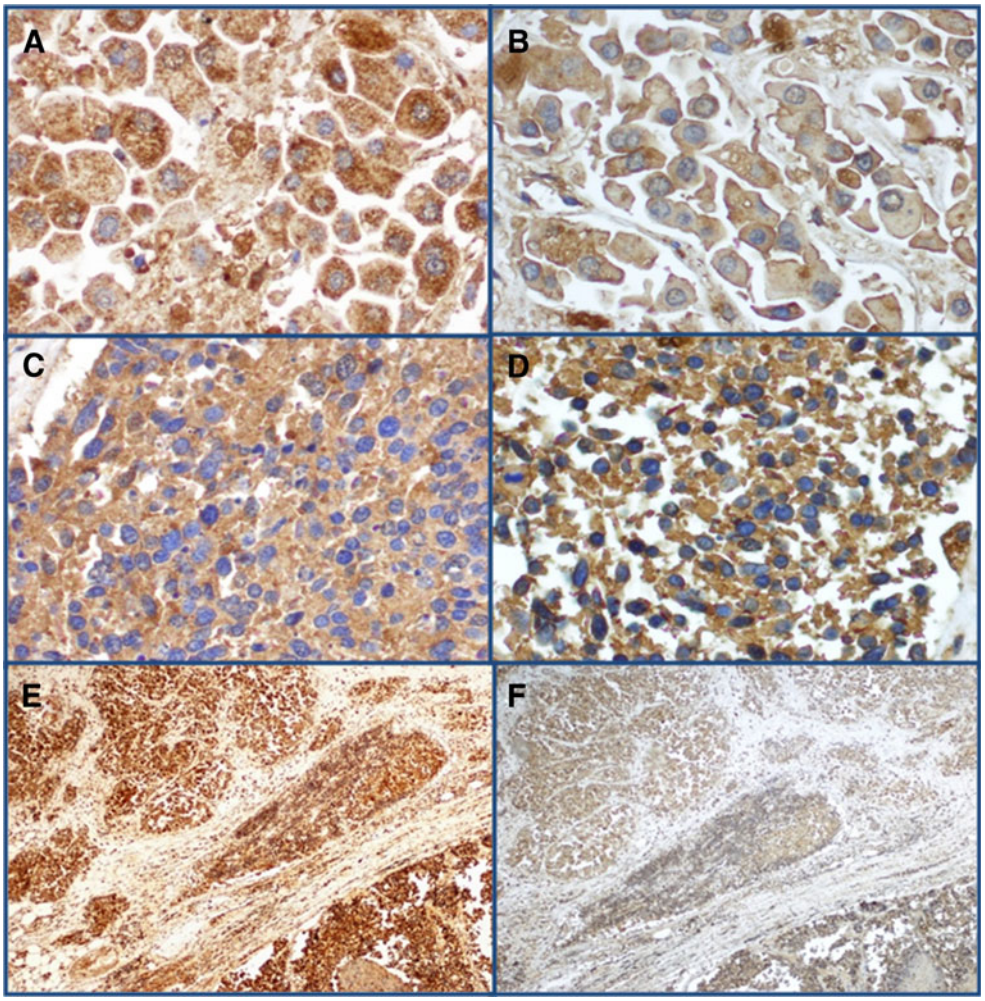

Fig. 2 Expression of CCR6 and CCR7. **a**, **b**—Immunohistochemistry with anti-CCR6 (**a**) and CCR7 (**b**) in hepatic nodules showed positivity for both receptors in breast carcinoma cells. **c**, **d**—Immunohistochemistry with anti-CCR6 (**c**) and CCR7 (**d**) in hepatic nodules showed positivity for both receptors in neuroendocrine carcinoma cells. **e**, **f**—The same was observed when immunohistochemistry with anti-CCR6 (**e**) and anti-CCR7 (**f**) was performed in the lymph nodes

leading to activation of Rac and Rho proteins, whose reciprocal activation and inactivation at the edges of the cell result in directional migration. According to the "chemoattractant" theory of tumor metastization, malignant cells that express functional chemokine receptors can respond to and migrate along chemokine gradients to distant organs, and settle secondary sites of tumor growth. Based on this hypothesis, numerous chemokine/chemokine receptor pairs have been subjected to research.

CCR7 is a seven-transmembrane-domain (G protein-coupled) receptor expressed on mature dendritic cells, B cells, naïve cells and some memory T cells. It binds two chemokines, namely CCL19 and CCL21, which are predominantly expressed by stromal cells in lymphoid organs and regulate the recruitment and homing of CCR7-positive cells to lymphatic tissue [8]. Neoplastic cells expressing functional CCR7 would therefore be more prone to homing to lymph nodes. The incidence of lymph node metastasis has been correlated with the presence of CCR7 on tissue sections of human cancers, namely breast cancer, melanoma, colorectal, head and neck, prostate, non-small cell lung, esophageal squamous cell and gastric cancers [3, 4, 8]. In our case, both tumours had a similar strong expression of CCR7, which would predict lymph nodes metastases. On the other hand, CCR6 is a seven transmembrane domain receptor expressed in lymphatic tissue as well as in intestinal mucosa, fetal liver and testis. It only binds CCL 20, which is normally expressed in mucosal-associated lymphoid tissues and in the liver, and regulates chemoattraction of T cells to the liver, as well as dendritic cells to the intestinal mucosa [9, 10]. Neoplastic cells bearing functional active CCR6 are therefore expected to preferentially settle liver mets and the incidence of hepatic metastasis from colorectal malignancies has been strongly correlated to CCR6 expression [9, 10]. In our case, both tumours had a strong similar expression of CCR6, which could have been a "facilitator" of liver metastasis.

We were also able to demonstrate the presence of a CCR6 and CCR7 similar expression pattern in the primary neuroendocrine carcinoma. Comparison with the primary breast tumour was necessary for further conclusions, but this leads us to reason that this pattern was most probably an inherent feature of this neoplasm, retained during its dissemination and conditioning its metastatic spread.

We can conclude then that the similar chemokines receptors profile of both tumors in our case could explain its unusual metastatic pattern. As both tumours have similar expression of CCR7 and CCR6, this could account for a directed migration of detached cells to specific lymph nodes with higher levels of CCL19/CCL21 (in our case, in pulmonary hilar region) and to the liver, generating the collision metastasis. Common chemokines receptors profile of neoplastic cells may contribute to explain the reason why different malignant tumours metastasize to the same organs, even in the same patient.

Appendix 1. Material and Methods

Immunostaining was performed by the peroxidase-indirect-polymer method. Sections 3 μm thick were cut, unto Superfrost plus slides, from paraffin-embedded routine tissue blocks. The sections were de-waxed, rehydrated and subjected to epitope antigen retrieval (20 min, 94°C) with Target Retrieval Solution High pH 50x Envision™ Flex (Ref.: DM828) in a pre-treatment module PTlink (Dako, Code No. PT 10130).

After blocking nonspecific staining primary monoclonal mouse antibodies anti-human CCR6 (Clone 53103.111; R&D Systems ref.: MAB195, 1:40), CCR7 (Clone 150503; R&D Systems ref. MAB197, 1:20), Synaptophysin (Clone SY38; Dako ref. MO776, 1:20), anti-GCDFP-15 (Clone 23A3; Novocastra NCL-GCDFP15, 1:60) and polyclonal rabbit anti-human Chromogranin A (Dako ref. A0430, 1:9000), were incubated for 30 min at room temperature. Endogenous peroxidase was blocked using Peroxidase Blocking Reagent Envision™ (Ref.: SM801). A labelled polymer HRP anti-mouse/rabbit (EnVision™ Flex ref. SM802) was used for all immunohistochemistry and incubated at room temperature for 30 min. DAB (3,3′—diaminobenzidine) was used as chromogen and Mayer Haematoxylin for counterstaining. Positive controls: tonsil and colon adenocarcinoma were used for CCR6 and CCR7 and appendix, pancreas and sweat glands for Chromogranin A, Synaptophysin and GCDFP-15 respectively. For negative controls, primary antibodies were omitted during the staining.

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