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Intraductal papillary mucinous neoplasm of the pancreas associated with neuroendocrine tumor: A case report

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ABSTRACT

INTRODUCTION: Intraductal papillary mucinous neoplasm is an uncommon cystic tumor of pancreas that can be associated with ductal adenocarcinoma. Coexistence of pancreatic IPMN and neuroendocrine tumor is very rare. Here, we report the imaging features of mixed type intraductal papillary mucinous neoplasia of the pancreas with high grade dysplasia together with neuroendocrine carcinoma and perform review of the literature.

PRESENTATION: A 68-year old patient has been evaluated for possible IPMN that was suspected during ultrasound. MRI revealed main and side branch duct dilatations. At the head, a contrast enhancing nodular lesion was identified. Due to the presence of high risk stigmata according to guidelines, surgery was performed. Histopathological examination revealed an unusual association, including mixed type IPMN and neuroendocrine carcinoma.

DISCUSSION: The concomitant occurrence of pancreatic IPMN and neuroendocrine tumor has been reported in case studies and brief reviews. Yet, the imaging findings and underlying molecular mechanisms of this entity has not been fully understood. In addition to this unusual association, pancreatic intraepithelial neoplasia was also detected in the present case. Although majority of neuroendocrine tumor associated IPMNs were reported to be having low grade dysplasia, our patient had high grade dysplasia. Further studies and reviews with larger groups are needed to establish imaging features and underlying molecular mechanisms of this rare association.

CONCLUSION: Although the major concern during work-up of IPMN is presence of associated pancreatic ductal adenocarcinoma, the possibility of neuroendocrine tumor, in the presence of a hypervascular solid foci on imaging studies should be kept in mind.

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1. Introduction

Intraductal papillary mucinous neoplasms (IPMN) are mucinous cystic tumors of the pancreas that originate from mucin secreting cells in the main pancreatic duct and/or its branches. IPMNs are more commonly seen in males, at the 6th–7th decade. They constitute about 20% of all cystic pancreatic neoplasia's. They are categorized as main duct, branch duct and mixed type according to macroscopic features. It is well known that patients with IPMN, especially involving the main pancreatic duct, have the potential to synchronously or met asynchronously develop pancreatic ductal adenocarcinoma (PDAC). There are certain criteria that favor

the presence of malignancy defined by consensus guidelines [1]. Neuroendocrine tumor (NET) of the pancreas is a unique type of pancreatic tumor, which constitute 1–2% of all pancreatic neoplasms [2]. They most commonly occur between 3rd–6th decades, without any gender predilection. Co-occurrence of pancreatic IPMN and neuroendocrine tumor is a very rare entity and has been presented as case reports in the literature [3]. Here, we report a patient having concomitant mixed type IPMN and NET of the pancreas and make a review of the relevant literature. The work has been reported in line with the SCARE criteria [4,5].

2. Case presentation

A 68-year-old male with a 20 year history of type 2 diabetes mellitus was admitted to our hospital for further evaluation of a possible pancreatic IPMN that was suspected during a routine abdominal ultrasound examination. He was also diagnosed as hav-

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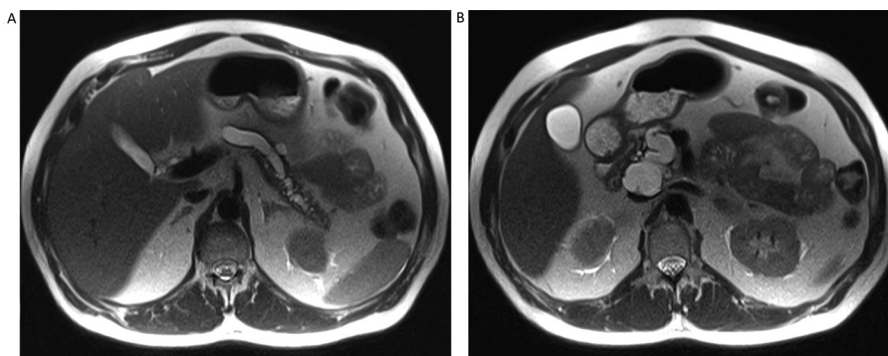


Fig. 1. a, b. Axial T2 weighted MR image showing pancreatic main ductal dilatation in the body and tail (a) and head (b) portions.

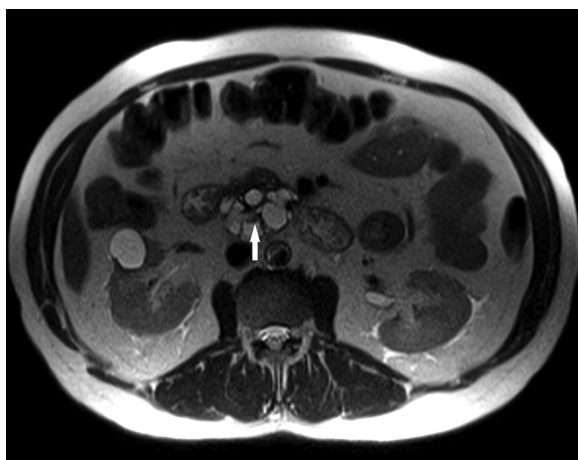


Fig. 2. A hypointense nodular intensity (arrow) is seen at the head of the pancreas inside the dilated duct close to the papilla level on axial T2 weighted MR image.

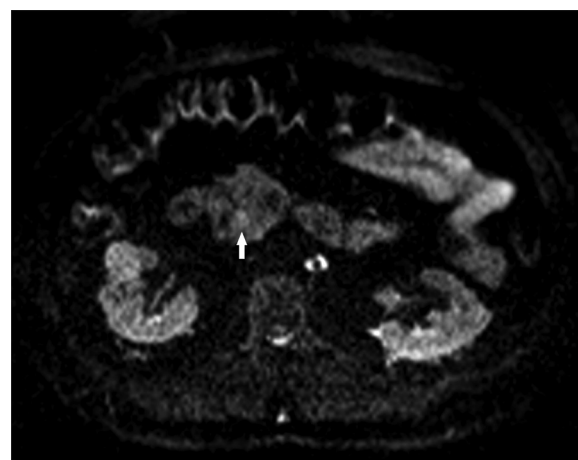


Fig. 3. Axial DWI image showing hyperintensity (diffusion restriction) of the nodular intensity (arrow) shown in Fig. 2.

ing diabetic nephropathy. There was a mild degree of renal failure. Magnetic resonance imaging (MRI) revealed dilatation of the main pancreatic duct throughout the gland, measuring up to 35 mm, accompanied by mild side branch dilatations (Fig. 1a, b). There was marked atrophy in the pancreatic parenchyma in all parts of the gland. The MR features were suggestive of a mixed type IPMN throughout the pancreas. A mural nodularity measuring 1.5 cm, that is similar to pancreatic parenchyma on pre-contrast images was noticed in the head region close to ampulla (Fig. 2). This nodular lesion exhibited hyperintensity on DWI (b: 800 s/mm²) images with hypointensity on ADC map (restricted diffusion) (Fig. 3). After intravenous contrast administration this lesion enhanced with contrast and this finding was further verified with subtraction images that were obtained after subtraction of pre from post-contrast data (Fig. 4). As far as recent international consensus guidelines about pancreatic mucinous neoplasia's are concerned [1], the imaging features revealed the presence of both high risk stigmata's (main pancreatic duct measuring >1cm and presence of contrast enhancing solid component). Tumor markers (serum CA 19-9 and CA 125) were in normal limits.

In accordance with the imaging features, total pancreatectomy, partial duodenectomy, cholecystectomy, subtotal gastrectomy, splenectomy and peripancreatic lymphadenectomy was performed. Since mixed type IPMN with high risk stigmata is detected, total pancreatectomy was performed. Although not seen on imaging tests, there was the probability of malignant foci on other parts of the pancreas. The surgery was done by a specialized hepatobiliary surgeon with 30 years of experience. The postoperative course of the patient was uneventful and he was discharged from the hospital at the end of the second postoperative week.

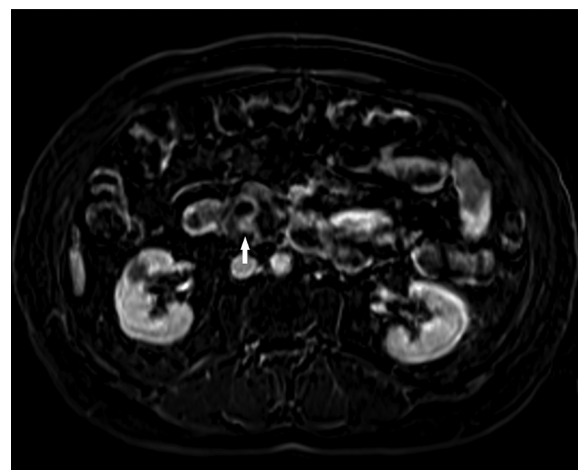


Fig. 4. Subtracted (precontrast from post contrast) T1weighted axial image showing that the nodular lesion is enhanced markedly with contrast (arrow).

For diabetes he has been using insulin subcutaneously before the operation, after surgery insulin was continued at the same dosage, pancreatic enzyme substitute (Kreon 25.000 Unit/3 times a day) was added to therapy.

Histopathological examination revealed high grade, mixt type IPMN containing gastric, intestinal and biliary type of epithelium. At the pancreatic head adjacent to the IPMN, presence of neuroendocrine carcinoma with perineural invasion was detected, that corresponded to the contrast enhancing nodular lesion seen on

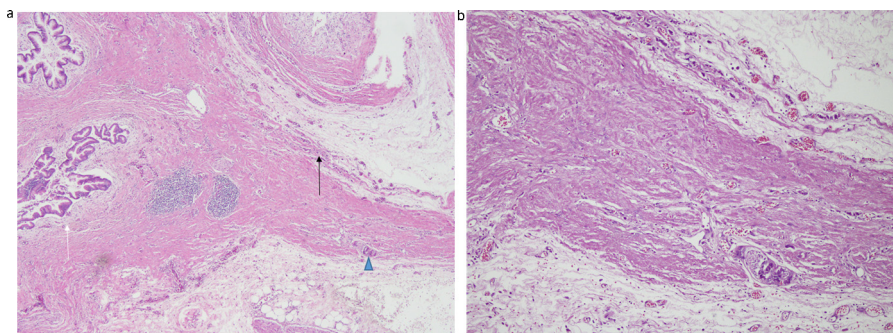


Fig. 5. a, b Histopathological images of resected pancreatic specimen on 40 hpf (a) and 100 hpf (b) showing IPMN (white arrow) and cells of NET (black arrow), at the right lower part of both figures perineural invasion (arrow head) is observed.

MRI (Fig. 5a, b). Histopathological analysis of a total of 33 regional resected lymph nodes revealed presence of neuroendocrine tumor metastases in four, without any perinodal invasion. Additionally, non-neoplastic pancreas parenchyma contained chronic pancreatitis-related changes and low grade pancreatic intraepithelial neoplasia (PanIN) foci were identified in some side branch ducts of the pancreas. The neuroendocrine tumor and 4 of the 33 resected peripancreatic lymph nodes demonstrated positive staining for chromogranin A and synaptophysin.

According to these histopathological and immunohistochemical findings, concomitant mixed type high grade IPMN and accompanying NEC with lymph node metastases of the pancreas was the final diagnosis.

3. Discussion

Pancreatic IPMN is regarded as a potential preneoplastic cystic lesion of the pancreas with a number of well-defined radiological findings that favor malignancy. According to the latest consensus guidelines, for the evaluation of pancreatic mucinous cystic lesions there are certain criteria that belong to the so called “worrisome feature” and “high-risk stigmata” groups. Presence of an enhancing solid nodular component or diameter of main pancreatic duct exceeding 1 cm are two criteria that make up the high risk stigmata. In the presence of high risk stigmata, as in the present case, surgery is indicated unless there is a contraindication. The classical type of malignancy accompanying IPMN is pancreatic ductal adenocarcinoma. The frequency of PDAC occurrence has been reported with a spectrum of 1.9–9.2% in different literature data [1,2]. On the other hand, concomitance of IPMN and NET is very unusual.

In 2013, Kadota et al., performed a literature review that revealed a total of 20 patients with this rare co-existence [3]. Eight of the patients were male and the remaining 12 female with a mean age of 63.7 (age range: 40–76 years). Although our patient is also male, there seems to be a female preponderance, as far as reported cases in the literature are concerned. Surgical excision and histopathological analyses was performed in 19 of those patients in that review. Eight of the patients had mixed, 9 had side branch and 1 had main duct type IPMN. All patients were diagnosed with associated neuroendocrine tumor, 6 of them localized in the tail, 10 in the head and 4 located in the body portion of the pancreas. Among all patients, head was the most common location of the neuroendocrine tumor, similar to our patient. Seven of the neuroendocrine tumors were detected to be malignant, and 4 among 7 had peripancreatic or regional nodal metastases, similar to our patient. Four of the total 20 patients were diagnosed as well differentiated neuroendocrine tumor (WDNT) and 7 were reported to be benign. Histopathological analysis of the IPMN component revealed three borderline, five benign, five malignant lesions and

four patients with low grade dysplasia. As far as we could review the literature the most common degree of dysplasia in coexistence of IPMN and NET, is low grade. High grade dysplasia was a very rare finding for the concomitant IPMN. However, the IPMN lesion of our patient has high grade dysplasia.

Following the largest literature review, performed by Kadota et al., only a few case reports have been published till now. In 2016, a patient having IPMN associated with a functioning neuroendocrine tumor (VIPoma) was presented as the first case in literature [6]. In the same year, de Sousa et al. presented the co-occurrence of nesidioblastosis and IPMN in the pancreas which presented with hyperinsulinemic hypoglycemia [7]. Although majority of the NETs associated with IPMN have been non-functioning type, as in our patient, the possibility of a functioning NET should also be kept in mind.

Previous reports suggest that probably this entity is more frequent than has been reported due to a variety of reasons, the most important being in the past due to underdiagnoses. The mechanism of this coexistence still is not clear. Marrache et al. hypothesized that the two distinct entities may have a common progenitor or this may result from transdifferentiation of cell types [8]. Later, genetic studies showed that there are obvious differences between genetic mechanisms between IPMN and NET [9,10]. Interestingly, our patient also had PanIN foci in the side branch ducts. This association makes the possible underlying molecular mechanism more complicated. Molecular studies with larger groups are still needed to clarify this entity.

From imaging point of view, specific radiological findings that may aid in the differentiation have not yet been defined due to limited number of reported cases. The neuroendocrine tumor that is detected in our patient had marked enhancement with intravenous contrast material that accounts for the hypervascular nature. In case of a hypervascular lesion accompanying high risk IPMN, especially in the presence of clinical symptoms that can be attributed to hormone overproduction, the possibility of a neuroendocrine primary, rather than classical hypoattenuating ductal adenocarcinoma should not be overlooked.

In conclusion, co-existence of IPMN with high grade dysplasia with neuroendocrine carcinoma having lymph node metastasis and PanIN is presented in this report. The major contribution of this report to literature is from the imaging point of view. We believe that this very rare association, still of unknown molecular basis, should be kept in mind, especially when there is a hypervascular foci in the setting of IPMN during imaging evaluation.

Conflicts of interest

All authors disclose any financial and personal relationships.

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Ethical approval

Our manuscript is a case report and review of the literature.

Consent

Informed written consent was obtained from the patient.

Author contribution

All authors contributed equally.

Guarantor

Bengi Gurses, MD.

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