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Mixed Acinar- Neuroendocrine Carcinoma of the Pancreas: A Rare Case Report with Comprehensive Review of Literature

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1. Abstract

There are two types of pancreatic tumors. Those arising from either endocrine component (neuroendocrine cells) or exocrine component (ductal and acinar cells). Mixed Acinar-Neuroendocrine Carcinoma (MANEC), is a unique entity comprising of both neuroendocrine and acinar components, with neuroendocrine cells comprising of more than 30% of the tumor. Less than 52 cases have been reported in the literature between 1982-2019. There is paucity of literature on clinical course, diagnostic criteria, management guidelines and molecular alterations of this carcinoma. It is considered as a subtype of acinar cell carcinoma and hence treated similarly as there are no established guidelines and standard of management. However, the treatment response and disease progression data are not encouraging. We present a rare case of MANEC in a 51-year-old male, with intermediate neuroendocrine component, invading the duodenum and surrounding structures and with lymph node metastases. The patient underwent surgical resection and received neoadjuvant chemotherapy. The patient died after 26 months due to complications of malignancy. Accurate diagnosis is important, as these tumors do not very well respond to the chemotherapy give for other pancreatic cancers. Hence, reporting of these cases should be encouraged to further our understanding on this entity and help identify the underlying molecular and genetic alterations and aid in improving the standard of care of these patients.

2. Introduction

Pancreatic cancer is one of the lethal malignancies and carries significant morbidity and mortality. Tumors comprising of both acinar and neuroendocrine components are called Mixed Acinar-Neuroendocrine Carcinoma (MANEC). So far 52 cases (Table 1) have been reported in the literature. Most tumors of the pancreas arise from a single cell of origin. It is either ductal, acinar or endocrine. MANEC was first described in 1982 by Ulich et al [1]. When the endocrine cells represent more than 30% of the tumor, along with the acinar component the tumor is called MANEC. There is paucity of data and the clinical features and pathogenesis remain unclear. It is not possible to distinguish MANEC from other pancreatic cancers on imaging, since the findings are nonspecific. Definitive diagnosis is highly reliant on Pathologic evaluation and microscopy. No specific classification exists and reporting of these cases is important to establish a classification, definitive standard of care and management protocol.

We present a case of 51-year-old male who presented with a mixed acinar- neuroendocrine carcinoma of the pancreas with neuroendocrine component and also present a comprehensive review of literature to contribute towards better understanding of this entity, aid in establishing diagnostic criteria, and management guidelines.

3. Case Report

A 51-Year-old male presented with a change in bowel habits, right upper quadrant abdominal pain in the setting of acalculous cholecystitis, dilated CBD and hydropic gallbladder. His Alkaline phosphatase was elevated at 181 units/L. An MRI cholangiopancreatography was performed to evaluate the pancreatic cysts seen on imaging. A

2.4 x 1.2 cm area of abnormal signal intensity was found within the inferior aspect of the head of the pancreas. A whipple procedure was performed and on gross examination there was a poorly circumscribed mass measuring 2.5 x 1.9 x 1.0 centimeters in the head of the pancreas (Figure 1).

Microscopically, the tumor comprised of acinar and neuroendocrine cells. The tumor showed extension into peripancreatic fat and perineural and lymphovascular invasion present. The operative margins were free of malignancy. The neuroendocrine neoplasm was well differentiated, intermediate grade and invaded the duodenal wall at the junction of first and second part of duodenum. The tumor invaded the ampulla of vater. Twenty-six out of 35 submitted lymph nodes were positive for metastatic carcinoma and multiple lymph nodes showed extracapsular extension. There was extensive fat necrosis and the neoplasm involved small bowel muscularis propria and fibroadipose tissue of small bowel mesentery. There were 15 mitotic figures per high power field and Ki67 was at 65%. The tumor showed positive immunoreactivity to Chromogranin, synaptophysin and trypsin. The pathologic stage of the tumor was pT3 pN1. There was chronic pancreatitis in the uninvolved pancreas (Figure 2).

He was treated with 4 cycles of Carboplatin/ Etoposide but the disease progressed and was switched to Octreotide and Everolimus. There were distant metastases and the chemotherapy was discontinued because of the disease progression. The patient died after 26 months of his surgical resection due to complications secondary to malignancy.

Table 1: Mixed Acinar Neuroendocrine Carcinoma of Pancreas Reported in the Literature

S. No	Age (yrs)	Sex	TUMOR LOCATION	COURSE	RADIOLOGY FINDINGS	Year reported	Author reported
1	30	F	Head of pancreas	Alive after 4 motnhs	Partly solid and patly fluid mass in the area of pancreas	1982	Ulich et al[1]
2	50	M	Pancreatic head	Alive after 18 months	3cm solid mass in pancreatic head	2000	Ogawa et al[1]
3.-4	i)39	i)M	i)Uncinate process	i)Alive	i)3.6 x 2.9 cm mass in the uncinate process	2018	Strait et al[3]
	ii) 66	ii)M	ii) Pancreatic tail	ii)lost to follow up	ii) 10 cm partially cystic and necrotic mass in the pancreatic tail		
5	62	F	Pancreatic tail	unknown	Cystic , solid and hemorrhagic well circumscribed mass	2016	Jakobsen et al [4]
6	56	F	Stomach (may originate from ectopic pancreas in stomach)	Died after one month	Large extragastric mass	2009	Kusafuka et al [5]
7	45	F	Tail of pancreas	Survived 7 years and 2 months after resection	Hypervascular tumor	2017	Hara et al [6]
8	48	M	Duodenum	Died 6 months after surgery	Hypoattenuating mass involving the mesenteric aspect of 2nd portion of duodenum	2019	Pheonix et al
			(pancreatic heterotopia)				
9	63	F	Pancreas body	Alive 8 months after surgery		2010	Terashi et al
10	65	F	Head of Pancreas	Alive 12 months after resection	8 x 6 cm mass on MRI	2015	Liu et al [7]
11	63	M	Pancreatic tail	Died 18 months after initiation of chemotherpay	6cm mass lesion in the pancreatic tail with multiple liver metastases	2013	Kanemasa et al [8]
12	66	M	Uncinate process	Died 21 months after intial diagnosis	3.1 x 2.8 x 2.7 cm mass in uncinated process of pancreas	2011	Lee et al [9]

13	59	F	Tail of the pancreas	Unknown	1.5 cm hypervascular, heterogenous, nodule.	2010	Chung et al [10]
14	60	F	Pancreatic head	Unknown	Large tumor in pancreatic head	2008	Nishii et al
15	57	F	Body of pancreas	Lost to follow up	2.5 cm mass in the body of pancreas	2013	Ogbonna et al [11]
16	75	M	Pancreatic tail	Alive 6 months after surgery	7cm homogenous mass in the pancreatic tail	2010	Kobayashi et al [12]
17		M	Tail	Died 10 months later	19 x 18 x 18 cm mass in tail of panceas	1993	Hassan et al [13]
18	51	F	Tail	Alive at 2 years post resection	10 x10 mm hyperdense mass in the tail of pancreas	2008	Shi et al [14]
19	72	M	Body to tail of pancreas	Died in 3 months	12 x 10 x 13 cm tumor in the body to tail region of the pancreas directly extending into the stomach.	2000	Muramatsu et al [15]
20	46	M	Head of pancreas	unknown	4 x 5 cm mass in the head of pancreas	2001	Tobita et al [16]
21	70	F	Tail	Alive at 22 months	12.5 x 9.5 x 8 cm horse shoe shaped mass, hypervascular mass	2006	Minkawa et al [17]
22	51	F	Tail	Died after 1 year	22 x 15 x 13 cm mass in the body and tail of pancreas	2010	Ohike et al [18]
23-27	48-81 yrs ,mean age 68 yrs,	2 MALES	Head: Body: multiple = 2:2:1	Two patients died (mean = 10.5 months)	Ranging in size from 3-11 cm, Mean size 8 cm	1994	Klimstra et al [19]
		AND		Two patients alive at 12 months, one patient lost to follow up			
		3 FEMALES					
28	52	M	Body of pancreas with metastases to liver	Died after 5 months	Unknown	2019	Tang et al [20]
29-34	6 patients mean 58.4 years	2 M, 4F	Location unknown		Mean tumor size 8.2 cm	2004	Ohike et al [21]
35	6 yr	F	Tail of pancreas	Tumor free after 13 years of resection	8 centimeter mass in the tail of pancreas	1985	Ichijima et al [22]
36-40	59-89 years	5 M	4 in head of pancreas and one in body	2.5 months to 3 years survival	Tumors ranging from 3.9 to 16 cm	2013	Yu et al [23]
41-42	i)51 ii)75	2M	i.) body	Unknown survival	i.)16 mm tumor in body of pancreas	2013	Sullivan et al [24]
			ii.) genu		ii)6mm tumor in genu of pancreas		
43	52	M	Ampulla of vater	Alive after 4 months of surgery	Dilated common bile duct and mass in the vicinity of ampulla of vater obstructing the lumen	2011	Soubra et al [25]
44	35	F	Head of pancreas	Alive after 9 years on Sunitinib therapy	2.5 cm cystic tumoral lesion in the head of the pancreas	2017	De Both et al [26]

45	72	F	Body of pancreas	Unknown	Tumor in the body of pancreas	2001	Tanakaya et al [27]
46	65	M	Tail of pancreas	Alive at 12 months	8.0 cm mass in the tail of pancreas and multiple liver metastases	2017	Yokode et al [28]
47	74	M	Head	Alive after 3 months of resection	6.8 cm large well circumscribed mass	2009	Kyriazi et al [29]
48	80	M	Head	Unknown	Unknown	2008	Imaoka et al [30]
49-50	i)75	i)M	i)Tail	i)10 months without recurrence	NA	2000	Skacel et al [31]
	ii)69	ii)M	ii)Head	ii)dead at 20 months			
51	61	M	Head and body	Died 43 months	A solid 4.9 x 3.6 x 2.8 cm irregular tumor in head and body of pancreas	1998	Frank et al [32]
52	28	M	Tail	Dead at 10 months	NA	1997	Shimoike et al [33]
53	51	M	Head of pancreas	Died after 26 months	2.4 x 1.2 cm area of abnormal signal intensity was found within the inferior aspect of the head of the pancreas	2020	Our case

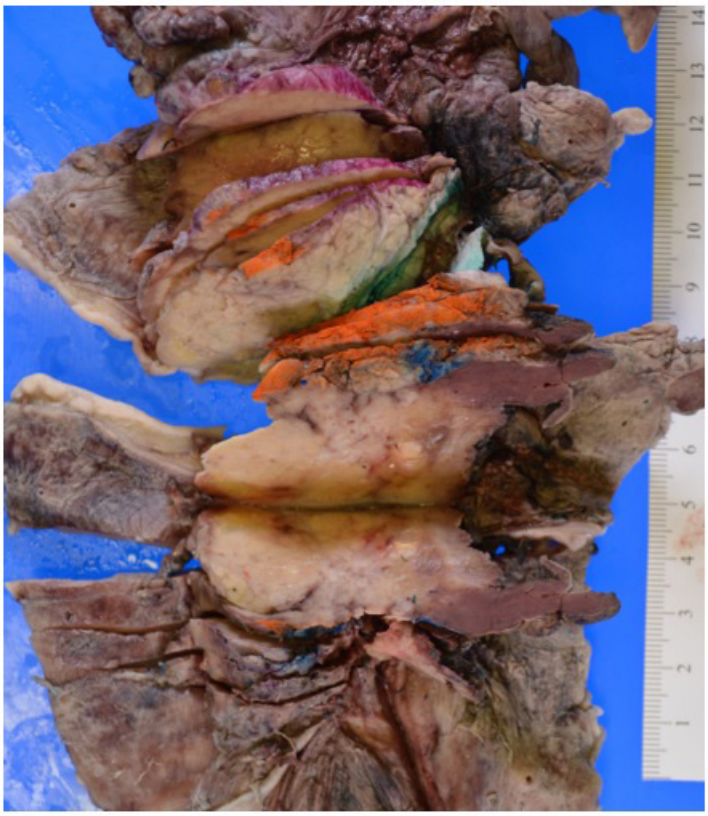

Figure 1: Gross photograph showing ill -defined tumor in the head of pancreas.

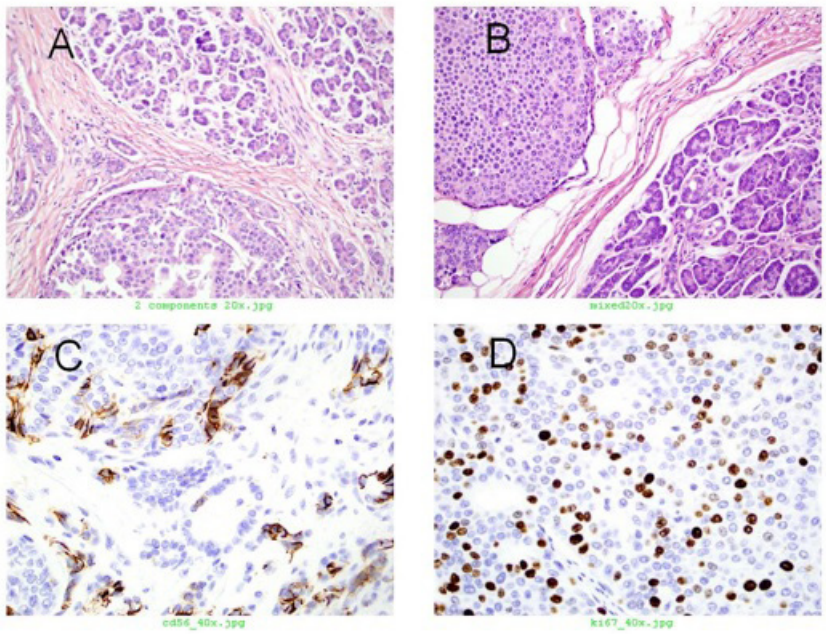

Figure 2: A. and B. H &E section of mixed acinar neuroendocrine carcinoma showing distinct acinar and neuroendocrine components (200x). C. CD56 stain highlighting the neuroendocrine cells (400x) D. Ki- 67 proliferation index of 65% in the neuroendocrine component at 400x

4. Discussion

Pancreatic mixed neuroendocrine neoplasm is a rare cancer of pancreas and rare cases have been reported in pancreatic heterotopia [2]. Tumors of the Exocrine Pancreas are histologically ductal, acinar, neuroendocrine, pancreatoblastoma mesenchymal or lymphomas. Ductal adenocarcinomas and its variants are the most common neoplasms in the pancreas constituting about 85-90% of all pancreatic neoplasms. Acinar cell carcinomas represent about 1-2 % of all pancreatic tumors. The histology is remarkable for large nodules of cells separated by hypocellular fibrous bands and acinar pattern is the most characteristic form. The neuroendocrine tumors of pancreas are classified by WHO based on the ki-67 proliferative index and are considered less aggressive than pancreatic ductal and acinar cell carcinoma. "Salt and pepper chromatin" is the characteristic feature and they may present as solid sheets, nests, trabeculae, gyri or cords. Mixed acinar neuroendocrine carcinoma (MANEC) are currently classified as a subtype of acinar cell carcinoma of pancreas. Presence of >30% of neuroendocrine cells in acinar cell carcinoma classifies them as MANEC. The acinar cell carcinoma is considered to be more aggressive than the neuroendocrine carcinoma of pancreas but the prognosis of MANEC is unknown [34].

Imaging often shows single mass in the pancreas which is either ill-defined [32] or well circumscribed [29]; solid [1], cystic [26], hemorrhagic [4], hypervascular [6, 10, 17] or necrotic mass often with metastases, especially of the liver [8, 9, 20] and ampulla of vater [25].

The acinar component if functional may secrete amylase or lipase and can present with skin lesions resembling erythema nodosa [1]. There are two histologic patterns observed, one is where the neuroendocrine and acinar component are segregated as in our case while in the other type neoplastic cells show concurrent expression of both acinar and neuroendocrine features. The latter is a more challenging diagnosis to make and use of electron microscopy is essential to distinguish zymogen granules (acinar component) from the secretory granules of neuroendocrine component [19]. These type of mixed acinar neuroendocrine carcinomas are thought to arise from pluripotent stem cells [21].

Immunohistochemistry is usually positive for Trypsin, chymotrypsin, lipase and elastase in the acinar cells and Neuroendocrine component is usually positive for chromogranin and synaptophysin. Mixed acinar neuroendocrine carcinoma of Pancreas is a rare neoplasm with 2 components each from exocrine and endocrine pancreas, i.e acinar and neuroendocrine, with acinar forming majority of the tumor and neuroendocrine component constituting >30% of the tumor. Shared mutations in different histologic components are thought to be responsible for mixed pattern of these tumors but it has not been proven. It is also conceptualized that epithelial cancers can differentiate into two different subgroups [1]. Diagnosis of mixed acinar- neuroendocrine carcinoma can be challenging based on histology alone and immunohistochemistry and ultrastructural examination is often necessary to arrive at definitive diagnosis [1]. Presence of both zymogen and neuroendocrine granules within the same cell has been observed, strengthening the hypothesis that both components are derived from a common progenitor cell [1].

Acinar cell carcinomas have alterations in the Adenomatous polyposis coli(APC)/ Beta catenin pathway. The molecular alterations seen in Acinar cell carcinomas are loss of heterozygosity at p1, 5q25 at the APC locus, 9p21 at the p16 locus, and 17p3 at the p53 locus [35]. Neuroendocrine tumors may occur sporadically or may be associated

with specific syndromes like Neurofibromatosis (NF-1), Von-Hippel Lindau (VHL) disease, Tuberous Sclerosis (TSC) or Multiple Endocrine Neoplasia-1 (MEN-1) syndromes. In each of these syndromes, MEN-1 is related to germline loss of function in MEN-1 gene and alteration of menin protein by alteration of 11q13, NF-1 is related to loss of function of neurofibromin protein and alteration of 17q 11.2 and VHL is associated with HIF (hypoxia inducing factor) dependent activation of mTOR (mammalian target of Rapamycin) and 3p25.5 alterations. Tuberous sclerosis is associated with alteration in tuberin protein and 9q34 (TSC-1) and 16p13.3 (TSC-2). Loss of chromosome 1 and 11q and gain of function at 9q are usually seen in sporadic pancreatic endocrine neoplasms [36]. Both these tumors have distinct molecular alterations. However, shared loss of heterozygosity in chromosomes 5q, 11q, 17p and 18 q have been thought to be associated with MANECs [37].

The diagnosis of MANEC is made by histological and immunohistochemical evaluation alone as there are no specific radiologic findings. Surgical resection is the first line of therapy and the efficacy of chemotherapy and radiotherapy is not well known. Due to paucity of data, there are no established management guidelines and neoadjuvant therapy is often disappointing.

5. Conclusion

MANEC is a poorly understood, infrequently encountered aggressive neoplasm, and with nonspecific radiologic and cytologic findings. Diagnosis based on radiology findings and Fine needle aspiration is a challenge. Surgical resection is the main treatment modality and diagnosis is only by histological and immunohistochemical evaluation. It is important to recognize this type of mixed tumor, since there are no management guidelines. Here we present a case of MANEC in a 51-year-old male along with a comprehensive review of literature.

References

1. Ulich T, Cheng L, Lewin KJ. Acinar-endocrine cell tumor of the pancreas. Report of a pancreatic tumor containing both zymogen and neuroendocrine granules. Cancer. 1982; 50:2099–105.
2. Bell PD, DeRoche TC, Huber AR. Mixed Acinar-Endocrine Carcinoma (MAEC) Arising in Duodenal Pancreatic Heterotopia. Case Rep. Pathol. 2019; 2019: 1713546.
3. Strait AM, Sharma N, Tsapakos MJ, Vaickus LJ, Liu X. Pancreatic mixed acinar-neuroendocrine carcinoma, a unique diagnostic challenge on FNA cytology: A small series of two cases with literature review. Diagn. Cytopathol. 2018; 46: 971–76.
4. Jakobsen M, Kloppel G, Detlefsen S. Mixed acinar-neuroendocrine carcinoma of the pancreas: a case report and a review. Histol. Histopathol. 2016; 31: 1381–8.
5. Kusafuka K. Pancreatic-type mixed acinar-endocrine carcinoma with alpha-fetoprotein production arising from the stomach: a report of an extremely rare case. Med. Mol. Morphol. 2009; 42: 167–74.
6. Hara T. Metastatic mixed acinar-endocrine carcinoma of the pancreas treated with a multidisciplinary approach: a case report. Surg. Case Rep. 2017; 3: 51.
7. Liu Z. Mixed acinar-endocrine carcinoma of pancreas: A case report and brief review of the literature. OncoTargets Ther. 2015; 8: 1633–42.
8. Kanemasa Y. Mixed acinar-endocrine carcinoma of the pancreas treated with S-1. Clin. J. Gastroenterol. 2013; 6: 459–64.
9. Lee L, Bajor-Dattilo EB, Das K. Metastatic mixed acinar-neuroendocrine carcinoma of the pancreas to the liver: A cytopathology case report with review of the literature. Diagn. Cytopathol. 2013; 41: 164–70.
10. Chung WJ, Byun JH, Lee SS, Lee MG. Imaging findings in a case of mixed acinar-endocrine carcinoma of the pancreas. Korean J. Radiol. 2010; 11: 378–81.
11. Ogbonna OH, Garcon MC, Syrigos KN, Saif MW. Mixed acinar-neuroendocrine carcinoma of the pancreas with neuroendocrine predominance. Case Rep. Med. 2013; 2013: 705092.
12. Kobayashi S. Mixed acinar-endocrine carcinoma of the pancreas with intraductal growth into the main pancreatic duct: Report of a case. Surg. 2010; 40: 380–4.
13. Medhat OH, Prema AG. Malignant Mixed Exocrine-Endocrine Tumor of the Pancreas with Unusual Intracytoplasmic Inclusions. Ultrastruct. Pathol. 1993; 17; 483–93.
14. Shi C, Jin D, Lou W. Mixed acinar-endocrine carcinomas of the pancreas: Case report and literature review. Surg. Pract. 2008; 12: 89–92.
15. Muramatsu T. Acinar–Islet Cell Tumor of the Pancreas: Report of a Malignant Pancreatic Composite Tumor. J. Clin. Gastroenterol. 2000; 31: 175-8.
16. Tobita K. Pancreatic acinar cell carcinoma with endocrine differentiation: immunohistochemical and ultrastructural analyses. Anticancer Res. 2001; 21: 2131-4.
17. Minakawa K. Pancreatic endocrine tumor with partial acinar cell differentiation. APMIS. 2006; 114: 720–5.
18. Ohike N, Bastürk O, Klöppel G, Morohoshi T. Mixed Acinar-Endocrine Carcinoma of the Pancreas. AJSP Rev. Rep. 2010; 15: 205-9.
19. Klimstra DS, Rosai J, Heffess CS. Mixed acinar-endocrine carcinomas of the pancreas. Am. J. Surg. Pathol. 1994; 18: 765-78.
20. Tang XJ, Fang XF, Zhu LZ, Wei QC, Bai XL, Liang TB, Yuan Y. Metastatic mixed acinar-neuroendocrine carcinoma of the pancreas treated by a multidisciplinary team: A case report and brief review of the literature. J. Dig. Dis. 2019; 20: 318-22.
21. Ohike N, Kosmahl M, Klöppel G. Mixed acinar–endocrine carcinoma of the pancreas. A clinicopathological study and comparison with acinar-cell carcinoma. Virchows Arch. 2004; 445: 231-5.
22. Ichijima K, Akaishi K, Toyoda N, Kobashi Y, Ueda Y, Matsuo S, Yamabe H. Carcinoma of the Pancreas with Endocrine Component in Childhood: A Case Report. Am. J. Clin. Pathol. 1985; 83: 95–100.
23. Yu R, Jih L, Zhai J, Nissen NN, Colquhoun S, Wolin E, et al. Mixed Acinar-Endocrine Carcinoma of the Pancreas: New Clinical and Pathological Features in a Contemporary Series. Pancreas. 2013; 42(3): 429-35.
24. Sullivan PS, Sullivan PS, Clebanoff JL, Hirschowitz SL. Hints to the

Diagnosis of Mixed Acinar-Endocrine Carcinoma on Pancreatic Fine-Needle Aspiration: Avoiding a Potential Diagnostic Pitfall. Acta Cytol. 2013; 57: 296-302.

25. Soubra A, Faraj W, Saab J, Shamseddine A. Peri-ampullary mixed acinar-endocrine carcinoma. Rare Tumors. 2011; 3: 44–6.
26. De Both A, Man MD, Troisi R, Vlierberghe HV, Hoorens A, Geboes K. Treatment of a mixed acinar-endocrine carcinoma with uptake on 68Gallium-DOTATOC positron emission tomography-computed tomography: A case report. Oncol. Lett. 2017; 14: 547-52.
27. Tanakaya K, Teramoto N, Konaga E, Takeuchi H, Yasui Y, Takeda A, et al. Mixed Duct-Acinar-Islet Cell Tumor of the Pancreas: Report of a Case. Surg. Today. 2001; 31: 177-9.
28. Yokode M, Itai R, Yamashita Y, Zen Y. A case report of mixed acinar-endocrine carcinoma of the pancreas treated with S-1 chemotherapy: Does it work or induce endocrine differentiation? Medicine (Baltimore). 2017; 96: e8534.
29. Kyriazi MA, Dong C, Wang C, Liu Q, Sun D, Wang L. Mixed acinar-endocrine carcinoma of the pancreas: a case report and review of the literature. Cases J. 2009; 2: 6481.
30. Imaoka H, Amano Y, Moriyama I, Itoh S, Yanagisawa A, Kinoshita Y. Endoscopic Ultrasound-Guided Fine-Needle Aspiration of a Mixed Acinar–Endocrine Carcinoma: A Case Report. Am. J. Gastroenterol. 2008; 103: 2659-60.
31. Skacel M, Ormsby AH, Petras RE, McMahon JT, Henricks WH. Immunohistochemistry in the differential diagnosis of acinar and endocrine pancreatic neoplasms. Appl. Immunohistochem. Mol. Morphol. 2000; 8: 203-9.
32. Frank M, Bittinger A, Rothmund M, Arnold R. Immunohistochemical Analysis and Clinical Course of High-Malignant Composite Endocrine-Acinar Cell Carcinoma: A Case Report. Pancreas. 1998; 17.
33. Shimoike T, Goto M, Nakano I, Sato T, Migita Y, Ito T. Acinar-islet cell carcinoma presenting as insulinoma. J. Gastroenterol.1997; 32: 830-5.
34. Ogawa T, Isaji S, Yabana T. A case of mixed acinar-endocrine carcinoma of the pancreas discovered in an asymptomatic subject. Int. J. Pancreatol. 2000; 27: 249-57.
35. Chaudhary P. Acinar Cell Carcinoma of the Pancreas: A Literature Review and Update. Indian J. Surg. 2015; 77: 226-31.
36. Chen M, Van Ness M, Guo Y, Gregg J. Molecular pathology of pancreatic neuroendocrine tumors. J. Gastrointest. Oncol. 2012; 3: 182-8.
37. La Rosa S, Marando A, Sessa F, Capella C. Mixed Adenoneuroendocrine Carcinomas (MANECs) of the Gastrointestinal Tract: An Update. Cancers. 2012; 4: 11-30.