Heterotopic pancreas (HP) is defined as the presence of pancreas tissue outside the normally placed pancreas. Heterotopic pancreas represents a rare lesion, usually asymptomatic and discovered incidentally during surgery or necropsy. In theory, all the pathological conditions that are developing in the normal pancreas may be observed in HP. The classification of pancreatic neoplasms is based on the cell differentiation line as ductal, acinar and endocrine [1]. The large majority of the neoplasms have ductal differentiation including intraepithelial or infiltrative, cystic or solid type lesions. Malignant ductal lesions and their precursors are rarely seen in HP [2, 3].

Pancreatic intraepithelial neoplasia (PanIN) is a recently described lesion [4] and accepted as a preinvasive precursor of pancreatic ductal adenocarcinoma for the normal anatomical pancreas, and for the HP [3, 5]. These lesions are diagnosed only by microscopy; they appear in the small caliber (< 5mm) pancreatic ducts and are divided into three grades (PanIN 1 to 3) according to the degree of cytology and architectural atypia. No definite data exists in the literature regarding the outcome of this lesion in the HP and the need for negative resection margins [3].

Pancreatic endocrine neoplasms (PENs) are classified based on size, mitotic rate and Ki67 index. Endocrine microadenomas are defined as nonfunctional tumors, measuring less than 0.5 cm and considered clinically benign [6]. There are very few cases of endocrine tumors reported in HP, it being also difficult to appreciate if the endocrine tumors arise from ectopic pancreas or are distinct independent lesions [7, 8]. To our knowledge, no such cases have been described in the jejunum.

CASE REPORT

We report the case of a 58-year-old male patient who presented to the Emergency Department of the County Clinical Hospital in Timisoara with acute, severe epigastric and abdominal pain, which had intensified in the last couple of days. Other reporting symptoms were asthenia, altered general status and weight-loss in the past 6 months. Previous history was without any significance. Imaging investigations found a...
large gastric neoplasm, adenopathy on the lesser curvature, liver metastasis and ascites. Radiology did not identify any masses in the pancreas and the laboratory tests for pancreatic enzymes showed normal parameters. The patient was moved to the surgery department for the tumor excision. A total gastrectomy was performed. During the surgery, a tumor mass was also identified in the intestinal wall, and was considered an intestinal metastasis; therefore, a fragment of the small intestine was also resected and referred to the Pathology Department.

The intestinal lesion was macroscopically a nodular tumor in the wall of the jejunum, 1.2cm/1.3cm/1.2cm, yellowish-white in colour, with apparently normal mucosa. The resected margins were negative for the tumor.

Microscopically, the tumor was proved to be a HP with acinar, ductal and endocrine component (Langerhans islets), similar to a normal pancreas, and corresponding to type I in the Heinrich classification (Fig.1). In this setting, two pathologically distinct lesions were identified, both measuring < 5mm in the maximum length.

**Fig. 1.** Heterotopic pancreas. Submucosal pancreatic tissue in a jejunal wall containing ducts, acini and endocrine cells (H&E, x4).

At the level of a dilated duct (3.6 mm), with predominantly flat ductal-type epithelium, a focal intraductal papillary proliferation with a pseudostratified epithelium was seen, composed of columnar cells, with variable mucin production, round to oval nuclei, predominantly basally located, having some atypia (focal crowding, loss of polarity, enlarged and hyperchromic, some nucleolated) but without atypical mitotic figures (Fig. 2), histopathologic aspects which characterize an intraepithelial neoplasia with moderate dysplasia (PanIN-2). No other types of intraepithelial or invasive neoplasia were observed on repeatedly cut sections.

Another single, circumscribed area (0.9/0.5mm) of endocrine proliferation was identified, with trabecular, nested and tubular architecture, small/medium size cells with scant, slightly eosinophilic cytoplasm, and nuclei with dispersed, fragmented chromatin (salt and pepper pattern), without atypia and mitotic aspect (Fig. 3); it was diagnosed as an endocrine pancreatic microadenoma. On repeatedly cut sections this very small lesion finally vanished.

Post-surgery the clinical evolution of the patient was not favorable, two weeks after the surgical intervention the patient died due to complications: sepsis, bronchopneumonia and renal failure. The histopathological report of the gastric tumor concluded to a poorly differentiated, mixt (diffuse and intestinal) carcinoma, pT4bN2.

**DISCUSSION**

Heterotopic pancreas represents a rare finding in the intestinal wall, being observed in 0.5% of upper abdominal laparotomies and in 0.6-13% of necropsy studies [2, 9]. Usually it is discovered in the upper gastrointestinal tract, the stomach, duodenum and jejunum being the most common location [2, 9-11]. Frequently, HP is misdiagnosed as a submucosal primary tumor, usually mesenchymal type, polyps or metastatic tumor as this case was. The diagnosis of such lesions is usually histological, by identifying normal pancreatic tissue. The HP in our patient had acini, ducts and endocrine tissue, which is the commonest variety [12].

Generally, it is supposed that all the pathologic conditions that affect the normal pancreas may be seen in HP, such as acute/chronic pancreatitis, pseudocystic changes, intraductal papillary mucinous neoplasm (IPMN), intraepithelial lesions or pancreatic neuroendocrine tumors being described [10], but malignant transformation is exceedingly rare [2, 9, 12]. In the rare cases of PanIN lesions reported in the HP [3, 5, 13-15], the premalignant changes seemed to occur with approximately the same incidence in HP as in the orthotopic pancreas [13]. The progression model from low-grade intraepithelial lesions (PanIN-1) to ductal adenocarcinoma in HP was demonstrated...
by Zhang et al. [5]. The present case was not associated with chronic pancreatitis, and morphologically the pancreatic ectopic tissue displayed papillary proliferation in a dilated duct, with moderate atypia, compatible with PanIN-2 diagnosis, which is the most frequent type encountered [3, 13, 15]. For the differential diagnosis of the PanIN lesions, IPMN should be considered. The distinction between PanIN and IPMN is currently based on size and macroscopic appearance [16]; IPMN is a larger, visible lesion (> 1 cm), possibly associated with other type of precursors or invasive tumors. The cyto-architectural atypia present in our case was not prominent as that seen in carcinoma, and repeating the examined sections we did not see any association.

Extremely rare cases of PENs developed from HP have been described [8, 17, 18], therefore there exists the risk to misinterpret the normal endocrine tissue in HP as a possible endocrine tumor [19]. Endocrine microadenomas in the normally placed pancreas are rare lesions, mostly discovered incidentally, usually circumscribed, measuring 1-2 mm. No cases of endocrine microadenoma developed in HP have been published in the literature. Endocrine microadenomas must be differentiated from other PENs (>5 mm), and from an enlarged but non-neoplastic islet (<500µm), but because of the small size of our lesion that vanished at repeated histopathological sections, the lesion has been defined as such. More so, islet cell hyperplasia should also be mentioned in the differential diagnosis: this is a small and nonfunctional lesion, but usually multiple, irregular in shape and non-circumscribed.

The management of such cases is difficult to appreciate due to the different presentations of HP and the lack of clear criteria to detect them pre-operatively [12]. None of the cases with malignant and premalignant ductal lesions occurring in HP and reported in the literature had been diagnosed pre-operatively. Classically, a surgical intervention is required for symptomatic patients. In our patient, endocrine microadenoma being considered as a benign lesion, theoretically no further treatment was necessary, however all PENs pass through a microadenoma stage as they grow larger than 0.5 cm. Also, because the PanIN lesion in HP is considered as a precursor of ductal adenocarcinoma [5], the surgical excision was mandatory. Heterotopic pancreas should be considered in the differential diagnosis of gastrointestinal submucosal masses and retroperitoneal tumors and the treatment of choice for all these patients is resection due to possible presence of premalignant or malignant lesions. Moreover, a supplementary attention needs to be given for other exocrine pancreatic lesions, because concomitant neoplastic precursors for ductal lesions have been described in HP and in morphologically normal pancreas [16].

CONCLUSION

We report the first patient with concomitant lesions, an exocrine (PanIN-2) and an endocrine (endocrine microadenoma) component in a heterotopic pancreas located in the intestine. The extreme rarity of each of these lesions makes it difficult to appreciate the evolution, prognosis and management of such conditions, but one needs to be familiar with their existence for the differential diagnosis.

Conflicts of interest. None to declare.

Consent. Written informed consent was obtained from the patient prior to admission for teaching/scientific use of his images provided his identity will be protected.

Authors’ contribution. R.C. assigned the case in the hospital pathology department; R.C. and S.T. developed the study design and prepared the draft of the article; C.S. acquired the data, photographed and interpreted the images; C.L. collected literature data; A.D. critically revised the article. All authors approved the final version of the manuscript.

REFERENCES


