CASE REPORT

Differential diagnosis issues in a case of gastric carcinoma associated with leukemoid reaction

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Abstract
Gastric tumors share many characteristics, making a definitive diagnosis challenging. Gastric adenocarcinomas represent 90% of malignant stomach tumors, meanwhile the frequency of gastric lymphoma range between 1–5% of all gastric cancers. Gastric carcinoma bears resemblance with particular forms of non-Hodgkin’s lymphoma of the stomach, not only in morphological presentation, but also in clinical configuration and laboratory tests. We report a case of gastric carcinoma with abnormal hematological picture dominated by leukemoid reaction and peculiar histopathological aspect. Pleomorphism of neoplastic cells and distinct arrangement of these give rise to the need of differentiation between a carcinoma and a non-Hodgkin’s lymphoma of the stomach. On immnohistochemical grounds, we succeeded in our action of segregation between the two lesional entities and we establish as definitive diagnosis that of poorly differentiated gastric adenocarcinoma. Additionally, leukemoid reaction proved to be a manifestation of a bone marrow metastasis from gastric cancer.

Keywords: gastric adenocarcinoma, diffuse large B-cell lymphoma, anaplastic large cell lymphoma, immunohistochemistry, leukemoid reaction.

Introduction
Gastric tumors share many characteristics, making a definitive diagnosis challenging. Gastric adenocarcinomas represent 90% of malignant stomach tumors and most often appear as a heterogeneous mass with focal wall thickening, diffuse infiltration and possible ulceration, loss of rugal folds, abnormal perigastric fat, exophytic disease, possible metastasis, and involvement of the peritoneal ligaments [1].

Gastric lymphomas are usually focal homogeneous tumors originating in the distal two thirds of the stomach or antrum and arising from the sites of mucosa-associated lymphoid tissue (MALT) [2]. There is commonly gastric wall thickening in excess of 1 cm and more than 50% infiltration of the gastric wall, but often without significant distortion of the gastric rugae. Circumferential involvement of most of the stomach may be seen, as well as lymphadenopathy on either side of the mesenteric vessels [3].

The presence of lymphadenopathy can be used to differentiate lymphoma from other malignant gastric tumors, although lymphomas can also present as heterogeneous masses and may distort the rugal folds, highlighting the fact that gastric neoplasms are sometimes difficult to diagnose clinically and macroscopically [4].

The certain diagnosis of these two lesional entities is established on histopathological grounds and, in case of doubts, immunohistochemical techniques represent a valuable method for differential diagnosis [5].

Patient and Methods
We expose the case of a male patient, D.M., 74-year-old, diagnosed and surgically treated for a gastric malignant tumor. The gastrectomy specimen was processed in the Service of Pathology, Emergency County Hospital of Constanta. Fragments of tumor were paraffin-embedded, sectioned at 5-µm and stained with Hematoxylin–Eosin (HE) and van Gieson. Immunohistochemical analysis was based on a panel of antibodies:

1. Monoclonal Mouse antiAE1/AE3 pancytokeratin, Isotype IgG1, kappa (DAKO) – specific marker of epithelial cell differentiation, useful in tumor identification and classification; synergy between the various components results in staining amplification; the mixture may aid in the discrimination of carcinomas and nonepithelial tumors; it is also useful in detecting micro-metastases in lymph nodes, bone marrow and other tissues and for determining the origin of poorly differentiated tumors [6].

2. Monoclonal Mouse Anti-Human Cytokeratin 7, Clone: OV–TL 12/30, Isotype IgG1, kappa (DAKO) – specific marker of epithelial cell differentiation, useful in tumor identification and classification; synergy between the various components results in staining amplification; the mixture may aid in the discrimination of carcinomas and nonepithelial tumors; it is also useful in detecting micro-metastases in lymph nodes, bone marrow and other tissues and for determining the origin of poorly differentiated tumors [6].

3. Monoclonal Mouse Anti-Human Cytokeratin 20, Clone K,20.8, Isotype IgG2a, kappa (DAKO) – a major cellular protein specifically expressed in the gastric and intestinal mucosa, also in adenocarcinomas of digestive system [6].

4. Monoclonal Mouse Anti-Human Epithelial Membrane Antigen (EMA), Clone E29, Isotype IgG2a, kappa
(DAKO) – large cell surface mucin glycoprotein expressed by most glandular and ductal epithelial cells and some hematopoietic cells; intense reaction in most adenocarcinomas, associated with poor prognosis [6].

5. Monoclonal Mouse Anti-Human CD20cy, Clone L26, Isotype IgG2a, kappa (DAKO) – positive staining in most B-cells (considered a pan-B-cell antigen) and in 90% of B-cell lymphomas [7].


7. Monoclonal Mouse Anti-Human CD45, Leukocyte Common Antigen, Clone 2B11 + PD7/26, Isotype IgG1, kappa + IgG1, kappa (DAKO) – CD45 is expressed in cells of the human hematopoietic lineage and it is not detected on differentiated cells of other tissues; positive staining in anaplastic large cell lymphoma, most B- and T-cell lymphomas [7].

### Results

The patient presented in the Internal Medicine Clinic, Emergency County Hospital of Constanta, with symptoms of malaise, pallor, palpitations, fever and weight loss. Hematological investigations exhibit the picture of hypochrome anemia (RBC 4.28×10^6/µL, hemoglobin 10 g/dL, hematocrit 33%, MCH 23.4 pg/cell, MCHC 30.4%, MCV 76.9 fl, peripheral blood smear with presence of moderate hypochromia, rare target cells, anisocytosis, poikilocytosis, teardrop cells, schistocytes, spherocytes – indicators of severe iron deficiency). Other parameters included in hemoleukogram indicated different disturbances: leukemoid reaction 52×10^3 leucocytes/mL, abnormal leukocytic formula: increased number of neutrophiles 84%, low level of lymphocytes 8.5%, monocytes 6.6%, eosinophiles 0.6%, basophiles 0.2%, normal platelets number 290×10^3/mL. Further imagistic procedures applied to the patient, in order to discover the cause of anemia – barium meal, double contrast barium study, gastroscopy – highlighted the presence of a gastric ulceration with some characteristics (blunted radiating folds converging to the edge of the ulcer, large diameter and depth, focal wall rigidity, easy bleeding) suggestive for a gastric malignant lesion. The clinician decided to transfer the patient to Surgery Clinic, where a subtotal gastrectomy with lymphadenectomy of lesser curvature procedure was performed and the resected specimen was sent to the Service of Pathology, for a certain diagnosis.

Macroscopical examination revealed a stomach of 10/8/4 cm, presenting an ulcero-infiltrative lesion of 4/4 cm with elevated borders (1 cm) and irregular base, localized in the middle third of the lesser curvature; on section surface, a solid homogenous translucent appearance, white-yellowish color and firm consistency; the surgical borders were macroscopically normal (Figure 1). Separately, the surgeon sent to the Pathology Department a fragment of connective and adipose tissue of 5/3 cm from the lesser curvature, evidencing after dissection multiple nodules of varying diameter (0.2–0.5 cm), of grayish color and medium consistency.

Microscopical analysis identified a population of large neoplastic cells with polygonal and round shape, uni- or multinucleated, with karyomegaly, vesicular nuclei, conspicuous nucleoli, homogenous eosinophilic or vacuolar cytoplasm (Figure 2).

The examination of 15 lymph nodes evidenced the effacement of the normal architecture by a diffuse infiltrate of small lymphocytes and sinus histiocytosis, considered as reactive characteristics.

The clinical aspect and the described lesion evoke features of gastric lymphoma superposed over those of undifferentiated carcinoma, this observation leading to the necessity of supplementary immuno-histochemical investigations.

The use of monoclonal antibodies emphasized the developmental features of the neoplastic process, the immunohistochemical profile and the pathological response to therapy.
particular immunophenotype of neoplastic proliferation:

- positive cytoplasmic reaction (+) to pancytokeratin AE1/AE3, CK7 and CK20 in tumoral population and in epithelial cells of the neighboring normal mucosa (Figure 6);
- intense positive membranar reaction (+++) to EMA in neoplastic proliferation and in mucosa (Figure 7);
- negative immunomarking to CD45 in neoplastic cells, but positive on the cellular membrane of reactive lymphocytes (Figure 8);
- negative reaction to CD20 in malignant cells, but positive expression in lymphoid follicles of mucosa and in lymphocytic inflammatory infiltrate (cytoplasmic compartment) (Figure 9);
- negative expression to CD30 in tumoral cells, but membranous and Golgi-type staining in the constituent cells of the inflammatory infiltrate (Figure 10).
The outlined immunohistochemical profile proved its usefulness for establishment of the final diagnosis for the examined lesion: poorly differentiated gastric adenocarcinoma (G3). The evaluation of invasiveness was useful for tumoral staging: pT2aN0Mx.

Discussion

The particular features of the case, both from clinical and pathological point of view, determine us to take in consideration two different entities: adenocarcinoma and gastric lymphoma (diffuse large cell lymphoma and anaplastic large cell lymphoma).

Adenocarcinoma of stomach, representing 90% of all gastric malignancies, is localized more often at distal portion of stomach (antral or antro-pyloric region), rarely in the proximal half of the organ, like our case presented [9]. Histopathologically, the origin of the neoplastic cells lies in mucosa, so a strong connection between this layer and malignant proliferation is almost always obvious [10]. The neoplastic population described here is pleomorphic and infiltrates between glands, this pattern representing for us one of the reasons to consider non-Hodgkin lymphoma an alternative diagnosis [11]. The second motive to orient to a malignant lymphoid proliferation refers to the abnormal hematological profile – leukemoid reaction (possibly encountered in lymphoma) and hypochrome anemia (associated both to epithelial or lymphoid malignancies). The architectural distribution and the increased dimensions of tumoral cells lead us to distinguish gastric carcinoma from diffuse large B-cell lymphoma and anaplastic large cell lymphoma.

Diffuse large cell lymphoma is the most complex and heterogeneous of all the non-Hodgkin’s lymphomas. It is morphologically defined by the large size of the cells, their vesicular nuclei with prominent nucleoli, and their relatively abundant cytoplasm. As a group, large cell lymphoma occurs in both children and adults, but mostly in the latter. In comparison with other lymphomas, it has a greater tendency for extranodal presentation (mostly in digestive system) and for being localized at the time of diagnosis. All these characteristics share similarities with those presented in our case, but the negative immunoexpression of the neoplastic population for common leukocytic antigen (CD45) and for B-cell marker (CD20) exclude diagnosis of large cell lymphoma [12].

Anaplastic large cell lymphoma (Ki-1 lymphoma) occurs in all age groups, about 20% of the patients being under age of 20-year-old. Clinically, gastric localization belongs to the systemic form of disease. Microscopically, the infiltrate has a polymorphic appearance, with a variable admixture of neutrophils, lymphocytes, histiocytes, and large highly atypical cells showing marked pleomorphism. The nuclei of these cells are often multiple and nucleoli are prominent. The cytoplasm is abundant and eosinophilic. It is characteristic for these tumor cells to form in a cohesive fashion and to involve preferentially the lymph node sinuses. Immunohistochemically, the tumor cells are by definition CD30 (Ki-1) positive; also, a consistent positivity for EMA and for pan-lymphoid markers is reported. The features of our case that might plead for anaplastic lymphoma are cytologic pleomorphism, cohesive pattern of growth and positive immunolabeling for EMA, but the absence of malignant cells in lymph node sinuses and the negative reaction for CD30 in malignant cells represent decisive elements for us to consider that presented case doesn’t belong to the category of anaplastic lymphoma [13].

We decided as final diagnosis that of poorly differentiated gastric adenocarcinoma of intestinal type (G3), based on evident findings: positive reaction for epithelial markers (EMA, pancytokeratin) in tumoral cells, expression of both CK7 and CK20 – specific for gastric adenocarcinoma, absence from lymph node sinuses of malignant cells with lymphoid origin [14].

A late finding confirmed that the established diagnosis was correct, when an elevated level (34 ng/mL) of seric carcinoembryonic antigen (CEA) was identified.

An unanswered question remains to be clarified: the significance of fever and of the hematologic disturbances, particularly that of leukemoid reaction, which has no apparent correlation with the clinical evolution of gastric adenocarcinoma. Supplementary information
enlighten this dark area: the patient was diagnosed in a hematology clinic from another medical center with bone marrow metastasis of gastric cancer. This certainty is based on bone marrow puncture, where the hematopathologist described atypical cells with peculiar features that proved to originate from the gastric neoplasm, because cytokeratins were expressed in these cells from the smear. This observation constitutes a supplementary element of unfavorable prognosis in our case of poorly differentiated gastric adenocarcinoma [15, 16].

Conclusions

Gastric carcinoma bears resemblance with particular forms of non-Hodgkin’s lymphoma of the stomach, not only in morphological presentation, but also in clinical and hematological picture. The value of immunohistochemistry methods proved once again their irreplacability in segregation of these lesions. The particular clinical signs and abnormalities in blood cell count bring important information for disease configuration and for prognostic evaluation.

References


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