Journal of Pathology of Nepal (2025) Vol. **15**, 2402 -2407

Journal of
PATHOLOGY
of Nepal
www.acpnepal.com

Case series

Expecting the unexpected in Whipple procedures: A series of unusual conditions mimicking periampullary carcinoma

Prachi Nichat[1], Vandana Rana[1], Saranga Bharathi[2], Abhishek Mishra[3]

[1]*Department of Pathology, Command Hospital (Northern Comd), Udhampur, India*
[2]*Department of Surgery, Command Hospital (Northern Comd), Udhampur, India*
[3]*Department of Radiology, Command Hospital (Northern Comd), Udhampur, India*

Keywords:

Adenomyomas; Autoimmune pancreatitides; Eosinophilic gastroenteropathy; Pancreaticoduodenectomy;

ABSTRACT

Benign diseases centered around the periampullary/ pancreatic head region may mimic malignancy, sharing similar clinico-radiologic features, thereby creating grounds for surprises on pathologic examination.

Cases of pancreatoduodenectomy performed for suspected malignancy between August 2022 and August 2023 at a low-volume tertiary centre were retrospectively audited for discrepancies between pre-operative and final histopathologic diagnosis. Nine pancreatoduodenectomies were performed, of which 6 turned out to be malignant and 3, unexpectedly, turned out to be benign: 1 case each of adenomyomatous hyperplasia of the ampulla of Vater, autoimmune pancreatitis- II, and eosinophilic ampullitis.

There remains a clear and ever-present probability of encountering rare, unexpected benign pathology in a pancreas specimen resected suspecting malignancy. Ambiguous cases might benefit from further investigation to avoid morbid resectional surgery.

Correspondence:
Dr Abhishek Mishra, MD
Department of Radiology,
Command Hospital (Northern Comd), Udhampur 182101, Jammu and Kashmir, India
ORCID: 0000-0002-8434-426X
Contact: ochre23@outlook.com

Received : January 23, 2024; **Accepted :** August 25, 2025

Citation: Nichat P, Rana V, Bharathi S, Mishra A. Expecting the unexpected in Whipple procedures: A series of unusual conditions mimicking periampullary carcinoma. J Pathol Nep. 2025;15(2):2402-7. DOI: 10.3126/jpn.v15i2.62118

INTRODUCTION

Whipple's pancreatoduodenectomy (WPD) is a surgical procedure associated with significant morbidity and mortality.[1] It is performed primarily for periampullary/ pancreatic head neoplasms and a few benign conditions.[2] Differentiating the two, however, proves challenging as there exists considerable overlap both in their clinical and radiologic features.[3] The pancreas is deep-seated, rendering percutaneous tissue sampling with fine needle aspiration cytology for a firm diagnosis difficult, due to the fear of needle injury/tumor seeding.[1-4] The survival in periampullary/ pancreatic head carcinomas is dismal

unless curatively resected.[1] The region, being surrounded by vascular structures, restricts the window of opportunity for resection to a narrow timeframe. Therefore, it is the fear of malignancy, which, being more common, drives the performance of the procedure even in ambiguous cases.[3,4] This situation lends itself to the possibility that some masses suspected to be neoplastic turn out benign following resection, leaving one to introspect whether they could have been addressed without surgery or with surgery of lesser magnitude and consequence.[2-4]

This study audits the modest experience of a unit in WPD and addresses the above predicaments by focusing on the benign pathologies presented as a case series.

CASE REPORTS

All cases of WPD performed between Aug 2022 and Aug 2023 were audited, after obtaining clearance from the institutional ethics committee of the hospital (approval # 06/2023 dated 25 Aug 2023). Informed consent was not obtained, the study being a retrospective evaluation based on hospital records.

Table 1: List of all cases that underwent pancreatoduodenectomy

S. No.	Age (in years)/ Gender	Presentation	Indication of surgery	Histopathological diagnosis
1	74/F	Obstructive jaundice	Peri-ampullary mass	Intra-Ampullary Papillary tubular neoplasm with invasive carcinoma
2	47/M	Obstructive Jaundice	Mass in the lower one-third of the common bile duct and ampulla	Moderately differentiated adenocarcinoma
3	70/M	Abdominal pain, jaundice	Mass involving the entire pancreas	Invasive Colloid Carcinoma
4	48/F	Abdominal pain	Mass in the body of pancreas	Pancreatic ductal adenocarcinoma (PDA)
5	62/M	Obstructive jaundice	Periampullary carcinoma	Moderately differentiated adenocarcinoma of the intrapancreatic common bile duct (CBD)
6	70/F	Obstructive jaundice, pain abdomen	Mass in the head and uncinate process of the pancreas	Pancreatic ductal adenocarcinoma
7	58/F	Abdominal pain, intermittent jaundice	Periampullary carcinoma	Adenomyomatous hyperplasia of the Ampulla of Vater
8	23/M	Abdominal pain, intermittent jaundice	Periampullary carcinoma	Autoimmune pancreatitis, Type 2
9	31/M	Abdominal pain, obstructive jaundice	Ampullary mass, Scope not negotiable on ERCP	Eosinophilic Ampullitis

CASE 1: A 58-year-old male presented with abdominal pain and intermittent jaundice of 2 months' duration. Performance status was Zubrod -1, and icterus was absent.

Laboratory investigations: Total Bilirubin: 0.94 mg/dl, Direct Bilirubin: 0.62 mg/dl, Aspartate aminotransferase (AST) – 42 IU/L, Alanine aminotransferase (ALT) - 45 IU/L, Alkaline phosphatase – 279 IU/L.

Computerized tomogram (CT) showed a double duct sign. Endoscopy revealed a bulky ampulla. (fig.1A&1B) Suspecting periampullary carcinoma, laparoscopic WPD was performed. Pathologic examination findings: On gross examination, the common bile duct was markedly dilated with ampullary wall thickening of 0.4 cm, causing luminal narrowing such that the probe could not be negotiated through the ampulla. On microscopy, sections from the ampullary wall showed lobules of hyperplastic glands surrounded by fibromuscular stroma suggestive of Adenomyomatous hyperplasia. (fig.1C) Glands were variably sized, lined by a single layer of columnar epithelium surrounded by moderate lymphoplasmacytic infiltrate in the stroma. (fig 1D) No metaplasia or dysplasia was noted.

CASE 2: A 23-year-old male presented with recurrent abdominal pain and intermittent jaundice of 3 months' duration. Performance status was Zubrod-0, had icterus, and a palpable gallbladder. Lab investigations showed deranged liver functions and elevated CA 19.9 (37 IU/L). Serum CEA levels: 1.3 ng/ml (< 5 ng/ml).

Endoscopy revealed a normal ampulla over a bulge in the duodenum. CT revealed an ill-defined 3 cms mass in the head of the pancreas/ uncinate, marked dilatation of the bile duct with abrupt cut off. (fig.2A & 2B) The lesion had an indistinct plane with the superior mesenteric vein; however, without contour aberration. Suspecting malignancy, a WPD was done. Gross pathologic examination revealed a normal ampulla; a firm pancreatic cut surface, which was gray-white and lobulated. Microscopy showed preserved pancreatic lobular architecture with pronounced inter/ intralobular fibrosis; a typical granulocytic epithelial lesion, and periductal lymphoplasmocytic infiltrates, typical of *autoimmune pancreatitis (AIP) II*. IgG4 was not elevated. (fig.2C)

CASE 3: A 31-year-old male presented with pain in the abdomen of 6 months' duration and progressive jaundice

of 6 weeks, along with loss of appetite and itching. Performance status was Zubrod-0, had deep icterus, and the gallbladder was palpable. Liver functions were deranged (bilirubin 15 mg%, direct- 9 mg%, SGOT/ SGPT- 253/276 IU/L); absolute eosinophil count was 189/ microlitre (2.1%); and tumor markers were borderline. Endoscopy revealed a bulge in the duodenum. Imaging revealed a heterogeneously enhancing mass lesion in the periampullary region projecting into the duodenum; the bile duct was dilated but not the pancreatic duct (Fig.3-A & B). Distal cholangiocarcinoma was suspected, and laparoscopic WPD was performed. Pathologic examination revealed a 1.2 cms nodule in the ampulla, which on histology was found to be composed of fibrocollagenous and hyalinized stroma with dense eosinophilic infiltrates. Eosinophilic infiltration was also observed in the gallbladder mucosa. No metaplasia or dysplasia was observed. This confirmed the diagnosis of *eosinophilic ampullitis* (Fig.3C). IgE levels were not elevated. He was put on long-term steroid therapy.

Follow-up: All three patients had an uneventful postoperative recovery and are doing well to date.

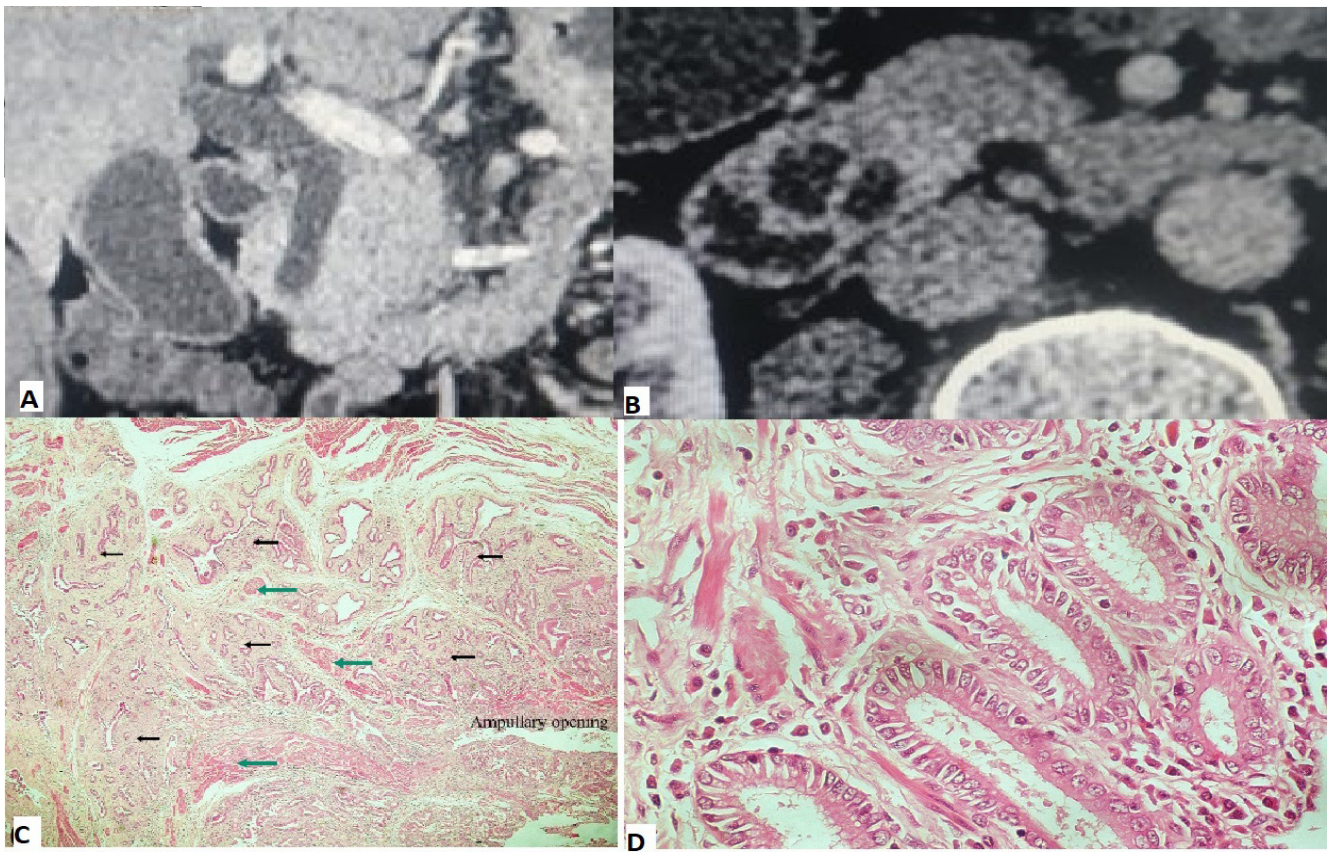

Figure 1: *Adenomyomatous hyperplasia. A) Coronal reformatted CT abdomen showing dilated bile duct with abrupt cut-off; B) CT abdomen axial section showing double duct sign; C) Lobules of benign glands surrounded by fibroblastic stroma, interspersed in the Vaterian musculature. Green arrows depicting the musculature interspersed among hyperplasic glandular lobules, highlighted by black arrows [H&E; 100x]; D) Benign columnar glands surrounded by lymphoplasmacytic infiltrate [H&E 400x]*

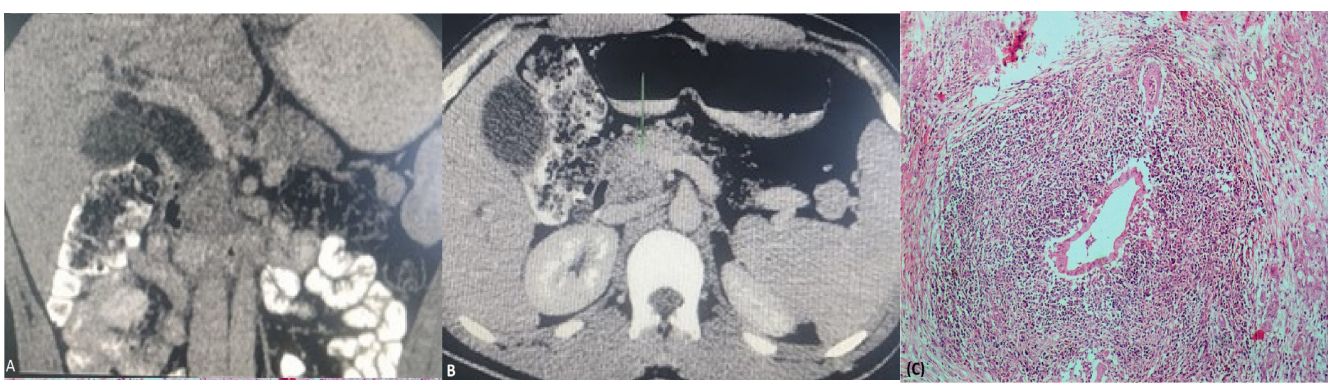

Figure 2: : *Autoimmune pancreatitis - II. A) Coronal reformatted CT abdomen showing dilated bile duct compressed by a pancreatic head mass. B) CT abdomen axial section pancreatic head mass with loss of interface with superior mesenteric portal vein. C) Photomicrograph showing medium-sized panreatic duct with a typical granulocytic epithelial lesion [H&E; 200x].*

DOI: 10.3126/jpn.v15i2.62118

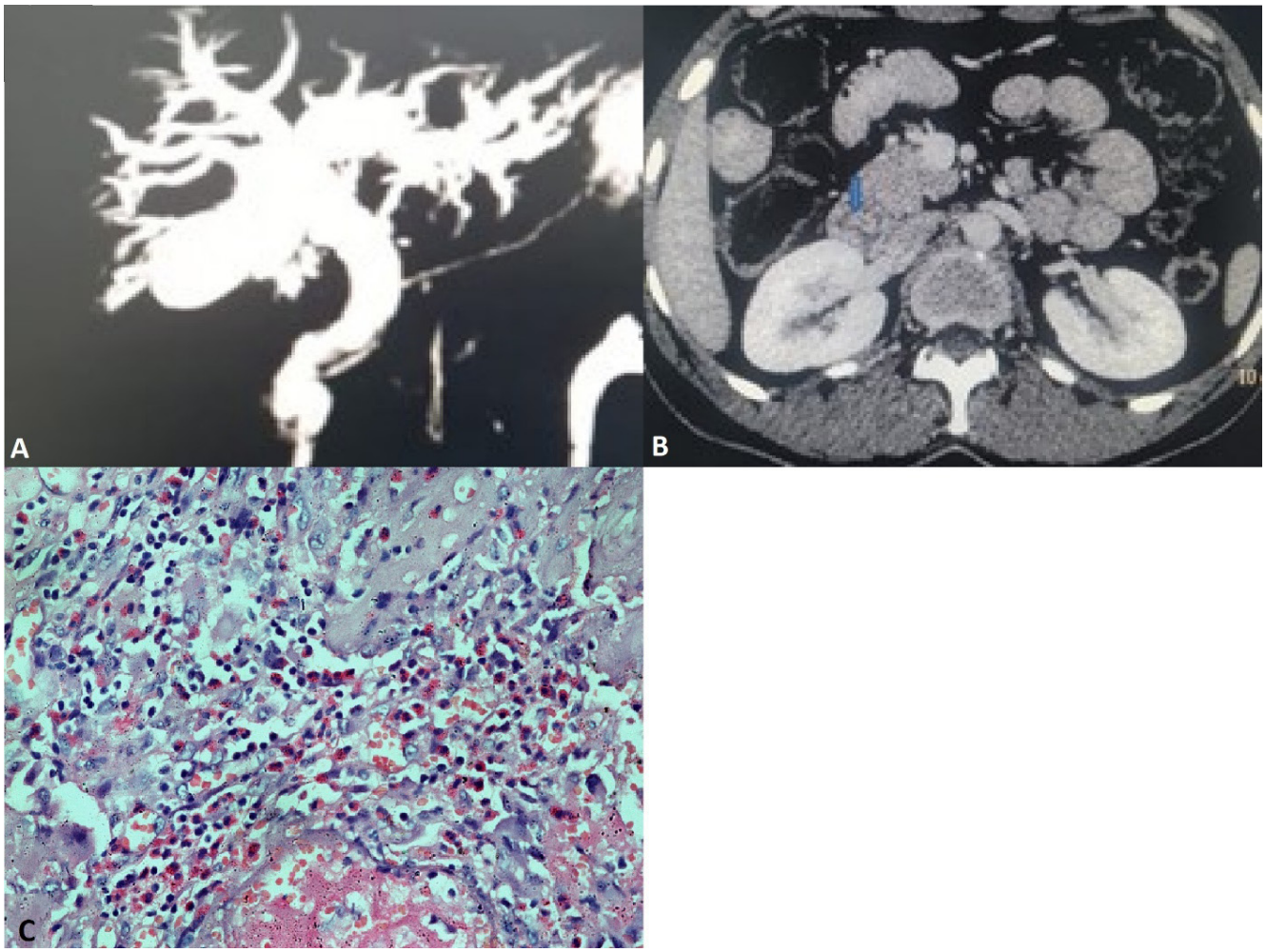

Figure 3: *Eosinophilic ampullitis. A) MRCP image showing dilated extrahepatic biliary tree with abrupt distal narrowing and a normal pancreatic duct. B) CT abdomen axial section showing an ill-defined heterogenously enhancing lesion (arrow) in the periampullary location projecting into the duodenal lumen. C) Photomicrograph showing dense eosinophilic infiltrate in the ampullary stroma [H&E, 400x].*

DISCUSSION

There has been a definite increase over the past 2-3 decades in the rate at which WPD is being performed worldwide.[2] This owes to the burgeoning population, increased longevity, improved connectivity, better diagnostics and treatment facilities, in addition to the rising incidence of the disease and diminishing surgical mortality.[2] The cornerstone is the increase in the detection rates. The detection of pancreatic/ periampullary malignancy rests on 4 pillars *viz* clinical picture, tumor markers, radiologic evidence, and tissue biopsy. Of these, clinical features and tumor markers are at best indicative/ corroborative, not conclusive, whereas tissue biopsy is.[1]

Percutaneous biopsy is difficult owing to the aforementioned reasons, and the yield of endoscopic retrograde cholangio-pancreatography (ERCP) guided brush cytology is relatively low.[3,4] This shortcoming is overcome by endoscopic ultrasonography (EUS) guided fine needle aspiration cytology (FNAC)/ biopsy.[3-6] This facility, however, has a learning curve and is not as universally available as CT/ MRI, especially in peripheral hospitals. Additionally, even in apex centers where EUS FNAC is performed expertly, there is a paradoxical increase in the number of WPD specimens turning out benign.[5] This owes to the low negative predictive value of this modality and also a fear of sampling error.[3-6] Positron emission tomography CT) are again limited by the inability to distinguish inflammation from malignancy. Therefore, guidelines direct proceeding with surgery based on imaging findings alone.[1] This gives rise to approximately 10% (5%-35%) incidence of benign pathology in WPD specimen resected for suspected malignancy, worldwide.[4] Though most turn out to be of inflammatory pathology, such as focal/ chronic pancreatitis, a minority turn out to have unusual pathology, such as some encountered in this study.[2-6]

Adenomyomatous hyperplasia (AH) is the benign proliferation of epithelium, glands, and smooth muscles without cellular atypia.[7-9] Etiology being unknown, it is hypothesized that the lobules represent glandular rests.[7-9] With an incidence of 0.13%, it is seen incidentally in the gallbladder as well as other parts of the gastrointestinal tract and is of little clinical consequence.[7-9] On the other hand,

DOI: 10.3126/jpn.v15i2.62118

biliary tract AH, especially of the ampulla, which may appear as round masses or as stenosis, causes biliary obstruction and masquerade sinister malignancy, as in our case.[7-9] However, with less than 50 reported cases in the literature, it is quite rare.[7-9] AH may also cause inflammatory complications, cystic degeneration/ dystrophy of the duodenal wall, and intestinal obstruction.[7] Although amenable to biopsy, the low negative predictive value, sampling error, and cellular atypia observed in > 66% in such biopsies render preoperative diagnosis difficult.[7-9] Limited surgery, such as ampullectomy or sphincterotomy have been attempted but is fraught with risk of failure owing to recurrence. [7-9] Hence, the treatment of choice remains WPD, especially when faced with diagnostic ambiguity or suspicion of malignancy, as in our case.[7-9]

AIP is responsible for upto 6% of chronic pancreatitis.[10-12] It exists in 2 distinct forms: AIP- I or lymphoplasmacytic sclerosing pancreatitis and AIP-II or idiopathic duct centric pancreatitis/ granulocyte epithelial lesion (GEL).[10-12] Although considered to be pathognomonic for AIP type II, neutrophic ductal injury akin to GEL may also be encountered in peritumoral pancreatitis.[13] AIP-I presents in the majority with jaundice, extra-pancreatic involvement, and raised IgG4, and is diagnosed more readily than AIP-II, which is restricted to the pancreas alone and coexists with inflammatory bowel disease in a third to half of the cases.[10-12] AIP II is frequently diagnosed only after resection, as in our case, owing to a lack of definitive features.[10-12] However, the younger age profile (< 43 years) and infrequent jaundice may indicate the diagnosis.[10-12] Their response to steroids is excellent, although some resolve spontaneously, and those resected seldom recur.[10-12] The diagnostic criteria comprising points outlined above are based upon radiologic demonstration of diffuse parenchymal enlargement and ductal narrowing/ stricture without much proximal dilatation (< 5mm), for suspicion of AIP.[10-12] If the radiologic picture is not classic, as in our case, other investigations are not even thought of. Hence, in the presence of diagnostic ambiguity, surgery remains a saner option, malignancy being commoner with anecdotal coexistence with AIP.[10-13]

Eosinophilic gastrointestinal disorders (EGID) refer to abnormal infiltration of segments of the gastrointestinal tract by eosinophils.[14,15] It may be consequent to hyper-eosinophilic syndrome, allergy, parasitic infestation, autoimmune disorders, or drugs.[14,15] It may manifest with raised IgE and peripheral eosinophilia or may occur frequently without them, lacking any allergic basis, as in our case.[14,15] The symptoms are dictated by the gut layer infiltrated, with diarrhea/ malabsorption, obstruction, or ascites depending upon the level of infiltration, whether mucosa, muscularis, or serosa, respectively.[14-18] Periampullary involvement as pseudotumor is perhaps the rarest amongst the spectrum of EGID, with 3 cases reported in the literature.[16-18] One manifested as an ampullary adenoma and 2 with stenosis causing biliary obstruction, as in our case.[16-18]

An analysis of the above cases and comparison with those with malignancy (Table 1) reveals a few features that might hint at benign disease: Patients were significantly younger. Patients' performance status was excellent, in contrast to those with malignancy. Jaundice was intermittent and mild except in the patient with eosinophilic ampullitis. The tumor markers were normal/ borderline elevated. The above features must prompt further evaluation to avoid unnecessary resectional procedures. Further evaluation may include EUS-guided brush cytology and ERCP-guided biopsies, but these have variable sensitivity (44 to 80%).[14] Other modalities, including ERCP with fluoroscopic imaging, intraductal ultrasound, digital image analysis, and fluorescence in situ hybridization (FISH) analysis. Diagnosis must be based on findings of all modalities available after due consideration of clinical features and, in certain cases, the nature of response to steroids in possible inflammatory conditions.

CONCLUSIONS

Despite advances in diagnostic modalities, pancreatoduodenectomy for suspected periampullary or pancreatic head malignancy continues to yield occasional unexpected benign diagnoses. This series underscores rare benign entities that closely mimic malignancy clinically and radiologically. Younger age, good performance status, intermittent jaundice, and normal or borderline tumor markers may provide clues to benign disease and should prompt normal or borderline tumor markers may provide clues to benign disease and should prompt further evaluation in ambiguous cases. Increased awareness of these mimickers may help reduce potentially avoidable major resections.

Conflict of interest: None

REFERENCES

1. Winter K, Talar-Wojnarowska R, Dąbrowski A, et al. Diagnostic and therapeutic recommendations in pancreatic ductal adenocarcinoma. Recommendations of the Working Group of the Polish Pancreatic Club. Prz Gastroenterol. 2019;14(1):1-18. DOI: 10.5114/pg.2019.83422

2. Schmidt CM, Powell ES, Yiannoutsos CT, et al. Pancreaticoduodenectomy: a 20-year experience in 516 patients. Arch Surg. 2004;139(7):718-27. DOI: 10.1001/archsurg.139.7.718

3. Kavanagh DO, O'Riain C, Ridgway PF, et al. Radical pancreaticoduodenectomy for benign disease. ScientificWorldJournal. 2008;8:1156-67. DOI: 10.1100/tsw.2008.147

4. Surci N, Rösch CS, Kirchweger P, et al. The Rate of Avoidable Pancreatic Resections at a High-Volume Center: An Internal Quality Control and Critical Review. J Clin Med. 2023;12(4):1625. DOI: 10.3390/jcm12041625

5. Yarandi SS, Runge T, Wang L, et al. Increased Incidence of Benign Pancreatic Pathology following Pancreaticoduodenectomy for Presumed Malignancy over 10 Years despite Increased Use of Endoscopic Ultrasound. Diagn Ther Endosc. 2014;2014:701535. DOI: 10.1155/2014/701535

6. Manzia TM, Toti L, Lenci I, et al. Benign disease and unexpected histological findings after pancreaticoduodenectomy: the role of endoscopic ultrasound fine needle aspiration. Ann R Coll Surg Engl. 2010;92(4):295-301. DOI: 10.1308/003588410X12628812458374

7. Frutuoso L, Pereira AM, Carvalho L, Gonçalves G, Nora M. Adenomyomatous Hyperplasia of Ampulla of Vater and a Concomitant Renal Tumor: A Case Report. Cureus. 2021;13(12):e20258. DOI: 10.7759/cureus.20258
8. Gouveia C, Fidalgo C, Loureiro R, Oliveira H, Maio R, Cravo M. Adenomyomatosis of the Common Bile Duct and Ampulla of Vater. GE Port J Gastroenterol. 2021;28(2):121-33. DOI: 10.1159/000507788
9. Handra-Luca A, Terris B, Couvelard A, Bonte H, Flejou JF. Adenomyoma and adenomyomatous hyperplasia of the Vaterian system: clinical, pathological, and new immunohistochemical features of 13 cases. Mod Pathol. 2003;16(6):530-6. DOI: 10.1097/01.MP.0000073525.71096.8F
10. Blaho M, Dítě P, Kunovský L, Kianička B. Autoimmune pancreatitis - An ongoing challenge. Adv Med Sci. 2020;65(2):403-8. DOI: 10.1016/j.advms.2020.07.002
11. Rana SS, Gupta R, Nada R, et al. Clinical profile and treatment outcomes in autoimmune pancreatitis: a report from North India. Ann Gastroenterol. 2018;31(4):506-12. DOI: 10.20524/aog.2018.0267
12. Zen Y. Type 2 Autoimmune Pancreatitis: Consensus and Controversies. Gut Liver. 2022;16(3):357-65. DOI: 10.5009/gnl210241
13. Chandrasegaram MD, Chiam SC, Nguyen NQ, et al. A case of pancreatic cancer in the setting of autoimmune pancreatitis with nondiagnostic serum markers. Case Rep Surg. 2013;2013:809023. DOI: 10.1155/2013/809023
14. Rothenberg ME. Eosinophilic gastrointestinal disorders (EGID). J Allergy Clin Immunol. 2004;113(1):11-29. DOI: 10.1016/j.jaci.2003.10.047
15. Collins MH, Capocelli K, Yang GY. Eosinophilic Gastrointestinal Disorders Pathology. Front Med (Lausanne). 2018;4:261. DOI: 10.3389/fmed.2017.00261
16. Madhotra R, Eloubeidi MA, Cunningham JT, Lewin D, Hoffman B. Eosinophilic gastroenteritis masquerading as ampullary adenoma. J Clin Gastroenterol. 2002;34(3):240-2. DOI: 10.1097/00004836-200203000-00009
17. O'Toole D, Palazzo L, Vullierme MP, Maire F, Levy P, Ruszniewski P. Bile duct obstruction caused by an eosinophilic papillary pseudotumor. Gastrointest Endosc. 2003;58:445-8. DOI: 10.1067/s0016-5107(03)00027-0
18. Nyabera A, Shah K, Nso N, Eskaros S, Niknam N. A Rare Case of Eosinophilic Gastroenteritis and Ampullitis Leading to Benign Papillary Stenosis. Case Rep Gastrointest Med. 2021;2021:5597578. DOI: 10.1155/2021/5597578