

Case Report

Clear cell sarcoma of the pancreas: a case report and review of literature

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Abstract: Clear cell sarcoma (CCS), is an uncommon malignant soft tissue neoplasm that displays melanocytic differentiation with a distinct molecular profile. It is very rarely localized in gastrointestinal tract. We reported the first case of a primary CCS arising in pancreas. A 36-year-old man presented with jaundice for one month. A preoperative abdominal computer tomography showed a low-density mass in the head of pancreas. Whipple procedure was performed and the tumor was resected. Pathological examination showed polygonal or fusiform cells arranged in a uniform nested to fascicular growth pattern with thin fibrous septa. Immunohistochemical studies revealed positivity for HMB-45, Melan A, S-100, MiTF and vimentin protein. Fluorescence in situ hybridization on paraffin section showed a translocation involving the EWSR1 gene region. No BRAF and NRAS mutation was detected. The patient underwent transcatheter arterial chemoembolization (TACE) six times and eventually died of diffuse liver metastasis 10 months later. This case illustrates that the pancreas is a potential site for primary clear cell sarcoma and molecular studies play an important role in making a conclusive diagnosis.

Keywords: Clear cell sarcoma, pancreas, immunohistochemistry, FISH, EWSR1, translocation

Introduction

Clear cell sarcoma (CCS) is an aggressive, rare soft tissue tumor and their classification among melanoma or sarcoma is still undetermined due to their clinical, pathologic and molecular properties found in both types of tumors. It is very rarely localized in gastrointestinal tract [1]. Herein, we present the first case of a primary clear cell sarcoma in the pancreas, and discuss its clinicopathological features and differential diagnosis. In addition, we discuss this rare type of sarcoma that affects young adults and has a poor prognosis characterized by the balanced chromosomal translocation $t(12;22)(q13;q12)$ with special emphasis on the necessity for pathologists to be able to distinguish it from melanoma [2, 3] -- potentially a major pitfall in diagnosis.

In this study, we report a case of CCS arising in the pancreas of a 36-year-old man. The present case, together with a detailed review of the literature on this topic, demonstrates that the pancreas is a possible site of CCS of soft tissues and that making a reliable diagnosis of

this tumor requires cytogenetic or molecular diagnostic investigations.

Case report

A 36-year-old male presented with anorexic, icteric and discharging acholic stool for one month. There was neither an overlying skin lesion nor a history of previous soft tissue excision. A preoperative abdominal computer tomography showed the enlarged pancreatic duct and a low-density lesion in the pancreas head, between the common bile duct and the head of pancreas (**Figure 1A, 1B**). Among the possible preoperative diagnoses, duodenal stromal tumor was suspected. Whipple procedure was performed. The tumor was located in the head and descending duodenum. It was found that the transverse mesocolon was infiltrated locally, the full-thickness of duodenum was invaded, the pancreas was involved which caused the formation of a diverticulum.

Grossly, the mass measured 3.9×3×2.2 cm and appeared multilobulated. The cut surface of mass was gray-tan, firm and homogenous, with

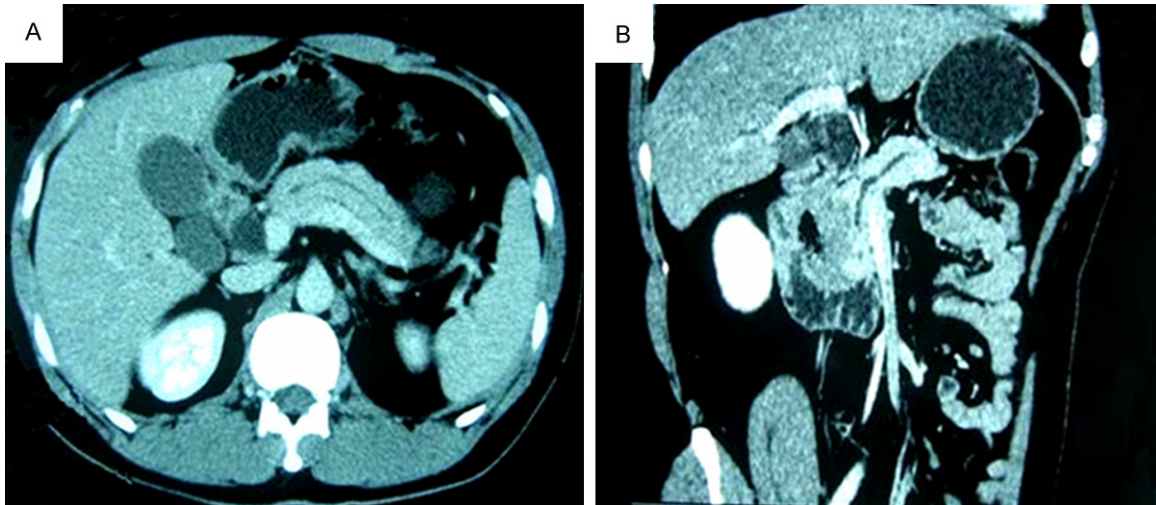


Figure 1. Abdominal computer tomography (CT) shows (A) the dilated pancreatic duct; (B) a low density lesion between the common bile duct and the duodenum.

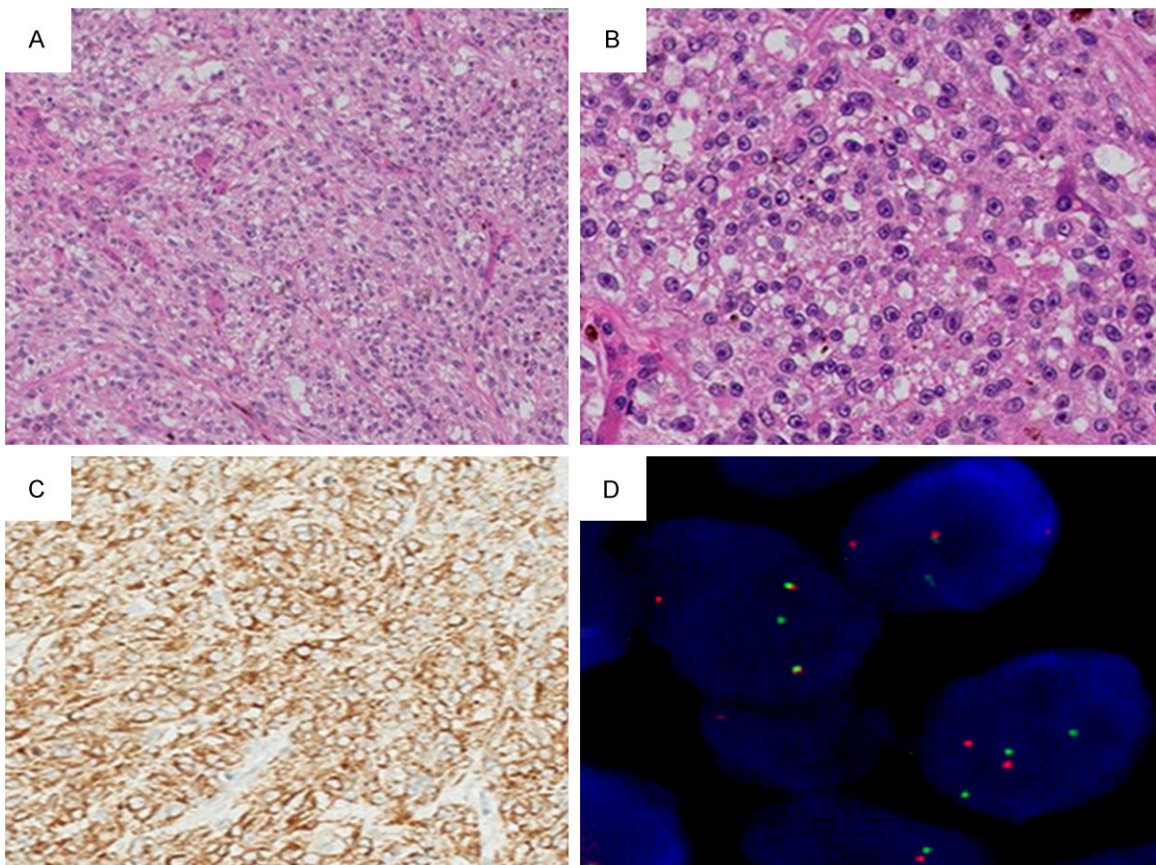


Figure 2. HE stained photomicrographs show (A) the tumor is mainly composed of polygonal and spindle cells (original magnification $\times 200$) and (B) the tumor cells exhibit oval nuclei with characteristic prominent nucleoli (original magnification $\times 400$). (C) The tumor cells are positive for HMB-45 (original magnification $\times 200$). (D) Representative micrographs of FISH with a EWSR1 dual color break-apart probe exhibit separate green and red signals, indicative of rearrangements of copies of the EWSR1 region in clear cell sarcoma (original magnification $\times 1000$).

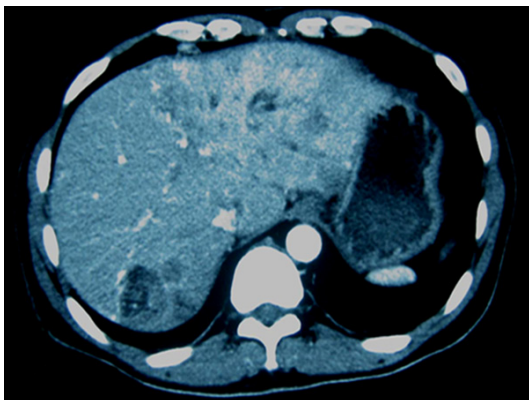


Figure 3. Abdominal computer tomography (CT) shows intrahepatic multiple round hypodense lesions of inequality of sizes, with scattered spots and flaky and nodular lipiodol deposition after transcatheter arterial chemoembolization.

no hemorrhage, necrosis or cystic change. Microscopically, tumor cells were polygonal or fusiform (**Figure 2A**), with clear or eosinophilic cytoplasm, arranged in a uniform nested to fascicular growth pattern with thin fibrous septa. The nuclei were vesicular with prominent eosinophilic nucleoli (**Figure 2B**). There was low mitotic activity (3~5/10HPF). Histologically, the tumor involved the entire thickness of the pancreas head and infiltrated the duodenal wall. Melanin was seen in focal area on both H&E and Fontana-Masson stains. Giant cell was not identified. Immunohistochemical studies revealed strong positivity for HMB-45 (**Figure 2C**) and Melan A and scattered tumor cells were also positive for S-100, MITF and vimentin protein. Cytokeratins, EMA, MyoD1, desmin, smooth muscle actin, CD34, CD31, CD117, CD99, synaptophysin, chromogranin A, CD56, and NSE were negative. Fluorescence in situ hybridization (FISH) with LSI EWSR1 Dual Color Break Apart Rearrangement Probe (Abbott Molecular Inc. Des Plaines, USA) analysis was performed on paraffin section, showing positive break-apart signals >20% of the tumor cell (**Figure 2D**). No BRAF and NRAS mutation was detected.

Discussion

A total of 22 GI CCS cases have been reported in literature, more often arising in the ileum and less commonly in other sites, such as jejunum (7 cases) [4, 5], the colon (3 cases) [6-8], stomach (2 case) [9, 10] and the duodenum (1 case) [11]. The present one is the first case of CCS

arising in the pancreas reported in the literature. The median size of the reported cases is 5 cm and average age of patients at diagnosis is 37 years old [12]. These characteristics are similar to the CCS of tendons and aponeuroses as presented in one of the largest and latest series. The diagnosis of CCS in the GI tract is often challenging, due to the inconsistent expression of melanocytic markers and its unusual site of presentation, require more than one approach. We review the differential diagnosis of CCS, which includes PEComa, malignant melanoma, epithelioid gastrointestinal stromal tumors, alveolar soft part sarcoma, leiomyosarcoma with HMB45 expression, and paraganglioma, malignant peripheral nerve sheath tumor (MPNST), deep-seated epithelioid sarcoma, monophasic synovial sarcoma and anaplastic carcinoma of pancreas (ACP). Immunohistochemistry can rule out many of these morphologically similar tumors but differentiation from clear cell sarcoma may require molecular genetics study.

PEComa is a rare mesenchymal tumor including different morphological entities, supposed to derive from perivascular epithelioid cells and characterized by a coexpression of myogenic and melanocytic markers. Given the melanocytic phenotype, immunostaining with nearly all melanocyte markers and the ultrastructural features showing the presence of premelanosomes, under some circumstances, the differential between a PEComa and clear cell sarcoma could represent a diagnostic challenge. Differentiation between these entities requires correlation of clinical, histological, and immunophenotypical findings. There is a marked female preponderance and approximately one-third of the cases occur in the pediatric age group [13]. Morphologically, this tumor is composed of cells arranged in nests or large cords separated by fibrous stroma, with abundant clear cytoplasm and with round regular small nuclei without atypia. Their clinical behavior is not predictable, and there is not strictly histological criterion for malignancy, although larger tumor with infiltrative growth, hypercellularity, cellular atypia, atypical mitoses, and necrosis generally has a malignant course. Immunohistochemically, the tumors cells stained for HMB45. Only 18 cases have been reported in GI in literature.

MPNST is immunopositive for S-100, but the staining is usually only focally. Moreover, it is

negative for HMB-45 and Melan A [14]. Synovial sarcoma is generally positive for cytokeratin, EMA, CD99, bcl-2 and calponin. S-100 protein may be detected in 30% SS. It is characterized by the SYT-SSX1/2, detectable by RT-PCR or FISH. Epithelioid sarcoma is immunoreactive for vimentin, low and high-molecular cytokeratin, and EMA, partial active for CD34, occasional active for SMA and S-100, and frequently negative for INI1. Anaplastic carcinoma of pancreas is positive for epithelial markers such as pan-cytokeratins and negative for HMB-45 and vimentin [15]. The most troubling differential is metastatic malignant melanoma. CCS shows phenotypic, ultrastructural features, and immunohistochemical overlap with MM. Combination of BRAF and NRAS mutation analysis with fusion gene detection contributes to diagnosis of MM and CCS. CCS generally lacks BRAF and NRAS mutation, and in the majority cases it harbors a chromosomal translocation t(12;22)(q13;q12), which leads to the formation of ESWR1/ATF1 fusion transcript, which is absent in MM [16]. Insulin-like growth factor 1 receptor might be a novel marker for CCS and treatment target [16-18].

Overall, GI CCS has an aggressive behavior, with a high incidence of local (lymph node) and distal (most commonly liver) metastasis. In about 50% of the cases reported, lymph node metastasis was present at the time of diagnosis [19] and only one case had metastases to the liver [20]. During the follow-up, liver metastasis developed in 32% of the patients reported, 27% have died and only three patients (14%) showed no evidence of the disease after resection of the primary lesion. Unfortunately, the small number of cases with adequate follow-up does not allow the determination of specific prognostic factors. In this case, however, liver metastasis was found at the time of diagnosis (**Figure 3**). Although TACE was performed 6 times, the patient died of diffuse metastasis 10 months after operation.

Clear cell sarcoma (CCS) is a high grade soft tissue sarcoma with a distinct molecular profile and with morphological features resembling those of melanoma. This case demonstrates that the pancreas is a potential site for primary clear cell sarcoma of soft tissues, and, furthermore, that cytogenetics and/or molecular techniques play a central role in the diagnosis.

Disclosure of conflict of interest

None.

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