Large cell neuroendocrine carcinoma of the midgut with anaplastic features: a case report
Carcinoma neuroendocrino de células grandes del intestino medio con características anaplásicas: reporte de un caso

ABSTRACT
Neuroendocrine neoplasms (NENs) of the digestive tract are currently classified as well differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine tumors also called neuroendocrine carcinomas (NECs). NECs can be small cell (SCNEC) or large cell (LCNEC). Herein, we report a 50-year-old female, who was previously diagnosed with diabetes mellitus type1 (T1DM), that was brought to the emergency room, due to acute abdominal pain. A computed axial tomography (CT scan) revealed a tumour involving the cecum with a secondary obstruction, and the patient was submitted to an emergency right hemicolectomy. After the surgery, the patient underwent a lung and abdominal CT scan, both with contrast and without contrast, showing the presence of multiple nodules in the liver, consistent with metastatic disease. The patient started palliative chemotherapy and died of the disease six months after surgery. Grossly, the tumor involved the cecum, the ileo-cecal valve and the terminal ileum. Histologically, it was composed mostly of mononuclear pleomorphic cells intermingled with large multinucleated cells with anaplastic-like morphology reminiscent to anaplastic T-cell lymphoma. The malignant cells were positive for CKAE1-AE3, CD56, chromogranin, and synaptophysin. The ultrastructural study showed dense core neurosecretory granules in the cytoplasm of the neoplastic cell. The diagnosis of “Large cell neuroendocrine carcinoma with anaplastic features” was rendered. NECs of the gastrointestinal tract have an aggressive clinical evolution; this is the first reported case of LCNEC with anaplastic features, is not possible at moment to know if the anaplastic features conferred a different prognosis.

Keywords: Anaplastic features, digestive tumors, large cell neuroendocrine carcinoma, Neuroendocrine carcinoma.
RESUMEN

Las neoplasias neuroendocrinas (NEN) del tracto digestivo se clasifican actualmente como tumores neuroendocrinos bien diferenciados (NET) y tumores neuroendocrinos pobremente diferenciados, también llamados carcinomas neuroendocrinos (NEC). Los NEC, histológicamente pueden ser de células pequeñas (SCNEC) o células grandes (LCNEC). En este artículo, informamos de una mujer de 50 años, a quien se le diagnosticó previamente diabetes mellitus tipo 1 (DM1), que fue traída a la sala de emergencias debido a dolor abdominal agudo, por el que se realizó una tomografía axial computarizada (TC) que evidenció una tumoración en ciego con obstrucción secundaria, por ello se decidió realizar la hemicolecotomía derecha de emergencia, luego de la cirugía se le realizó una tomografía computarizada torácica y abdominal, ambas con y sin contraste, evidenciando la presencia de múltiples nódulos en el hígado, compatibles con enfermedad metastásica. La paciente inició quimioterapia paliativa y falleció de la enfermedad seis meses después de la cirugía. La tumoración macroscópicamente comprometía el ciego, la válvula ileocecal y el íleon terminal. Histológicamente estaba compuesta en su mayoría por células mononucleares pleomórficas entremezcladas con grandes células multinucleadas con morfología anaplastica que recuerda al linfoma anaplásico de células T. Las células malignas fueron positivas para CKAE1-AE3, CD56, cromogranina y sinaptofisina. El estudio ultraestructural demostró gránulos neurosecretorios de núcleo denso en el citoplasma de la célula neoplásica. Se concluyó el diagnóstico de “Carcinoma neuroendocrino de células grandes con características anaplasticas”. Las NEC del tracto gastrointestinal tienen una evolución clínica agresiva; este es el primer caso reportado de LCNEC con características anaplasticas, por el momento no es posible saber si las características anaplasticas confirieron un pronóstico diferente.

Palabras clave: Características anaplasticas, tumores digestivos, carcinoma neuroendocrino de células grandes, carcinoma neuroendocrino.

1. Introduction

In the current World Health Organization (WHO) classifications of digestive tumors (5th edition), the neuroendocrine neoplasms (NENs) of the digestive system are classified depending on their localization and histopathologic features (1).

By localization, there are classified as foregut, midgut, and hindgut (2). The foregut includes tumors from the oropharynx to the upper duodenum, liver, gallbladder, and pancreas, the midgut corresponds to the middle part of the duodenum to the right two-thirds of the transverse colon, and finally the hindgut corresponding to the left one-third of the transverse colon including the upper anal canal.

The main way to classify NENs is through histopathological study which incorporates both the morphology of the tumor and the proliferation rate evaluated by mitotic rate and Ki67 proliferation index, with these NENs can be classified as well-differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (NECs), this classification can be used in all the digestive system (1,3,4). In summary tumors with “carcinoid” or well-differentiated morphology can be graded as low grade G1 (<2 mitoses/2 mm2 or Ki-67 index <3%), intermediate grade G2 (2-20 mitoses/2 mm2 or Ki-67 index 3-20%) and high grade G3 (>20 mitoses/2 mm2 or Ki-67 index >20%). NECs don’t need to be graded, they are high grade (poorly differentiated) by definition, and they can be classified as NEC small-cell type (SCNEC) and NEC large cell type (LCNEC). Finally, there is another category called mixed neuroendocrine non-neuroendocrine neoplasms (MiNENs), these are defined by the presence of a neuroendocrine tumor and a not neuroendocrine tumor, where one of the 2 constitutes at least 30% of the total tumor (1,3)

Midgut NETs (defined as the middle middle part of duodenum, jejunoileal, and proximal colon) as a group, are the most common type of gastrointestinal NETs and are associated with common metastasis to the mesentery, peritoneum, and liver, frequently associated with carcinoid syndrome, and the 5-year survival is less of 50% among persons with metastasis disease (5,6).

There are few data or recent reports about the incidence, epidemiology, and histopathologic characteristics of midgut NENs after the new WHO classifications of digestive tumors (5th edition), so to date there is no study that focuses on the histopathological characteristics and the division of well differentiated NETs in grade (G1, G2 or G3) or the use of the name NECs (poorly differentiated).

The morphology of NECs can be small cell or large cell, however, NECs with large multinucleated cells and with anaplastic features are not reported in English literature. Here we present a case report of a LCNEC with anaplastic features of the midgut.

2. Case report

A 50-year-old woman, who was previously diagnosed with diabetes mellitus type1 (T1DM), was brought to the emergency room, due to acute abdominal pain. The patient presented with a 4-month history of colic pain, dyspepsia, postprandial distension, change in bowel habits and weight loss of 12 kg. A simple not contrasted computed axial tomography (CTscan) revealed a tumor involving the cecum, with secondary obstruction. The patient underwent and emergency hemicolectomy for the clinical diagnosis of acute intestinal obstruction. After the surgery, and the histopathology diagnosis, the patient underwent a lung and abdominal CAT, both with contrast and without contrast, showing the presence of
multiple nodules in the liver, consistent with metastatic disease. The patient started palliative chemotherapy and died of the disease six months after surgery.

3. Pathological findings

Grossly, the tumor involved the cecum, the ileo-cecal valve and terminal ileum, it measured 20 x 12 x 12 cm and it was ovoid, lobulated and firm; the periphery was solid with a pale pink cut surface, and was in contact with the serosa. 14 lymph nodes were resected, 4 of them being positive for metastasis (Figure 1). Histologically, the tumor was composed mostly of large mononuclear cells intermingled with large cells with anaplastic-like morphology, arranged in solid sheaths. The anaplastic-like large cells showed abundant amphophilic cytoplasm, and multiple nuclei arranged in a wreath-like pattern, with open chromat and visible nucleoli, the morphology reminiscent of anaplastic T lymphoma. The mononuclear large cells had moderate amphophilic cytoplasm with nuclear pleomorphism, some with disperse chromatin and inconspicuous nucleoli, others with hyperchromatic nuclei (Figure 2). The mitotic count was high (>20 mitoses/2 mm2), with many atypical mitoses. Lymphovascular invasion was present, perineural invasion and necrosis were not found.

By Immunohistochemistry, both the large anaplastic-like cells and mononuclear large cells were positive for cytokeratin AE1-AE3 (membranous and para nuclear “dot-like”), CD56, chromogranin and synaptophysin (Figure 3); negative for CD3, CD20, CD30, CK20, EMA, CD5, CD4, CD8, CDX2, PAX5, SALL4, SATB2 and ALK. The results of immunohistochemistry and the antibodies used are summarized in Table 1.

Ultrastructure showed polygonal cells with scant cytoplasm that contained few organelles and dense core neurosecretory granules. The nuclei were large with finely dispersed euchromatin and small clumps of heterochromatin, most displayed a small nucleolus (Figure 4).

Figure 1. Gross appearance, the tumor is large and shows a central cavity (asterisk), the wall is infiltrated by a neoplastic solid pale tumor (arrowhead).

Figure 2. There are two types of neoplastic cells. One are large multinucleated cells with a wreath-like configuration and a anaplastic morphology similar to the cells of anaplastic large T cell lymphoma, (arrow), also there a component of mononuclear large cells, and multiples atypical mitosis (hematoxylin and eosin (H&E); 40x).

Figure 3. The neoplastic cells are positive for cytokeratin AE1AE3 (CKAE1-3), CD56, Chromogranin (CR-GR) and Synaptophysin (SYN) (x40).
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Figure 4. Ultrastructurally the cells show large nuclei with fine dispersed chromatin, most displayed a small nucleolus (A). The cytoplasm contains neurosecretory granules (B).

Table 1. Results of the immunohistochemical analysis.

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Results</th>
<th>Pattern</th>
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<tr>
<td>CKA1/3</td>
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<td>Biogenex</td>
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<td>Cytoplasmatic strong</td>
<td>Dako</td>
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<td>5H7</td>
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<tr>
<td>CD 56</td>
<td>+3</td>
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<td>CD 3</td>
<td>-</td>
<td></td>
<td>abcam</td>
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<td>-</td>
<td></td>
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With the morphology of the tumor, immunophenotype and the ultrastructural characteristics, a diagnosis of large cell neuroendocrine carcinoma was done, but due to the presence of anaplastic large cells, we decide to call this tumor as “Large cell neuroendocrine carcinoma of with anaplastic features”.

4. Discussion

Is well known that many tumors can have “anaplastic” morphology, especially some types of carcinomas (thyroid, pancreas, lung), and anaplastic T cell lymphomas. The anaplastic morphology in NECs of the digestive tract is not mentioned in the literature. The tumor presented in this case displayed a solid pattern, most of the neoplastic cells were mononucleated large cells intermingled large multinucleated cells showing an anaplastic like-morphology, the tumor showed brisk mitotic activity (> 20 mitoses/2 mm2).

By histology the differential diagnoses are; anaplastic adenocarcinoma, anaplastic T cell lymphoma, melanoma or dedifferentiated Gastrointestinal Stromal Tumor (GIST). In this case the diagnosis of neuroendocrine neoplasm was evident by the expression of CD56, chromogranin and synaptophysin and confirmed ultrastructurally by the presence of dense core neurosecretory granules.

In our search of the literature, we only found one article that emphasis in the histologic findings of a LCNEC, it is a report of a LCNEC of the esophagogastric...
juncture with rhabdoid features (7). There is a possibility that are more unusual histologic features of LCNECs, but that are unrecognized because the rarity of LCNECs of gastric digestive system.

NECs of the gastrointestinal tract have an aggressive clinical evolution regardless of the site or origin, with early metastasis and poor prognosis (8), the patient presented aggressive clinical with documented metastasis to liver by CAT and die of disease 6 months after the surgery, it is not clear if the anaplastic morphology conferred a prognosis different from that described in these neoplasms.

5. Conclusions
We herein report the first case large cell NEC with anaplastic features involving the midgut, corroborated by immunohistochemistry and ultrastructure, this variant should be included in the differential diagnosis of anaplastic tumors of the intestine. The prognosis of NECs of the gastrointestinal tract is poor, anaplastic features may confer a different prognosis, but this should be confirmed with larger studies.

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Declaration of Competing Interest
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Abbreviations
World health organization (WHO)
Neuroendocrine neoplasms (NEs)
Neuroendocrine tumors (NETs)
Neuroendocrine carcinomas (NECs)
Small cell type neuroendocrine carcinoma (SCNEC)
Large cell type neuroendocrine carcinoma (LCNEC)
Computed axial tomography (CT scan)