CASE REPORT

Morphological and immunohistochemical characteristics of a gastric amphicrine tumor: differential diagnosis considerations

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Abstract
Gastric amphicrine tumors, lesions in which dual epithelial and neuroendocrine differentiation occurs in the same cell, represent neoplasms with a very low incidence. We present the case of a male patient, who suffered a subtotal gastrectomy. Histopathological examination showed a malignant proliferation with glandular, solid and trabecular pattern, composed of round/polygonal, monomorphic cells admixed with scattered signet ring cells. The use of monoclonal antibodies revealed positive immunoreaction of malignant cells for epithelial and neuroendocrine markers. These characteristic features plead for the final diagnosis of amphicrine tumor, based on the co-expression of both epithelial and neuroendocrine markers in the same cells. Differentiation of this entity must be done with collision tumor and with composite tumor, with distinct histopathological features. Rigorous interpretation of dual immunohistochemical expression of neoplastic cells of amphicrine tumor is useful in distinguishing this entity from others with similar morphological characteristics, in order to assure an adequate targeted therapy.

Keywords: amphicrine tumor, gastric adenocarcinoma, epithelial membrane antigen, neuron specific enolase, synaptophysin.

Introduction
In adenocarcinomas of the stomach, the presence of scattered neuroendocrine cells is a well-recognized pattern. On the other hand, the existence of gastric mixed endocrine and non-endocrine tumors has been a subject of debate and classification of these neoplasms comprised various categories, according to different authors. One of these groups is represented by gastric amphicrine tumors, lesions in which dual epithelial and neuroendocrine differentiation occurs in the same cell and constitutes neoplasms with a very low incidence.

Materials and Methods
We present the case of a male patient (D.T.), 52-year-old, who complained of epigastralgia, loss of appetite and weight loss. A double-contrast barium upper gastrointestinal radiograph revealed a cause for his symptoms an ill-defined mass indenting the gastric contour.

Endoscopic examination evidenced a Borrmann’s type II tumor located in the median part of the lesser curvature. The biopsy procedure disclosed a malignant epithelial proliferation, considered as poorly differentiated (G3) adenocarcinoma. The patient was then referred to the Second Department of Surgery, Clinical Hospital of Constanța. A subtotal gastrectomy was performed, associated with lymphadenectomy, splenectomy and omentectomy. The macroscopic, histopathological and immunohistochemical analysis was performed in the Clinical Service of Pathology, Emergency County Hospital, Constanța. The specimen was fixed in 10% formalin and paraffin-embedded, using the standard histological procedure. Five microns thick sections were stained with Hematoxylin–Eosin and, afterwards, monoclonal antibodies were applied, methods that revealed particular features of this neoplasm. Macroscopic image was taken with a Nikon Camera and microscopic images, with a Nikon Eclipse E600 Microscope.

Results
Gross examination of the distal polar subtotal gastrectomy specimen revealed, on the lesser curvature, the presence of an ulceroinfiltrative lesion of 7.5/5.5 cm with elevated borders, irregular base, whitish translucent cut surface and firm consistency (Figure 1). Residual gastric mucosal folds were flattened. Serosal surface correspondent to the lesion apparently was not involved. The omentectomy specimen showed no macroscopic particular features. The splenectomy specimen contained multiple lymph nodes of 0.5–1 cm diameter, tan-gray and firm; seven nodules were identified, dissected and submitted to microscopical
examination. The lymphadenectomy specimen taken from the area adjacent to the left gastric artery was 1/1 cm diameter, gray-reddish and with elastic consistency.

Histopathological examination showed a malignant proliferation composed of round/polygonal, relatively monomorphic cells, with well-defined cytoplasmic borders, loss of polarity, granular/vacuolar cytoplasm, karyomegaly, hyperchromatism, prominent nucleoli, intense mitotic activity; the disposition of this cellular population consisted of solid areas, nests, trabeculae and pseudoglands, that focally ulcerated the mucosa and infiltrated the tunica muscularis (Figures 2 and 3); admixed with this uniform cells, there were signet ring cells, with a diffuse configuration and formation of mucin pools (Figure 4).

Figure 1 – Gross aspect.

Figure 2 – Solid pattern of malignant proliferation (HE stain, 100×).

Figure 3 – Pseudoglandular and trabecular disposition of neoplastic cells (HE stain, 100×).

Figure 4 – Signet ring cells interspersed in malignant population (HE stain, 200×).

Light microscope examination of lymphadenectomy specimens showed the involvement of lymphoid tissue by the previously described malignant population. The splenectomy specimen was microscopically unaffected by the neoplastic proliferation.

Our preliminary diagnosis was that of poorly differentiated gastric adenocarcinoma (G3) of mixed type according to Lauren’s classification, stage pT2N3M0.

We considered that further evaluation by immunohistochemical methods was mandatory. The application of monoclonal antibodies revealed some peculiar characteristics of malignant cells:

• Monoclonal Mouse anti-Human Epithelial Membrane Antigen, Clone E29, Isotype IgG2a, kappa (DAKO) – positive reaction in all neoplastic cells, including signet ring cells (Figure 5);

• Monoclonal Mouse Anti-Human Neuron-Specific Enolase, Clone BBS/NC/V1-H14, Isotype IgG1, kappa (DAKO) – diffuse cytoplasmic reaction in monomorphic malignant cells; focal positive reaction in signet ring cells (Figure 6);

• Monoclonal Mouse Anti-Synaptophysin, Clone SY38, Isotype IgG1, kappa (DAKO) – positive reaction in solid, trabecular and pseudoglandular areas; focal reaction in signet ring cells (Figure 7).

The characteristic features of immunohistochemical response pleaded for the final diagnosis of amphicrine tumor, based on the co-expression of both epithelial and neuroendocrine markers in the same neoplastic cells.
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Discussion

Recently, Fujiyoshi Y et al. [1] revised the classification of mixed endocrine and non-endocrine epithelial tumors and established the following groups: (1) neuroendocrine cells interspersed within carcinomas; (2) carcinoids (neuroendocrine tumors/NET) with interspersed non-endocrine cells; (3) composite glandular–neuroendocrine cell carcinomas containing both areas of carcinoid and conventional carcinoma; (4) collision tumors in which neuroendocrine tumors and conventional carcinomas are closely juxtaposed, but not admixed; (5) amphicrine tumors predominantly composed of cells exhibiting concurrent neuroendocrine and non-endocrine differentiation; (6) combinations of the previous types.

The entity of amphicrine tumor was first described by Feyrter F [2] in his “Diffuse endocrine epithelial system”, where he revealed the coexistence of endocrine and exocrine secretory products within single cells. Ratzenhofer M and Leb D [3] used for the first time the term “amphicrine” to describe cells containing both neuroendocrine granules and mucin vacuoles. Chejfec G et al. [4] brought unequivocal proofs for neuroendocrine differentiation and mucin production within the same cells in two cases of well or moderately differentiated adenocarcinoma in the stomach. Yang GCH and Rotterdam H [5] described two cases of gastric malignant tumor characterized by mixed glandular–endocrine features of neoplastic cells and offered ultrastructural evidence for the coexistence of neuroendocrine granules and mucin droplets in the same cell.

Our case showed widespread immunoreaction in malignant cells for both epithelial marker EMA (Epithelial Membrane Antigen) and neuroendocrine markers (Neuron Specific Enolase and Synaptophysin). Furthermore, the tumoral configuration in pseudo-glands, cords and sheets sustained both cellular lines: epithelial and neuroendocrine.

Distinction of this entity must be done with collision tumor, characterized by a clear demarcation between the two types of malignant proliferations – epithelial and neuroendocrine, and with composite tumor, remarkable for the intimate mixture of two cellular populations, with distinct immunohistochemical profiles [6].

Composite or mixed glandular–neuroendocrine cell carcinomas are defined as an intricate admixture of both elements, which are present in equal proportions and show two distinct neoplastic phenotypes. One type is composed of gastric-type epithelial cells with a high nuclear to cytoplasm ratio that diffusely permeate the mucosa and wall in an infiltrative growth pattern. The cytomorphology of these cells supports the diagnosis of signet-ring cell adenocarcinoma. The second type is composed of smaller uniform neoplastic cells arranged in islands, cords, glands or solid sheets. These tumor cells have scant, eosinophilic granular cytoplasm and a centrally located round nucleus with finely dispersed (“salt and pepper”) chromatin, outlining the diagnosis of malignant neuroendocrine tumor. Immunohistochemically, each neoplastic population reacts separately: one with epithelial markers and the other with neuroendocrine markers, respectively, without interferences between them [7].

Collision type neoplasms occur as exocrine and neuroendocrine tumors that arise adjacent to one another and do not originate from the same cell type.
The tissue components apparently grow from opposite sides with a readily identifiable line of interface. This particular neoplasms are composed of one cellular line with features of adenocarcinoma and another cellular population, with histological and immunohistochemical characteristics of neuroendocrine tumor, with no intermingling or merging of tissue components at the interface of the growth [8].

A supplementary argument supporting the diagnosis of amphicrine tumor in the presented case consisted of the appearance of lymph node metastases, outlining dual immunohistochemical features identical to those of the primitive tumor, observation that excludes collision tumor, where secondary tumors are characterized by the presence of only one of the two involved cell lines and composite tumor, associating the lesions of adenocarcinoma and neuroendocrine tumor in lymph nodes [9].

Our case report sustained the idea that amphicrine carcinomas arise from immature multipotential stem cells in the endodermal origin, clonal cells that possess both character of exocrine and endocrine natures, theory suggested by Alipov G et al. [10] in their study.

Regarding the prognosis, amphicrine carcinomas showed aggressive behavior. Ito H and Tahara E [11] reported ten cases of adenocarcinoma cell carcinomas with a diffuse growth pattern and five patients died within the first year. On the contrary, composite tumors are presented as neoplasms with favorable prognosis [7]. The prognosis of collision tumors is uncertain, but it seems that the presence and degree of differentiation of the adenocarcinoma component have a greater negative impact than do those of the carcinoid component [8]. In reference to our patient, the presence of lymph node metastases of amphicrine carcinoma represented supplementary elements of unfavorable prognosis and supported the need of a complex oncologic treatment.

The recognition of amphicrine carcinomas may be of relevance for an accurate clinico-radiological monitoring of the patient and for targeted therapeutic strategy, foreseeing the use of biotherapies similar to those proposed for pure neuroendocrine tumors [12]. Further evaluation of cases that will benefit of multimodal therapy will bring additional elements to complete the picture of this clinico-pathological entity.

Conclusions

Rigorous interpretation of dual immunohistochemical expression of neoplastic cells of amphicrine tumor is useful in distinguishing this entity from others with similar morphological characteristics, in order to assure an adequate targeted therapy.

References