Unexpected Pancreatic Tumor: Report of an Exceptional Case

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1. Abstract
Pancreatic tumors are essentially primary tumors. Secondary tumors of the pancreas are less common as they represent only 2-5% of all pancreatic malignancies. Secondary tumors are dominated by the lung cancer, renal and colorectal carcinomas. Pancreatic Metastasis of thyroid carcinoma is rare finding with few reports in literature, and mostly dominated by the papillary variant.

This report will shed light on an exceptional case of a pancreatic metastasis of medullary thyroid carcinoma discovered after Whipple surgery for a clinically and radiological misdiagnosed primary pancreatic tumor in a patient with unknown past history of thyroid disease. Histological study combined with immunostaining and clinical data lead to retain the final diagnosis of a metachronous pancreatic metastasis of a medullary thyroid carcinoma.

As far as to our knowledge, this case is the fourth reported case of pancreatic metastasis of medullary thyroid carcinoma, it illustrates the rarity of such secondary tumors and the challenge of differential diagnosis leading, as in this case, to a large surgery.

2. Introduction
Pancreatic tumors are essentially primary tumors; the vast majority of them are of ductal origin (90%). Secondary tumors of the pancreas are rare findings accounting only for 2% to 5% of all pancreatic malignancies [1]. However, there are a variety of tumors involving this organ secondarily as mass lesions, most frequently at the late stage of disseminated disease; they account for 3 to 12% such as Renal Cell Carcinoma (RCC), colon rectal cancer, liver, breast cancer, ovary, urinary bladder, prostate, Merkel cell carcinoma, uterus, lymphoma and melanoma [1,2,3].

The vast majority of metastases are from lung cancer in autopsy series [1]. Pancreatic metastases from well-differentiated thyroid carcinoma are rare findings with few reported cases, dominated by the papillary variant and the follicular variant. Only three cases of pancreatic metastasis of medullary thyroid carcinoma have been reported to date. Herein, we report an exceptional case of a secondary pancreatic tumor accidentally discovered on a classic specimen of pancreaticoduodenectomy and the histological and immunohistological studies, combined with clinical data lead to diagnosis of a metachronous metastasis of medullary thyroid carcinoma. As far to our knowledge, this case will be the fourth case reported of this exceptional secondary pancreatic tumor. A brief literature review of this particular condition will also be included.

3. Case Presentation
We received a classic Pancreaticoduodenectomy (PDD) specimen from a 64-years-old woman at the pathology lab, with no clinical past history. According to the link card, the patient was suffering from paroxystic epigastralgia with vomiting episodes during two months, without fever and without weight loss. The clinical examination on admission was practically normal except for slight epigastric tenderness. The ultrasound tomography carried out had shown a mass at the expense of the head of the pancreas measuring 6cm of long axis without dilatation of the bile ducts. The abdominal computed tomography was carried out and had identified tumor mass within the pancreas head, without dilatation of the bile ducts and without infiltration of the peri-pancreatic fat. The pancreatic lesion was an isolated mass; the other viscera were free (Figure 1).
Figure 1: Abdominal CT-scan showing a pancreatic head-tumor (arrow) with bumpy outlines and suspicious necrotic center measuring 6 cm on long axis.

Biological analysis showed elevated levels of tumoral markers; carcino-embryonic antigen (CEA = 6.64 ng/ml) and CA19-9 (89 u/ml). The calcium and phosphor values were within the normal range. Once the surgical management performed, the specimen was sent to the pathology lab.

Grossly, the PDD showed the presence of a tumor with a discreetly bumpy appearance on the surface and well circumscribed margins, measuring 6x4x2.5 cm. The cut surface was pearly white and the tumor was well demarcated from the remaining pancreatic tissue and located 1 cm from the pancreatic margin. The lymph node dissection found eight lymph nodes.

Microscopically, the histological study of the tumor showed a proliferation of solid pattern, made of trabeculae, cords, solid islets and sometimes of pseudo-glandular structures. The tumoral cells were round, monomorphic showing small nuclei and "Salt Pepper “-type chromatin with many figures of mitosis. The stroma was subtle and showed focally amphophilic hyaline deposits. The entire lesion was circumscribed by a demarcating fibrous tissue. There was no evidence of infiltration of the remaining pancreatic tissue but a slight pushing effect (Figure 2 a, b). The obvious neuroendocrine pattern and the hyaline deposits lead us to achieve a special Congo red-coloration which has shown a brick-red appearance of the deposits with apple-green birefringence in polarized light confirming their amyloid nature (Figure 3 a-b).

The clinical investigation resumed with the patient and her children, had revealed the past history of a thyroidectomy dating back to 8-10 years ago (without histological data), an ovarian cystectomy six years ago, the absence of hormone syndromes related to pancreatic hypersecretion, and the absence of family history of thyroid pathology.

The diagnosis of pancreatic metastasis from medullary thyroid carcinoma has been mentioned strongly.

An immuno-histochemical study was therefore launched and had shown intense expression by tumor cells of neuroendocrine markers; synaptophysine, chromogranine A, and CD 56. The Lack of cytokeratin 20 (CK20), Thyroglobulin (Thg), and TTF1 antibodies. Finally, and specifically, the intense expression of Calcitonin by tumor cells (Figure 4 a, b, c, d). Thus, a final diagnosis been retained; metachronous pancreatic metastasis of a medullary thyroid carcinoma. Therefore, a measurement of circulating calcitonin levels did not reveal high levels.

4. Discussion

The vast majority of pancreatic tumors are primary carcinomas of ductal origin; as a consequence, pancreas cancer may be used as a synonymous of ductal adenocarcinoma. The propensity of primary pancreatic tumors can consequently make misdiagnosed other tumors occurring in the pancreas and lead to consider them primary pancreatic tumors.

Even rare (2-5%), secondary pancreatic tumors can represent an interesting variety of neoplasms that could fall in the differential diagnosis of pancreatic neoplasms making a real diagnostic challenge [1-3]

The largest study to determine types and frequency of secondary tumors involving the pancreas was undertaken by N. VOLKAN ADA-SAY [1] in 2004, it concerned autopsy and surgical specimens. There were 81 cases of secondary pancreatic tumors within 190 cases of pancreatic tumors among the autopsy series: the epithelial-origin tumors were predominant, decreasingly represented by: lung, Gastro-intestinal tract, Kidney, Breast, Liver, Ovary, and Gallbladder.
**Figure 2a:** low power [Hex20]: tumoral proliferation of organoid pattern showing a well demarcated mass lesion by fibrous with pushing effect on the remaining pancreatic tissue. The neuroendocrine pattern is obvious.

**Figure 2b:** High power magnification [HEX40]: tumoral monomorphic cells with stromal hyaline deposits.
Figure 3a: Red-Congo special coloration highlighting the amyloid nature of the deposits [HEX20].

Figure 3b: Green fluorescence of the amyloid deposits on polarized light exam.
**Figure 4:** Immuno-histochemical study [HEX20] showing positive expression by tumoral cells of

![Image of Synaptophysine](figure4a.png)

**Figure 4a:** Synaptophysine

![Image of CD56](figure4b.png)

**Figure 4b:** CD56
Less frequent, the non-epithelial tumors were essentially lymphomas, melanomas, mesotheliomas, myelomas and sarcomas. These findings were also noted in the previous literature published before 2004 [1, 4-7]. Among the surgical series, 38 cases within 973 specimens were secondary pancreatic tumors, dominated by lymphomas and lung carcinomas [1].

Well-differentiated thyroid carcinoma metastasizing to pancreas are rare findings; only twenty-six cases have been reported in the literature up to 2020, with fifteen cases published in the English literature [8-11], six cases in Japanese literature with English abstract [12, 13], and five cases in the Japanese literature [14-17]. The cases were respectively; 18 cases of papillary variant, 3 cases of medullary variant
and 4 cases of follicular variant. The mean age was 59.3 years (range 39–82 months) and the mean interval between initial thyroidectomy and pancreatic metastasis was 83.4 months (range 0–192 months); data in accordance with our case.

The time of occurrence of pancreatic metastasis of thyroid carcinomas ranges from 1 month to 13 years with an average of 7 years in another previous study by Davidson [18], which also in concordance with our case.

The pancreatic metastasis was solitary in twenty-one cases and multiple in four cases; occurring as solitary mass, metastasis can fall seriously in the differential diagnosis of pancreatic tumors both clinically and radiologically. In the case under study, the solitary mass lead to misdiagnose the metastasis as a primary pancreatic carcinoma and consequently to assess a large surgery. According to previous literature, the current case may be the fourth case of pancreatic metastasis of medullary thyroid carcinoma reported up to date.

In the case series reported by Davidson [18], pancreatic metastasis of thyroid carcinoma (12 cases of papillary variant), express thyroglobulin (Thg) in ten cases, TTF1 in four cases, CD15 in one case of tall-cells variant of papillary carcinoma. Authors reported also the BRAF V600E gene mutation as a frequent associated molecular abnormality with metastasis to the pancreas [8, 18].

In our case, the tumor did not express nor the Thg, neither the TTF1; medullary thyroid carcinoma is known to lack the Thg-antibody. TTF1 is known to be expressed in almost 90% of thyroid metastasis [19]. Nevertheless, in our case the tumor cells lack the TTF1 expression. Tumor cells also lack CK20 expression repressing a gut origin.

There was an over expression of neuroendocrine markers (ChgA, synap, CD56), and of the hallmark antibody of medullary thyroid carcinoma; the Calcitonin. Thus, we strongly favor the diagnosis of pancreatic metastasis of medullary thyroid carcinoma rather than a Calcitonin Secreting Pancreatic Neuroendocrine Tumor (CT-PETS) which is a rare lesion. Major criterions militate against this differential diagnosis:

Clinically, there were no hormone syndromes consecutive to tumor secretions; in the series reported by Schneider [20] bearing on 37 patients, the predominant symptoms of those tumors were watery diarrhea (51, 4%), abdominal pain (35,1%), and weight loss (32,4%), vomiting, nausea, flushing, polyuria, polydipsia, ascites or hematemesis were rarely described. In ancillary tests, all patients presented high levels of circulatory Calcitonin, even measured after radiological diagnosis of the tumor.

In our case the clinical symptoms were slight and nonspecific with no evidence of hormone syndromes. The circulating levels of calcium and phosphor before surgery were indicative of a CT within the normal range, confirmed by measurement after histological diagnosis. Finally, even with no histological data, the past history of thyroidectomy leads us to dismiss the eventual diagnosis of (CT-PETS) and strongly favors the farmer. According to Schneider [20], the CT-PETS are so rare that a history of thyroid disease can dismiss the diagnosis.

Secondary tumors of the pancreas may be very challenging as differential diagnosis; the symptoms, if present, can be very subtle and nonspecific [1, 2, 3, 4]. They often occur as a solitary mass of the pancreas; consequently, fall in the differential diagnosis of primary tumors as in our case. Adsay [1] reported in his surgical series the difficulty differential diagnosis of melanomas, sarcomas, and lymphomas from anaplastic pancreatic carcinomas. A melanoma with pseudo papillary pattern was also misdiagnosed as a Frantz-tumor in a young female. Other misdiagnosed secondary tumors have been also found in autopsy series [1].

In summary, this case report illustrates the rarity of such secondary pancreatic tumor and some diagnostic challenges. This case is the fourth case reported of metastatic medullary thyroid carcinoma to the pancreas. It confirms that secondary pancreatic tumors could be easily misdiagnosed as they occur like solitary mass of the pancreas making a challenge diagnosis even clinically, radiologically, and histologically.

References:


