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First pancreatic perivascular epithelioid cell tumor (PEComa) treated by mTOR inhibitor

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ABSTRACT

Background: Perivascular epithelioid cell tumor, an extremely rare mesenchymal tumor, could be ubiquitous but rarely arises from pancreas. Surgery is considered the most appropriate treatment. Nevertheless, activation of mTOR pathway seems to be a common pathogenic event in PEComas paving the way to chemotherapy by mTOR inhibitor.
Method: A 17 year-old man presented a hypervascular tumor of 55 mm, located in the head of pancreas without bile duct or pancreatic duct compression.
Results: Histopathology showed epithelioid cells with clear or focally granular eosinophilic cytoplasm with melanocytic (HMB-45, Melan-A) and myoid markers which confirmed diagnosis of PEComa. Given the absence of worrisome feature, we ruled out surgery and decided to initiate treatment with Sirolimus, an mTOR inhibitor. After 3.5 years, we showed a significant reduction in size of the tumor.
Conclusion: This first case of pancreatic PEComa treated by mTOR inhibitor without surgery suggests a good efficiency of this therapy.
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Case report

A 17 year-old man, without past medical or surgical history, presented weight loss, asthenia and flu-like syndrome. Laboratory tests showed anemia due to iron deficiency with moderate inflammatory syndrome.

Abdominal Computed Tomography (CT) revealed a hypervascular tumor of 55 mm, located in the head of pancreas without bile duct or pancreatic duct compression (Fig. 1A). Duodenoscopy, endoscopic ultrasound (EUS) and magnetic resonance imaging (MRI) confirmed the lesion which didn't involve the papilla, was well delimited without vascular or lymph node invasion, heterogeneous and contained necrotic areas (Fig. 1B and C).

Histological examination (Fig. 1D, E, F, G) showed epithelioid cells with clear or focally granular eosinophilic cytoplasm, with oval nuclei, and inconspicuous nucleoli. Immunocytochemistry showed strong positivity for HMB-45 (50%), Melan-A (100%) and S100. Some cells were positives for smooth muscle actin. No epithelial markers (cytokeratin pan (AE1/AE3)), desmin, CD117, CD31, endocrine markers (synaptophysin, chromogranin A), and inhibin were found. The proliferation index was 10%. No necrosis nor mitotic activity nor cellular atypia, known as worrisome histo-prognostic criteria, were found. We confirmed the diagnosis of Perivascular Epithelial Cell tumor (PEComa).

Mainly based on morphological criteria of the Folpe's classification [1], because interpretation of histopronostic criteria from a single biopsy could be questionable, we classified this tumor as malignant given size, infiltrative pattern and necrosis. After multidisciplinary discussion, and given the age of the patient and the localization of the tumor, we ruled out surgery which would be pancreaticoduodenectomy, a morbid surgery (1% mortality, 7% morbidity [2]) for a relatively benign tumor, and decided to initiate Sirolimus tablets, an mTOR inhibitor, 3 mg then 6 mg q24 h per os. After 1 month, a significant clinical and radiological response with weight recovery and cytoreduction of 50% (26 × 22 mm vs 54 × 42 mm) was observed without any toxicity. After 4 months, a stable disease on MRI and a high serum concentration of sirolimus on blood tests led to a reduction of dose to 4 mg q24 h per os for

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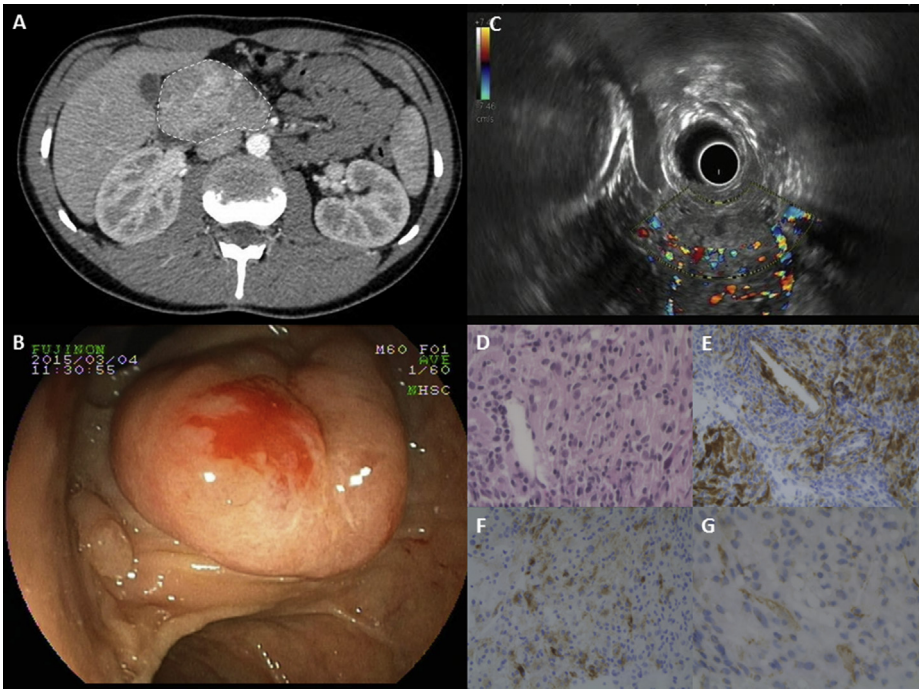

Fig. 1. PEComa: initial exams A) Abdominal CT: hypervascular tumor of 55 cm in the head of the pancreas with central necrosis and invasion of duodenal wall without bile or pancreatic duct compression. B) Duodenoscopy: bleeding duodeno-pancreatic mass, apart from the papilla. C) EUS: hypervascular mass of the head of the pancreas. D) Epithelioid cells with clear or focally granular eosinophilic cytoplasm, with oval nuclei. E) Melan A+ cells, F) HMB45 + cells, G) smooth muscle actine + cells.

7 months. Treatment was well tolerated but resulted in an increasing size. Thus we re-increased sirolimus tablets to 6 mg q24 h per os for 14 months and MRI demonstrated a substancial reduction in size of the tumor (6 × 4 mm, 88.8% reduction from baseline) (Fig. 2). Given the residual size and adverse effects of Sirolimus (asthenia, folliculitis and mouth ulceration) a new dose reduction to 4 mg q24 h per os during 3 months then 2 mg q24 h per os was applied. Thirteen months after dose reduction, no side effects were noticed and the MRI showed stable disease. We're now thinking about a definitive but mini-invasive therapy such as EUS guided radiofrequency ablation.

Discussion

PEComa is a rare mesenchymal tumor composed of distinctive perivascular epithelioid cells that exhibit both melanocytic and myoid markers. The PEComa family includes lymphangioleiomyoma, angiomyolipoma, clear cell "sugar" tumors and a variety of unusual tumor developing from different visceral sites and soft tissues morphologically and immunohistochemically similar called PEComa-NOS (PEComa not otherwise specified). PEComas arising from the pancreas are extremely rare (24 cases at present). Pancreatic PEComas could be found in patients, mostly women, of any age (median age: 48.8 year-old), but given its rarity and the extremely wide range of age (17–74 year-old), this case report of a young man is not surprising. Histologically, pancreatic PEComas are composed of epithelioid or spindle cells possessing clear to focally granular eosinophilic cytoplasm, a round to oval nucleus and a prominent nucleolus. Pancreatic PEComas have a strong positivity for HMB-45, Melan-A, and α-SMA. Other relevant positivities were desmin and S-100. No expression of epithelial and endocrine markers is seen.

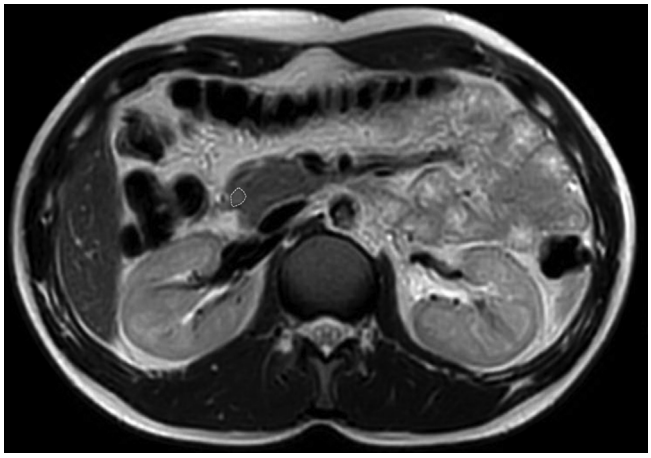

Fig. 2. MRI after 3 years of treatment with mTOR inhibitors. Residual tumor (4 × 6 mm).

Folpe et al. [1] proposed 6 features defined as « worrisome »: lesion larger than 5 cm; infiltrative growth pattern; high nuclear grade and cellularity; mitotic rate greater than 1/50 high power fields; necrosis and vascular invasion. One limitation is that histopathological criteria have been defined on surgical specimens. Thus it could be difficult to extrapolate prognostic factors from biopsies. Authors classify PEComas into three categories: benign, uncertain malignant potential and malignant according to the number of worrisome features (respectively 0, 1 or ≥ 2).

Treatment of pancreatic PEComa is still under debate. Surgery is considered the most appropriate treatment. With the exception of one single case, all pancreatic PEComas reported have been surgically treated, regardless of their Folpe's category. Given the morbidity and mortality associated with pancreatic surgery (especially for pancreaticoduodenectomy), some authors wondered if surgery is appropriate in any case. Adjuvant therapy for tumor with worrisome features isn't routinely performed. Only one case [3] described adjuvant chemotherapy (four 21-day cycles

of epirubicin plus ifosfamide plus endostar) for large pancreatic PEComa involving adjacent organs. Some authors showed that the activation of mTOR pathway through loss of the TSC1/TSC2 repressor complex seems to be a common pathogenic event in PEComas [4]. Thus, mTOR inhibitors could appear as a new therapeutic approach for PEComas [5]. Our case is the first pancreatic PEComa treated by mTOR inhibitor. This significant response tends to confirm that mTOR inhibitors could be considered for pancreatic PEComa. However, to maintain tumor control, it seems necessary to have prolonged treatment.

Conclusion

Activation of mTOR signaling pathway, a common pathogenic event in PEComa, suggested the use of mTOR inhibitor as a new therapeutic way. We reported the first case of pancreatic PEComa successfully treated by mTOR inhibitor confirming the efficacy of this treatment. The association with mini-invasive therapies (e.g. radiofrequency ablation) could be of great interest for treatment of PEComa with high surgical risk.

Conflicts of interest

All authors declare they have no conflicts of interest or source of funding

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