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Primary signet ring cell carcinoma of the pancreas. A case report about an extremely rare variant of pancreatic carcinoma.

INTRODUCTION: *Primary signet ring cell carcinoma of the pancreas (PSRCCP) is an extremely rare histologic variant of pancreatic carcinoma, which cells are characterized by large mucin vacuoles and peripheric nucleus that producing a signet ring aspect.*
CASE REPORT: *We present a case about 66 years old man, with history of chronic pancreatitis and Wirsung stenosis of unknown origin, came to our attention for abdominal pain compatible with pancreatitis exacerbation. A TC scan showed a head of pancreas' neoformation, and a MRI showed numerous metastatic liver lesions confirming the presence of pancreatic lesion (52x46) mm. Fine needle aspiration biopsy of liver was suggestive of signet ring cell carcinoma. As second step, an ERCP was performed in order to get a biopsy of pancreatic lesion and drain the biliary tract. No surgical approach was possible as well as the progressive complications arised after diagnosis contraindicated chemotherapy. The patient died 3 month after diagnosis.*
CONCLUSION: *PSRCCP is an aggressive malignancy with low survival rate, because of high metastatization rate. Only 9 cases are described in literature at December 2019, so we consider our work a precious contribute to knowledge.*

KEY WORDS: Pancreatic tumor, Pancreas, Pancreatic carcinoma, Primary signet ring cell carcinoma of the pancreas. Signet ring cell carcinoma

Case Report

We present a 66 years old male patient, known for chronic pancreatitis of biliary origin since 2013. He was also affected by ischemic heart disease (aortocoronary triple bypass in 1998), peripheral artery disease and non-insulin dependent diabetes mellitus type 2. He smoked 60 py and had moderate alcohol consumption. In April 2019 he had his annual check-up with the gastroenterologist, who asked for a MRI of the pancreas, one year after the previous MRI. The exam showed complete stability of pancreatic morphological changes, with the presence of a sub-stenosis at the level of the pancreatic isthmus with slight expansion of the Wirsung duct, and a fair hypotrophy of the parenchyma. In addition, the known small cystic formation remained stable, at about 11 mm, always at the isthmus level; gastroenterologist proposed a subsequent check in a year. Unluckily, from the end of October, the patient suffered abdominal pain, so he was hospitalized with the hypothesis of exacerbation of chronic pancreatitis. He didn't feel nausea, he had normal stool but he reported 7 kg weight loss in one month despite normal nutrition. He underwent a CT scan, which detected a mass in the head of the pancreas, then a MRI, which confirmed the pancreatic lesion, localized in the head of pancreas, maximum size

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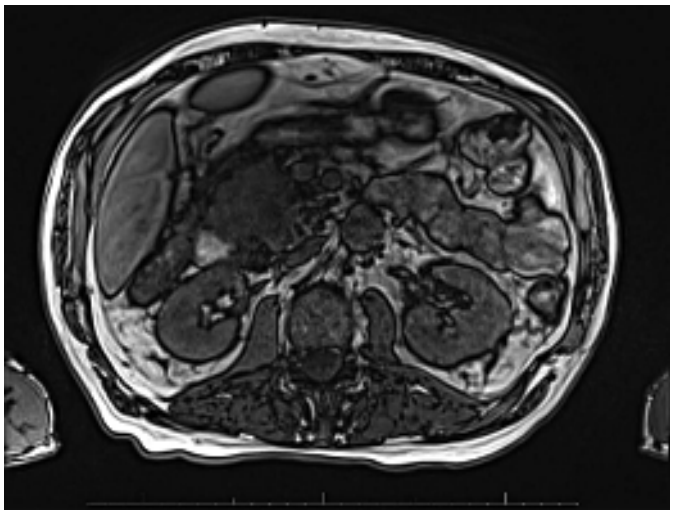

Fig. 1: MRI showing a 52 x 46 mm pancreatic lesion, localized in the head of pancreas.

52 x 46 mm (Fig. 1), in contact with the upper mesenteric vein for less than 50% of the circumference. Moreover, the MRI detected, in the liver parenchyma, innumerable areas of impaired signal intensity, with a diameter ranging from a few millimeters to 1.9 cm, compatible with secondary lesions. The heteroformative picture appeared inseparable from the gastric antrum and the first portion of the duodenal C. Lymph node formations compatible with secondary disease involvement were recognizable posterior to the pancreatic head and tripod (maximum diameter 14 mm). Biopsies were performed on one epatic lesion (performed with percutaneous echo-guided fine needle biopsy) and on the pancreatic mass performed through eco-endoscopic fine needle biopsy); adenocarcinoma with signet-ring cells was identified. The patient was discharged from the hospital and the multidisciplinary oncological board proposed to start palliative chemotherapy. A couple of week later, the patient was hospitalized for mechanical obstruction of the small bowel, ascites and sepsis, secondary to tumor progression. The situation was critical and a surgical treatment was not indicated. The patient received an antibiotic treatment and a palliative care treatment was started. He died in three weeks.

Discussion

Primary signet ring cell carcinoma of the pancreas (PSRCCP) is a particular histotype of pancreatic carcinoma. Tumor's cells are characterized by large intracytoplasmic mucin vacuoles which push the nucleus at the periphery of the cell, causing the signet ring aspect [1,2]. PSRCPP is a very rare type of pancreatic tumor. In fact, if pancreatic cancer annual incidence is about 12.5 cases per 100.000 people in the USA [3], the 85% – 90% of these cases are pancreatic ductal carcinomas [4]. In a large retrospective study, based on National Cancer Institute's Surveillance, Epidemiology and End Result (SEER) database, Patel M. et al [5] found out just 497 PSRCCP confirmed cases between January 1th 1973 and December 31 2013 in USA population. The literature currently avaible about PSRCPP includes only 9 case reports [6-14] .Primary signet ring cell carcinoma occurs most frequently in the stomach (96% of cases), while in less than 1% of cases it involves the pancreas [2]. The tumor involves mostly the head of the pancreas (49,7% of cases) and it is poorly differentiated in 42,5% of cases [5]. According to the study of Patel M. et al., the median age of patients is 68 years old, with a range starting from 18 to 97 years old, with a slight prevalence for males (55% vs 45% for female). There's a significant prevalence in white race (82,7%), but the 10% of black people affected by PSRCCP shows a worse prognosis. Case reports about PSRCPP show both an higher median age of patients (74 years old) and an higher male prevalence (87.5%) even though the limited number of cases is not representative. Molecular characteristics of this tumor were widely described by Patel M. et al. [5]. Neoplasm's cells show a costitutive activation of ErbB2/ErbB3 pathway, which allows the tumor to metastasize and increases its aggressiveness [5]. In a paper published in 2019, El Hussein S. et al. [13] highlight how the endoscopy guided-fine-needle aspiration (EUS-FNA) is widely used in the diagnosis of pancreatic tumors. They also describe the importance of immunohistochemistry (IHC) in the differential diagnosis of pancreatic lesions with signet ring-like morphology. In particular, PSRCCP's stains shows a positivity for MUC1 and MUC5. Furthermore, El Hussein S. et al. affirm that cytopathology examination alone could lead to misdiagnosis of pancreatitis, basing only on the presence of inflammatory cells [15]. Therefore, both IHC and cytomorphological examination of PSRCCP are mandatory for a precise diagnosis. Regarding prognosis, pancreatic cancer has a 5-years survival rate of 6% [16], while PSRCCP has a lower but similar survival rate (4%). This poor prognosis is due to the advanced stage of the tumor at the diagnosis, when only the 3% of cases is still localized to the pancreas [5]. Patient's age can be considered a negative prognostic factor, considering the higher prevalence of comorbidities in older patients, which leads to a higher risk for treatments like chemotherapy and radiotherapy [17]. Whenever possible, surgery is the first choice for PSRCCP when the tumor is localized in the pancreas or it has locoregional involvement. The procedure includes a duodeno-cephalo-pancreasectomy which can be followed by a gastrectomy. After that, adjuvant radiotherapy can be performed. While surgery can increase survival rate by a 64%, radiotherapy alone can improve it till 41%. Combined surgery and radiation can rise by 71% the 5-year survival rate. Treatment for metastatic PSRCCP includes various chemotherapy reg-

imens which aim to improve overall survival (OS) of patients, to induce a regression of the lesion and to control its symptoms. Among these cytotoxic regimens, best results can be obtained with FOLFIRINOX (5-FU, leucovorin (LV), irinotecan, and oxaliplatin), gemcitabine/nab-paclitaxel and nanoliposomal irinotecat/5FU [18]. There are also recent evidences about the efficacy of combined adjuvant chemotherapy and surgery for resectable or even borderline resectable pancreatic tumors [19]. In a 2017 case report, Radojkovic M et al [12] shows the efficacy of a combined theraphy with a gemcitabine/oxaliplatin regimen, which reduced the pancreatic mass, followed by a surgical treatment of the lesion. However, in their case, due to the low creatinine clearance rate of the patient, it was possible to use gemcitabine alone. Nevertheless, this regimen allowed to downsize the tumor from 4,5 cm to 1,5 cm, making it surgically treatable. Authors highlight also the role of adjuvant chemotherapy in treating possible distant micrometastasis, moreover it helps reducing peritoneal tumor implantation after the surgery. Unfortunately, in our case we discovered the tumor in an advanced stage, even if the patient was strictly followed by physicians and by imaging because of his chronic pancreatitis, so no therapy has been tested as well as no kind of surgical intervention.

Conclusion

PSRCCP is a really rare pancreatic cancer histotype, poorly described in literature and with just one retrospective cohort study available nowadays, edit by Patel M. et al. Moreover, in that paper, it's reported that only the 16% of diagnoses were made in the decades between 1973 and 2000, and the 84% were made between 2000 and 2010. Probably in the last decades this variety of pancreatic tumor was underestimate, and that in next years, thanks to the implementation of diagnosis methods, ever more cases of PSRCCP will be diagnosticated. For these reasons, in our opinion, is essential to improve the knowledge about PSRCCP, reporting updated cases about management of this pathology and treatment approach.

Riassunto

Il carcinoma con cellule ad anello con castone primitivo del pancreas (PSRCPP) è una entità nosologica estremamente rara, con soltanto 9 casi riportati in letteratura. Esiste un unico studio retrospettivo condotto negli Stati Uniti e basato sul database del National Cancer Institute's Surveillance Epidemiology and End Result, in cui sono emersi documentati soltanto 497 casi di PSRCPP in una finestra temporale che va dal gennaio 1973 al dicembre 2013. In questo Caso Clinico, presentiamo un paziente di 66 anni, seguito dal nostro centro per pancreatite cronica dal 2013. Ad un precedente controllo, svoltosi ad Aprile 2019 mediante Risonanza Magnetica Nucleare, il quadro pancreatico appariva stabile, con una piccola lesione cistica alla testa del pancreas stabile dai precedenti controlli, con un diametro di 11 mm. Tale stabilità, ha portato a pianificare un successivo controllo ad un anno di distanza, senonché il paziente venne ricoverato ad Ottobre 2019 per dolori addominali in un quadro clinico di sospetta pancreatite acuta su cronica. Durante gli accertamenti atti a confermare il sospetto, una TAC addome e quindi un nuova Risonanza Magnetica, misero in luce una massa pancreatica di 52x46 mm, con infiltrazione di antro gastrico e C duodenale, oltre che secondarismi epatici. Le biopsie condotte a livello sia epatico che pancreatico posero diagnosi di adenocarcinoma con cellule ad anello con castone. Il quadro clinico, discusso collegialmente, venne reputato candidabile a chemioterapia palliativa, sfortunatamente, il paziente morì poche settimane dopo per shock settico a partenza da un ileo meccanico indotto dalla massa tumorale. Abbiamo reputato interessate per la comunità medico-scientifica proporre questo caso in quanto trattasi di un istotipo oncologico rarissimo e poco discusso in letteratura. Sebbene lo studio retrospettivo citato abbia preso in analisi quasi cinquecento casi, non possiamo non considerare come nell'ultimo decennio le tecniche chirurgiche e le soluzioni chemioterapiche siano evolute ad un ritmo incalzante, pertanto è nostra convinzione che sia fondamentale pubblicare casi aggiornati e attuali su questo argomento.

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