Article published online: 2022-12-30

Rare Columnar Cell Variant Papillary Thyroid Carcinoma with Metastasis to Pancreas and Lungs at Initial Presentation: A Case Report and Review of Literature

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J Gastrointestinal Abdominal Radiol ISGAR 2023;6:62–66.

Abstract

Papillary thyroid cancer (PTC) is the most common endocrine malignancy, accounting for 85% of differentiated thyroid cancers. A small percentage of PTC variants are considered more aggressive, such as the tall cell variant associated with the V600E mutation in the *BRAF* gene and the rarer columnar variant, which is described in only 0.2% of cases and has a poor prognosis. Although locoregional metastases to neck lymph nodes are common, distant metastases of PTC are rare at presentation with only 5 to 7% reported in the literature. We present a very rare case of columnar cell variant PTC with synchronous metastasis to the lungs and indolent focus in the pancreas at initial diagnosis, which has never been reported in the literature. Our patient presented with non-radioactive iodine (RAI) responsive PTC with diffuse metastases to the lungs and one synchronous focal metastatic lesion in the pancreas. After multidisciplinary discussions, pancreatectomy/metastasectomy was deferred due to the disseminated PTC with multiple metastases to the lungs, lack of pancreas-related symptoms in the patient, and inherent complication risks. The patient was treated with systemic therapy using a tyrosine kinase inhibitor (lenvatinib), which is the standard of care for non-RAI responsive PTC and showed a complete radiologic resolution of the pancreatic lesion, however, with partial yet nonprogressive metastatic disease in the lungs.

Keywords

- papillary thyroid cancer
- columnar cell variant
- pancreatic thyroid metastasis
- PTC metastases

Introduction

Papillary thyroid cancer is the most common endocrine malignancy and is generally associated with an excellent long-term outcome.[1–4] In a 16-year follow-up study, cancer-related mortality in patients without metastatic disease at presentation was only 6%.[5] Other studies report > 95% 10-year survival rate and almost 100% 5-year survival in patients with localized disease.[4,6] Risk of death from PTC increases with older age (over 55 years) at diagnosis, invasion of major neck structures, and lymphatic/distant metastases at presentation. The follicular variant of PTC, which is the most

article published online
December 30, 2022

DOI https://doi.org/10.1055/s-0042-1758122.
ISSN 2581-9933.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

common, has a favorable prognosis. Though PTC constitutes the largest percentage of differentiated thyroid cancers, literature reports 10 different variants of PTC with a small percentage of PTC variants being considered more aggressive. These include the tall cell variant associated with the V600E mutation in the *BRAF* gene reported with an incidence of 3.2 to 19%, the even rarer columnar cell variant with an incidence of 0.15 to 0.4%, and the hobnail variant.[4,7,8] The three aggressive variant forms of PTC have a few common features of large size of the tumor at presentation, frequent extrathyroidal extension, increased locoregional lymph nodal metastasis, and overall poor prognosis.[4,7]

Locoregional metastasis to cervical lymph nodes is common but distant metastases of PTC are rare with only 5 to 7% exhibiting distant disease at presentation.[6] Additionally, when metastatic cancer is present at the time of primary PTC diagnosis, it is most often found in the bones, lungs, and thoracic lymph nodes.[2,9–11] The frequency of metastasis to the pancreas from any tumor is very low between 3 and 16%, and only 1.8% to 7.6% of pancreatic biopsies result from thyroid metastatic disease, which is diagnosed based on immunohistochemical findings for thyroglobulin/thyroid transcription factor 1 and cytomorphology.[9,11,12] There are only 13 cases reported in our literature search since the first report of metastatic PTC to the pancreas in 1991,[2,9,13] with most pancreatic metastases identified anywhere from 1 month to 13 years after the primary thyroid cancer detection.[2] However in general, a long latency period spanning several years with an 8 to 9 year average is reported in other primary malignancy metastases to the pancreas, common primaries being renal cell carcinoma, bronchiolar carcinoma, colorectal cancer, breast cancer, and gastric cancer.[11,14,15] Most of the pancreatic metastatic cases reported are from the classic and follicular variants, two were tall cell variants, and a third were poorly differentiated/classical variant mix. Based on the literature review, our patient is the only reported case to date with the aggressive columnar cell variant of PTC metastatic to the pancreas and indolent at initial presentation.[1,2,6,9] Another unique feature of our case is that our patient's diagnosis of pancreatic metastasis was based on imaging with the resolution of findings following treatment and without pathological confirmation.

Case Report

Our patient was a 50-year-old man who presented with a single episode of cough and hemoptysis. He had an abnormal chest radiograph that was followed with a computed tomography (CT) of the chest revealing bilateral pulmonary nodules with the largest measuring 1.9 cm (►**Fig. 1A**), mediastinal and left hilar lymphadenopathy measuring up to 2.1 cm in its largest dimension. (►**Fig. 1B, C**). The findings were suspicious of malignancy. The CT also reported an enlarged thyroid gland with a large thyroid nodule (►**Fig. 1D**). Dedicated ultrasound of the thyroid showed a large, solid, heterogeneous hyperechoic nodule with irregular margins and stippled microcalcifications in the right lobe (►**Fig. 2A, B**). No left thyroid nodule or cervical lymphadenopathy was identified.

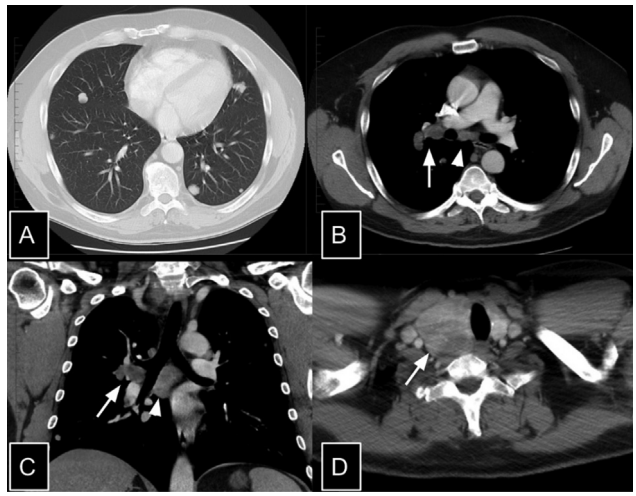

Fig. 1 (**A**) (top left image): CT of the chest in the lung window at the level of the heart shows multiple bilateral pulmonary nodules in the right middle lobe, lingula, and left lower lobe. (**B, C**) (top right image [1B] and bottom left image [1C]): CT chest in mediastinal window demonstrates enlarged right hilar nodes (arrow) and subcarinal mediastinal node (arrowhead). (**D**) (bottom right image): CT chest in soft tissue window at the level of the lower neck shows an asymmetrically enlarged right lobe of thyroid with an ill-defined heterogeneous hypodense nodule (arrow).

The patient was examined by an endocrinologist. He denied palpitations, heat/cold intolerance, dysphagia, dysphonia, muscle weakness, or facial weakness, all common symptoms of thyroid cancer. The patient is a never smoker without personal or family history of malignancy. Biopsies of the right thyroid nodule were reported as papillary thyroid carcinoma, and one of the biopsied left lung nodules was reported as metastatic papillary thyroid carcinoma. He subsequently underwent a total thyroidectomy with central neck dissection. The final pathologic diagnosis was columnar cell variant PTC, measuring 8.0 cm, involving almost the entire right lobe thyroid but confined to the thyroid parenchyma. The margins were uninvolved and there was no extra-thyroid extension. The left lobe was free of malignancy. One of two central neck lymph nodes contained metastatic carcinoma without extranodal extension. His follow-up serum thyroglobulin level at 2 months post-surgery was $>$ 500 ng/mL, which prompted a whole-body scan with sodium iodide I-131 that demonstrated thyroid remnants within the

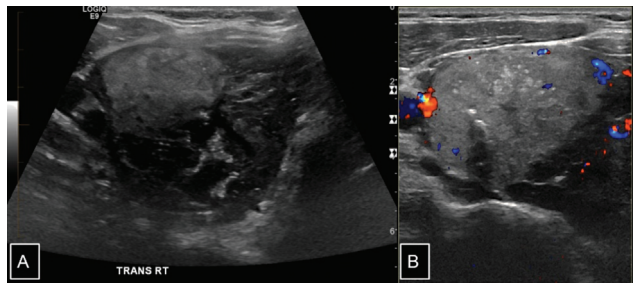

Fig. 2 (**A, B**) Grayscale image on the left demonstrates the right lobe of the thyroid replaced by a large heterogeneous solid mass with stippled micro-and macro calcifications. Color doppler images on the right show increased peripheral vascularity.

surgical bed (►**Fig. 3**). No I-131 uptake was noted in the lungs, a finding consistent with iodine-resistant lung disease, which has a worse prognosis. Subsequently, the patient was treated with 150 mCi of I-131. A staging F18-fluorodeoxyglucose (FDG) positron emission tomograph/ computed tomography (PET/CT) after radioactive iodine therapy demonstrated hypermetabolic pulmonary nodules (SUV max of 8.1), mediastinal and hilar lymph nodes (SUV max of 33 in right hilar node), which were unchanged in size compared to the preoperative CT, and an additional subcentimeter hypermetabolic pancreatic nodule (SUV max of 6.7) (►**Fig. 4A, B, C**). A dedicated CT of the abdomen and pelvis showed an exophytic, lobulated, mildly enhancing pancreatic lesion with a central hypodensity in the body of the pancreas, measuring 1.4 × 1.0 cm corresponding to the FDG avid lesion seen on PET/CT (►**Fig. 5A, B**). There was no vascular encasement or abutment. A repeat neuroendocrine-specific Dotatate PET/CT was not performed because the management would not have changed whether there was uptake or no uptake on that scan. A biopsy of the pancreatic lesion was not performed for the following reasons: the imaging presentation was consistent with PTC metastatic focus, high-risk procedure given the size and location of the lesion, and management would have remained the same, regardless of the pathologic diagnosis of the pancreatic lesion.

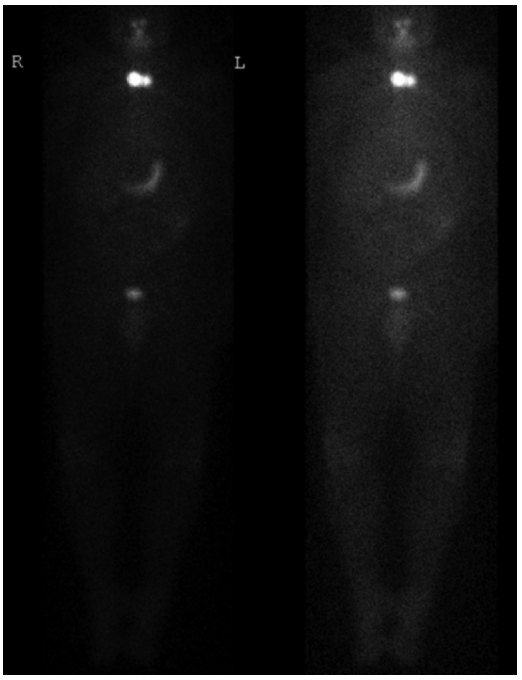

Fig. 3 Whole-body scan with sodium iodide I-131 at 2 months post thyroidectomy demonstrated increased tracer uptake at the surgical bed representing thyroid remnants.

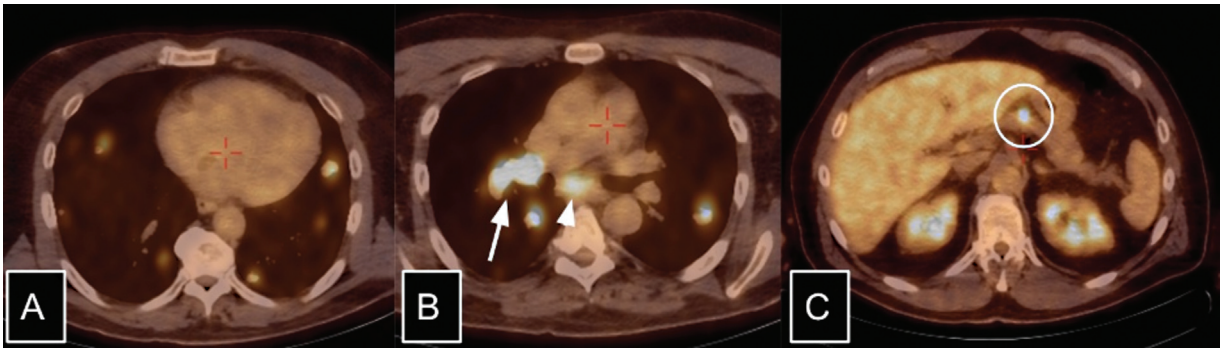

Fig. 4 FDG PET-CT: (**A**) Multiple bilateral hypermetabolic pulmonary nodules with an SUV max of 8.1 noted corresponding to the nodules seen on the preoperative CT chest. (**B**) Hypermetabolic enlarged right hilar lymph node with an SUV max of 33 (arrow) and enlarged subcarinal lymph node with SUV max of 6.0 (arrowhead). (**C**) Hypermetabolic focus in the body of pancreas with SUV max of 6.7 (circled) suspicious for metastatic focus.

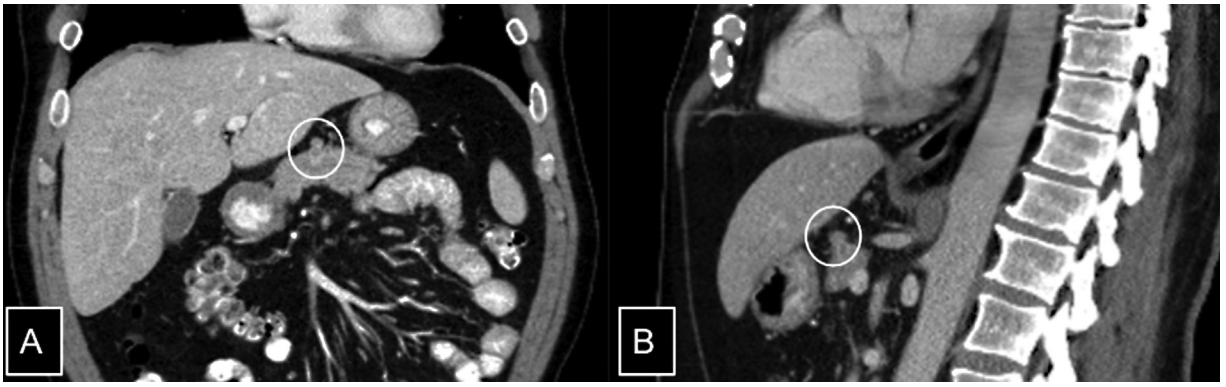

Fig. 5 Coronal (**A**) and sagittal (**B**) views of the contrast-enhanced CT of the abdomen and pelvis demonstrate a 1.4 × 1.0 cm exophytic, lobulated, mildly enhancing pancreatic lesion with a tiny central hypodensity in the body of the pancreas (circled) and this corresponded to the FDG avid lesion on the PET/CT. No vascular encasement or abutment was noted.

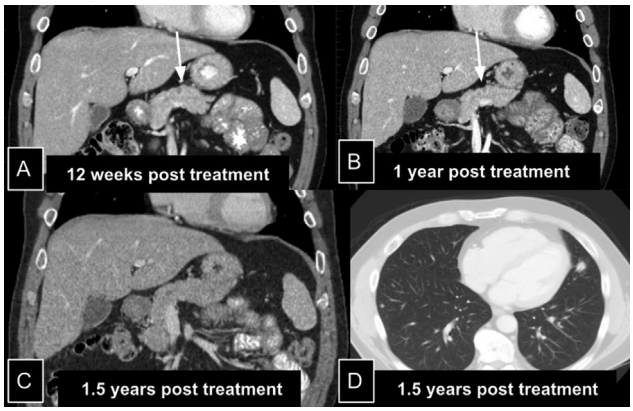

Fig. 6 Coronal view of the contrast-enhanced CT of the abdomen was performed at 12 weeks (**A**), 1 year (**B**), and 1.5 years post-RAI treatment (**C**), which shows a continued decrease in size and enhancement of the pancreatic lesion at 6 weeks and 1 year (arrows) with non-visualization of the lesion at 1.5 years post-treatment representing resolution. (**D**) CT chest in lung window shows persistent pulmonary nodules.

The patient was initiated on systemic treatment with lenvatinib, a tyrosine kinase inhibitor (TKI), for his radioactive iodine-resistant metastases involving the lungs and pancreas. After 12 weeks of therapy, follow-up imaging with CT revealed a decrease in the size of the pancreatic lesion (►**Fig. 6A**) and a decrease in the number and size of the pulmonary nodules representing a favorable response. Follow-up CTs at 1 year and 1.5 years post radioactive iodine therapy showed resolution of the pancreatic lesion, while the pulmonary nodules were unchanged in number and size (►**Fig. 6B, C, D**). No new metastatic disease or recurrence since treatment. The last serum thyroglobulin was 51.4 ng/mL, which is 2 years since the initial presentation. The patient continues treatment with lenvatinib at the time of reporting this case though with changes in his doses due to intermittent toxicity related to immunotherapy.

Discussion

PTC is a common endocrine malignancy with an average age at diagnosis reported as 55 years though the initial case reports had mostly been patients aged 80 years and above with large male predominance.[2,12] PTC rarely presents with distant metastases though metastasis is the common cause of mortality in this common thyroid malignancy.[9] Apart from the common sites of metastasis from PTC in the bones, lungs, and thoracic lymph nodes, other sites of unusual metastasis include the kidneys, liver, adrenals, skin, and muscles.[2,3,9–11] A very rare site of metastases is the pancreas.[9,11] The median time interval from the detection of primary PTC to the diagnosis of metastasis has been reported as 110 months.[14] However, simultaneous detection of primary and metastatic thyroid malignancy is reported only in 3 to 5% of patients while up to 20% of patients have a metachronous occurrence.

The literature mentions that patients with pancreatic metastases usually present with symptoms of abdominal pain, signs of acute or chronic recurrent pancreatitis, or rarely obstructive jaundice.[3,9,12,13] The long latency period described above has been attributed to the extensive asymptomatic phase of pancreatic metastases before they manifest with symptoms such as chronic pancreatitis.[12] There are also reports mentioning elevation of CA 19-9, amylase, and lipase in patients with metastatic pancreatic disease.[9,11] On the contrary, our patient did not have any symptoms related to the pancreas throughout the course of the disease, and hence the serum lipase, amylase, and CA 19-9 were not tested.

Early detection and appropriate management of distant metastases are crucial for improved patient management. To identify the primary tumor, immunohistochemistry for thyroglobulin and thyroid transcription factor 1 are tested.[13,14] Pathologic diagnosis with the accurate classification of the cell type of thyroid carcinoma is crucial as the treatment and follow-up planning depend on the type of PTC.[4] As pancreatic symptoms often manifest late in metastases, these cancers will result in diagnostic challenges that will lead to delays in treatment. Cho et al reported several years of delay in the diagnosis of their patient, resulting in several rounds of ineffective I-131 treatment.[6] Hence, imaging diagnosis is imperative in these patients for metastatic workup, which can be achieved by one of the following: contrast-enhanced multidetector computed tomography (MDCT), endoscopic ultrasound (EUS), magnetic resonance imaging (MRI), and positron emission tomography-CT (PET-CT). Whole-body scans and CT are not as sensitive and studies show PET-CT and EUS to be superior with sensitivity up to 94 to 100%.[3,8,12,13] However, the particular diagnostic tool can be chosen based on symptoms and clinical scenarios guided by serum tumor marker levels and during various treatment planning phases.[3,13] A feature shared by different metastatic thyroid cancers is the loss of radioactive iodine uptake. This can make diagnosis more challenging and RAI whole-body scans are unreliable for surveillance, which are the commonly used imaging modality to follow up patients with PTC.[2] It is usually difficult to differentiate primary from metastatic pancreatic tumors, especially when solitary; however, a few imaging findings on CT will help to differentiate the two. The findings that usually favor metastasis include multiplicity of lesions, low-attenuating lesions on contrast-enhanced CT, lack of encasement of vessels or pancreatic/biliary ducts, and accompanying liver and/or splenic metastatic lesions.[15] However, these are not always present as in our case where there were only two of the above-mentioned four features: hypodense lesion, and lack of vascular or ductal invasion. There was no multiplicity or liver/splenic lesions accompanying the pancreatic lesion.

The approach to treatment is tailored and will vary based on multidisciplinary discussions but various principles have been accepted. Authors have recommended management guidelines as resection of primary thyroid cancer should be performed first, followed by radioactive iodine ablation of surgical bed and aggressive surgery for metastasis to help prolong the survival of patients if there is no widespread metastasis.[9,13,15] On the contrary, if there is widespread metastasis at diagnosis, aggressive management for metastatic tumors is questioned due to the increased risk of morbidity and mortality especially those associated with

pancreatectomy or metastasectomy.[9,13,15] Additionally, for pancreatectomy considerations, the primary tumor should have a good prognosis, metastases must be limited to the pancreas and the patient be clinically able to tolerate the pancreatectomy surgery.[9,15] Also, controversial and debated is the simultaneous resection of primary and isolated pancreatic metastasis.[15] Most of the management guidelines for pancreatic metastases are based on more common primary cancers because PTC to the pancreas is exceedingly rare. In cases of widespread metastatic disease or involvement of an inoperable organ, systemic therapy is the best strategy.

PTC has a very good prognosis when confined to the primary site or when associated with limited locoregional metastases.[6] The common classical and follicular variants also have a very good prognosis.[5,7] Mortality increases with more aggressive PTC variants such as the tall cell and columnar cell variants.[7] The columnar cell variant PTC was first described by Evans et al in 1986 and to date remains a challenge for cytopathologists to make the diagnosis on fine-needle aspiration samples.[8] However, the following cytologic features are more characteristic of columnar cell variant PTC: hypercellular smear exclusively composed of papillary structures with pseudostratified nuclei with rare nuclear grooves and intranuclear pseudo inclusions.[8]

Though there is no significant difference in the clinicopathologic findings between the columnar cell variant and classical PTC, the disease-free survival is significantly poor, and higher rates of recurrence and increased number of incomplete responses to treatment reported with columnar cell variant as opposed to classical PTC.[4] Also, studies have shown that columnar cell variant PTC has the worse clinical outcome compared to classical PTC and even the other aggressive tall cell variant PTC.[4] Pancreatic metastases in our patient were concerning for aggressive and advanced diseases along with other factors including the most aggressive and rare form of columnar cell variant and widespread metastases to the lungs. His prognosis was very poor and hence systemic therapy was initiated after primary resection. The literature reports longevity of approximately 8.7 months for patients with pancreatic metastases from PTC.[15] In more fortunate patients with a solitary metastatic lesion to the pancreas, metastasectomy increases the 5-year survival to 31%.[15]

In light of the rarity of reported cases of metastases to the pancreas, more information and research are required to have an evidence-based approach to help guide appropriate workup and treatment. At present, it seems warranted that if a PTC diagnosis is made, an F18-FDG PET-CT (in addition to RAI whole-body scan), should be considered part of the work-up. This will save time by avoiding delay in diagnosis and timely determination of appropriate medical and/or surgical treatment.

In conclusion, for patients with a history of PTC, regardless of the remoteness of the diagnosis, clinical symptoms of pancreatitis, with or without elevation of serum markers, metastases should be high on the differential, especially when there is decreased RAI uptake but increased FDG avidity on PET-CT. Management is tailored depending on locoregional metastases, which warrant aggressive surgical management as opposed to distant metastases that warrant systemic therapy in lieu of its poor prognosis, especially in aggressive variants of papillary thyroid carcinoma.

Note
This study received funding in the form of imaging equipment. The patient described in the manuscript was from the Department of Radiology, Loyola University Medical Center, Maywood, IL, USA. The pathology examination was from the Department of Pathology, Loyola University Medical Center, Maywood, IL, USA.

Conflict of Interest
None declared.

References

1 Farina E, Monari F, Tallini G, et al. Unusual thyroid carcinoma metastases: a case series and literature review. Endocr Pathol 2016;27(01):55–64
2 Davidson M, Olsen RJ, Ewton AA, Robbins RJ. Pancreas metastases from papillary thyroid carcinoma: a review of the literature. Endocr Pract 2017;23(12):1425–1429
3 Rossi G, Petrone MC, Schiavo Lena M, et al. Pancreatic metastasis of papillary thyroid carcinoma with an intraductal growth pattern. Endoscopy 2020;52(12):E452–E453
4 Song E, Jeon MJ, Oh HS, et al. Do aggressive variants of papillary thyroid carcinoma have worse clinical outcome than classic papillary thyroid carcinoma? Eur J Endocrinol 2018;179(03):135–142
5 Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med 1994;97(05):418–428
6 Cho M, Acosta-Gonzalez G, Brandler TC, Basu A, Wei XJ, Simms A. Papillary thyroid carcinoma metastatic to the pancreas: case report. Diagn Cytopathol 2019;47(03):214–217
7 Cho J, Shin JH, Hahn SY, Oh YL. Columnar cell variant of papillary thyroid carcinoma: ultrasonographic and clinical differentiation between the indolent and aggressive types. Korean J Radiol 2018;19(05):1000–1005
8 Bongiovanni M, Mermod M, Canberk S, et al. Columnar cell variant of papillary thyroid carcinoma: cytomorphological characteristics of 11 cases with histological correlation and literature review. Cancer Cytopathol 2017;125(06):389–397
9 Ren H, Ke N, Tan C, Wang X, Cao W, Liu X. Unusual metastasis of papillary thyroid cancer to the pancreas, liver, and diaphragm: a case report with review of literature. BMC Surg 2020;20(01):82
10 Angeles-Angeles A, Chable-Montero F, Martinez-Benitez B, Albores-Saavedra J. Unusual metastases of papillary thyroid carcinoma: report of 2 cases. Ann Diagn Pathol 2009;13(03):189–196
11 Yoon JH, Jeon MJ, Kim M, et al. Unusual metastases from differentiated thyroid cancers: a multicenter study in Korea. PLoS One 2020;15(08):e0238207
12 Chen L, Brainard JA. Pancreatic metastasis from papillary thyroid carcinoma diagnosed by endoscopic ultrasound-guided fine needle aspiration: a case report. Acta Cytol 2010;54(04):640–644
13 Tunio MA, Alasiri M, Riaz K, Alshakweer W. Pancreas as delayed site of metastasis from papillary thyroid carcinoma. Case Rep Gastrointest Med 2013;2013:386263
14 Smith AL, Odronic SI, Springer BS, Reynolds JP. Solid tumor metastases to the pancreas diagnosed by FNA: a single-institution experience and review of the literature. Cancer Cytopathol 2015;123(06):347–355
15 Li XO, Li ZP, Wang P, et al. Pancreatic metastasis of papillary thyroid carcinoma: a case report with review of the literature. Int J Clin Exp Pathol 2014;7(02):819–822

