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პაციენტი პანკრეასის აცინური კარცინომით - იშვიათი კლინიკური შემთხვევის აღწერა

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პანკრეასის კიბო კიბოთა 5%-ზე ნაკლებს შეადგენს და მათგან ყველაზე იშვიათი ტიპია პანკრეასის აცინური კარცინომა, რომელიც ყველა კიბოს 0,05%-ზე ნაკლებს შეადგენს. აცინური კარცინომა არის უაღრესად აგრესიული ნეოპლაზია. საერთო 5-წლიანი გადარჩენის მაჩვენებელი პაციენტებში ქირურგიული ჩარევით მერყეობს 36.2%-დან 72.8%-მდე.

21 წლის მამაკაცს აღენიშნებოდა არასპეციფიკური სიმპტომები, როგორიცაა პროგრესირებადი მუცლის ტკივილი, წონის დაკლება, გულისრევა და პირღებინება, მელენა, სისუსტე, ანორექსია. პაციენტი მწეველი იყო და ზომიერი რაოდენობით მოიხმარდა ალკოჰოლს. არ ჰქონდა კუჭ-ნაწლავის დაავადების ოჯახური ისტორია. ჩატარდა გამოკვლევები მუცლის და მენჯის გაძლიერებული კომპიუტერული ტომოგრაფიის, გულმკერდის რენტგენის, მუცლის ღრუს ულტრაბგერითი, სიმსივნური მარკერების, ღვიძლისა და თირკმელების ფუნქციის და კოაგულაციის ფუნქციის ჩათვლით.

ვიზუალიზაციის მიხედვით დიფერენციალური დიაგნოზი მერყეობდა კარგად დიფერენცირებულ პანკრეასის ენდოკრინულ ნეოპლაზმებს, მყარ ფსევდოპაპილარულ ნეოპლაზმებს, შერეულ აცინურ ნეოპლაზმებსა და პანკრეატობლასტომებს შორის.

იგი გადაიყვანეს ონკოქირურგიულ დეპარტამენტში სიმსივნური წარმონაქმნის ამოსაკვეთად. მეორე დღეს ჩატარდა მოდიფიცირებული ლაპაროსკოპიული Whipple პროცედურა (პილორუსის შემანარჩუნებელი პანკრეატიკოდუოდენექტომია), რადგან აგრესიული ქირურგიული რეზექცია ასოცირდება ხანგრძლივ გადარჩენასთან. პოსტოპერაციულმა ჰისტოლოგიურმა ანალიზმა გამოავლინა უხვი მასალა უჯრედებით, რომლებიც ასახავს სხვადასხვა ხარისხის აცინური დიფერენციაციას და სადინრის და ენდოკრინული უჯრედების ნაკლებობას. ნეოპლასტიკური უჯრედები არ აჩვენებდნენ ნორმალური ეპითელიუმის კომპაქტურ, მოწესრიგებულ ლობულურ „ყურძნის მტევანს“.

საკვანძო სიტყვები: ვიპლის პროცედურა, პანკრეასის აცინურუჯრედოვანი კარცინომა, აგრესიული ნეოპლაზია.

A patient with pancreatic acinar carcinoma a - a rare clinical case report

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Abstract

Pancreatic cancer accounts for less than 5% of all cancers. And the rarest type of them all is the pancreatic acinar cell carcinoma accounting for less than 0.05% of all cancers. Acinar cell carcinomas are highly aggressive neoplasms, with a median DFS (Disease Free State) for patients with localized disease and metastatic disease of 47 and 14 months, respectively, and an overall 5-year survival rate ranging from 36.2% to 72.8% in surgically resected individuals.

A 21-year old man presented with non-specific symptoms like progressive abdominal pain, weight loss, nausea and vomiting, melena, weakness, anorexia. Patient was a smoker and consumed moderate amounts of alcohol. There was no family history of gastrointestinal disease. Examinations including enhanced abdominal and pelvic CT scans, chest X-ray, abdominal ultrasound, tumour markers, liver and renal function and coagulation function were performed.

With the imaging, the differential diagnosis could be well-differentiated pancreatic endocrine neoplasms, solid pseudopapillary neoplasms, mixed acinar neoplasms and pancreatoblastomas.

He was referred to surgical oncology for tumour resection. The following day, a modified laparoscopic Whipple (pylorus preserving pancreaticoduodenectomy) was performed. The reason being, aggressive surgical resection with negative margins is associated with long-term survival. Negative margins were obtained in the pancreatectomy specimen. Post operative histological analysis revealed abundant material with cells depicting varying degrees of acinar differentiation and lack ductal and endocrine cells. The aspirates contained mostly cohesive fragments forming acini, cellular cords or solid nests of neoplastic epithelium. The neoplastic cells did not show the compact, orderly lobular “bunch of grapes” arrangement of normal epithelium.

Key words: Whipple procedure, acinar cell carcinoma (PACC) of the pancreas, aggressive neoplasia.

Introduction

Pancreatic cancer, constituting less than 5% of all cancers, presents as one of the most challenging malignancies with limited treatment options and a dismal overall prognosis. Within this heterogeneous group,

pancreatic acinar cell carcinoma (PACC) emerges as an exceptionally rare subtype, accounting for less than 0.05% of all cancers.[1-3] PACC is a rare and aggressive neoplasm that arises from the exocrine portion of the pancreas. The median Disease-Free State (DFS) for patients with localized disease and metastatic disease is reported at 47 and 14 months, respectively, underscoring the formidable challenges associated with both early and advanced stages.

Unlike the more common pancreatic ductal adenocarcinoma, PACC is characterized by its unique histopathological features, predominantly composed of acinar cells that closely resemble normal pancreatic acinar tissue. [4] Despite its infrequency, PACC poses significant diagnostic and therapeutic challenges due to its ability to mimic other pancreatic neoplasms both clinically and radiologically. The distinct molecular and genetic alterations underlying PACC further differentiate it from other pancreatic tumours [5], highlighting the need for a comprehensive understanding of its pathogenesis for the development of targeted therapeutic strategies. In this clinical case report, we present a detailed analysis of a case of pancreatic acinar cell carcinoma, discussing its clinical presentation, diagnostic workup, treatment modalities, and outcomes, with the aim of contributing to the growing body of knowledge surrounding this rare malignancy.

Case report

Anamnesis and Presentation:

A 21-year old man presented with non-specific symptoms like progressive abdominal pain, weight loss, nausea and vomiting, melena, weakness, anorexia. Patient was a smoker and consumed moderate amounts of alcohol. There was no family history of gastrointestinal disease. Examinations including enhanced abdominal and pelvic CT scans, chest X-ray, abdominal ultrasound, tumour markers, liver and renal function and coagulation function were performed.

Diagnostic Workup:

The diagnostic methods for PACC include ultrasonography (US), endoscopic ultrasonography (EUS), computed tomography (CT), and magnetic resonance imaging (MRI).

The patient had an elevated lipase (initial lipase unavailable). white blood cell (WBC) count, 4.6 × 109/L (normal: 4.0–10.0 × 109/L); WBC count, 6.9 × 109/L; RBC count, 4.6 × 1012/L; Hgb, 151 g/L; AFP, 4.0 ng/mL; CEA, 1.49 ng/mL; CA 19–9, 14.2 U/mL; AST, 57 U/L; ALT, 73 U/L; TBIL, 11.5 μmol/L; and DBIL, 4.4 μmol/L.

A CT (Images attached) of the abdomen and pelvis with intravenous contrast revealed a bulky, ovoid, predominantly solid mass with or without clear margins in the pancreas or peripancreatic fat. The 3 × 3.2 cm solid mass in the head of the pancreas.

An MRI (Images attached) performed concurrently showed that the pancreatic mass was homogenously hypointense on T2-weighted (T2W) images with marked restricted diffusion as well as heterogeneous enhancement on postcontrast T1-weighted (T1W) gradient echo (GRE) subtraction images and a tumoural cystic component.

This case report underscores the exceptional nature of the presentation, considering the atypical age of onset for pancreatic cancer. Typically, pancreatic malignancies manifest in individuals between the ages of 60 and

80.[6] The occurrence of this rare cancer in a 21-year-old patient represents a significant anomaly within the demographic spectrum of pancreatic neoplasms.

With the imaging, the differential diagnosis could be well-differentiated pancreatic endocrine neoplasms, solid pseudopapillary neoplasms, mixed acinar neoplasms and pancreatoblastomas.

Recently, EUS-guided fine needle aspiration (EUS-FNA) has been widely advocated as a standard method for the histopathological diagnosis of a pancreatic mass.[7] Although EUS-FNA is a highly effective diagnostic tool, the preoperative diagnosis of PACC is rare. Considering the unusual presentation, FNAC wasn't performed and the patient was referred to surgical oncology for tumour resection.

Treatment and Post-Op Analysis:

The following day, **a modified laparoscopic Whipple** (pylorus preserving pancreaticoduodenectomy) was performed. In comparison with a conventional pancreaticoduodenectomy, PPPD has been associated with decreased blood loss, shorter operating times, and similar morbidity and mortality.[8] PPPD involves removal of Head of the pancreas, Duodenum, Common bile duct, Gallbladder (if deemed necessary), and Regional lymph nodes (as part of the lymphadenectomy).

Aggressive resection was carried out till negative margins were obtained in the pancreatectomy specimen. The reason being, aggressive surgical resection with negative margins is associated with long-term survival.

Post operative histological analysis revealed abundant material with cells depicting varying degrees of acinar differentiation and lack ductal and endocrine cells. The aspirates contained mostly cohesive fragments forming acini, cellular cords or solid nests of neoplastic epithelium. The neoplastic cells did not show the compact, orderly lobular "bunch of grapes" arrangement of normal epithelium. The cells had an eccentrically placed nuclei and granular, often basophilic cytoplasm. Numerous naked nuclei resembling lymphocytes were present in the smear background (The neoplastic cells often lose their fragile cytoplasm).

In general, immunohistochemical staining of pancreatic cancers has acinar cell carcinoma (ACC) showing positive staining of acinar cell markers, trypsin, and BCL10. The component of ductal adenocarcinoma (DAC) show positivity for ductal markers, MUC1, and Alcian blue with the positive expression of p53 and loss of p16 and Smad4. [9]

In the case of the patient, the tumour cells were positive for Cytokeratin 7 (CK), Pan CK, trypsin, and chymotrypsin and were negative for CK 20, chromogranin, synaptophysin, and classification determinant 56 (CD). The tumour marker, carbohydrate antigen (CA) 19-9, was elevated at 82 U/mL (normal range: 0-37 U/mL) which was unusual for ACC. The tumour cells were also negative for mucicarmine and showed diastase resistance cytoplasmic granules. These findings are consistent with ACC of pancreas.

Discussion

The occurrence of pancreatic acinar cell carcinoma (PACC) is estimated to be less than 1% among all pancreatic malignancies. At the time of diagnosis, over 50% of PACC patients exhibit metastatic disease. Despite a relatively better reported prognosis compared to pancreatic ductal adenocarcinoma (PDAC), the overall prognosis for PACC remains grim.[10] The overall survival (OS) time for patients with metastatic PACC is reported to be 19.6 months.[11,12] Surgical resection is frequently highlighted as the most efficacious

therapeutic approach, with the efficacy of systemic therapy being a matter of debate. The patient under discussion, diagnosed with metastatic PACC, demonstrated a survival exceeding 5 years following a multi-therapeutic approach involving radiation therapy, chemotherapy, antiangiogenic therapy, and combined immunotherapy.[13]

PACC presents distinctive features in terms of biological behavior, imaging, and prognosis compared to PDAC, including variations in alpha-fetoprotein (AFP) levels.[14] In the presented case, monitoring AFP levels proved valuable in assessing treatment benefits, while levels of CA 19-9 and CEA, typical markers for pancreatic cancer, remained within the normal range.

Surgical resection stands as the cornerstone of PACC treatment, with patients undergoing surgery showing significantly improved median survival compared to those who do not (36 months vs. 14 months). The recommendation for adjuvant therapy post-surgery is a subject of controversy, and the utilization of chemotherapy often depends on individualized factors and variable response rates. Due to the presence of genetic variants in the APC gene/β-catenin pathway in PACC patients, chemotherapy regimens proven effective in PDAC or colorectal cancer are commonly applied. [15]

Notably, there is no established standard chemotherapy regimen for unresectable or recurrent PACC due to the rarity of the disease, and large-scale randomized controlled trials are lacking. Combination chemotherapy regimens based on gemcitabine or fluoropyrimidine are frequently used, and the choice depends on the patient's fitness status.[16, 17] For instance, patients with good physical condition may receive folinic acid/fluorouracil/oxaliplatin or folinic acid/fluorouracil/irinotecan, while those in poorer physical condition might be treated with gemcitabine/protein-bound paclitaxel.[17,18]

PACC exhibits a distinct genomic profile compared to PDAC, with rare mutations in TP53, KRAS, and p16. Notably, approximately 20% of PACC cases involve APC or CTNNB1 mutations affecting the WNT signaling pathway. Various genes implicated in DNA repair, such as ATM, BRCA1, BRCA2, PALB2, and MSH2, contribute to genomic instability. Despite the rarity of PACC, comprehensive molecular analysis can reveal actionable molecular targets, eg by the detection of NRAS. [19,20,21]

Angiogenesis inhibition is an established strategy for treating solid tumours, yet antiangiogenic therapies have not demonstrated efficacy in pancreatic cancer, with limited exploration in PACC. Anlotinib, a novel tyrosine kinase inhibitor, achieved a noteworthy progression-free survival (PFS) time of 23 months in advanced metastatic PACC after multiple chemotherapy failures. [22,23]

Radiotherapy is commonly employed in the management of PACC, aiming to downstage tumours or alleviate symptoms. The developed radiotherapy protocol in the presented case potentially contributed to the patient's improved condition. Notably, radiotherapy's immunogenic effects, especially with stereotactic body radiotherapy (SBRT), can enhance systemic antitumour responses.[24,25]

Immunotherapy remains experimental in pancreatic cancer treatment. Pembrolizumab, recommended for tumours with high microsatellite instability (MSI-H) or DNA mismatch repair deficiency (dMMR), demonstrated a favorable response in a significant proportion of pancreatic cancer patients. Tislelizumab, a PD-1 monoclonal antibody, is designed to minimize antibody-dependent phagocytosis. [26, 27]

Combining immunotherapy with granulocyte-macrophage colony-stimulating factor (GM-CSF) can enhance efficacy by promoting antigen presentation and T-cell infiltration into the tumour microenvironment.

Preclinical data also suggest that combining GM-CSF with radiotherapy may improve the abscopal effect, a systemic antitumour response outside the radiation field. [28,29]

The combination of high-dose radiotherapy, GM-CSF, and immunotherapy yielded positive disease control outcomes in the presented case. Anlotinib's ability to downregulate PD-L1 expression on vascular endothelial cells may influence the tumour immune microenvironment, although the exact mechanism remains unclear. [30] Further research is needed to elucidate the role of anlotinib in PACC treatment.

Conclusion

We describe a rare pancreatic acinar cell carcinoma that could be adequately treated using preoperative precise imaging, PPPD and postoperative histopathological evaluations.

When tumour in the pancreas is encountered within an unusual demographic and with lack of risk factors, the diagnosis of a rare pancreatic tumour should be considered, as in our case.

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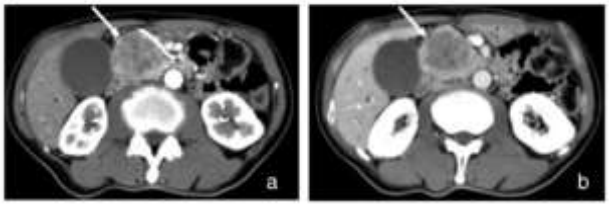
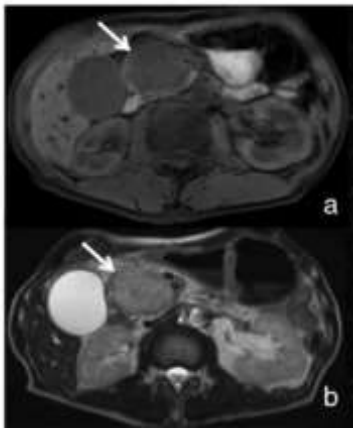
Images

Fig. 1



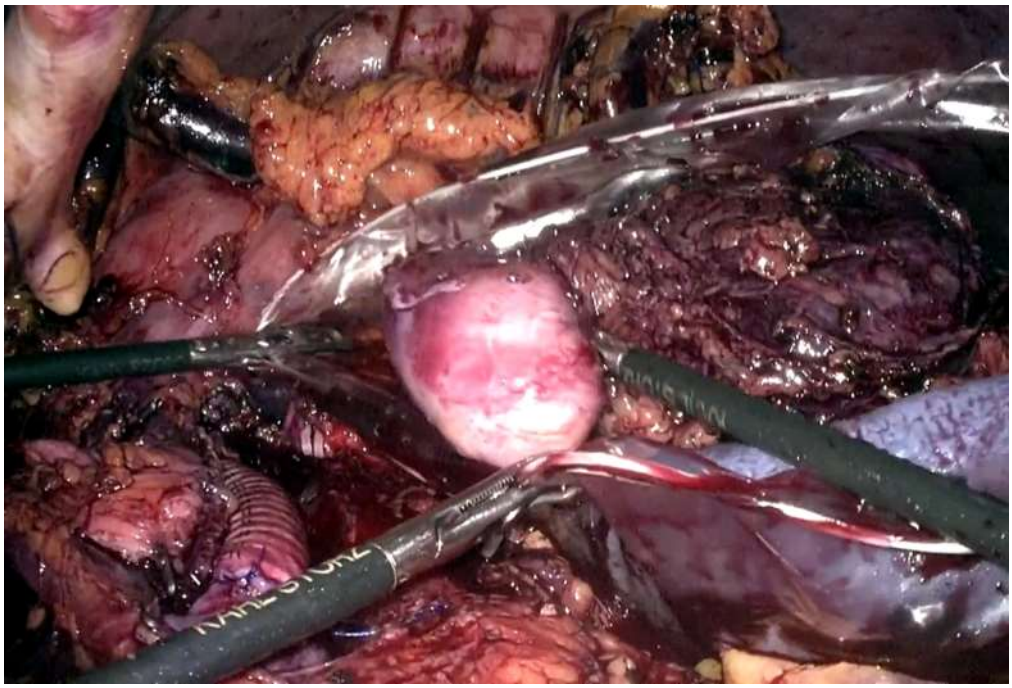
Contrast-enhanced CT revealed a slight enhancement with a poor enhanced spot in the solid tumour with an indistinct border (arrow). **a** Early phase, **b** late phase

Fig. 2



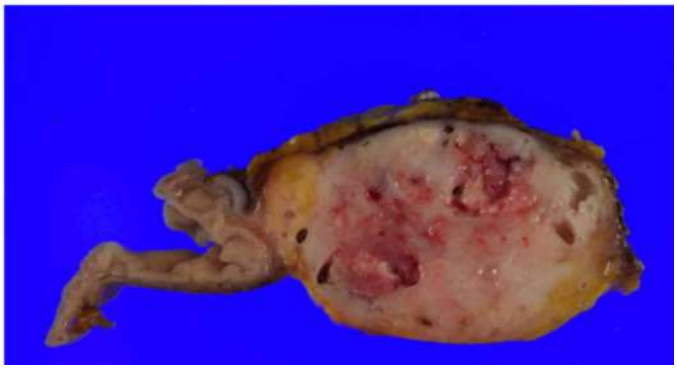
MRI showed a tumour in the pancreatic head showing low intensity on T1-weighted images (**a**) (arrow) and high-intensity images on T2-weighted images (**b**)

Fig 3.



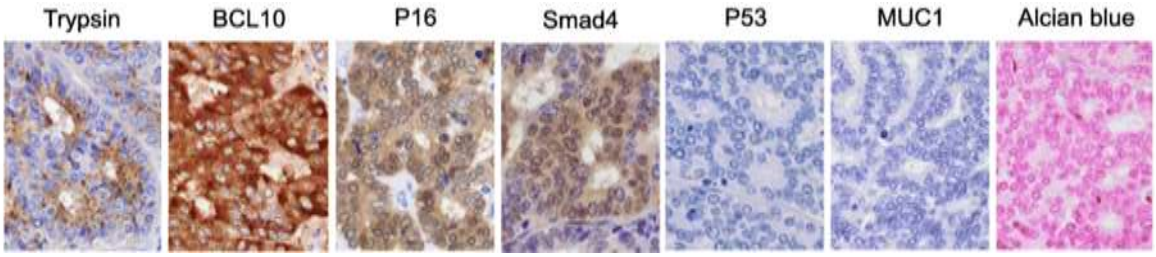
Laparoscopic pancreatic resection: Intraoperative view of enucleation of the tumor followed by PPPD

Fig 4.



Macroscopic fresh cut view of the resected specimen showing the main tumour, the macroscopic abnormalities are not recognized.

Fig 5.



Results of immunostaining and mucin staining. Acinar cell carcinoma (ACC) showed positive staining of acinar cell markers, BCL1-, Smad4, trypsin, and BCL10 but negative for MUC1, p53, and Alcian blue.