Concurrent Invasive Ductal Carcinoma and Pancreatic Intraepithelial Neoplasia in Duodenal Heterotopic Pancreas: A Case Report

Sara Al Harthi1* and Mohammed Al-Masqari2

1Anatomical Pathology, Oman Medical Speciality Board, Muscat, Oman
2Anatomical Pathology, Royal Hospital, Muscat, Oman

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*Corresponding author: r2053@resident.omsb.org
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Abstract

Heterotopic pancreatic tissue is defined as the presence of pancreatic tissue outside of its usual site with no vascular or anatomic association with the normal pancreas. This is most commonly found in the stomach, duodenum and proximal jejunum. The majority of diagnosed pancreatic heterotopia cases are an incidental finding. Yet, the heterotopic pancreas can occasionally produce symptoms such as bleeding, abdominal pain and symptoms related to gastrointestinal obstruction. They can also develop malignant and pre-malignant lesions that are normally reported in the native pancreas. The following report details a rare case of a 77-year-old male with concurrent invasive ductal carcinoma and low-grade pancreatic intraepithelial neoplasia involving a heterotopic pancreatic tissue located at the duodenum.

Keywords: Adenocarcinoma; Pancreas; Duodenum; Neoplasms; Ductal Carcinoma; Oman.

Case Presentation

A 77-year-old man with an intermittent fever, widespread pruritus, and jaundice presented with them. CT, US, and magnetic resonance cholangiopancreatography (MRCP) revealed a pancreatic head mass with characteristics favoring adenocarcinoma. None of the imaging modalities indicated a submucosal lesion involving the duodenum.

The patient underwent a Whipple procedure.

On gross inspection of the specimen, a firm, ill-defined mass surrounding the intrapancreatic common bile duct and pancreas head was detected. The duodenum had a well-defined intramural lesion with a consistently yellow sliced surface measuring 2 cm in maximum dimension. The overlying mucosa was unremarkable (Figure 1).
Microscopy of the pancreatic head mass revealed a moderately differentiated ductal adenocarcinoma (PDAC). The surrounding pancreatic parenchyma showed high-grade pancreatic intraepithelial neoplasia (HG-PanIN). Microscopic examination of the duodenal lesion revealed ectopic pancreatic tissue with low-grade PanIN (LG-PanIN) (Figure 2).

Immunohistochemical analysis using p16 and p53 markers showed complete loss of p16 in both the PDAC and ectopic LG-PanIN. The p53 revealed variable expression (i.e., wild-type staining pattern) in PDAC and no expression in ectopic PanIN (i.e., aberrant staining pattern) (Figure 3).
Figure 2: (a) a microscopic image of the ectopic submucosal pancreatic tissue composed of acini and ducts (black arrow) with a low-grade PanIN lesion (red arrow) with overlying unremarkable duodenal mucosa (green arrow) (H&E; X4 magnification). (b) A higher magnification of the ectopic foci exhibiting LG-PanIN lesion (red arrow) (H&E; X10 magnification).
Figure 3: (a) The PDAC in the native pancreas expressing p53 IHC stain with variable nuclear expression (stained brown) (H&E; X10 magnification). (b) The PanIN involving the ectopic pancreas showing complete loss of p53 nuclear stain (red arrow) (H&E; X10 magnification).

Discussion

Heterotopic pancreatic (HP) tissue is discovered in an unusual location, complete with its own vascular supply and duct system [1, 2]. It most typically appears in the upper gastrointestinal tract (GIT), especially the duodenum [2, 3]. Several hypotheses have been proposed to explain this phenomenon, including totipotent endodermal cell development into mature pancreatic tissue, misplacement of pancreatic tissue during GIT formation, and metaplastic pancreatic tissue migration from the GIT mucosal surface to the submucosa [4-6].

HP affects 0.5% to 13.7% of the population, three times more common in men than in women [5]. It is typically discovered incidentally during endoscopic or imaging workup, postoperatively, or at autopsy [1, 2, 6]. Most HP’s lack symptoms, according to published case studies [1, 7-9]. The most commonly reported symptoms are vomiting, nausea, and weight loss [2,5]. A series of studies discovered that symptomatic HP lesions are larger than 2 cm in size, occur more frequently in younger individuals, associated with a lymphoid cuff and are more likely to be located in the stomach [10]. Larger lesions are related to more severe symptoms [8]. Moreover, HP is prone to acute pancreatitis, neoplasia, and other pathologies that can occur in the normal pancreas. Malignant conditions are extremely rare [1, 11].

HP appears as a poorly defined, homogeneous and hypoechoic lesion in the endoscopic US that coincides with the acinous components and dispersed adipose tissue [6]. The diagnosis based on imaging remains challenging [6, 11]. Leiomyoma, gastrointestinal stromal tumor (GIST), and other lesions with comparable characteristics might also be included in the differential diagnosis [12]. Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) might be the most reliable modality to confirm the diagnosis [1].

The heterotopic pancreas in the GIT presents macroscopically as a hard, well-defined subepithelial lesion that can be comparable to a GIST or leiomyoma [12]. Microscopically, it is composed of a variable combination of the normal pancreatic constituents, including acini, ducts or islet cells [5]. Type I is distinguished by the presence of all three elements; type II by the predominance of acini without islet cells; and type III by the presence of pancreatic ducts without islet cells [6, 12]. They are typically seen in the submucosa, but may also be found
Submucosal lesions can be missed during endoscopic biopsies due to the limited depth of the procedure, so the use of EUS-FNA has shown to provide superior results [1, 12].

In this report, we examine the case of a PanIN lesion discovered after a Whipple procedure.

PanIN is a microscopic (<5 mm), non-invasive neoplastic lesion arising within the pancreatic ducts [13]. It’s the most important risk factor for developing pancreatic invasive ductal adenocarcinoma [4]. They are classified as low and high-grade lesions, depending on the degree of cytological and architectural atypia [13, 14].

The incidence of PanIN increases with age. LG-PanINs are more frequent, and they can be found in over 50% of people over the age of 50 [15]. They either progress to a HG-PanIN and eventually develop into a carcinoma, or persist as low-grade for decades [16, 17]. LG-PanIN can seldom progress to cancer, and it’s only reported in 1.5% of males and 1.3% of females with a LG-PanIN. On the other hand, the risk of developing cancer from a HG-PanIN is reported to be as high as 33% [16].

Molecular studies support the hypothesis that PanIN can progress to (PDAC) with accumulation of genetic alterations overtime [4, 16, 17]. The majority of LG-PanIN’s harbor telomerase shortening and KRAS activating point mutation, both of which are thought to represent early molecular aberrations in PDAC [14, 18]. Telomeres are DNA repeats that protects chromosome ends from damage or loss during the cell cycle [17].

At the intermediate stages of neoplasm growth, the tumor suppressor gene cyclin-dependent kinase inhibitor 2A (CDKN2A/p16) is inactivated, which favors the establishment of a HG-PanIN [14, 15, 17, 18]. This is present in the great majority of pancreatic carcinomas [4]. In the late stages (i.e., invasive PDAC), the tumor suppressor genes TP53 and SMAD4 are frequently inactivated [14, 18]. The TP53 gene encodes for the p53 protein, which regulates cell division and apoptosis. This absence of this protein enhances the accumulation of genetic variations, which promotes cell growth and survival [4, 19]. The SMAD4 protein is also important in cell cycle control [4].

One study found HG-PanIN-associated PDAC carried more KRAS mutations, while PDAC with no HG-PanIN in the background harbored TP53 and SMAD4 inactivating mutations [14]. This highlights the possible different molecular pathways that PDAC can arise from, including the case described in this report where the p53 exhibited wild-type expression in the PDAC but aberrant expression in the ectopic LG-PanIN.

Due to the rarity of PanIN lesions arising within a HP, guidelines for treatment and follow-up have not been established. Endoscopic resection has been suggested with endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) if EMR is difficult [1, 6]. HP PanIN lesions are best treated surgically due to the risk of bleeding and perforation during endoscopic excision. Safe resection margins are undefined [1, 5]. It's unclear whether these patients require further follow-up.

Reference


