Clear Cell Carcinoma of the Pancreas Infiltrating Duodenum: A Case Report of a Multiface Aspect of an Intriguing Entity

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Abstract

Background: Although Clear-cell carcinoma has been found in various organs as a variant of ductal carcinoma of the pancreas, it still hasn't been well recognized. According to the WHO classification, primary Clear-cell carcinoma of the pancreas is rare, and it is classified as a "miscellaneous" carcinoma. To date it has been poorly characterized and only few cases have been reported in the literature [1].

Case presentation: We report here an unusual case of Clear-cell carcinoma in a 59-year-old man involving the head of the pancreas and the second part of the duodenum initially misconceived as pyloric gland adenoma, a rare duodenal entity. Nevertheless, duodenal sub stenosis was suspected of malignancy, so further investigations were made. Subsequent abdominal computed tomography (CT) detected not only a duodenal vegetation but also an alteration of the duodenal-pancreatic interface with thickening of the duodenal wall and a common bile duct dilatation. The malignant clinical aspect and behavior of the lesion, associated to the impossibility of further investigations due to the duodenal sub stenosis, led to an exploratory laparotomy.

The laparotomy revealed a retracting area straddling the duodenum and the pancreatic head. A duodenum pancreatectomy of the head of the pancreas with extended lymphadenectomy was performed and the histological evaluation showed a ductal Clear-cell adenocarcinoma of the pancreas infiltrating the duodenum. The postoperative course was characterized by a pancreatic fistula grade B. At 6 months from the surgery, the patient hasn't had recurrence.

Conclusion: Because it is a rare tumor with very few cases reported previously, the incidence and prognosis are not well known for this neoplasm. The report of our case would aid in the identification of this rare neoplasm. Further studies and more case reports are needed to clarify the diagnosis and prognostic significance of the clear cell differentiation of these tumors.

Background

Adenocarcinomas of ductal origin accounts for 85–90% of all pancreatic exocrine tumors. The World Health Organization (WHO) recognizes several histo-morphologic variants of ductal adenocarcinoma in addition to the classical form and in particular Clear-cell carcinoma, a "miscellaneous" carcinoma characteristically rich in glycogen and poor in mucin (1)

Unfortunately, few data are available regarding the incidence and the characteristics of this type of tumor.

We report an unusual case of ductal adenocarcinoma with predominantly clear cell morphology at the duodeno-pancreatic interface which mimicks, in the first phase of approach, a pyloric gland adenoma.

Case Presentation

A 59-year-old man was admitted at Spedali Civili Hospital of Brescia, Italy, in August 2020, having developed icterus, pale stool and brown urine. At the initial diagnostic work up, a computed tomography scan of the abdomen revealed a vegetation in the second part of the duodenum, with an alteration of the duodenal-pancreatic interface and thickening of the duodenal wall, and a common bile duct dilatation. A inhomogeneous pancreatic head with dilatation of the proximal part of the pancreatic duct and dilatation of the extra and intra-pancreatic bile ducts was also discovered. Tumor markers CEA and CA19-9 were within normal limits.

Subsequently, a magnetic resonance cholangiography was executed to rule out the presence of gallstone in the biliary tree liable for an intra-pancreatic biliary duct dilatation.

With this suggestion, an endoscopic retrograde cholangiopancreatography was attempted, but the instrument failed to pass the superior duodenal flexure due to a sub stenosis of the second part of the duodenum. (Fig. 1A-B) A series of biopsies of the duodenal vegetation were performed during the procedure without solving the biliary obstruction.

Histological examination of the biopsy specimen in a background of mild chronic duodenitis suggested the possibility of a pyloric-type glands adenoma with low grade dysplasia, but the unusual imaging made it necessary to carry out further instrumental investigations (Fig. 2A-B)

Patient underwent endoscopic ultrasound (EUS) performed with 3870UTK linear scope (Pentax, Tokyo, Japan). The narrow of the duodenal lumen denied the access to the Vater papilla. However, the endosonographic view from the duodenal bulb window showed a periampullary neoformation (EUT3N1) 22 mm in diameter with secondary biliary dilation (Fig. 3A-B). A fine needle aspiration with 22G EchoTip Ultra needle (Cook, USA) was performed. The cytological evaluation was consistent with a diagnosis of low-grade epithelial dysplasia.

Since the ERCP failed to solve the jaundice, the patient underwent a percutaneous cholecystostomy (total bilirubin/direct 3,70/3,21 mg/dL). Once the icterus was solved, we proposed to the patient an exploratory laparotomy to solve the diagnostic dilemma and obtain a reliable diagnosis. The laparotomy revealed a retracting area straddling the duodenum and the pancreatic head that made it impossible to proceed with a conservative resection. A macro biopsy was considered useless owing to the clear evidence of infiltration. Therefore, a duodenopancreatectomy with extended lymphadenectomy was performed. Gross examination of the surgical specimen showed no evidence of a macroscopic lesion along all the duodenal mucosae. (Fig. 4A) Cut sections uncovered a firm, whitish and poorly defined lesion of the pancreatic head, with a maximum extension of 2,5 cm, and macroscopic infiltration of duodenal wall (Fig. 4B). Macroscopic involvement of the intrapancreatic bile duct was also detected.

Histological examination of the specimen evidenced a moderately differentiated infiltrating neoplasia, forming atypical glandular-like structures and solid nests, surrounded by a desmoplastic stroma. The pancreatic neoplasia was composed of polygonal cells with marked clarification of cytoplasm. Nuclei were hyperchromatic, predominantly eccentrically located and with moderate pleomorphism. (Fig. 5A).

Additional findings were the presence of vascular and perineural invasion and concomitant low grade intrapancreatic neoplasia. (PIN1).

PASD (Periodic Acid-Schiff with predigestion with diastase) staining highlighted diffuse mucin accumulation in neoplastic cells (Fig. 5B). CA 19-9 immunostain showed strong but patchy cytoplasmatic positivity. HNF-1 β immunostain has been reported to be specific for clear cell variant of pancreatic ductal adenocarcinoma [2]; in this case HNF-1 β has shown diffuse and moderate to strong nuclear immunostaining in neoplastic cells. (Fig. 5C-D). Negative immunostain for PAX-8, accordingly with no clinical and radiological evidence of a renal neoplasm, definitely excluded a clear cell renal carcinoma metastasis [3], [4].

An unusual feature was the histological behavior of the pancreatic neoplasia that spreaded from the pancreatic core through the duodenal muscular layer up to the mucosa changing its phenotype throughout the invasion. The clear cell phenotype turned into a well-differentiated adenocarcinoma, composed of columnar cells with low to moderate grade atypia and a foamy cytoplasm resembling a foamy gland pattern of pancreatic ductal adenocarcinoma, is reported as an apparently benign variant [5]. Notably, where the neoplasia reached the duodenal mucosa, these neoplastic cells resembled the features detected in the previous biopsy specimen that was mis-interpreted as a duodenal pyloric gland adenoma. (Fig. 5E-F)

Final diagnosis of ductal adenocarcinoma with clear cell morphology, moderate grade of differentiation, duodenal infiltration and 2/26 positive nodes (pT2N1; AJCC 7th edition) was made.

Discussion

We describe a case of carcinoma in the duodenal-pancreatic interface, firstly misdiagnosed as a duodenal pyloric gland adenoma. Final diagnosis of clear cell carcinoma belonging to the pancreas was made with an unusual difficulty to obtain a preoperative diagnosis.

In this case, CT and MRI, the well accepted tools to study the pancreatic lesions, failed. This is not a rare situation because atypical imaging features may be present and, in addition, many other diseases may mimic pancreatic adenocarcinoma [6, 7] even if usually a strong suspect arises when used sequentially.

In this patient, CT scan showed an inhomogeneous head of the pancreas, an alteration of the duodenal-pancreatic interface, a thickening of the duodenal wall, a modest proximal ectasia of the Wirsung duct and no signs of atrophy of the rest of the gland. Cholangio-MRI confirmed the over distension of the gallbladder but mentioned the presence of an hypointense in T2 mass in the papilla compatible with a gallstone and, again, no evidence of malignant lesions. So, direct, and indirect signs of cancer of the head of the pancreas were lacking. ERCP and echoendoscopy also failed to solve the problem because the instrument did not pass through the superior duodenal flexure for a partial stenosis. At the end of the diagnostic process, we solved the icterus with a percutaneous procedure, but we had no definitive diagnosis. The biopsy of the duodenal vegetation made during the cholangiopancreatography suggested

a probable duodenal pyloric gland adenoma (PGA), originally defined in 1976 by Kurt Elster [8, 9]. This kind of lesion is typically found in the stomach, but it can also originate from duodenum (9% of the reported series) (9), gallbladder, bile duct, pancreas, rectum and in Barrett's esophagus. It is most common in females in their 8th decade of life [8] likely due to their association with autoimmune gastritis. The identification of these lesions is important because they have a malignant potential, although this evolution is rarely reported (....).

At that point, we proposed an explorative laparotomy; the duodenal lesion compromised the duodenal lumen and determined an obstructing icterus. Furthermore, we considered the direct visualization and the intraoperative biopsy as the final steps to obtain a diagnosis. Literature permits an extensive resection till the duodenopancreatectomy without a histologic proof, but this strategy accounts for a rate of 7-8% of false positive diagnosis and resection is finally performed for a benign lesion of the pancreas (10). In this case, no evidence was clear towards a diagnosis of a pancreatic lesion; really, the most probable diagnosis was a benign process of the peri-ampullary area and not a pancreatic cancer.

The complicated and inconclusive diagnostic process was certainly the first unusual characteristic of this case, but the real unexpected feature was the histopathological result.

Histopathological examination of the surgical specimen revealed Clear-cell ductal adenocarcinoma of the pancreas with an unusual behavior regarding the invasion of the duodenum. This feature consisted of a changing in the phenotype of the neoplasia, starting from a clear cell component to a well-differentiated adenocarcinoma where the neoplasia infiltrated the duodenum up to the mucosa. Notably, where the neoplasia reached the duodenal mucosa, a various degree of dysplasia was observed and cells resembling the features detected in the previous biopsy specimen, which was mis-interpreted as a duodenal pyloric gland adenoma, were also found.

We were confident about the final diagnosis. Carcinomas with solid clear cell features are rare in the pancreas but common in other organs; the differential diagnosis must first consider the possibility of a metastasis of an extra pancreatic primary tumor, notably a renal Clear-cell carcinoma [10]. The specific criteria to confirm this tumor have not yet been established. Kim L et al, Luttges J et al. and Ray S et al. classified Clear-cell carcinoma as those tumors with more than 75%, 90%, 95% respectively of the tumor cells being clear cells [13, 14]. To define this disease entity and prognosis further investigation with other methods is needed. The finding, however, that our case of Clear-cell carcinoma had an intraductal papillary component excluded the possibility of a metastasis from a renal Cell-carcinoma or other similar extra pancreatic cancers, such as the carcinoma of the adrenal cortex or lung. Furthermore Clear-cell carcinomas of the kidney often stain not only for keratin but also for vimentin [11] and for the other non-pancreatic cancer, an intraductal papillary component is unusual. Moreover, the negativity for chromogranin A and synaptophysin excluded an endocrine neoplasm and the negativity for neuron-specific enolase (NSE), alpha-1-antitrypsin and vimentin a solid pseudo-papillary tumor [12, 13]. All these data give strength to our final diagnostic suggestion.

There are not clear treatment guidelines for Clear-cell carcinoma. In our case, the patient started adjuvant chemotherapy with FOLFIRINOX 3 months after surgery, which was replaced, after the first cure, with FOLFOX because he suffered profuse diarrhea, hyperpyrexia, and abdominal pain.

To date, 4 months later, there are no signs of disease recurrence.

Conclusion

Clear cell carcinoma of the pancreas remains a poorly characterized and understood disease. It is currently listed under “miscellaneous” as part of the World Health Organization (WHO) classification. We have presented a rare case of clear cell carcinoma of the pancreas. The specific criteria to confirm this tumor have not yet been established. To define this disease entity and its prognosis, further investigation with other methods such as biomarker studies, gene analysis and immunohistochemistry are needed to differentiate clear cell carcinoma of the pancreas from other pancreatic tumor. Our case might be a contribute for further review in order to study the presentation and the behavior of these rare entity.

Declarations

- **Ethics approval and consent to participate:** the report was approved by the appropriate ethic review board.
- **Consent for publication :** the participant provided informed consent.
- **Availability of data and materials :** the datasets used for the report are available from the corresponding author on reasonable request.
- **Competing interests :** the authors declare that they have no competing interests.
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Figures

Figure 1

A – B: endoscopic view of the duodenal stenosis due to “ab estrinseco” compression from the pancreatic mass.

Figure 2

The so-called pyloric gland adenoma with low dysplasia H&E A x 4 B x 20.

Figure 3

A: EUS view of the neoplastic mass and biliary dilation from the duodenal bulb ultrasonographic window.
 B: EUS FNA.

Figure 4

Surgical specimen A- duodenal mucosa without macroscopic lesions; B Tumor of the pancreatic head.

Figure 5

A adenocarcinoma with clear cell H&E x 20 B PAS-Diastase accumulation of mucus in neoplastic cells C-D diffuse nuclear positivity for HNF-1 β C x20 D x60; E-F tumor in the duodenal mucosa H&E e x 10 F x 40.