Case Report: Primary pure clear cell gastric carcinoma

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Abstract
Clear cell carcinoma has been described in numerous anatomic sites, but the renal location is the most frequent. Its occurrence in the stomach is exceptional. Here, we report the case of a 51-year-old woman who presented with epigastric pain of four months. The upper gastrointestinal endoscopic examination revealed a polypoid tumor of the greater curvature of the stomach. Biopsies showed a poorly differentiated carcinoma with a signet-ring cell component. The CT scan revealed a polypoid mass of the vertical part of the greater gastric curvature. There was no renal lesion. A distal subtotal gastrectomy was performed, and the post-operative course was uneventful. The gross exam showed a 6.5 cm, polypoid ulcerated tumor of the antrum. Histological analysis showed a clear cell gastric carcinoma. The immunohistochemical study, performed to rule out a metastasis from renal carcinoma, showed that tumor cells didn't express CD10 and vimentin. We therefore retained the diagnosis of a primary gastric clear cell carcinoma. Pure primary clear cell carcinomas of the stomach are exceedingly rare and are associated with a poor prognosis. Immunohistochemistry is the cornerstone of the diagnosis of these tumors to rule out metastases from a renal clear cell carcinoma.

Keywords
Clear cells, gastric cancer, gastrectomy
Introduction
Clear cell carcinoma (CCC) generally develops in organs originating from the Mullerian system, such as the lower urinary and female genital tracts. Its occurrence in the gastrointestinal tract is uncommon, and cases occurring in the stomach are exceedingly rare. Clear cytoplasm, and hence clear cells, are the result of intracellular accumulation of glycogen, lipid, water, or mucin. Due to its rarity, the clinicopathological and biological behaviors of this entity remain unclear.

Until now, only a few cases of gastric CCC have been reported in the English literature. These reports generally included gastric carcinoma with focal clear cell changes. We report herein the third case of a pure gastric CCC.

Case report
We report the case of a 51-year-old north African woman, who presented with a history of epigastric pain of four months. The abdominal examination found mild epigastric tenderness but no palpable mass. The upper gastrointestinal endoscopic examination revealed a polypoid tumor of the greater curvature of the stomach measuring 6x4 cm (Figure 1). Biopsies were performed using digestive endoscopic biopsy forceps. The anatomopathological examination showed a poorly differentiated carcinoma with a signet-ring cell component. No immunohistochemical examination was performed.

A CT scan of the thorax and abdomen, performed as part of the extension assessment, showed a pedicled budding mass with endoluminal development of the vertical part of the greater gastric curvature measuring 6 x 4 x 5cm (Figure 2). Otherwise, it did not show evidence of any renal tumor or hepatic or pulmonary localization.

In order to reduce tumor volume and improve the R0 resection rate, the patient received four courses (one course per two weeks) of perioperative chemotherapy with 5-fluorouracil (2600mg/m2), folinic acid (350mg), oxaliplatin (85mg/m2) and docetaxel (50mg/m2) according to the FLOT regimen, administered through a totally implantable venous access port via the internal jugular left vein. Then the patient underwent distal subtotal gastrectomy with a manual Roux-en-Y esophagojejunostomy, via a midline incision. This was the procedure of choice of the clinical lecturer who performed the intervention in case of proximal gastric cancer.

Gross examination revealed an ulcerated polypoid tumor with endoluminal development. The histological exam showed an invasive tumor arranged in lobules, clusters, and nests within a highly vascularized stroma (Figure 3a). There were necrotic changes. Tumor cells had abundant clear cytoplasm and well-defined cytoplasmic borders. The nuclei had marked atypia and prominent eosinophilic nucleoli (Figure 3b). The tumor infiltrates to the subserosa without serosal invasion. Moreover, we noted the absence of vascular emboli, perineural tumor invasion and lymph node metastasis. Periodic acid-Schiff and alcian blue stains were negative. An immunohistochemical study was performed to rule out a renal origin. The tumor cells were negative for CD10 and vimentin. They were positive for cytokeratin with diffuse cytoplasmic and membranous staining. The diagnosis of primary gastric CCC in its pure form was made.
The postoperative course was uneventful and the patient was discharged on the fifth postoperative day on analgesic treatment and low-molecular-weight heparin for thirty days. The patient received four courses of adjuvant chemotherapy (FLOT regimen). The CT scan done after six months showed no local or distant recurrence.

Discussion

A CCC can develop in various organs, and the most common sites are the kidneys and the female genital tract. Its occurrence in the gastrointestinal tract is uncommon. Only few case reports or small series have been described in the colon, pancreas, and the biliary system.

Even though the presence of clear cell changes in gastric carcinoma has been reported in 8.5% of cases, the pure form of CCC of the stomach is an extremely rare oncologic entity. There is no specific reference to CCC in the latest WHO classification of gastric carcinoma. This entity has not been well documented, with only limited literature available on the topic.

Regarding the clinical characteristics, Kim et al. have demonstrated, in a large cohort study, that gastric carcinomas with clear cell changes were associated with younger age and tended to be located in the gastric antrum. However, Ghotli et al. showed that gastric CCC had a predilection for the gastroesophageal junction. Moreover, these tumors are polyloid and histologically characterized by a tubulo-papillary pattern. These features are consistent with the characteristics of the tumor in our case, which was polypoid and located in the vertical part of the greater gastric curvature.

What makes this case remarkable is that the present tumor is composed of more than 10% of clear cells. Kim et al. reported 65 cases and defined CCC as a carcinoma composed of more than 5% of clear cells. To the best of our knowledge, only Terada and Yamada et al. have reported the pure form.

It has been shown that the presence of clear cell changes is an independent indicator of poor prognosis since it is associated with advanced depth of invasion, presence of lymphovascular tumor emboli, and lymph node metastases, compared to gastric adenocarcinoma without clear cell changes.

Advances made in techniques used for pathological examinations and immunohistochemistry made the diagnosis of gastric CCC easier. Immunophenotypically, it has been demonstrated that CCC carcinoma shows overexpression of cyclin D1. It has also been noted that clear cell tumors of the stomach may produce alpha-fetoprotein (AFP) in the serum and within the tumor. In our case, AFP was not measured.

Recently, hepatocyte nuclear factor-1b (HNF-1b) has been accepted as a unique biomarker of CCC for tumors of the female genital tract, bladder, and pancreas. In the stomach, carcinomas with clear cell changes also show increased positive immunostaining of HNF-1b as it has a role in cellular glycogen synthesis. Nevertheless, until now, there has been no reports about the role of HNF-1b in gastric adenocarcinomas.

Due to its rarity, there are no therapeutic guidelines for CCC. It is managed like conventional gastric carcinomas, and its surgical treatment depends on its localization. In our case, the tumor was located in the vertical part of the great gastric curvature and necessitated total gastrectomy.

Conclusions

Pure primary CCC of the stomach are exceedingly rare and are associated with a poor prognosis. Immunohistochemistry is the cornerstone of the diagnosis of these tumors to rule out metastases from a renal CCC.
Data availability
All data underlying the results are available as part of the article and no additional source data are required.

Consent
Written informed consent for publication of their clinical details and clinical images was obtained from the patient.

References


Open Peer Review

Current Peer Review Status:  

Version 1

Reviewer Report 06 July 2021

https://doi.org/10.5256/f1000research.28482.r88574

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This case report is concise, nicely written and presented with clear concept for an important topic.

However, due to its rarity, some more details may be required, both clinically and histopathologically.

1. Being an exceedingly rare tumor, all available clinical and demographic data are required; e.g. origin, ethnicity, martial status of the patient, history of dyspepsia or indigestion, nausea or vomiting, loss of appetite or weight, smoking, drug histories, etc.

2. Have the authors considered that neoadjuvant chemotherapy might have altered the immunohistochemical reactivity of this tumor?

3. The authors relied on minimal immunohistochemical markers as a diagnostic tool to exclude renal origin. They should have exhaust all possible markers to exclude a renal and other less common origins and to prove a gastric origin: Please, see below: [(The commonly used immunarkers can differentiate and distinguish most of the clear-cell tumors. Clear cell carcinoma (CCC) of female genital tract (FGT) are CD15, Napsin A, and CA125 positive and estrogen receptor (ER), Wilms tumor 1 (WT1),carcinoembryonic antigen(CEA), inhibin, and alpha-fetoprotein (AFP) negative; clear cell renal cell carcinoma (CCRCC) are CD10, epithelial membrane antigen (EMA), vimentin, Pax 2, and CK20 negative; variable CK7 andmelanomas are HMB45 and Melan A positive; skin CCCs are CK and HMWK positive; sarcomas are positive with vimentin and variably positive for desmin, smooth muscle actin, S-100, and CD68. In the central nervous system (CNS), immunomarkers such as glial fibrillary acidic protein (GFAP), neuron-specific-enolase (NSE), S-100, vimentin, and EMA are used for differentiation of entities. By combining morphology with]
immunohistochemistry (IHC)). Even Perivascular Epithelioid Cell (PEComa) must be excluded. **This is a major drawback on the report.**

4. They also did not specify **which cytokeratin** was used (pancytokeratin, CK7 or CK20?

5. Also **H&E images are insufficient.** They should provide more photos of H&E as well as for **all immunohistochemical markers used** to convince the reader of a primary pure CCC of stomach.

6. Tumor stage was not precisely determined. It must be clearly mentioned.

7. Clear cell carcinomas are usually aggressive and carry a poor prognosis. Have the authors **followed the case up** and for how long?

8. Being an aggressive tumor, **why have you tried the conventional treatment for adenocarcinoma?** would a more aggressive therapy been more appropriate?

9. The authors have stated that ((Then the patient underwent distal subtotal gastrectomy with a manual Roux-en-Y esophagojunostomy, via a midline incision)) in case report section, but later in discussion they state that ((In our case, the tumor was located in the vertical part of the great gastric curvature and necessitated total gastrectomy)). **Would that be considered a controversy?**

10. A statement that **all authors have approved** the submitted manuscript and all subsequent revisions is required and must be added.

**Is the background of the case's history and progression described in sufficient detail?**
Partly

**Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?**
No

**Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?**
Yes

**Is the case presented with sufficient detail to be useful for other practitioners?**
Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Medical human genetics, clinical genetics, cytogenetics, molecular diagnosis, biochemical genetics, birth defects and teratology, and genetic counseling.

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have
significant reservations, as outlined above.

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