A pancreatic adenocarcinoma mimicking hepatoid carcinoma of uncertain histogenesis: A case report and literature review

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Abstract. In rare cases, metastatic adenocarcinomas of different origin may exhibit the features of hepatoid carcinoma (HC), a rare malignant epithelial tumor, most commonly occurring in the ovaries and stomach, as well as in the pancreas and biliary ducts. A case of a 72-year-old female patient who developed a highly aggressive, poorly differentiated pancreatic ductal adenocarcinoma with peritoneal carcinomatosis, demonstrating hepatoid differentiation upon conventional hematoxylin and eosin staining is reported in the present study. The patient presented with severe abdominal pain, and the radiological investigations performed revealed ovarian and hepatic tumor masses and peritoneal lesions, which were surgically removed. The gross examination of the peritoneum and omentum revealed multiple solid, firm, grey-white nodules, diffusely infiltrating the adipose tissue. The microscopic examination revealed a malignant epithelial proliferation, composed of polygonal cells with abundant eosinophilic cytoplasm and irregular, pleomorphic nuclei. Certain cells presented with intracytoplasmic mucus inclusions, raising suspicion of a HC with an uncertain histogenesis. Immunohistochemical staining was performed, and the tumor cells were found to be positive for cytokeratin (CK)7, CK18 and mucin 5AC, whereas negative staining for CK20, caudal-type homeobox transcription factor 2, α-fetoprotein, paired box gene 8, GATA-binding protein 3 and Wilms tumor 1 were documented. Thus, the diagnosis of metastatic pancreatic adenocarcinoma was established. The main aim of the present study was to provide further knowledge concerning poorly differentiated metastatic adenocarcinoma resembling HC, emphasizing the histopathological and immunohistochemical features of these malignant lesions and raising awareness of the diagnostic difficulties that may arise, as well as the importance of the use immunohistochemistry in differentiating carcinomas of uncertain histogenesis.

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Abbreviations: AFP, α-fetoprotein; CDH1, cadherin-1; CDH2, cadherin-2; CDKN2A, cyclin-dependent kinase inhibitor 2; CDX2, caudal-type homeobox transcription factor 2; CK, cytokeratin; CRS, cytoreductive surgery; Dkkl, Dickkopf-1; DUPAN-2, duke pancreatic monoclonal antigen type 2; EMT, epithelial-to-mesenchymal transition; FOLFIRINOX, folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin; HC, hepatoid carcinoma; HIPEC, hyperthermic intraperitoneal chemotherapy; mPDA, metastatic pancreatic adenocarcinoma; MUC 5AC, mucin 5AC; nab-paclitaxel, nanoparticle albumin-bound paclitaxel; PAC, pancreatic adenocarcinoma; PAX8, paired box gene 8; PARP, poly ADP-ribose polymerase; PC, pancreatic cancer; PD, pancreaticoduodenectomy; PIVKA II, protein-induced by vitamin K absence or antagonist-II; SNAI1, Snail family transcriptional repressor 1; SPan-1, s-pancreas-1 antigen; Six1, sineoculis homeobox homolog 1; US, ultrasound; VIM, vimentin; VR, vascular resection; WT1, Wilms tumor 1; ZEB1, Zinc finger E-box-binding homeobox 1

Key words: hepatoid, pancreatic, carcinoma, peritoneal, carcinomatosis

Introduction

Hepatoid carcinoma (HC) is a rare extrahepatic epithelial malignancy exhibiting morphological and immunohistochemical features similar to hepatocellular carcinoma (1). HC most frequently occurs in the ovaries, colon or stomach, with only a few cases of pancreatic adenocarcinoma (PAC) of the hepatoid subtype having been reported (2-6). However, several metastatic lesions, including the poorly differentiated adenocarcinoma of the pancreas and stomach, have been reported to exhibit hepatoid morphology (2,7). The clinical course and prognosis of patients developing hepatoid or high-grade adenocarcinoma are always poor, as they rapidly develop metastatic lesions (2). The positive and differential diagnosis

of these entities may be challenging, always requiring ancillary studies and good knowledge of the clinical history of the patient (1,7,8).

The pathological entity with which pancreatic HC is related is PAC, which is one of the leading causes of cancer-related mortality worldwide, mainly presenting at advanced stages, frequently metastatic, with limited conventional treatment efficacy (9,10). As the fourth most lethal form of cancer in the USA, PAC is associated with high mortality and poor survival rates. The incidence of pancreatic carcinoma is increasing worldwide and in western countries (9,11), with its annual incidence having been reported as high as 50,000 patients (12). PAC is estimated to be the eleventh most reported cancer in 2018 (13) or the fourteenth most common cancer, as reported in 2021 (14); however, it is the third or the seventh leading cause of cancer-related mortality, as reported in 2018 (13) and 2021 (14), respectively, mainly affecting older adults. The incidence of PAC is expected to increase further (9), and it is predicted to become the second leading cause of cancer-related mortality in western countries by the year 2030. The median age of diagnosis is 71 years in the USA, with only <1% of diagnoses performed prior to the age of 50. Inherited pancreatic cancer (PC) syndromes and familial PC comprise ≤10% of PAC cases. Despite having been reported as one of the most lethal solid tumors (15), early diagnosis is not frequently achieved, and reliable diagnostic biomarkers are currently lacking.

Identifying modifiable and non-modifiable risk factors for PAC is essential for developing effective preventive strategies and improving patient outcomes. At least 20 possible risk factors for PAC have been identified in prospective cohort studies, with lifestyle and metabolic factors being the most common. These include tobacco smoking, obesity, a sedentary lifestyle, alcohol consumption, an increased fat and red meat intake, a decreased fruit and vegetable intake (16), populations of African descent (17), cadmium, arsenic and lead exposure (18). Other risk factors include a family history (14,19), genetic predispositions (19) or disorders (mutational status of several genes such as BRCA2 or PRSS1, but not only associated with a familial component) (18), long-term diabetes (14,16,17,19-21), chronic pancreatitis (14,16,18,19), certain infectious diseases (involving *Helicobacter pylori*, Hepatitis B virus and human immunodeficiency virus) (18) and intraductal papillary mucinous neoplasms (14). Inherited PC syndromes (hereditary pancreatitis, familial atypical multiple mole melanoma syndrome, and Peutz-Jeghers syndrome) and familial PC comprise 10% of PAC cases (22). Risk prediction models have demonstrated good discrimination and calibration, providing the possibility of early identification and prevention of the disease (16). A recent review (23) proposed a model about how the dysbiosis of microbial and mycobial species may contribute to the development of PAC. The model suggested that bacterial and fungal species in the oral cavity and gut microbiome, including *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, the Proteobacteria, *Helicobacter* spp., and *Malassezia globosa* can cause inflammation and chronic pancreatitis, ultimately leading to PC.

A significant metabolic heterogeneity has been observed in PAC, arising within the ducts of the pancreas (24) and has been linked to the highest rate of cancer-associated venous thromboembolic disease (25). In total, >50% of PAC patients develop liver metastases (26,27). Tumor initiation leading to PC occurs through acinar to ductal cell metaplasia (28). Previous studies have suggested several causes for pancreatic tumorigenesis. The dysbiosis of micro- and mycobiota contribute to tumorigenesis in PAC (23), while the intratumor microbiome modulating carcinogenesis, has been recently introduced as a new component of the tumor microenvironment (11). Dickkopf-1 (Dkkl), a protein that inhibits the Wnt/β-catenin pathway and induces apoptosis, exhibits an increased expression in specimens from patients with PAC, and the serum Dkkl-cytoskeleton associated protein 4 (CKAP4)-PI3K/AKT signaling pathway in serum also participates in PC cell proliferation (29). Retinoids play a critical role in maintaining normal pancreatic functions, and the dysregulation of retinoid functions is observed in PAC (30).

Several genetic predispositions and molecular alterations (31) have been found to be associated with this highly lethal entity. The most common mutated oncogenes in PAC and that were among the first to be reported in the literature are KRAS (32) and Bcl-2 (21), while p53 (33-35), deleted in pancreatic cancer 4 (21), cyclin-dependent kinase inhibitor 2 (CDKN2A) (17,35,36), retinoblastoma protein (17,21,33,34,36) are the most frequently deleted tumor suppressor genes. CDKN2A is a gene that encodes proteins involved in regulating the cell cycle, and mutations in this gene are commonly detected in PAC (36). Pathogenic germline alterations are common in individuals with PAC, and ~10% of patients have familial inheritance (17). DNA repair dysfunction involving breast cancer BRCA mutations (19,34,35,37-42), and the polyADP-ribose polymerase (PARP) enzyme (31,34,35) play a crucial role in the pathogenesis of PAC. Next-generation sequencing (26,31) is a technology that allows for the rapid sequencing of DNA or RNA, providing the opportunity for targeted therapy of other mutated genes, including neurotrophic receptor tyrosine kinase (26,33), anaplastic lymphoma kinase (26) and HER2 (31). The TGF-β signaling pathway is frequently altered in PC and acts as an inhibitor and inducer of tumor progression (43). TGF-β signaling was identified as a potent inducer of epithelial-to-mesenchymal transition (EMT), a significant factor in PAC progression and the development of metastases (43). The downstream effects of this duality are critical in the development of metastatic disease, immunologic response, and EMT (44-46). The PI3K pathway (29,47) modifies the tumor microenvironment, and some components of this signaling cascade (such us subunit α of phosphoinositide 3-kinase, phosphatase and tensin homolog, protein kinase B or subunits of PI3K such as p85α or p110α) are frequently mutated in PAC. Understanding the genetic and molecular alterations in PAC can lead to targeted therapies and improved treatment outcomes for this highly lethal disease.

Pancreatic HC is a distinct subtype of PAC, hence similar to that of PAC, its pathology is expected to have the same poor prognosis, poor long-term survival (48) and limited availability of therapeutic strategies (49). Late symptoms and treatment resistance contribute to its highly fatal nature, and despite recent improvements, the median overall of patients survival remains as low as ~11 months (43), while the 5-year survival rate ranges from 5 to 17% (25,50-58). Several factors including a lack of screening (54,59,60) and peritoneal metastases

Table I. Immunohistochemistry antibody information.

Antibody type	Staining method	Manufacturer and catalog information	Catalog number	Clone number, clonality	Dilution
AFP	Automatic BOND Leica Biosystems™	MilliporeSigma	A8452-100UL	C3, MMab	1:500
CK 8.18	Automatic BOND Leica Biosystems™	Thermo Fisher Scientific, Inc.	MA5-14088	5D3, MMab	1:50
WT1	Automatic BOND Leica Biosystems™	GeneTex, Inc.	GTX01958	WT49, MMab	1:100
CEA	Automatic VENTANA Roche™	Abcam	ab193372	CEA31, MMab	1:100
PAX8	Automatic VENTANA Roche™	MilliporeSigma	363M-18	MRQ-50, MMab	Ready-to-use
MUC 5AC	Manual BSB	MilliporeSigma	MAB2011	CLH2, MMab	1:50
GLYPICAN	Manual BSB	MilliporeSigma	261M-9	1G12, MMab	1:200

AFP, α-fetoprotein; BSB, biotin-streptavidin-peroxidase; CK, cytokeratin; PAX8, paired box gene 8; Mmab, mouse monoclonal antibody; MUC 5AC, mucin 5AC; 3WT1, Wilms tumour 1.

also affect prognosis (58). With a relatively better prognosis, pancreatic acinar cell carcinoma has a 5-year survival rate of ~15% (28). Prognostic factors include tumor size (58), differentiation (58,61), margins (58,62), lymph node invasion (58,62) and high-grade tumor budding (63). Exercise during treatment is crucial for the optimization of the quality of life; however, well-designed trials are required (64). The low socio-economic status of patients in Europe and North America is associated with a reduced access to surgery or an increased likelihood of refusing surgery, which is influenced by a low income, poor levels of education, insurance coverage and rural areas (65).

Surgical resection is the only curative option limited to a limited number of candidates (56). Multidisciplinary therapy (12,66,67) is required for locally advanced disease, and suboptimal chemotherapy response is a major concern. Recent chemotherapy, radiation, and immunotherapy advancements have improved short-term survival, and new therapeutic regimens are being developed (68). Artificial intelligence can potentially improve diagnosis and treatment, and novel approaches are undergoing preclinical and early clinical evaluation (54).

Case report

A 72-year-old female patient presented to the Emergency Clinical Unit and further hospitalized in the Second Department of Surgery, University Emergency Hospital of Bucharest (Bucharest, Romania), where laboratory tests and radiology investigations, including ultrasonography and CT scan, indicated the presence of hepatic and ovarian tumor masses and aroused suspicion for peritoneal carcinomatosis. Therefore, the affected peritoneum and omentum were surgically excised and submitted to the Department of Pathology. The samples were fixed with 10% neutrally buffered formalin at 4-8˚C overnight (20 h) and then processed by conventional histopathological methods using paraffin embedding, sectioning (3-5 mm) and hematoxylin-eosin staining at room temperature (5-10 min for hematoxylin and 1-5 min for eosin). The slides were observed using light microscopy. Afterwards, the sections were deparaffinized in toluene and alcohol, washed in PBS (phosphate saline buffer), incubated with normal serum, and then incubated with primary antibody overnight. Subsequently, washing in carbonate buffer and developing in 3,3'-diaminobenzidine hydrochloride/hydrogen peroxide (MilliporeSigma) and nuclear counterstain with Meyer's hematoxylin (MilliporeSigma) was performed according to the provided manufacturer's protocol, at room temperature for 1-5 min. Normal human serum (MilliporeSigma) at a concentration of 10% was used as the blocking reagent, performed at room temperature. Overall, the following immunohistochemical markers and corresponding antibodies were used: Cytokeratin (CK)7, CK20 and CK8/18, α-fetoprotein (AFP), paired box gene 8 (PAX8), caudal-type homeobox transcription factor 2 (CDX2), GATA-binding protein 3, mucin 5AC (MUC 5AC) and Wilms tumor 1 (WT1) (Table I). Staining was performed either manually using a biotin-streptavidin-peroxidase complex technique or automatically with the Leica Biosystems Bond™ or Roche Ventana™ immunohistochemistry staining systems. The staining method is specified along with the automatic staining system in the second column of Table I. The antibody clone information as listed by the manufacturers is also stated.

Furthermore, inserting the search query '[pancreas(Title) OR pancreatic(Title)]) AND hepatoid carcinoma[Title]' into the PubMed database, all English language cases published until February, 2023 were reviewed, by also including all reported patients of any age and sex developing metastatic pancreatic carcinoma confirmed by histopathologic examination and immunohistochemical analysis, further investigating the cases with hepatoid morphology. All of the reported cases which referred to metastatic HC of ovarian, gastric and colonic origin were excluded.

The case of a 72-year-old female patient with a medical history of hypertension under treatment and grade II obesity

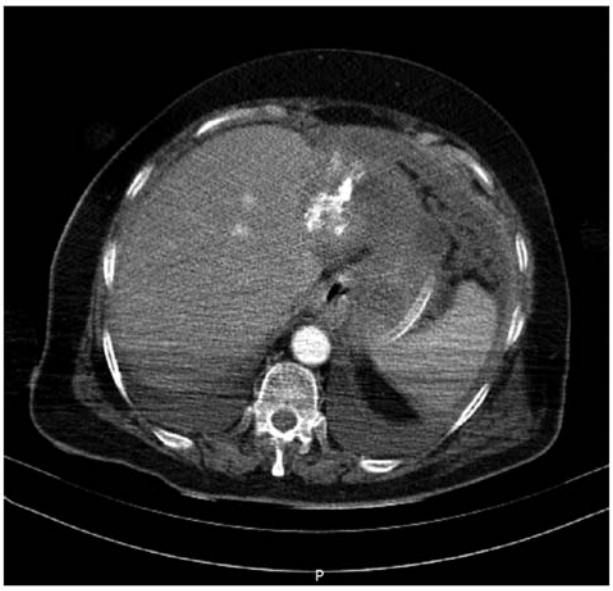

Figure 1. Computed tomography abdominal scan showing hepatic tumor, ascites and peritoneal nodes.

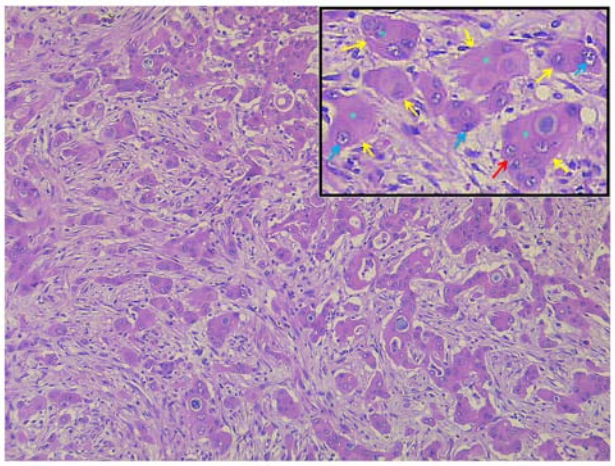

Figure 2. Highly pleomorphic epithelial proliferation exhibiting a diffuse sheet-like growth pattern and marked desmoplasia (hematoxylin and eosin staining, x10 magnification). Cell-level features are shown in the inserted zoomed-in image (200%): Loss of nuclear polarity and polygonal morphology (yellow arrow), marked nuclear pleomorphism and prominent nucleoli (black arrow), atypical mitoses (red arrow), abundant eosinophilic cytoplasm containing mucin granules (green star).

was investigated in the present study, who presented to the Emergency Clinical Unit of the University Emergency Hospital of Bucharest with complaints of severe abdominal pain and abdominal distension. The patient was further hospitalized in the Second Department of Surgery. Blood biochemistry later revealed that the patient had chronic high glucose levels with HbA1c levels at 7.1%, which is a diagnostic criterion of type 2 diabetes (69). A computed tomography (CT) scan (Fig. 1) was performed, revealing hepatic and ovarian tumor masses and multiple nodular lesions of the peritoneum and greater omentum, raising concern about an extensive abdominal neoplasm. The hepatic lesion involved segments II and III presented with multiple calcifications. On the CT scan, the clinical image of the pancreas appeared to be within normal limits.

Ascitic fluid was observed, and a sample was submitted for cytological analysis upon which malignant epithelial cells and acute inflammatory infiltrate were identified. The serum tumoral markers analysis revealed the following values: CA125, 280.9 U/ml; CEA, 18.8 ng/ml; CA19-9, >1,972 U/ml; and AFP, 3.11 ng/ml. The peritoneum and greater omentum were surgically excised during open surgery and submitted to the Department of Pathology. The gross examination of the specimens revealed multiple infiltrative, solid, firm, grey-white nodules involving the entire adipose tissue.

The histological examination of the fragments revealed a malignant epithelial proliferation exhibiting a diffuse sheet-like growth pattern, occasionally forming cords and pseudoglandular structures (Fig. 2). The neoplastic cells demonstrated a particularly polygonal morphology, with marked nuclear pleomorphism, loss of nuclear polarity, atypical mitoses and prominent nucleoli, and abundant eosinophilic cytoplasm containing mucin granules (Fig. 2). The malignant tumor exhibited a deeply infiltrative growth pattern and marked desmoplastic stromal proliferation. The angiolymphatic neoplastic invasion was also documented. As the histopathological aspect of the lesion and clinical data were highly suggestive of HC, several immunohistochemical examinations were performed. Firstly, AFP, PAX8 and WT1 expression analysis revealed negative staining of the neoplastic cells, excluding an ovarian HC origin (Fig. 3). The absence of CDX2 expression within the tumor cells excluded a presumptive colonic origin of the metastatic lesion (Fig. 4). The possible pancreatic-biliary origin of the malignant lesion was later studied by using low molecular weight MUC 5AC (Fig. 5A) and CKs (Fig. 5B and C). The tumor cells demonstrated CK7-positive (Fig. 5B) and CK20-negative (Fig. 5D) staining. The intense expression of MUC 5AC (Fig. 5A) and CK18 (Fig. 5C) within the neoplastic cells eventually established the diagnosis of metastatic PAC.

Due to advanced metastatic neoplastic condition, the patient passed away shortly after the surgery, and no specific oncological treatment had been established due to the fulminant lethal course of her disease. The histopathological diagnosis was finalized at approximately the same time. No non-surgical treatment was initiated due to the fulminant lethal course of the disease.

Discussion

HC is a rare epithelial neoplasm with an uncertain histogenesis, which most frequently involves the ovaries or the digestive tract, particularly the colon and stomach (8). Although very few cases have been reported, the described tumor can also develop in the pancreatic head (2,8).

Rare tumors are classified *a priori*, within the predictive, preventive and personalized treatment spectrum; however, since they are only detected with a reduced frequency in the total population, their susceptibility to adverse disease progression and the response to targeted therapeutic strategies remains to be investigated further with the use of genomics. Immunohistochemical analysis provide results that, considered that they provide information concerning pathological

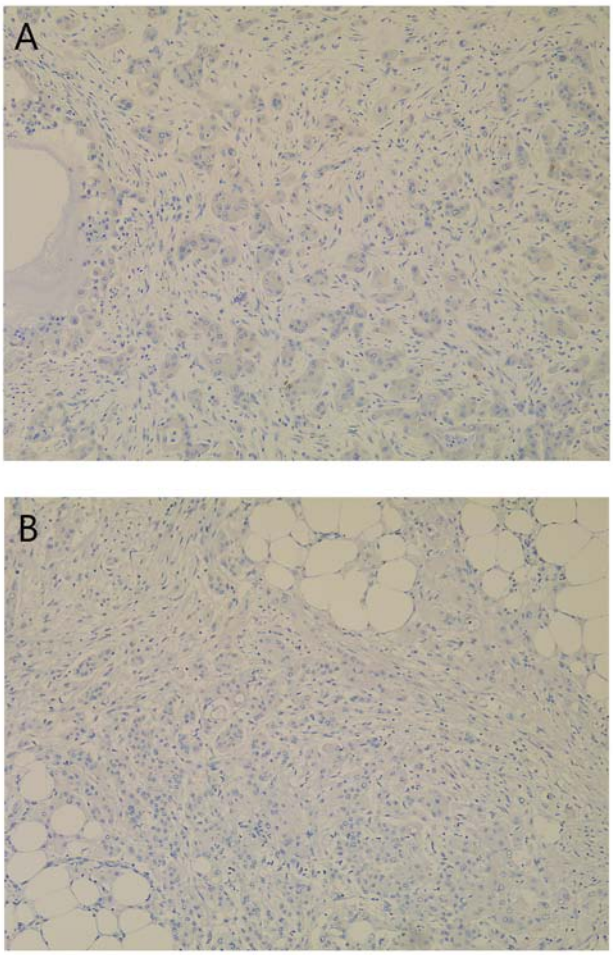

Figure 3. Imunohistochemistry images (x10 magnification): (A) Absence of AFP expression in the tumor cells ruling out hepatoid differentiation of the malignant lesion; (B) negative paired box gene 8 staining within tumor cells ruling out ovarian origin of the malignant lesion of the greater omentum.

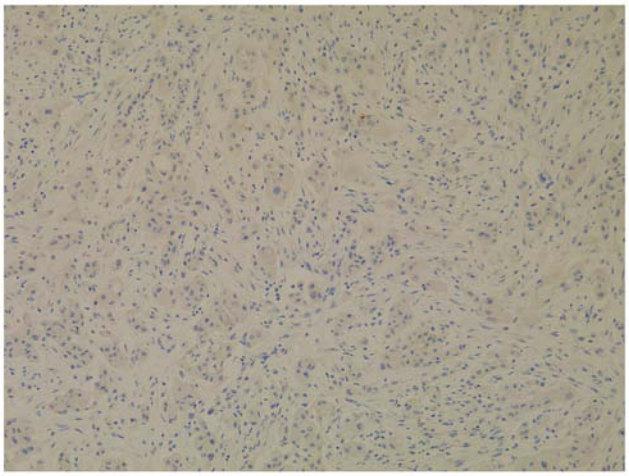

Figure 4. Negative caudal-type homeobox transcription factor 2 staining in the neoplastic epithelial cells excluding the presumptive 'intestinal' differentiation of the epithelial neoplasm (imunohistochemistry images, x10 magnification).

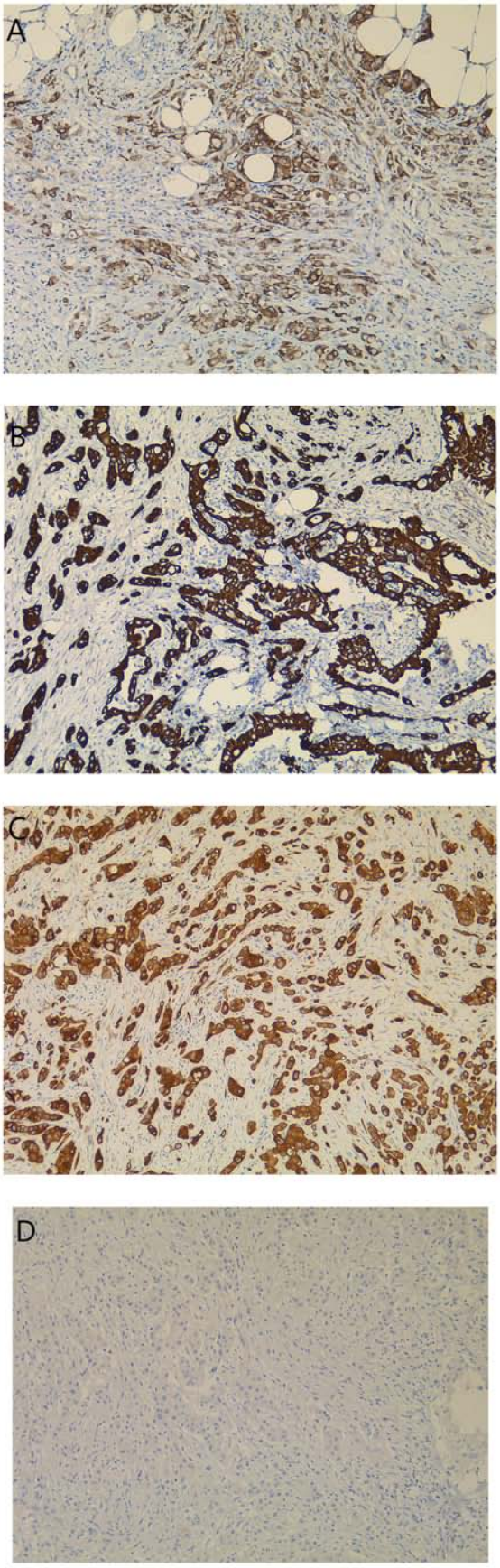

Figure 5. Imunohistochemistry images (x10 magnification): (A) Diffuse intense expression of mucin 5AC within the malignant epithelial proliferation. (B) Intense cytoplasmatic and membranous expression of cytokeratin 7 within neoplastic cells. (C) Diffuse intense cytokeratin 18 positivity within tumor cells, suggesting pancreatobilliary origin of the neoplastic proliferation. (D) Absence of cytokeratin 20 expression within tumor cells.

mechanisms, can be incorporated in genetic tests with a predictive role for tumor development and with a possible supporting

role in decision-making, in relation to therapeutic strategies targeted at specific patient groups.

Although not well defined, the pathogenesis of pancreatic HC can be summarized into three hypotheses (70) (Fig. 6). The first one is the ectopic tissue hypothesis, according to which HC may have origins in ectopic hepatic tissue in the pancreas (71,72). Secondly, the pancreas to hepatic transdifferentiation hypothesis explores the possibility of the pancreatic cells being able to transdifferentiate into hepatocytes. Lastly, the pancreatic multipotent stem cell hypothesis states that the liver and pancreas have the exact embryological origin in the foregut endoderm and share activating genes that control differentiation during carcinogenesis (70-72). Considering the morphological and immunohistochemical aspect, pancreatic HC can be further classified as a pure or mixed type, and the latter can be associated with other component types, including ductal adenocarcinoma and acinar cell carcinoma (73). Using the PubMed search query, '[Pancreatic(Title) OR pancreas(Title)] AND adenocarcinoma[Title]', 9,800 studies related to PAC were discovered (on February 19, 2023) in the literature, of which 39 were pure-type and 16 were mixed-type pancreatic HCs (6,70). Regardless of the affected organ, this malignancy is always associated with aggressive clinical behavior, as the patients either decease due to the rapid disease progression or develop multiple recurrences and distant metastases (2,74). PACs are rapidly progressive epithelial neoplasms which may exhibit hepatoid features upon microscopic examination (75,76). This diagnosis is associated with a poor prognosis, due to early micrometastatic spread with a limited 5-year survival of <3% (77).

The poorly-differentiated variants of PAC can present as deeply infiltrating lesions, composed of large, polygonal neoplastic cells with abundant eosinophilic cytoplasm and pleomorphic nuclei with open chromatin, prominent nucleoli, mimicking hepatoid tumors and even hepatocellular carcinoma (75,78,79). Some patients developing this highly lethal malignancy are frequently diagnosed with a metastatic lesion at the time of first diagnosis (80). Although PAC and HC are rapidly progressive tumors associated with metastases, including peritoneal carcinomatosis, patients developing hepatoid lesions may exhibit elevated serum levels of AFP (1,2,6,79,81). In the case described in the present study, the initial presentation implied the identification of peritoneal carcinomatosis, with no increase in serum AFP levels. However, the histopathological examination of the specimens revealed malignant epithelial proliferation, mainly composed of large, polygonal cohesive neoplastic cells with abundant eosinophilic cytoplasm, displaying a sheet-like growth pattern, with occasional forming of cellular cords and pseudoglandular structures. The most peculiar aspect identified within the tumor was intracytoplasmic basophilic granules, raising concern about HC with an ovarian origin, particularly considering that an ovarian mass was detected by the CT scan. The neoplastic cells within hepatoid ovarian carcinoma usually exhibit AFP expression; however, they are also positive for PAX8 and WT1, with their origin being the surface ovarian epithelium (2,8,82). In the case described herein, no expression of PAX8 or AFP was detected in the tumor cells, simultaneously excluding the possibility for the ovarian origin of the lesion and an hepatoid phenotype. However, as mentioned earlier, the microscopic

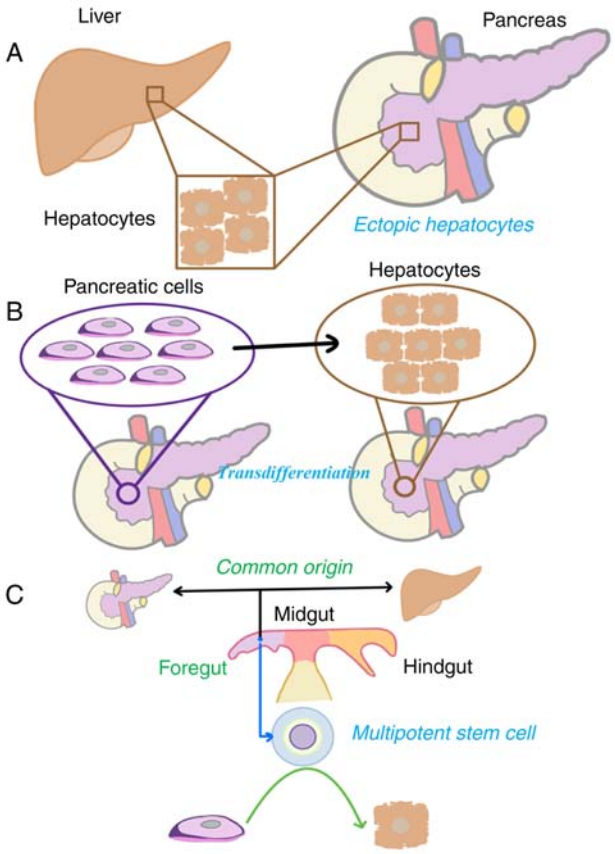

Figure 6. Hypotheses of the pathogenesis of hepatoid carcinoma: (A) Hypothesis of ectopic liver tissue; (B) hypothesis of transdifferentiation of pancreatic cells into liver cells; (C) hypothesis of common genetic activation of pancreatic and liver cells due to the common origin of the two types of cells in the embryonic foregut.

examination of the fragments obtained from the peritoneum and omentum revealed a deeply infiltrative tumor proliferation, predominantly composed of atypical cells, exhibiting mucus secretion and pseudoglandular structures, distorted by a thick fibrous and inflammatory stroma.

Hepatoid tumors are often negative for CK7 and positive for the pan-cytokeratin markers, AE1/AE3 (92%), CK19 (94-100%), glypican-3 (78%), arginase-1 (75%), CK20 (25-47%) and CK18 (70,81,83). The possibility of the tumor being classified as a poorly differentiated adenocarcinoma with a gastric or pancreatic origin was also considered; thus, further concomitant analyses were performed. Firstly, CK7, CK20 and MUC 5AC staining was performed, in order to investigate the hypothesis of the pancreato-biliary or gastric origin of the neoplasm. Furthermore, CK18 was considered as a valuable marker for the confirmation of the pancreatic origin of the peritoneal metastases, as several studies previously suggested that it can be detected in metastatic PAC and cholangiocarcinoma (84,85). It is considered that positive CK18 staining of neoplastic cells has a more optimal diagnostic value when CK20 is not expressed within the tumor (85,86). MUC 5AC expression in the neoplastic cells has also been analyzed, since there is significant evidence of the critical role of mucin expression in colorectal and pancreatic carcinogenesis (86,87). Eventually, positive CK7, CK18 and MUC 5AC staining, correlated with the lack of CK20 expression within

the patient examined or the present case report, confirmed the diagnosis of metastatic poorly differentiated PAC.

In simple, pseudostratified, ductal epithelium, mesothelium, and urothelium, CK7 has a similar, although more restricted expression than CK8 and CK18. It is a cytoplasmic or membranous marker that is detected in both normal epithelia and generally expressed in a broad spectrum of malignancies, albeit with considerable variation. CK18 is predominantly expressed in simple epithelial cells, eccrine glands (88), small dimension vessels (89) and trophoblasts (90). MUC 5AC is expressed in various parts of the digestive system, particularly in the gastric antrum, superior airways and metaplastic endometrium (91).

Despite the widespread distribution of CK7 expression, it is a valuable component of a panel for diagnosing the primary location of metastatic cancer. Its expression is usually concurrently analyzed with CK20 in tumors of various types and localizations. Similarly, CK7 and CK18 are expressed in various tumors, as presented in Table II.

Several other immunochemical biomarkers are mentioned in the literature; however, relevant techniques for their identification were unfortunately unavailable for the present study. The lack of the evaluation of the aforementioned markers would constitute a limitation of this diagnostic and treatment strategy of the present case report. For instance, a recent study proposed that cadherin-1 (CDH1), cadherin-2 (CDH2), Vimentin (VIM), Zinc finger E-box-binding homeobox 1 (ZEB1), and Snail family transcriptional repressor 1 (SNAI1) could be potential diagnostic, prognostic, and therapeutic targets for PAC (92).

The most frequently mentioned, CDH1, is a protein associated with cell adhesion and known be involved in tumor progression, invasion and metastasis (93,94). Moreover, the complete or partial loss of CDH1 expression plays a predictive role in the development of the disease, as it is an independent predictor of poor outcomes among patients with PAC undergoing pancreaticoduodenectomy (PD) (95), being primarily related to a worse median survival than in patients with a uniformly intact CDH1 expression, but also to frequent lymph node metastasis and an advanced clinical stage (96). More precisely, the CDH1 gene polymorphism is associated with an increased risk of PC in the Chinese population; however, larger samples are required to confirm these findings (97). In particular, a higher histological grade PAC is related to CDH1 methylation promoter encountered in long-term diabetes patients with pancreatic cancer (98). A similar effect in tumorigenic transformation through EMT is exerted by CDH2 (99,100).

However, CDH1 is not PAC-specific, being also a biomarker involved in the diagnosis of hereditary diffuse gastric cancer, and may not always initiate the development of PAC when both pathologies are present in the same patient (101). In the absence of conclusive imaging results regarding the damage to abdominal organs, CDH1 positivity would support the hypothesis concerning the gastric origin of the tumor.

Along with the investigation of ZEB1, VIM, or SNAI1, the detection of CDH1 could have contributed to finalizing the diagnosis and disease development prediction. ZEB1 is an EMT-related transcription factor. ZEB1 levels have been negatively associated with PC, through its involvement with inositol-3-phosphate synthase 1 into a pathway that enhances cancer cell migration and invasion (102). Additionally, ZEB1, in combination with CDH1, has already been confirmed as a negative prognostic biomarker by previous studies (99,103), ZEB1 acting as a repressor of both CDH1 (104) which is a controller and of epithelial cell adhesion molecule, which is a regulator of the migrating cells adhesiveness (105). Metastatic tumors with a larger diameter exhibit an increased expression of CDH1 and a decreased expression of ZEB1 and SNAI1, as compared with smaller metastases (104). VIM has been suggested as a predictive biomarker for the PC evolution (106) in parallel with CDH1 (107). Additionally, CDH1, VIM and ZEB1 have been suggested as diagnostic and predictive biomarkers for intraductal papillary mucinous neoplasm (108).

Following surgery survival or in the absence of surgical indication, the evaluation of those biomarkers could have allowed the administration of targeted treatment since they have been proposed as possible therapeutic targets. Blocking CDH1 inhibits PAC progression by facilitating its expression through the enforced expression of miRNA-101 (93,96). The metastasis-associated with colon cancer protein 1/SNAI1 complex in EMT, a therapeutic target in PC, has been reported to downregulate CDH1. CDH1 is downregulated when sineoculis homeobox homolog 1 (Six1) is inhibited, and tumors with impaired Six1 expression exhibit loss of the $CD24^{+}/CD44^{+}$ phenotype. Therefore, Six1 may be a potential therapeutic target for PC (109). The downregulation of VIM inhibits cancer cell migration and may affect the response to chemotherapy (106). Along with ZEB1, SNAI1, SNAI2 and CDH2, VIM is involved in the NF-κB signaling pathway, inducing EMT and promoting lymphovascular and neural invasion; thus, over the past decade, these markers have been proposed as potential therapeutic targets for inhibiting PC progression (110). However, the positive results of such targeted treatments are not supported by extensive studies, being otherwise currently unavailable in the literature.

Early PC detection is hindered by the lack of a strategy to identify high-risk individuals (14). It has been suggested that a more targeted screening approach based on modifiable and non-modifiable risk factors might be more efficient, particularly for individuals with inherited and familial PC syndromes (22). Early detection of PAC is crucial for improving therapeutic outcome, and current screening methods are primarily imaging-based. The interest in detecting PAC and precursor lesions at an early stage has led to the developing PC screening programs (56).

The accurate staging of PAC is essential, due to the metastatic nature and course of treatment of the disease (111). Therefore, imaging techniques are essential in differentiating metastatic disease from other entities (56). Novel imaging techniques (56), including dual-energy CT, diffusion-weighted MRI and positron emission tomography/MRI, are being developed to improve the accuracy of diagnosing PC. Multimodality imaging (pancreatic protocol CT and magnetic resonance cholangiopancreatography) and interventional endoscopy [endoscopic retrograde cholangiopancreatography and endoscopic ultrasound (US)] are currently used for diagnosis and staging (50); however, monitoring treatment response remains challenging. Complete surgical resection should be mandatory whenever possible, followed by adjuvant chemotherapy and

Table II. Common immunochemical features (CK7, CK18, CK20 and MUC 5AC) of tumors with various localizations, according to the literature.

Tumor	CK7	CK18	CK20	MUC 5AC	(Refs.)
Gastrointestinal tumors					
Esophageal adenocarcinoma	+	NA	-	NA	(159)
Gastric adenocarcinoma	+	+	+	NA	(160)
Diffuse carcinoma	NA	NA	NA	+	(161)
Lymph nodes of gastric carcinoma	NA	+	NA	NA	(161)
Small intestinal adenocarcinoma (67%)	+		+	NA	(162)
Colon carcinoma (in lymph nodes)	NA	+	NA	NA	(163)
Pancreatic adenocarcinoma					(8,70)
Poor prognosis	+	NA	+	NA	
Good prognosis	+	NA	-		
Hepatocellular adenocarcinoma		+		NA	(164)
Hepatoid carcinoma mimicking hepatocellular adenocarcinoma		+		NA	(165)
Carcinoma of the bile duct					(166)
Extrahepatic	+	NA	+	NA	
Intrahepatic	+		-	NA	
Gynecological tumors					
Endometrial adenocarcinoma	+	NA	-	NA	(167)
Ovarian mucinous tumors	+	NA	+	+	(80,81,168)
Cervical and uterine cancer	+	NA	+	NA	(169,170)
Breast cancer					(171,172)
Invasive disease	+	+	-	NA	
Other					
Head and neck cancer					(70,173,174)
Sinonasal	+	NA	+	NA	
Lung adenocarcinoma	+	NA	-	NA	(175)
Urinary tract cancer	+	+	+	NA	(176)

Existing studies prove that the maker is positive (+) or negative (-) in the listed localisations. NA, non-available information; CK, cytokeratin; MUC 5AC, mucin 5AC.

depending on the case of metastatic disease, hyperthermic intraperitoneal chemotherapy (HIPEC) can be considered (76,112,113). A review of four studies evaluating the use of HIPEC in PAC after surgical resection demonstrated overall survival rates ranging from 2 to 62 months with an 8.5% hospital mortality rate (114). However, due to a small sample size and low-quality evidence, no valid conclusions could be drawn. In a study in which three therapeutic strategies were used [cytoreductive surgery (CRS) with HIPEC, prophylactic HIPEC, and neoadjuvant intraperitoneal chemotherapy], it was concluded that the use CRS and HIPEC in peritoneal carcinomatosis of pancreatic origin was considered not useful and unsafe (115).

Several studies have demonstrated the benefits of surgery even for isolated recurrences of PAC (116). However, <20% of patients are candidates for curative resection (117). Attempted resection rates, margin negative resection rates and pathological response are the outcomes measured for surgical resection (118). Palliative local treatments are preferred alternatives to surgery (26). However, although only 10-20% of patients are candidates for curative resection, vascular bypass graft techniques and neoadjuvant treatment regimens have increased the curative resection rate (56,117). Attempted resection rates, margin negative resection rates, and pathologic response are the outcomes measured for surgical resection (118). Radical resections increase margin negativity and life expectancy (48).

Conversion surgery for initially unresectable tumors is associated with improved survival, and no significant difference in survival was observed between patients with locally advanced disease and those with distant metastases after conversion surgery (119). A systematic review of published evidence on locally advanced PC treatment strategies with curative intent (120) reported that the median resection rate was 25%, with 33.5% of patients proceeding to surgery after completion of the neoadjuvant pathway (121). Median progression-free and overall survival for resected patients may reach 12.9 (122) and 30 (123) months, respectively. The extent of surgery applied is controversial; lymphadenectomy, nerve plexus, retroperitoneal tissue, vascular and multi-visceral resections,

total pancreatectomy, and liver metastases are discussed in a review of the basic underlying concepts and the roles of radical surgery (48). In a systematic review comparing PD with and without vascular resection (VR) in pancreatic head adenocarcinoma, it was reported that the PD+VR group demonstrated lower 1-, 3- and 5-year overall survival rates. The PD+VR group presented with larger tumors, positive lymph nodes, and higher R1 resection. The reported 30-day mortality was higher in the PD+VR group, and no differences were observed between groups in post-operative complications (124). Hepatic resection for patients with PC with hepatic metastases is a safe procedure and provides an additional survival benefit in the medium term (<3 years); however, further randomized, controlled trials are urgently required (27).

Laparoscopic pancreatic surgery is a safe and feasible option for carefully selected patients and has been suggested to improve surgical outcomes; however, further confirmation is necessary through randomized controlled studies (125). Irreversible electroporation is being explored as a potential treatment for locally advanced PC, and while some preliminary evidence is promising, IRE should only be used after conventional treatments and within the research context (126). Minimally invasive distal pancreatectomy is safer than open distal pancreatectomy for patients with PAC, with lower positive surgical margin rates, less blood loss, a shorter hospital stay, and lower morbidity and mortality (127). High-intensity focused US (HIFUS) is an emerging therapeutic modality for PC, inducing mechanical effects for targeted drug delivery and pain management in palliative care and for downstaging borderline resectable tumors (53). With the advancement of emerging therapeutic modalities including sonodynamic therapy and immunomodulation, HIFUS may be a promising option for improving outcomes.

However, due to its aggressive nature and the possibility of early hepatic metastasis, some authors present the utility of neoadjuvant chemotherapy, surgery and adjuvant chemotherapy with results that are yet unclear and remain to be elucidated further (41,128-130). The standard treatment care for PC in clinical practice is the application of combination chemotherapy (131,132). Conventional chemotherapy offers a low 5-year survival rate due to its limited efficacy and suboptimal response (133). Patients with DNA repair dysfunction, including BRCA mutations, benefit from platinum chemotherapy and PARP inhibitors (31). Limited success has been reported concerning the use of therapies, including gemcitabine (134). The use of folinic acid, 5-fluorouracil, irinotecan and oxaliplatin (FOLFIRINOX) has been reported to exhibit comparably increased efficiency, although presenting with an increased toxicity (135). FOLFIRINOX and nanoparticle albumin-bound paclitaxel (nab-paclitaxel) plus gemcitabine have demonstrated benefit (134), while a modest improvement in survival has been observed with gemcitabine-erlotinib and FOLFIRINOX (135). The median overall survival for patients with metastatic pancreatic adenocarcinoma (mPDA) treated with first-line regimens remains as low as 1 year, indicating a significant need for effective later-line options, nab-paclitaxel being one such example (31).

The global analyses of gene expression in PC led to the discovery of several potential new PC markers (52). Database searches in a previously published study identified 76 independent prognostic and predictive molecular markers implicated in pancreatic tumor growth, apoptosis, angiogenesis, invasion and resistance to chemotherapy. Researchers are investigating these biomarkers, in order to capture phenotypic variability and identify PC earlier, including small extracellular vesicles, microbial signatures, proteins, metabolites, genetic and epigenetic markers (52). CA19-9 is the most commonly used biomarker, although with limited specificity for PC and sensitivity in the early PC stages (136); thus, new biomarkers clinically validated by prospective studies are needed for early detection and subsequent death rate reduction (137). Of these, 11 markers (Ki-67, p27, p53, TGF-β1, Bcl-2, survivin, VEGF, cyclo-oxygenase 2, CD34, S100 calcium-binding protein A4 and human equilibrative nucleoside transporter 1) provided independent prognostic or predictive information in two or more separate studies. In addition, thrombospondin-2, insulin-linked binding protein 2, lysophosphatidic acid, autotaxin, inflammatory factors, coagulation factors (61) and Dkkl (29) are possible simple protein biomarker candidates. Mesothelin was identified by serial analysis of gene expression as overexpressed in 80-90% of PC cells. However, limited expression of mesothelin has been observed in normal tissues, being thus a valuable diagnostic aid and a therapeutic target (137). Soluble mesothelin-related proteins may potentially be part of a panel of markers for pancreatic carcinoma, along with previously used markers, including CA19-9, CEA, and tissue inhibitor of metalloproteinases-1 (138,139).

Several serum biomarkers, including protein-induced by vitamin K absence or antagonist-II (PIVKA II), Duke pancreatic monoclonal antigen type 2 (DUPAN-2), and s-pancreas-1 antigen (Span-1) in conjunction with 'classical' non-specific tumor markers (for example, CA19-9 or CEA) have been studied as risk factors for the evolution of patients with PAC. PIVKA II was identified as having higher serological levels in PC, thus being considered as a possible biomarker for this pathology (140). A subsequent study by the same group of authors revealed that PIVKA II is can also be used as a predictive biomarker of postoperative evolution in small stages (141). In addition, it has been demonstrated that PIVKA II can function as an excellent marker in rare cases of hepatoid pancreatic adenocarcinoma demonstrated, while its increased levels have also been associated with a positive diagnosis of hepatocellular carcinoma (142).

DUPAN-2, CEA and CA19-9 positivity, in conjunction with certain levels for the first two and tumor sizes >30 mm, are indications of resectable or non-resecable tumors (143). In addition, DUPAN-2 has been used to monitor the response to chemotherapy (144). DUPAN-2 can potentially predict the prolonged survival of patients with PC during initial systemic therapy and may be useful in determining the optimal timing for conversion surgery in initial systemic therapy (145). Thus, together with CA19-9, DUPAN may aid in patient stratification and personalized treatment decisions (146).

SPan-1 is a biomarker used in PC that plays a predictive role in the evolution of the disease. Preoperative serum SPan-1>37-41 U/ml (147,148) levels are significantly associated with a higher early recurrence risk following the curative resection of PC. Therefore, SPan-1 may be useful for determining the best treatment option for patients with resectable PC.

Span-1 is as useful as CA19-9 for monitoring the success of gemcitabine chemotherapy (149). Moreover, SPan-1 and CA19-9 have been identified as independent risk factors for early recurrence in patients who underwent surgical resection for PC: Patients with both biomarkers presented with a higher rate of lymph node metastasis than patients with one increased biomarker or none altered (150), whereas higher levels of CA19-9, SPAN-1 together with low mitochondrial OGG1 expression are indicators of perineural invasion (151).

Recently, the former two biomarkers have been included in various scores, e.g., a preoperative tumor marker index whose high values have been associated with larger tumors, lymph node metastases, and worse prognostic outcomes in terms of both relapse-free survival and overall survival (152). Another example of a predictive score is the early recurrence prediction score, which identifies patients with poor prognoses and avoids unnecessary surgery (153). However, elevated post-operative CA19-9 instead of either Span-1 or DUPAN-2 (154), was identified as the strongest predictive marker of poor survival in the pre- and post-operative period, being thus a biomarker of choice for post-operative evolution. However, complementing the preoperative serum levels of CEA, CA19-9 with values of Span-1 and DUPAN-II would have been necessary to further support surgical indication.

Liquid biopsies and next-generation sequencing of circulating tumor cells enable novel PC diagnostics and therapeutics, allowing prognosis (57,155) by detecting circulating nucleic acid-based biomarkers (42,156), including non-coding miRNAs (157). Genetic testing for germline BRCA1 and 2 pathogenic variants is crucial for all newly diagnosed patients with mPDA, considering the solid hereditary component of the disease (31,37,39). Additionally, identifying active oncogenic pathways and gene-gene interactions has been suggested to reveal oncogene addiction and synthetic lethality, which can provide a basis for developing personalized treatments (155). Additionally, identifying active oncogenic pathways and gene-gene interactions can reveal oncogene addiction and synthetic lethality, which can provide a basis for developing personalized treatments (155). However, challenges including sensitivity and analytical limitations still exist, which require further research (156).

Identifying biomarkers that accurately predict disease recurrence or response to chemotherapy would substantially aid individual risk assessment and treatment selection, possibly also leading to novel therapies by becoming targets for molecular intervention in specific subsets of patients.

In conclusion, the positive and differential diagnosis of metastatic adenocarcinoma with hepatoid morphology revealed associations between standard histopathological examination and the expression of immunohistochemical markers. Furthermore, due to the highly aggressive clinical outcomes of this malignancy, establishing the origin of peritoneal metastases is crucial for the evaluation of the prognosis and response of the tumor to surgical and oncological treatment. The establishment of a neoadjuvant therapy for pancreatic neoplasms in general (118,158), and for tumors as uncharacteristic and as aggressive as the hepatoid pancreatic adenocarcinoma presented in the present study is rare; however, immunohistochemical studies contribute to opening up new perspectives for early diagnosis and improvement of neoadjuvant treatments or curative strategies. Case report studies should not be considered solely as descriptions of rarely occurring tumors but an opportunity to gain further immunological insight. As has been demonstrated in the present study, pancreatic adenocarcinoma is very aggressive, regardless of its histopathological typology, mainly associated with other aggravating factors including multi-organ dissemination and risk factors (comorbidities, old age).

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

AI, RVT and LB participated in the conceptualization of the study. LB performed the validation of the manuscript plan according to available data. RC and NZ performed the surgery, while AI and AMC conducted the medical investigation of the pathology slides. AI, AMC, RC and NZ gathered all necessary resources. AI and RVT conducted all data curation. AI, LB and RVT prepared the original draft of the manuscript. AI, RVT, NZ, RC, and AMC reviewed and edited the manuscript. LB and RVT realized the Figures. AI, LB and RVT supervised the present study. AI and LB confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient's informed consent was obtained to use the biological material for ancillary studies, including also the consent for the publication of personal information as presented in imaging body scans.

Competing interests

The authors declare that they have no competing interests.

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