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Case Report

Granular cell tumor of the ampulla of Vater: report of a unique case with emphasis on immunohistochemistry for TFE3 antigen expression

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Abstract: Granular cell tumor (GCT) is uncommon benign mesenchymal neoplasm of Schwann cell origin,which can arises in any part of the body, and the most common locations are the tongue, oral cavity, skin, and subcutaneous tissue, occasionally occurs in the gastrointestinal tract and the biliary tract. Primary GCT of the ampulla of Vater is an extremely rare, the first case of ampullary GCT was described in 2005, to the best of our knowledge, this is the second report of such cases appearing in the English language literature to date. Herein, we report a unique case of ampullary GCT presenting as no obvious cause abdominal distension for 6 months in a 63-year-old Chinese woman without evidence of a primary soft tissue tumor elsewhere at the time of initial diagnosis. Computed tomography and Magnetic Resonance Imaging revealed a 20 mm × 18 mm soft tissue nodule in the ampulla of Vater region. The patient underwent Whipple resection. Histological examination demonstrated an ampulla of Vater tumor measuring 25 mm × 20 mm × 20 mm with gray-whitish and hard consistency. The tumor was composed of a nested growth of large tumor cells with ample eosinophilic granular cytoplasm. Immunohistochemically, the tumor cells were positive for S-100, CD68, TFE3, and neuron-specific enolase, but were negative for CK, CD117, Dog-1, SMA and Desmin. The final histopathological diagnosis was ampullary GCT.

Keywords: Granular cell tumor, ampulla of Vater, TFE3

Introduction

Granular cell tumor (GCT), also called Abrikossof tumor, was first described by Alexis Abrikossof in 1926. GCT can arise in any part of the body, although their common locations are the tongue, skin, and subcutaneous tissue, occasionally occurs in the gastrointestinal (GI) tract and the biliary tract. GCT in the GI tract comprises approximately 5% of all GCT [1, 2], and less than 1% developing in the biliary tract [3, 4]. GCT in the ampulla of Vater is an extremely rare, to our knowledge, only one case has been reported in literature to date [5], and only seven cases of the pancreas GCT have been reported [6, 7]. Most GCT is benign, with 1% to 2% of all of these tumors considered to be malignant. Up to now there have been no reports about malignant GCT in the GI tract, the bile duct and the pancreas. A majority of the reported cases were females and black Americans with mean age of 35 years (range 11-63 years). Herein, we report the first case of ampullary GCT in a Chinese woman, including clinical, histopathological and immunophenotypic features, diagnostic and differential diagnosis. We emphasize the differential diagnoses engendered by GCT including a series of soft tissue tumors with eosinophilic cytoplasm which have nested and alveolar growth patterns, and demonstrate the utility of immunohistochemistry for TFE3 antigen expression for arriving at accurate diagnosis.

Case report

A 63-year-old Chinese woman was admitted to our hospital because she presented with no obvious cause intermittent abdominal distension for 6 months, accompanied by urine yellow

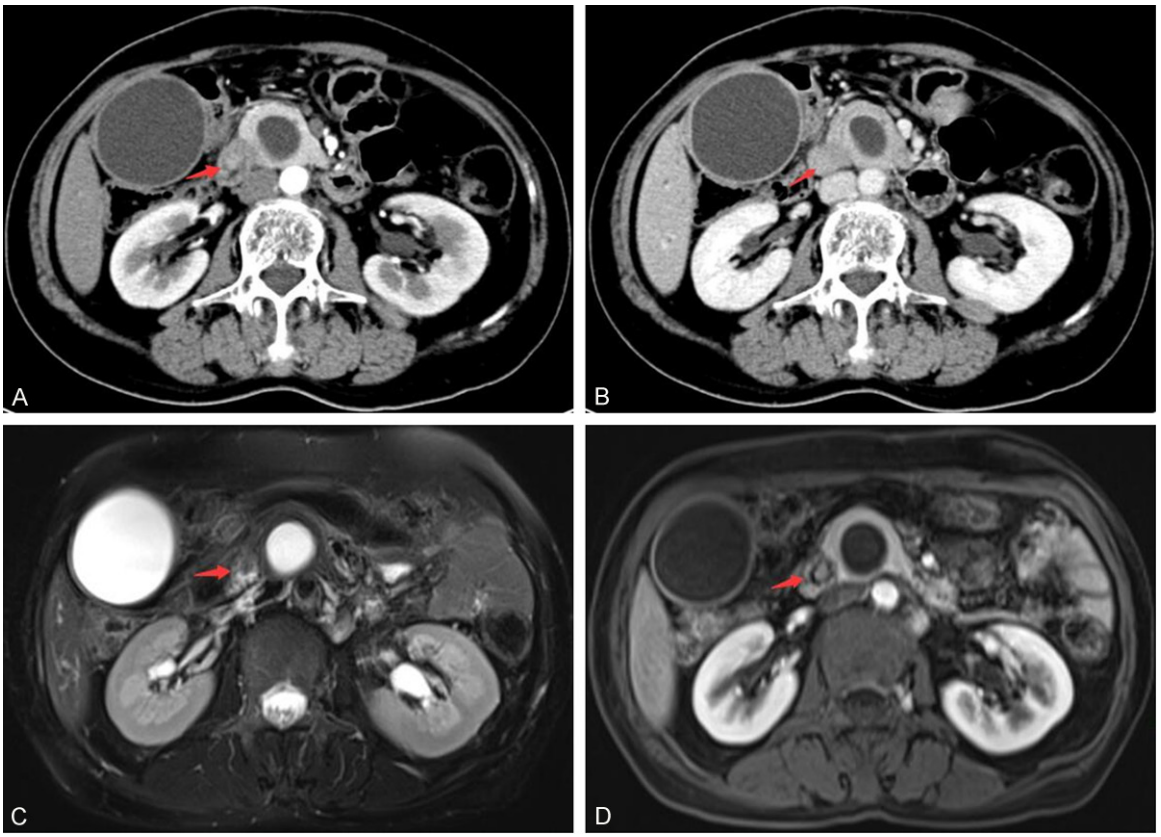

Figure 1. Enhanced CT revealed a 20 mm × 18 mm soft tissue nodule in the ampulla of Vater region, venous phase nodule strengthening was gradually fading (A and B); MRI showed that the nodule showed heterogeneous high signal intensity on T2-weighted images and slightly low signal intensity on T1-weighted images (C and D).

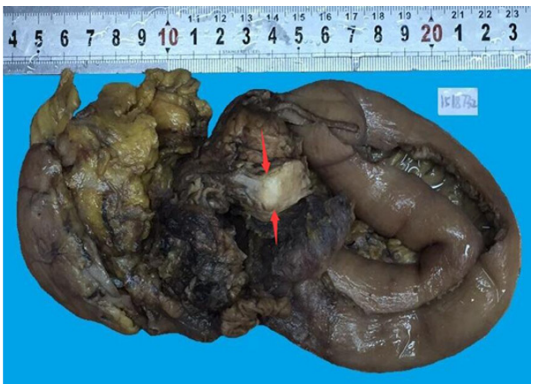

Figure 2. Gross pathologic findings that an ampulla of Vater tumor with cross-sections of the tumor was gray-whitish and hard consistency.

and poor appetite, without no obvious abdominal pain, jaundice and fever.Enhanced CT revealed a 20 mm × 18 mm soft tissue nodule in the ampulla of Vater region, venous phase nodule strengthening was gradually fading (**Figure 1A**, **1B**). MRI revealed that the nodule showed heterogeneous high signal intensity on T2-weighted images and slightly low signal intensity on T1-weighted images (**Figure 1C**, **1D**), dynamic enhanced scanning the nodule with an enhancement effect persisting into the portal phase, the edge of the nodule was blurring. Intrahepatic bile ducts, extrahepatic bile duct and common bile duct were more obvious expansion, and the pancreatic duct was mild expansion. Routine laboratory investigations were normal, including complete blood count and serum urea and electrolyte levels. The liver function tests were within normal limits. Tumor markers, including α-fetoprotein, carcinoembryonic antigen and carbohydrate antigen 19-9, were all within normal limits. The patient underwent Whipple resection. Our patient was not given any treatment after operation, and has been free from tumor recurrence and metastasis in the 4 months since surgery.

Pathological examination

On gross examination for the Whipple resection specimen, macroexamination demonstrated an ampulla of Vater tumor measuring 25 mm ×

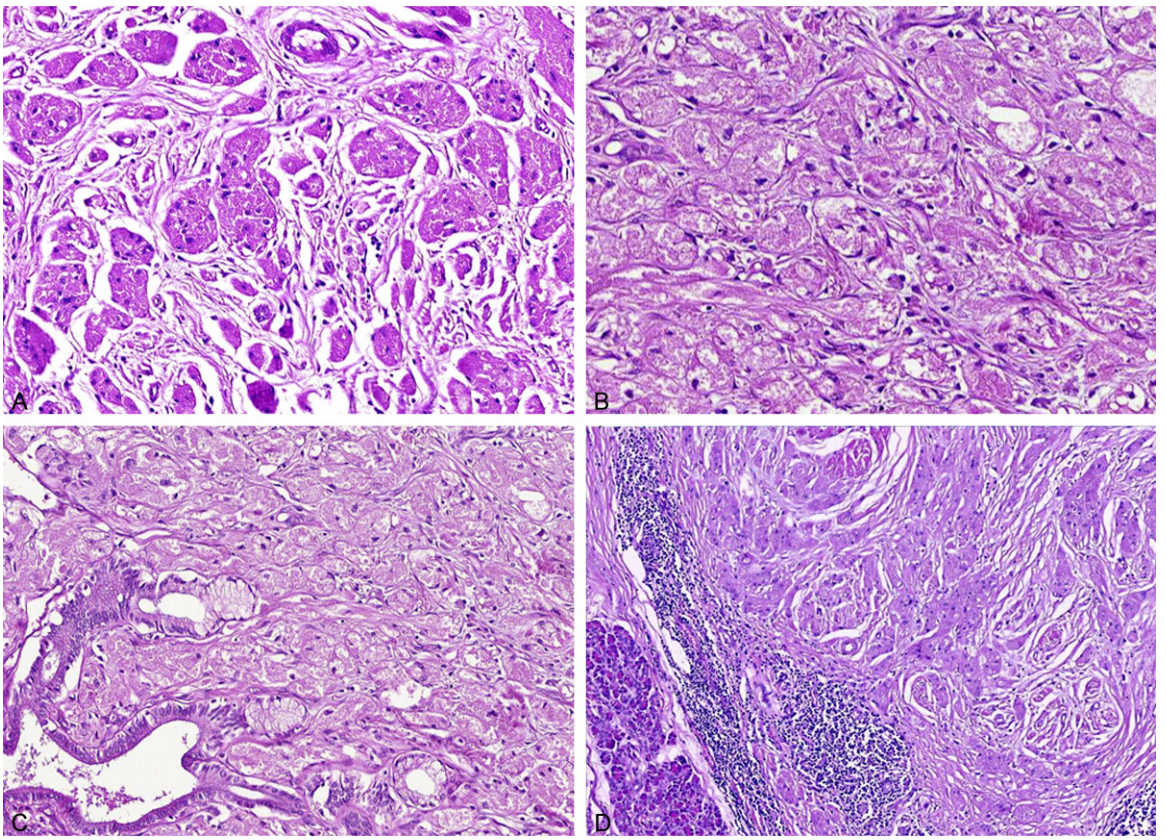

Figure 3. Microscopically, the tumor was composed of a nested and alveolar growth of large tumor cells with ample granular cytoplasm and small round nuclei (A and B); tumor cells infiltrated the mucous membrane epithelium of ampulla of Vater (C); the boundary of the tumor was clear and peritumoral lymphoid cuffs are noted (D).

20 mm × 20 mm with cross-sections of the tumor was gray-whitish and hard consistency (**Figure 2**). Microscopically, the tumor was composed of a nested and alveolar growth of large tumor cells with ample granular cytoplasm and small round nuclei (**Figure 3A**, **3B**); tumor cells infiltrated the mucous membrane epithelium of ampulla of Vater (**Figure 3C**); the boundary of the tumor was clear and peritumoral lymphoid cuffs are noted (**Figure 3D**). There was no tumor necrosis, the cellular atypia and mitosis were inconspicuous, and in addition, 16 regional lymph nodes were free from tumor. Immunohistochemically, the tumor cells were positive for S-100 (**Figure 4A**), CD68 (**Figure 4B**), TFE3 (**Figure 4C**), and neuron-specific enolase, but were negative for CK (**Figure 4D**), CD117, Dog-1, SMA and Desmin. These findings were compatible with benign GCT.

Discussion

GCT is uncommon benign mesenchymal neoplasm of Schwann cell origin, also called Abrikossof tumor, was first described by Alexis Abrikossof in 1926, which can arises in any part of the body, and the most common locations are the tongue, oral cavity, skin, and subcutaneous tissue [8]. GCT from the GI tract is relatively uncommon and comprises approximately 5% of all GCT [1]. The esophagus and colorectal are the most commonly reported locations of GCT in the GI tract, with the stomach being the third most common location [1, 2]. GCT in the ampulla of Vater is an extremely rare, to our knowledge, only one case has been reported in literature to date [5], and only two cases of the duodenum GCT have been reported [9, 10].

About the naming of GCT has been experienced some different changes. The previous reports focused on their histogenesis, originally been believed of skeletal derivation, therefore these tumors were called as granular cell myoblastoma; subsequently some authors noted that these tumors were frequently observed adjacent to peripheral nerves, the name was changed to granular cell neuroma; but later

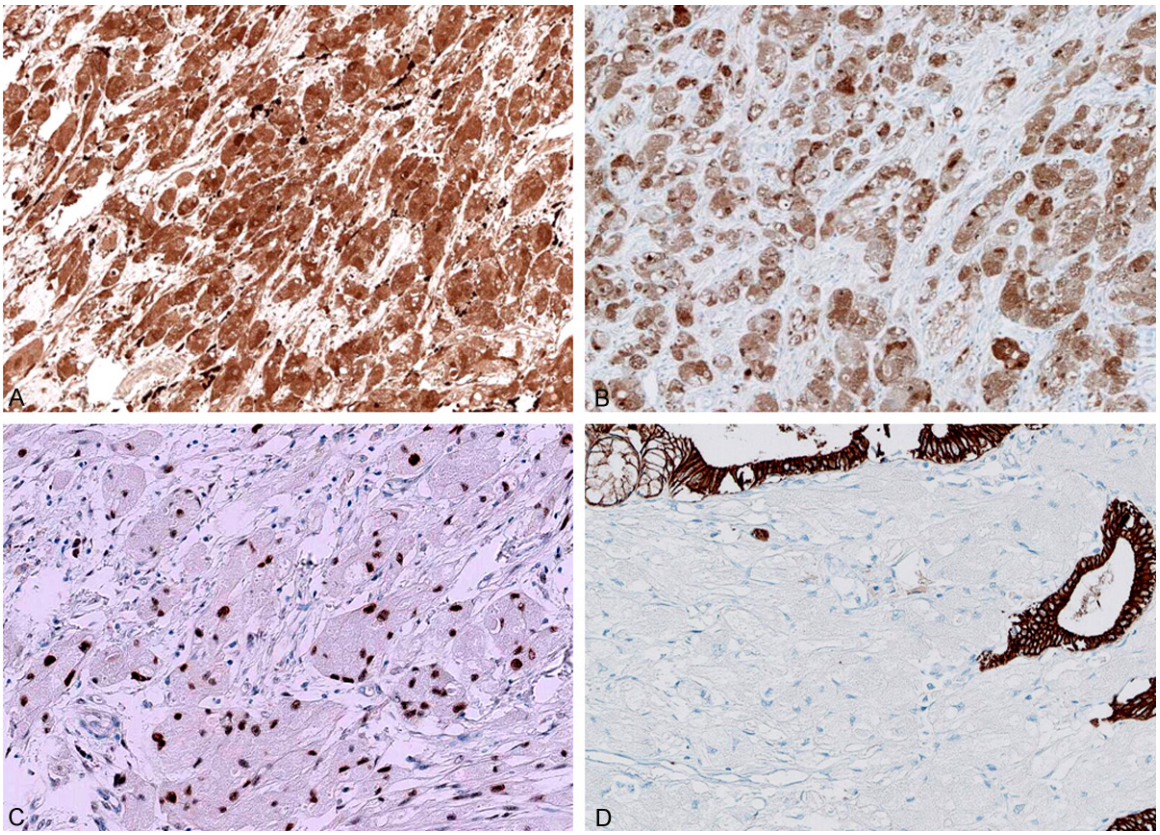

Figure 4. Immunohistochemically, tumor cells showed diffuse nuclear and cytoplasmic S-100 protein (A), diffuse cytoplasmic CD68 (B), nuclear TFE3 (C) labeling; but were negative for CK, compared with epithelial CK was positive (D).

proved to be of Schwann cells by immunohistochemical labeling of S-100 protein and electron microscopy, eventually these tumors were named as GCT.

There are no characteristic clinical manifestations about GCT, accuring in the different anatomical site, there have different clinical manifestations. Our patient was found to no obvious cause intermittent abdominal distension for 6 months, accompanied by urine yellow and poor appetite and imaging found periampullary occupying lesions. There are no tumor markers or imaging characteristics that allow a preoperative diagnosis for GCT, the diagnosis is based entirely on histopathological and immunohistochemical findings. Microscopically, the well circumscribed tumor was located mainly between the mucosa and subserosa, was composed of round to polygonal cells with abundant granular eosinophilic cytoplasm. Immunohistochemically, tumor cells showed diffuse nuclear and cytoplasmic positive for S-100 protein, diffuse cytoplasmic CD68 and nuclear TFE3 labeling; but were negative for CK, CD117, Dog-1, SMA and Desmin. Based on the pathological morphology and immunohistochemical result, the final diagnosis was benign GCT.

GCT is rare, small, slow-growing, solitary and painless tumor which behaves in a benign fashion, but can have a tendency to recur; in rare cases they can metastasize, when they became malignant, there are some clinical and histological criteria to suspect the malignance of this tumor, including rapid tumor growth, a large tumor size (>4 cm), increased cellularity, and cytologic atypia. Malignant GCT is extremely rare and is categorized into 2 types, one of which is both histologically and clinically malignant tumor and the other is clinically malignant despite a histologically benign appearance [11].

Our findings indicate an interesting phenomenon that TFE3 is overexpressed in GCT. The findings are consistent with the report of Chamberlain and his colleagues on their immu-

nophenotypic comparison of alveolar soft part sarcoma (ASPS) and GCT, they found that TFE3 was diffuse nuclear positive in 10 (91%) of 11 cases of GCT [12]. Later Schoolmeester and Lastra also observed that intense and diffuse TFE3 immunolabeling in 6 cases of GCT, but FISH was negative for TFE3 rearrangement in all cases [13]. The above results show that TFE3 is overexpressed in most GCT, but without corollary gene rearrangement detectable by FISH, further reflecting the presence of native TFE3 protein and is not indicative of TFE3 rearrangement. Although the intense and diffuse nuclear TFE3 positivity is considered sensitive and specific for tumors with TFE3 fusion, but GCT is an exception in that overexpression of TFE3 protein does not appear to be linked to separation of the TFE3 gene. In addition, significant TFE3 expression can ocassionally be seen in tumors that not harbor an associated gene fusion, such as adrenocortical carcinoma and paraganglioma [14].

At present the mechanism for overexpression of TFE3 protein is not known in the TFE3 tumor family, Roczniak-Ferguson research team [15] have proposed an error in native TFE3 degradation or promoter enhancement resulting in protein overproduction. It is likely that GCT harbor some kind of recurrent genetic alteration other than translocation of TFE3 to account for their increased levels of nuclear TFE3 protein. Schoolmeester and Lastra [13] have considered that TFE3 is instrumental in feedback regulation of phagosome/lysosome synthesis and the Golgi stress response and may induce the characteristic cytoplasmic accumulation of phagolysosomes in GCT and other TFE3-related tumors. On the contrary aberrant nuclear TFE3 accumulation in GCT may be the result of dysfunctional organellar or intracellular metabolic signaling pathways, such as deregulated lysosomal-mammalian target of rapamycin signaling.

The differential diagnosis in the current case is relatively broad that includes epithelioid PEComa [16], epithelioid GIST, epithelioid leiomyoma, ASPS [12], carcinoid [17]. Although careful histomorphologic investigation obviously plays a critical role in this differential diagnosis, IHC and occasionally molecular genetic analysis will prove decisive. The lack of HMB-45 and SMA protein expression can rule out PEComa, the lack of CD117 and Dog-1 expression can rule out GIST, the lack of SMA and Demin expression can rule out leiomyoma. Occasionally, ASPS and GCT show significant overlap in their histologic features on H&E-stained sections, rendering definitive diagnosis particularly challenging. S-100 is positive in GCT but negative in ASPS, molecular cytogenetic testing of TFE3 can be helpful in distinguish GCT from ASPS.

In conclusion, this is the first reported case of ampullary GCT in Chineses. Because of its unusual anatomic presentation, problems in diagnosis may arise. Histomorphology, immunohistochemical and molecular genetic studies may help separate it from other neoplasms, especially immunohistochemical expression TFE3 in identification of GCT and other soft tissue tumors have a very important role.

Disclosure of conflict of interest

None.

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