

CASE REPORT

Gastric-type Intraductal Papillary Neoplasm, Pyloric Gland Variant, of the Pancreas

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ABSTRACT

Context Gastric-type intraductal papillary neoplasm pyloric gland type of the pancreas is an uncommon neoplasm with indolent behavior in many cases, morphologically resembling pyloric gland adenomas of the gallbladder, with only few reported cases of concurrent malignancy. **Case Report** We report the case of an asymptomatic seventy-two-years-old woman accidentally diagnosed with main duct-intraductal papillary neoplasm. The lesion has been surgically removed due to the endosonographic features, similar to those of an intraductal papillary neoplasm with *high-risk stigmata*. Histologically the neoplasia was composed of tubular glands lined by epithelial cells with low-grade dysplasia, resembling gastric foveolar type epithelium and pyloric gland like epithelium. The lesion developed in an area of main duct-intraductal papillary neoplasm gastric-type. The expression of MUC5AC and MUC6 supported gastric type differentiation. **Conclusion** In the majority of cases intraductal papillary neoplasm pyloric gland type are considered to follow a benign course. However, malignant intraductal papillary neoplasm pyloric gland type has been reported. In order to avoid surgical overtreatment, the development of reliable criteria determining the course of the disease is an important task. Potentially, technical advances in molecular analysis of cystic fluids may aid in the assessment of cystic lesions to avoid overtreatment.

INTRODUCTION

The abundant use of advanced medical imaging, such as computed tomography (CT) and magnetic resonance imaging (MRI), has led to the detection of an increasing number of cystic intraductal pancreatic lesions [1]. Given the fact that these lesions are known precursors of pancreatic ductal adenocarcinoma (PDAC) [2], their specific identification in imaging studies is of great relevance for the clinical approach to the patient (surveillance vs. surgical resection) [3]. The current *WHO Classification of Tumors of the Digestive System* recognizes the following intraductal precursor lesions: Pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasm (IPMN),

intraductal oncocytic papillary neoplasm (IOPN) and intraductal tubulopapillary neoplasm (ITPN) [4].

Furthermore, there is another recently described entity, resembling morphologically the pyloric tubular/papillary adenoma of the gallbladder [2]. It is not mentioned in the current WHO classification and nomenclature proposals for it are "intraductal tubular adenoma pyloric-gland type" (ITA) or, as applied in this report, gastric IPMN pyloric gland variant (IPMN-PG) [5]. A total of 41 cases (hast du die neuen Fälle mitberüic ksic htigt?) have been documented in the literature [1, 5, 6, 7]. IPMN-PG has been firstly considered as a type of ITPN [5]. However, due to its genetic features and the coexistence with gastric-type IPMN [6], it is now considered a variant of gastric-type IPMN [4].

Due to its nodular growth IPMN-PGs commonly display high-risk stigmata in imaging studies⁷. Furthermore, some cases may develop malignancy. Hence it is of utmost importance to develop radiological and/or molecular algorithms, predicting the clinical course of the disease thus avoiding under- or overtreatment.

The purpose of this study is to report a further IPMN-PG, review the literature and delineate the clinical approach in diagnostic and further management.

CASE REPORT

We report the case of a seventy-two-year-old woman, who underwent a check-up CT-scan in the context of a progressive unspecific neurodegeneration. She was

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Abbreviations EUS endoscopic ultrasound; FNA fine-needle aspiration; HGD high-grade dysplasia; IPMN-PG Intraductal Papillary Mucinous Neoplasms pyloric gland type; IOPN intraductal oncocytic papillary neoplasm; ITA intraductal tubular adenoma pyloric-gland type; ITPN intraductal tubulopapillary neoplasm; NGS next generation sequencing
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accidentally diagnosed with a cystic dilatation of the ductal system in the left sided pancreas with multiple enhanced formations (**Figure 1**). EUS revealed a normal shaped pancreas with a 15 mm enlarged main duct with intraductal contrast-enhanced nodules. Moreover, a 2 cm sized intraductal mass lying to the duct-wall but not infiltrating the adjacent tissue was detected (**Figure 2**).

EUS features were considered consistent with MD-IPMN with *high risk stigmata* and according to the revised Fukuoka Guidelines surgical resection was recommended [3]. To avoid the development of a postoperative pancreatic fistula, the wide pancreatic duct was stented preoperatively via endoscopic retrograde pancreatography (ERCP). The onset of a subclinical post-ERCP pancreatitis resolved after single fluid administration and finally a laparoscopic distal pancreatectomy with splenectomy was performed. The postoperative outcome was uneventful, and the patient was discharged after 13 days. A follow-up after 6 months did not show any clinical abnormality.

Gross examination of the resection specimen revealed a dilated main duct in the left sided pancreas. Histologically the main pancreatic duct was lined by epithelial cells resembling gastric foveolar epithelium. The nuclei were basally located and showed only mild atypia. One area resembled pyloric metaplasia with antral type glands. Furthermore, a 11.5 mm well demarcated intraductal nodule, composed of regular tubular glands, was observed (**Figures 3, 4**). Two cell types have been observed: gastric foveolar type epithelial cells, MUC5AC and MUC6 positive, and a pyloric gland like differentiation of epithelial cells, MUC5AC negative and MUC6 positive (**Figures 5, 6**). Both MUC2 and CDX2 were not expressed. The cells were only mildly atypical. There were neither mitoses nor necrosis. Approximately 1% of tumor cells were Ki-67 positive. Furthermore, there were no signs of invasion and also no atrophic changes or hyalinization. NGS revealed a single mutation of KRAS in codon 12 G12R (34G>C), a mutation of GNAS in exon 8 (c.2531G>A) and a mutation of CTNNB1 in exon 3 (c.946G>A).

These features correspond to a low grade mixed-type IPMN with gastric differentiation and a pyloric gland like adenoma.



Figure 1. CT-Scan: Diffuse cystic dilatation of the main ductal system in the left pancreas.



Figure 2. EUS (Pancreatic body): Intraductal mass of ca 2cm diameter adjacent to the wall of the main pancreatic duct, without infiltration of the adjacent tissue.

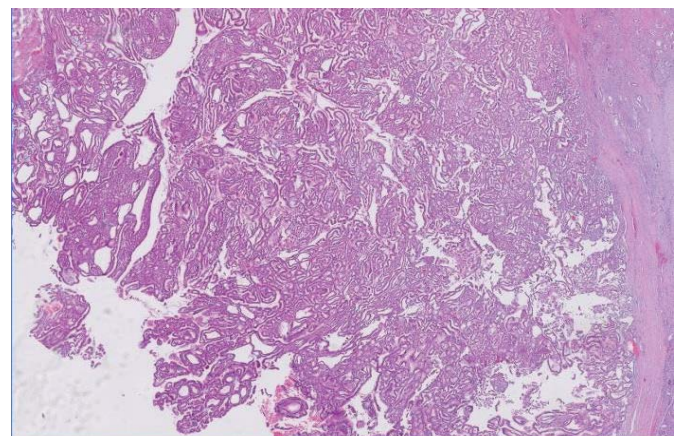


Figure 3. Histology - hematoxylin and eosin) Cross section of the main pancreatic duct showing an intraductal mass;

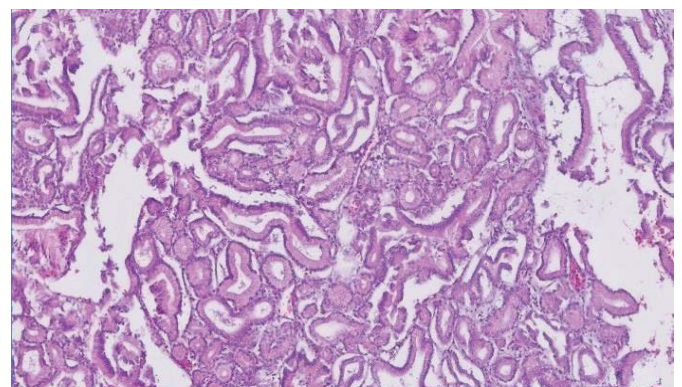


Figure 4. (Histology - hematoxylin and eosin) Higher magnification of the intraductal mass. It is composed of tubular glands. There are two types of epithelia to be observed: in the glandular area epithelia resembling those of pyloric glands and "covering" those glands epithelia resembling foveolar type epithelium.

MATERIALS AND METHODS

Next generation sequencing was performed on Illumina MiSeq. The Illumina Cancer Hotspot Panel v2 was used.

For immunohistochemistry the following antibodies were used: CK7, CK20, Ki-67, MUC2, MUC5AC, CDX2,

synaptophysin (all provided by DAKO) and MUC6 (Cell Marque).

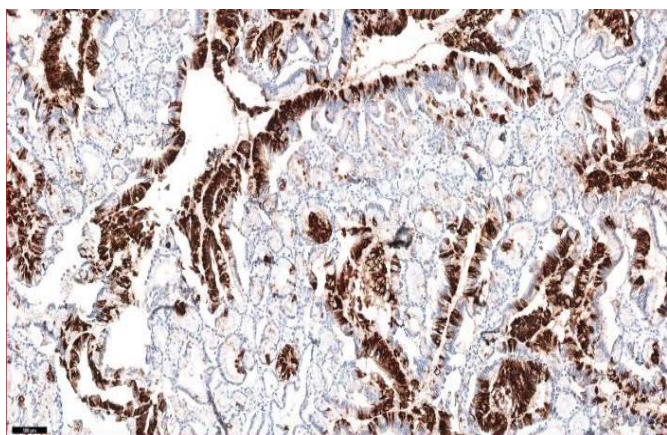


Figure 5. Only foveolar type epithelial cells are MUC5AC positive.

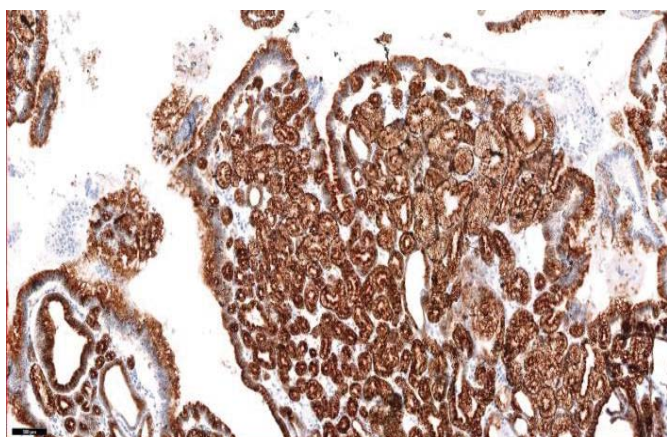


Figure 6. Essentially all epithelial cells are MUC 6 positive.

DISCUSSION

We report a case of a pyloric gland adenoma-like lesion arising in the main pancreatic duct, diagnosed incidentally in an asymptomatic patient. This is a rare pancreatic lesion. Essentially all cases have been reported in the Japanese and American literature whereas only one case was observed in Europe [1, 6]. Histologically, IPMN-PG is a neoplasm composed of tubular glands resembling pyloric glands. In our resection specimen an area with pyloric gland metaplasia was observed, supporting the hypothesis that such metaplasia could be a precursor lesion.

IPMN-PG has been described as low-grade neoplasms with good prognosis. In a minority of cases with IPMN-PG pancreatic duct adenocarcinoma may develop. Interestingly, in a recent study with 4 malignant IPMN PG cases, all were localized in the pancreatic head [7]. According to this study, there were no specific radiologic signs that indicated malignancy in IPMN PG.

In general, considering all types of IPMNs, most cases follow a benign course. Nevertheless, a subgroup may develop high grade dysplasia (HGD) and may be the progenitors of pancreatic carcinoma. Identifying patients who are at a higher risk of harboring lesions demanding resection and determining the mode of follow-up in the remainder was the aim in many studies and lead to the current guidelines. Although clinical decision should be individualized, findings on imaging studies called

“worrisome features” and “high risk stigmata” guide this decisional process. Patients with *worrisome features* should be evaluated by EUS to further stratify the lesion. Patients with *high-risk stigmata* IPMNs should undergo resection if feasible [3]. In our case an enhanced mural nodule >1 cm was observed and was interpreted as *high risk stigma*, thus a surgical resection was performed.

Clearly, although intramural nodules are commonly associated with high grade dysplasia and almost exclusively occur in pancreaticobiliary and intestinal type IPMN, they are also observed in benign pancreatic lesions. E.g. approximately 50% of IPMN-PGs arise in association with a gastric-type IPMN and present with nodular/polypoid intraductal masses inside a cystically dilated pancreatic duct in EUS [2] (**Figure 2**). Therefore, IPMN-PG may display high risk stigmata in imaging studies and when they present with an enlarged duodenal papilla with mucous hypersecretion at the endoscopic inspection [8], they perfectly imitate the features of a high grade IPMN. Furthermore, complicated branching of flat-type IPMN ducts and granulation tissue in ducts might result in radiological presentation as enhanced mural nodules [7].

To overcome these diagnostic drawbacks, several radiologic markers have been proposed. Since pancreatic parenchyma atrophy is known to be associated to IPMN malignancy, one group suggested to assess this feature using CT/MRI to predict IPMN-associated malignancy [7]. However, atrophic changes in distal pancreas may also be the result of ductal obstruction by a large benign IPMN-PG.

Molecular analysis of pancreatic material collected via EUS could provide additional information on the dignity of the intraductal tumor. It is well known, that KRAS and GNAS are early and relatively specific genetic alterations in IPMNs. Following these early events there is a convergent evolution in later driver genes such as RNF43, CDKN2A and TP53 finally leading to the development of PDAC [9]. Possibly a specific pattern of molecular events might indicate a high-risk situation. Another important finding which might be exploited diagnostically is the fact that driver gene heterogeneity is prevalent in IPMN with KRAS and GNAS mutations and that these mutations are more heterogenous in low-grade dysplasia when compared to high-grade dysplasia [9, 10].

Therefore, molecular analysis of fluid collected from pancreatic cysts by fine needle aspiration (FNA) could be useful in determining the risk of progression of lesions with *worrisome features* or *high-risk stigmata*. Furthermore, the assessment of ploidy by DNA cytometry may provide a simple method to suggest grade of dysplasia in cystic fluid [11]. Another technic to characterize the nature of a pancreatic lesion is based on the analysis of duodenal fluid collected after secretin stimulation: in this setting the detection of TP53 genetic alterations is a potential indicator of malignancy [12, 13].

CONCLUSION

IPMN-PG is rare pancreatic lesions which can occur both in coexistence with IPMNs gastric type or as isolate MD lesion. In imaging studies, they may resemble IPMNs with *high-risk stigmata* or *worrisome features*. In patients with incidentally detected pancreatic cysts with *high-risk stigmata*, this entity has therefore to be taken into account. In addition to classical imaging and endoscopic ultrasound, the availability of new analytic methods could be supportive in the differentiation of lesions with atypical morphologic features. In particular, the molecular analysis of cyst fluid might prove useful in determining the management of pancreatic cystic lesions.

Conflicts of Interest

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

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