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Original Research Article

Pancreatic heterotopia: An overview of a lesion often mimicking neuroendocrine tumour

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ABSTRACT

Background: Pancreatic tissue that has no direct or vascular connection to the main body of the pancreas constitutes ectopic pancreas or heterotopic pancreas (HP). Majority are located in the upper gastrointestinal tract (GIT). HP may be mistaken for neoplasms like neuroendocrine tumour (NET) and adenocarcinoma on endoscopy as well as on histopathology. We report six cases of HP along with review of literature; three of them were misdiagnosed as NET. To the best of our knowledge, this is the first case series of HP from India, rest being case reports.

Materials and Methods: Histopathological features of six cases of HP were analyzed. Variables examined were clinical presentation, age at diagnosis, location, histopathologic type and immunohistochemical profile.

Results: Two cases each were seen in duodenum and Meckel's diverticulum while one case each was seen in stomach and an atretic segment of ileum, a site never reported previously. There were five males and one female with age ranging from one day to 48 years. Patients with gastric and duodenal HP were symptomatic. On histopathology, four cases were intramuscular and two were submucosal. Four cases were of Type I and two cases were of type II.

Conclusion: HP should be considered in the differential diagnosis of submucosal upper GI lesions. Awareness, high degree of suspicion and thorough histopathological examination are necessary to arrive at a correct diagnosis. Immunohistochemistry for chromogranin and synaptophysin is useful for confirming the islets especially on small endoscopic biopsies.

Key messages: HP must be considered in the differential diagnosis of submucosal upper GI lesions. Knowledge about this entity, high degree of suspicion and thorough histopathological examination help in arriving at a correct diagnosis and excluding mimics.

1. Introduction

Ectopic pancreas or pancreatic heterotopia (HP) refers to pancreatic tissue that has no direct or vascular connection to the orthotopic pancreas. About 70 to 90 % of cases of HP are located in the upper GIT, stomach being the most common site.[1] HP is frequently asymptomatic but may present with ulceration, bleeding, pyloric obstruction, intussusception or rarely, neoplastic transformation.[2–4] On endoscopy, HP is seen as a submucosal nodule with characteristic central umbilication.[1,5] However, it is difficult to differentiate HP from well differentiated adenocarcinoma, well differentiated neuroendocrine tumour (NET) or gastrointestinal stromal tumour (GIST). In majority of the cases, correct diagnosis is established only after histopathological examination.[1] On microscopy, there

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are three types of HP depending on the composition of the lesion.[1,6] We report six cases of HP, three of which were misdiagnosed as NET initially on histopathology and referred to us for immunohistochemistry (IHC). This is probably the first case series of HP from India.

2. Materials and Methods

Total six cases diagnosed with HP were analysed. The clinical details were obtained from the medical records. The slides were reviewed. The locations of the lesion in the GIT as well as in the wall were noted. In all the cases, IHC for CK, CK7, chromogranin and synaptophysin was done. Endoscopic findings were also analysed.

Case 1 was a 48 years male with complaints of abdominal pain and loss of appetite of four months duration and vomiting of one month duration. CT scan showed a small nodular enhancing lesion in the body of stomach. Endoscopy revealed a 2x2 cm submucosal lesion on the anterior wall of body of stomach.

Case 2 was a 36 years male with complaints of abdominal pain, loss of appetite and weakness of six months duration. Endoscopy showed a small 1x1cm submucosal lesion in the second part of duodenum with normal overlying mucosa.

Case 3 was a 24 years female who presented with radiating pain and tenderness in the epigastric region. CT scan revealed a soft tissue lesion measuring 1x1.2 cm in the second part of duodenum. On endoscopy, the second part of duodenum showed thickening of the mucosal folds with central superficial ulceration. In all these three cases, we received slides and blocks with an outside histopathology diagnosis of NET, for IHC confirmation and grading.

Case 4 was a 29 years male operated for appendicectomy. Incidentally detected Meckel's diverticulum (MD) was resected and sent for histopathology.

Case 5 was the youngest patient in our series, a one day old male child who presented with intestinal obstruction. Further workup revealed atresia of ileal segment which was resected and sent to us for histopathology.

Case 6 was a seven-month old male child presenting with intussusception. Incidentally detected MD was sent to us for histopathology.

3. Results

We had total six cases of HP from 2012 to 2019. The details of the cases are presented in Table 1. There were five males and one female. The age ranged from 1 day to 48 years, average being 27.5 years.

Patients with gastric and duodenal HP presented with abdominal pain, loss of appetite and vomiting. In one patient (case 5) HP was found in a baby who presented with intestinal obstruction due to ileal atresia. In cases 4 and 6 HP was found in incidentally detected MD.

Endoscopy was done in three symptomatic cases. In case 1, the lesion was a 2x2cm, submucosal nodule located on the anterior surface of the body of stomach with normal overlying mucosa (Figure 1 A,B). In both cases 2 and 3, HP was located in the second part of duodenum and measured 1x1cm and 1x1.2cm respectively. In case 3, the overlying mucosa was ulcerated (Figure 1 C). In cases 4 and 6, HP was located in MD while in case 5, it was noticed in an atretic ileal segment (Figure 1 D).

On histopathology, four cases (case 1,3,4 and 6) were intramuscular (Figures 2 and 5) while two cases (case 2 and 5) were submucosal (Figures 4 and 6). Four cases (case 1,3,5 and 6) revealed all three elements i.e. acini , ducts and islets of Langerhans conforming to type I HP. (Figures 2 and 6). Cases 2 and 4 had only acini and ducts conforming to type II HP (Figure 4). On IHC, acinar cells, ductal cells and islets were positive for CK. Ductal cells were also positive for CK7 while islets were positive for chromogranin and synaptophysin (Figure 3, Figure 5 C,D, Figure 7 C and D). In cases 3 and 5, H and E stained slides showed only acini and ducts while islets were highlighted only after IHC for synaptophysin and chromogranin. The H and E slides were again reviewed thoroughly but still islets could not be demonstrated (Figures 5 and 7). Hence, IHC for chromogranin and synaptophysin was done in cases 2 and 4 for identifying islets, if any and were labelled as HP type II after confirming their absence.

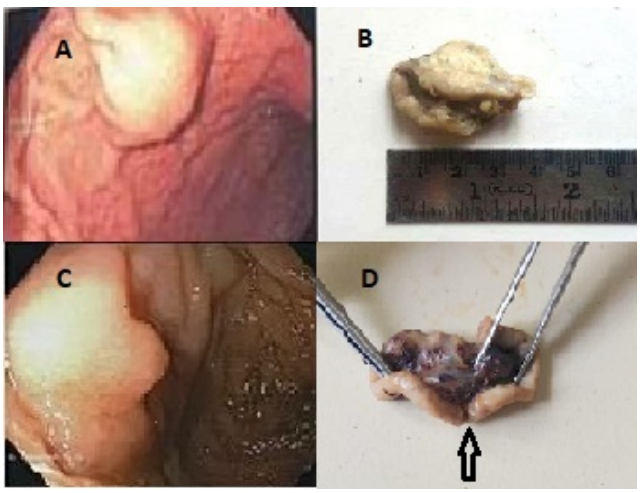

Fig. 1: (A) Case 1: Endoscopic image showing a nodular submucosal mass in the body of stomach; **(B):** Case 1: Gross photograph of resected mass; **(C):** Case 3: Endoscopic image showing a nodular mass in the second part of duodenum; **(D):** Case 5: Gross photograph of resected ileal segment. Arrow is pointing towards atretic portion

4. Discussion

First described in 1729 by Jean Schultz, HP is a congenital anomaly thought to result from separation of fragments

Table 1:

S.No.	Age/Sex	Site	Location in wall	Histopathologic Type
1	48years/M	Stomach	Muscularis propria	I
2	36 years/M	Duodenum	Submucosa	II
3	24 years/F	Duodenum	Muscularis propria	I
4	29 years/M	MD	Muscularis propria	II
5	1Day /M	Ileal atresia	Submucosa	I
6	7 months/M	MD	Muscularis propria	I

MD –Meckel's diverticulum

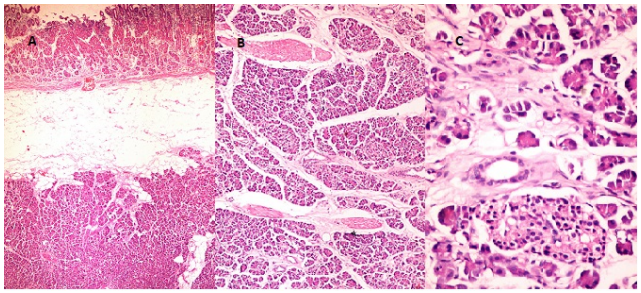

Fig. 2: H&E sections from case 1 showing **(A):** Intact gastric mucosa in upper portion with Pancreatic Heterotopic tissue (HT) in the gastric wall (x40), **(B):** Pancreatic HT infiltrating muscularis propria (x100), **(C):** Pancreatic HT showing all 3 elements – Acinar cells, ducts and islets (x400)

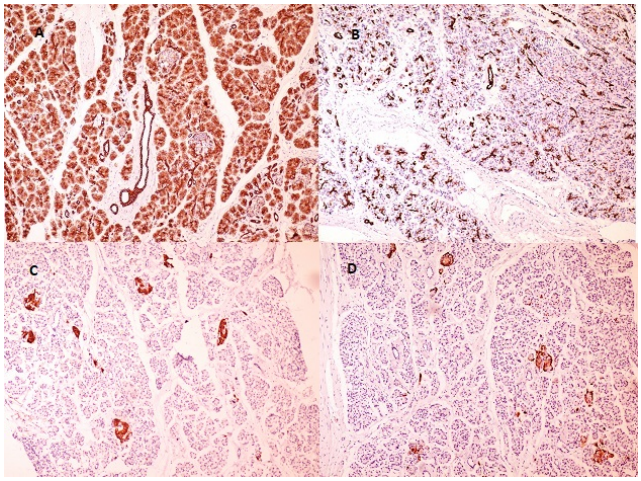

Fig. 3: IHC images from case 1 showing expression of **(A):** CK by all 3 elements; **(B):** CK7 by ductal cells, expression of **(C):** Synatophysin and **(D):** Chromogranin by islets. (A,B,C,D: x100)

from the main mass of the pancreas during rotation of the foregut.[7,8] The incidence is widely variable with 0.55 to 13.7% in autopsy studies and one in every 500 cases of upper abdominal surgical procedures.[9] This is probably the first case series of HP from India, rest all being case reports.

HP has been reported at all ages including children, average being 45 years.[5,9–11] In our study, the age ranged from one day to 48 years (average 27.5 years). Dolan et al

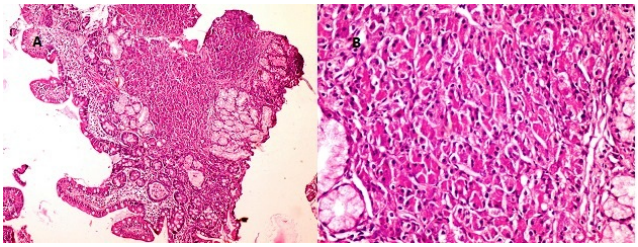

Fig. 4: H&E sections from case 2 showing **(A):** Submucosal duodenal pancreatic HT (x40), **(B):** Pancreatic HT showing acinar cells & ducts (x400)

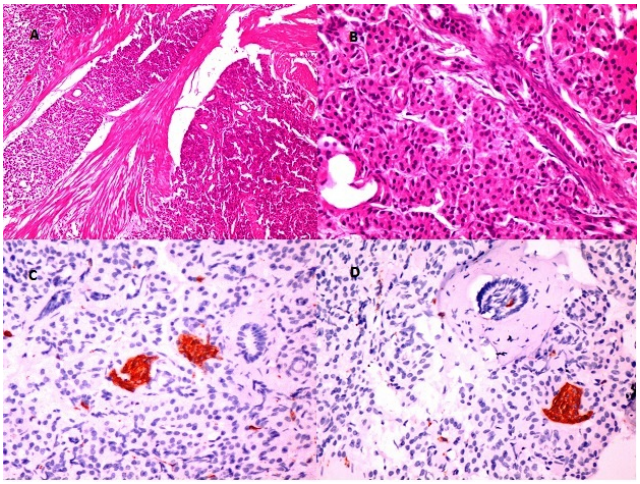

Fig. 5: Case 3: **(A and B):** H&E sections showing Pancreatic HT in the form of acini and ducts infiltrating muscularis propria.(Ax40 and Bx400); **(C and D):** IHC images showing islets cells expressing **(C)** Synaptophysin and **(D):** Chromogranin (C and D x400)

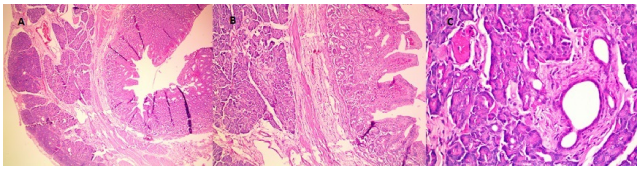

Fig. 6: H&E sections from case 6 showing pancreatic HT in Meckel's diverticulum showing all 3 elements (Ax40, Bx100 and Cx400)

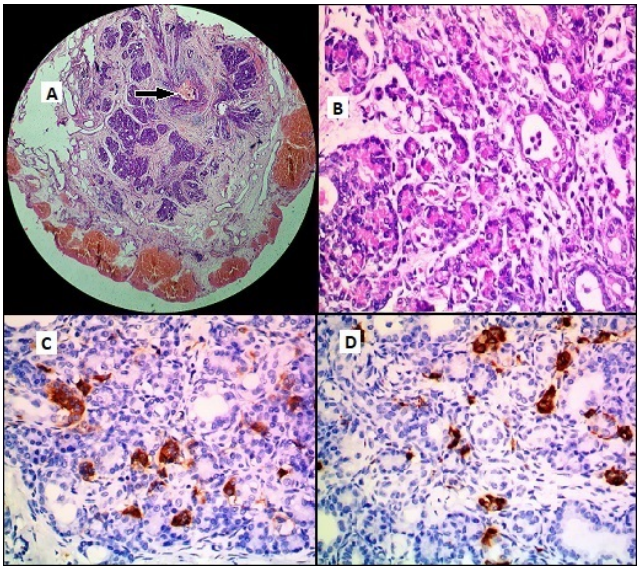

Fig. 7: Case 5: **(A):** H&E section showing PancreaticHT in the atretic ileal segment. Arrow is pointing towards narrowed lumen; **(B):** H & E sections showing acinar and ductal elements. (Ax40 and Bx400); **(C and D):** IHC images showing islets cells expressing; **(C)** Synaptophysin and **(D):** Chromogranin (C and D x400)

have reported the largest series of 214 cases of HP at Mayo clinic from 1952 to 1974.[12] Armstrong et al have reported total 34 cases of HP including 25 males and 9 females over a period of 20 years.[9] Lai and Tompkins have reported 37 cases of HP with 22 males and 15 femalesover a period of 25 years.[10] Bromburg et al have reported equal number of males and females in their series of 18 cases.[6] We had total six cases of HP, five males and one female.

Most of the HPs are asymptomatic.[1] Bromburg et al observed symptoms only in four out of 18 cases, Armstrong et al reported 13 symptomatic cases out of 34 while Lai et al had nine symptomatic patients out of 37.[6,9,10] In symptomatic cases, epigastric pain was the most frequent presenting complaint.[8,10] Other signs and symptoms include nausea, vomiting, jaundice, hematemesis, intussusception, acute and chronic pancreatitis, pseudocyst formation and rare malignant transformation.[1,5,6,10,13,14] A rare case of duodenal HP with carcinoid syndrome has also been reported.[2] In general, symptoms are related to site, size and presence of overlying mucosal ulceration.[10] In our study, patients with gastric and duodenal HP had abdominal pain, vomiting and loss of appetite. In cases 4 and 6, HP was located in incidentally detected MD while in case 5, it was noticed in an atretic ileal segment.

HP can involve any point along the GIT including the esophagus and rectum, the most recognized locations being proximal duodenum (17-36%), gastric antrum (25-38%), jejunum (15-21%) and ileum (5.8%).[6,8,10,15] Other sites include gall bladder, umbilicus, mesentery, common bile duct, fallopian tube and certain gastrointestinal malformations such as duplicated stomach and MD.[8] Ours is probably the first case of HP occurring in an atretic ileal segment as no similar case was found on reviewing the literature extensively.

HPs are invariably single and majority occur within 3 to 4 cm of either side of the pylorus, often on the greater curvature.[1,7] Rarely HP may be seen in the corpus or cardia.[5,16] In our series, two cases were from duodenum, two from MD and one case each from stomach and an atretic segment of ileum. The lesion was single in all the cases. In stomach, it was located in the body, a rare location.

HP is most commonly located in the submucosa, though cases may occur in muscularis or subserosa.[2,5,9] The proportion of HP in submucosa, muscularis and subserosa is 73%, 17% and10% respectively.[15] Bromburg et al have observed 15 out of 18 while Pang et al have reported 15 out of 32 cases of HP located in submucosa.[6,17] In the present study, four cases (case 1,3,4 and 6) were intramuscular while two (case 2 and 5) were submucosal.

On endoscopy, central dimpling is a characteristic feature of HP described in 35-90% of cases.[5,6] However, mucosal dimpling or umbilication may not be seen in lesions less than 1.5 cm in size. On the other hand, it may be observed in submucosal NETs, hamartomas or in large GIST or schwannoma with central necrosis.[6] In our study, endoscopy was done in three cases but none of them showed central dimpling.

Endoscopic ultrasound (EUS) is highly accurate for clarifying the layer of origin of upper GI subepithelial lesions. Majority of HPs involve the submucosa and muscularis propria while GIST, schwannoma and leiomyoma occur predominantly in muscularis propria. Other features suggestive of HP on EUS include heterogeneous echotexture, indistinct border, localization in gastric antrum, ductal or cystic anechoic structures and involvement of more than one layer.[18]

The CT features of HP are oval shape or flat surface, endoluminal growth pattern, antral gastric location and ill defined microlobulated margins. On Magnetic Resonance Imaging (MRI), the characteristic high signal intensity of the pancreas on T1 weighted images is particularly helpful in differentiating HP from other lesions.[19]

Microscopically, HP may be composed of any one or combination of the three normal components of pancreatic parenchyma i.e. ducts, acini and islets. Accordingly, lesions are characterized as type I with all three components, type II when any two components are present and Type III having only one component.[5,6] When only smooth muscle and ducts are present in HP, it is termed as adenomyoma.[5] Bromburg observed HP with type I morphology in 83.3% cases.[6] Endocrine component representing islets is found less frequently.[5,6] However Armstrong observed islets in 68% cases.[9] Histologically, each component in HP is

similar to that in normal pancreas. Thick disorganized bundles of hyperplastic smooth muscle are often admixed with acini and ducts. Cystic degeneration may also be seen in HP.[6,8] Cases with mucus inspissation and duct rupture may lead to an erroneous clinical and histological diagnosis of mucinous carcinoma.[12] In our study, four cases showed type I HP while type II HP was observed in two cases. Out of these four cases of type I HP, 2 cases (case 3 and 5) showed only acini and ducts on H & E sections and islets could be highlighted only after IHC for chromogranin and synaptophysin. Even after reviewing the H and E slides again, the islets could not be demonstrated. Hence, we emphasize the need of IHC to demonstrate islets.

Cases 1, 2 and 3 were diagnosed as NET outside and were referred to us for IHC confirmation and grading. Kanthan et al have reported 16 cases of HP, two of them masquerading as malignant tumours.[20] Baisakh et al have also reported a case of gastric HP mistaken for adenocarcinoma.[21] Submucosal location, superficial morphologic resemblance to NET and lack of awareness about the existence of HP may be the possible reasons for this error.

Endoscopic biopsies can be negative as HP is located submucosally. Literature search revealed cases of radical surgeries for HP since preoperative diagnosis was not possible.[2,8,14] This can be avoided by use of intraoperative frozen section.

The lesions of HP need to be differentiated from pancreatic acinar metaplasia (PAM) and well differentiated adenocarcinoma. PAM is much more common than HP, is located in cardia or antrum and is composed only of pancreatic acinar cells lacking ducts, islets, stroma or smooth muscle. PAM is either in direct continuity with gastric mucosa or is separated from it by smooth muscle.[5]

Malignant transformation of HP is rare, occurring most commonly in gastric lesions.[1] However, cases have been reported from HP in duodenum, rectum and HP located in hiatal hernia.[22–25] Adenocarcinoma is the most common malignancy arising in HP.[8] Well differentiated adenocarcinomas reveal architectural and cytologic atypia, atypical mitoses and other features of malignancy which are lacking in HP. Also the ducts in HP normally grow in a lobular fashion and have smooth rather than irregular profiles. Guillou et al have proposed three criteria for the diagnosis of carcinoma arising in HP –

1. The tumour must be located within or very close to the ectopic pancreatic tissue,
2. Transition between pancreatic structures and carcinoma must be identified,
3. The non-neoplastic pancreatic tissue must comprise fully developed acini and ducts[25]

In addition to adenocarcinoma, NET, acinic cell carcinoma and intraductal papillary mucinous neoplasm arising in HP have also been reported.[1,8,26]

5. Conclusion

This is probably the first case series on HP from India and also the first to document an atretic ileal segment as a site of HP. HP must be considered in the differential diagnosis of submucosal upper GI lesions and should not be misdiagnosed as NET due to superficial morphologic resemblance. In most cases, awareness of this entity and careful histopathological examination establish the correct diagnosis. Even on diligent search, islets may be missed occasionally on H and E stained sections. In such cases, IHC for chromogranin and synaptophysin confirms their presence.

6. Source of Funding

None.

7. Conflict of Interest

The authors declare that there is no conflict of interest.

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