CASE REPORT

SALL4 is expressed in pancreatic acinar cell carcinoma

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Abstract

Pancreatic acinar cell carcinoma (ACC) is a rare, malignant epithelial neoplasm. SALL4 is a zinc-finger transcription factor and a member of the SALL gene family that has been previously expressed in numerous malignancies including breast, lung, colorectal, and hepatocellular carcinomas but not in pancreatic adenocarcinoma. The expression of SALL4 is related to early clinical stage in breast and lung carcinomas but with early metastasis and an unfavorable prognosis in liver and colorectal carcinomas. In this study, we report two ACC cases with SALL4 expression. Interestingly, one of these two cases also had elevated alpha-fetoprotein (AFP) while both cases showed neuroendocrine features. Clinically, these two patients responded very well to chemotherapy, and the second patient is alive without recurrence and metastasis for more than four years. To our knowledge, these are the first reported cases of SALL4 expression in pancreatic acinar cell carcinoma, indicating a role of SALL4 in this tumor.

Key words

SALL4, Pancreatic, Acinar, Alpha-fetoprotein

1 Introduction

Pancreatic acinar cell carcinoma (ACC) is a rare, malignant epithelial neoplasm originating from acinar elements of the exocrine pancreas. ACC accounts for less than 1% of all pancreatic neoplasms [1, 2]. The tumor is typically seen in men over age 50 (mean age of 58 years) with no distinctive clinical presentation [3-5]. Most patients may present with nonspecific symptoms such as skin rashes, weight loss, nausea, vomiting, jaundice, polyarthralgias, fevers, and fat necrosis [2]. Symptoms relating to the overproduction and release of lipase into the circulation are present in 10%-15% of patients [2, 3]. Approximately 50% of patients present with metastasis, typically to the liver and regional lymph nodes, when original diagnosis is made [2]. The prognosis of ACC is intermediate between well-differentiated neuroendocrine tumors (PanNETs) and pancreatic ductal adenocarcinoma (PDA) with an average survival of 56.9 months in patients with localized, resectable disease and 19 months in patients with advanced disease [6].

Most pancreatic exocrine tumors are considered derivatives of ductal cell precursors. Serum alpha-fetoprotein (AFP) is known as a tumor marker of hepatocellular carcinoma (HCC) and rarely found in pancreatic carcinoma [7]. Only a small

number of ACC cases with elevation of AFP have been reported in the English literature with most of the cases identified in East Asia [8-10].

SALL4 is a zinc-finger transcription factor and a member of the SALL gene family, which was originally cloned based on sequence homology to Drosophila spalt (*sal*) [11]. In Drosophila, Sal is an essential homeotic gene for the development of the fly [11]. The human SALL gene family is involved in normal development. SALL4 is an important regulator of survival and phenotype, not only in several types of normal stem cells, but also in cancer cells and possibly cancer stem cells [12]. SALL4 expression is reported in numerous malignancies, such as breast cancer [13], lung cancer [14], colorectal carcinomas [15], hepatocellular carcinomas [16], and other malignant neoplasms [17-20]. It is suggested that SALL4 might be important in pathogenesis of germ cell tumors (GCT), and can be used as a highly specific marker to confirm the germ cell origin of a metastatic tumor, due to its sensitivity and specificity [18, 19]. Furthermore, it is proposed that SALL4 may have diagnostic and therapeutic value in breast, lung, liver, and colorectal cancers [15, 16].

Here, we report two cases of acinar cell carcinoma of the pancreas with elevated AFP in one case and positive SALL4 expression in both cases. To our knowledge, these are the first reported cases of SALL4 expression in pancreatic acinar cell carcinoma.

2 Case reports

The material used in this study was obtained from the Department of Pathology at New York University (NYU) Langone Medical Center (New York, NY).

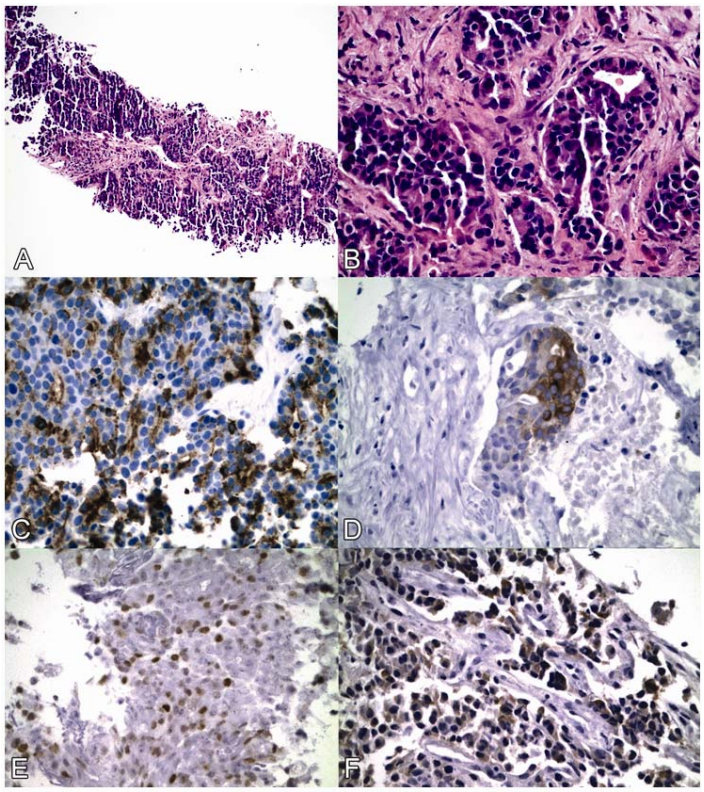

Figure 1. Case 1, A to F, Pancreatic acinar cell carcinoma characterized by trabecular and acinar growth pattern, hematoxylin and eosin ×100 (A). The tumor cells were relatively uniform with minimal pleomorphism, eccentrically-placed hyperchromatic nuclei, and finely granular cytoplasm, H&E ×400 (B). The tumor cells were positive for trypsin (C), focally positive for inhibin (D), focally positive for SALL4 (E), and weakly positive for AFP, ×400 (F).

The first patient was a 46-year-old Asian male who presented with low back pain, night sweats, decreased appetite, and 8 lbs weight loss for four months. His past medical history was not significant. Physical examination and radiological imaging at an outside institution showed numerous positive lymph nodes and liver lesions. Biopsy of the left clavicular lymph node showed a metastatic high-grade malignant neoplasm. The MRI scan of the abdomen showed an ill-defined

mildly hypointense mass in the body of the pancreas which measured 4 cm × 2.3 cm with distal atrophy of the pancreatic tail and mild ductal dilatation. His laboratory findings were significant for elevated serum AFP of 3490 ng/ml (< 44 ng/ml), elevated AST of 125 IU/L (8-40 IU/L), and elevated Alkaline Phosphatase of 234 U/L (53-128 U/L). Image guided biopsy of the liver was performed at NYU.

Histologically, routine paraffin sections showed a tumor with trabecular and acinar growth patterns. The tumor cells were relatively uniform with minimal pleomorphism. Nuclei were eccentrically placed with moderate hyperchromasia and high nuclear/cytoplasm ratio. The cytoplasm was finely granular. Extensive necrosis and fibrosis were noted (see Figure 1).

Immunohistochemical stains were performed. The tumor cells were positive for CK7, CK19, Cam 5.2, glypican 3, synptophysin, trypsin, focally positive for chromogranin, chymotrypsin, lipase, inhibin, SALL4, and weakly positive for AFP. They were not immunoreactive for CK20, PSA, PSMA, CDX2, TTF-1, and Heppar 1. Ki-67 stain shows 90% proliferative index, and beta-catenin stain showed membranous staining. Reticulin stain highlighted fibrosis surrounding the tumor. Taking together the morphology and immunohistochemical profile, this tumor most likely represented a metastatic pancreatic acinar cell carcinoma with neuroendocrine features. The patient received several cycles of chemotherapy with good response. The patient is currently still under treatment status.

The second patient was a 62-year-old female with past medical history significant for hypertension, gastroesophageal reflux, and migraine headaches who developed epigastric discomfort for one year. She was treated conservatively with various antacids without relief. An MRI of the abdomen revealed a mass in the body of the pancreas that measured 2.1 cm in greatest dimension. Endoscopic ultrasound disclosed a 2.6 cm × 2.0 cm hypoechoic lesion in the body of the pancreas in close proximity to the splenic vein. The patient had a laparoscopic distal pancreatectomy.

Histologically, routine paraffin sections displayed a moderately- differentiated pancreatic acinar cell carcinoma with focal neuroendocrine differentiation. The tumor showed focal weak positivity for synaptophysin and CD56 suggestive of neuroendocrine differentiation. The tumor was focally positive for SALL4 (see Figure 2). Following resection, the patient is alive without disease and metastasis for more than four years.

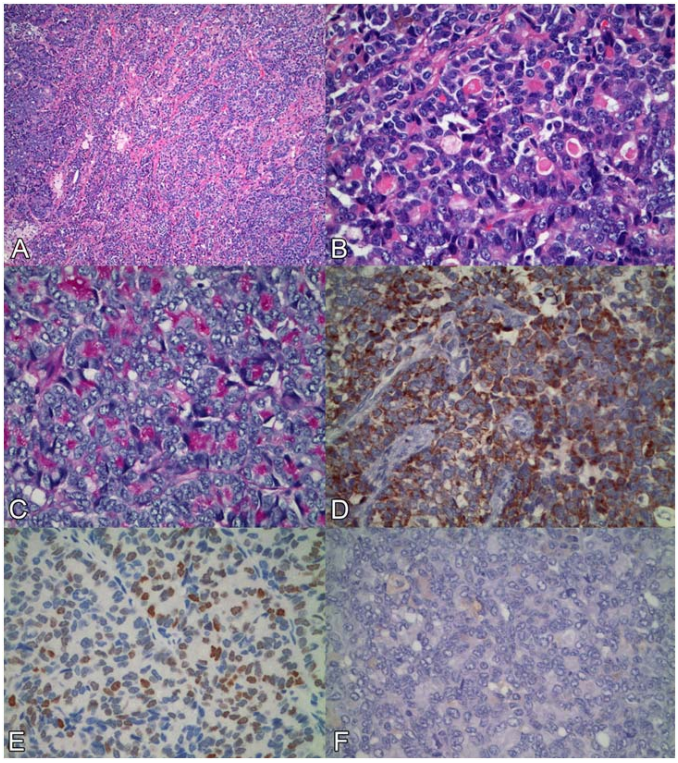

Figure 2. Case 2, A to F, Moderately differentiated pancreatic acinar cell carcinoma with fused acinar pattern and few fibrous septae, H&E ×100 (A); ×400 (B). The tumor cells had a granular eosinophilic cytoplasm with abundant zymogen granules that were positive for PAS stains and resistant to diastase digestion (C). The tumor cells were weakly positive for synaptophysin (D), focally positive for SALL4 (E), and negative for AFP, ×400 (F).

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3 Discussion

Acinar differentiated neoplasms of the pancreas are defined as neoplasms with production of pancreatic enzymes packaged in zymogen granules. Though acinar cells comprise most of the normal pancreas, acinar neoplasms are very rare, accounting for 1%-2% of pancreatic tumors in adults and 15% in children. Mean age in adults is 58 years, with a 3.6:1 male predominance [1, 2]. Patients generally present with nonspecific abdominal symptoms. Jaundice is rare. Lipase hypersecretion syndrome characterized by massive serum lipase elevation, subcutaneous fat necrosis, and polyarthralgias occurs in 10%-15% of patients, usually in the setting of hepatic metastasis [21]. Some reports, including one of these cases in this study, show elevated serum AFP, a finding more common in younger patients and most frequently reported in Asia.

ACC can occur in any portion of the pancreas, usually presenting as a large (mean size 10 cm) and circumscribed lesion. They are frequently encapsulated though invasion of tumor through the capsule is common. Grossly, the tumors can invade locally into adjacent organs including duodenum, mesenteric vessels, stomach, kidney, peritoneum, and spleen [22].

The diagnosis is made through a combination of morphology, special stains, and immunohistochemical stains. Solid and acinar patterns with a frequent mixed pattern are the most common low magnification architectural patterns. Other findings include glandular and trabecular patterns. In the acinar pattern, neoplastic cells form small lumina with basal nuclei and moderate eosinophilic granular cytoplasm representing abundant zymogen granules. The nuclei are uniform with a large, central nucleolus. Mitotic features are common [21]. Zymogen granules are positive for PAS stains and resistant to diastase digestion. Immunohistochemical staining for enzymes such as trypsin and chymotrypsin is 95% sensitive for identifying acinar differentiation and also highly specific. Staining for amylase is rare.

Focal neuroendocrine differentiation is also seen in approximately 40% of ACCs [1, 2] including both cases presented in this study. Exocrine and endocrine pancreatic cells develop from a common endodermal epithelium, and human tumors may mimic the relationship between ducts and islet cells during early developmental stages [23, 24]. ACCs are thus capable of differentiating into ductal and neuroendocrine components. Pancreatic tumors composed of all three components of acinar, ductal, and islet cells have been reported [24, 25]. Klimstra *et al.* 1994 proposed the term “mixed acinar-endocrine carcinoma” in ACCs with more than 25% of the tumor cells exhibiting endocrine features. Neuroendocrine cells were only a minor component of the cases presented, and the tumor still belongs to the conventional ACC type.

Staining for AFP can also be detected with immunohistochemistry in patients with and without serum AFP elevation [2, 21]. Clinically, the incidence of pancreatic tumors with elevated AFP level ranges from 6% to 24% [26, 27] while immune-histochemically-confirmed cases comprise 4.5% to 6% [1, 2]. AFP is produced in the liver, yolk sac, and in the fetal gastrointestinal tract [28]. Thus, tumors originating from these tissues may show AFP production [24] as seen in one case in this report.

Interestingly, both of the presented cases had neuroendocrine features and are also positive for SALL4 expression. These two patients responded very well to chemotherapy, and one patient is alive without recurrence and metastasis for more than four years. SALL4 expression was detected in variant carcinomas, such as breast, lung, colorectal and hepatocellular carcinomas. The expression of SALL4 is related to early clinical stage in breast and lung carcinomas [13, 14] but with early metastasis and an unfavorable prognosis in liver and colorectal carcinomas [15, 16]. More case analyses are needed to clarify the role of SALL4 in ACC. To our knowledge, there are no other reported cases of SALL4 positivity in ACC in the literature. With this unique aspect, these tumors need to be distinguished from metastatic germ cell tumors, which are also positive for this marker. In some cases, it may be challenging to make this distinction as germ cell tumors, particularly yolk sac tumor, exhibit diverse morphologic, overlapping features. Specific markers for pancreatic acinar cells can play important roles in this purpose, such as trypsin, chymotrypsin, and lipase. Surgical resection is the standard treatment for localized ACCs.

However, the treatment for metastatic or recurrent ACC remains controversial, and various treatment options have been reported including chemotherapy, chemoradiation therapy, and surgical resection. Suzuki *et al*. reported a successful aggressive surgical approach to treating hepatic metastasis from ACC. A multimodal approach that included preoperative chemoradiation and surgical resection was successful in a case of ACC metastatic to the liver in the form of a bile duct tumor thrombus [29]. Although multimodal approaches may be useful for ACCs [29], further studies would aid in evaluating the benefits of such treatment in cases of hepatic metastases as seen in this report as well as in recurrent ACC.

In conclusion, we reported two pancreatic acinar cell carcinoma cases with SALL4 expression. Both SALL4 positive cases had neuroendocrine features, and one patient is alive without recurrence and metastasis for more than four years. Our first SALL4 positive patient also had elevated AFP. He had numerous lymph node and liver metastases when original diagnosis was made, but responded very well to chemotherapy. To our knowledge, these are the first reported cases of SALL4 expression in pancreatic acinar cell carcinoma.

Competing interests

The authors declare that they have no competing interests.

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