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Pancreatic neuroendocrine neoplasms coexisting with biliary intraductal papillary mucinous neoplasm: A case report and literature review

Yi AQ *et al*. Unique pNENs and biliary IPMN case

Abstract

BACKGROUND

Pancreatic neuroendocrine neoplasms (pNENs) are rare, heterogeneous tumors accounting for 1%-2% of pancreatic tumors, with significant malignant potential. Intraductal papillary mucinous neoplasm of the bile duct (IPMN-B) is a rare precancerous lesion in the bile duct system, with potential for malignancy. The combination of pNENs and IPMN-B is exceptionally rare and often leads to misdiagnosis. This study aims to report a rare case of pNENs combined with IPMN-B treated at Yanbian University Hospital to improve understanding and management of this unusual tumor combination.

CASE SUMMARY

We retrospectively analyzed a case from Yanbian University Hospital. We reviewed clinical records, imaging findings, endoscopic retrograde cholangiopancreatography, surgical exploration, and histopathological examination. The patient was diagnosed with pNENs and IPMN-B. Surgical treatment was performed, with follow-up showing effective management and no significant recurrence.

CONCLUSION

This case represents the first report of pNENs combined with IPMN-B. It highlights the need for thorough diagnostic evaluation to prevent misdiagnosis and improve treatment strategies.

Key Words: Pancreatic neuroendocrine neoplasms; Intraductal papillary mucinous neoplasm of the bile duct; Malignant potential; Endoscopic retrograde cholangiopancreatography; Histopathology; Case report

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Core Tip: This case report presents the first documented instance of pancreatic neuroendocrine neoplasms coexisting with intraductal papillary mucinous neoplasm of the bile duct. The study highlights the importance of comprehensive diagnostic evaluation to distinguish between these two rare entities, which are often misdiagnosed. By detailing the diagnostic and therapeutic approaches taken, this report offers new insights into managing this unusual tumor combination, underscoring the need for heightened awareness and careful consideration in similar cases.

INTRODUCTION

Pancreatic neuroendocrine neoplasms (pNENs) are highly heterogeneous and rare tumors characterized by the excessive secretion of various hormones and peptides[1,2]. pNENs can occur throughout the body, including in endocrine organs, the gastrointestinal tract, the respiratory system, nervous structures, and skin. Over the past 30 years, neuroendocrine carcinomas (NECs) incidence has reached 5.25 per 100000 and has shown an upward trend[3-5]. PNENs account for one-third of all NECs and 1%-2% of pancreatic tumors, exhibiting significant malignant potential and high heterogeneity[6,7]. This complexity and rarity pose significant challenges for diagnosing and treating pNENs. Understanding the pathological features and mechanisms of pNENs is crucial for improving diagnostic accuracy and developing effective treatment strategies.

Despite the unique biological behavior of pNENs, their clinical manifestations are often nonspecific and can easily be confused with other types of pancreatic diseases[8]. Imaging examinations are crucial for diagnosing pNENs, but their results do not always provide definitive diagnostic information[9,10]. The diagnostic process becomes even more complex when pNENs coexist with other types of tumors, such as intraductal

papillary mucinous neoplasm of the bile duct (IPMN-B). IPMN-B is a unique type of tumor that occurs in the bile duct system and, as a precancerous lesion, has the potential for malignancy. In 2010, the World Health Organization classified it as intraductal papillary carcinoma and a precancerous lesion[1,11]. Due to its low incidence and atypical clinical presentation, IPMN-B is often diagnosed during endoscopic retrograde cholangiopancreatography (ERCP) or other surgeries when gelatinous mucus is found in the bile duct[12]. Because of its subtle clinical and imaging features, IPMN-B is frequently misdiagnosed or missed, affecting patient prognosis.

Existing literature includes numerous independent studies on pNENs and IPMN-B, but reports on cases where both occur together are extremely rare. Most research focuses on the individual diagnosis and treatment of pNENs or IPMN-B, lacking systematic exploration of their combined occurrence and clinical management. Current case reports are mostly isolated descriptions, lacking large-scale systematic studies, leaving us with limited knowledge about the clinical characteristics and optimal treatment strategies for pNENs combined with IPMN-B. A systematic review of the existing literature reveals an absence of standardized diagnostic and treatment guidelines, further complicating the clinical management of such complex cases[13-15]. Therefore, more case studies and comprehensive analyses are necessary to fill this research gap.

This paper presents a retrospective analysis of a recent case at Yanbian University Hospital involving a patient with pNENs combined with IPMN-B. Detailed records of the patient's clinical presentation, imaging results, pathological features, and treatment process were documented. Upon admission, the patient presented with upper abdominal discomfort and symptoms of indigestion. Imaging examinations revealed abnormal masses in the pancreatic and bile duct regions. Further diagnosis was conducted through ERCP and surgical resection, initially diagnosing the condition as pNENs combined with IPMN-B. Postoperative histopathological examination and immunohistochemical analysis confirmed the rare coexistence of pNENs and IPMN-B. Detailed pathologic analysis showed that the tumor cells exhibited typical

neuroendocrine and mucinous characteristics, and immunohistochemical staining results supported the diagnosis of dual tumors.

The primary aim of this study is to enhance the understanding of the rare coexistence of pNENs and IPMN-B and to prevent misdiagnosis, missed diagnosis, and delayed treatment due to unclear clinical manifestations. We hope to provide valuable reference points for clinicians managing similar cases by meticulously documenting and analyzing this case. Specifically, we emphasize the importance of comprehensive imaging examinations, histopathological analysis, and immunohistochemical testing in the diagnostic process. This multidisciplinary diagnostic approach improves diagnostic accuracy and lays the groundwork for developing individualized treatment strategies. As the first reported case of pNENs combined with IPMN-B worldwide, this study holds significant clinical importance. It fills a gap in the current research and offers new perspectives and methods for diagnosing and treating similar cases in the future. By highlighting the unique histological and immunophenotypic characteristics of both tumors, we provide new theoretical foundations and potential molecular targets for diagnosing and treating pancreatic NECs and IPMN-B. These findings are crucial for the future diagnosis and treatment of similar cases. However, this study has limitations due to the small sample size and the specificity of the case. Therefore, future research should aim to increase the sample size to obtain more representative data and conclusions. Additionally, we should enhance research on imaging and pathological examinations to improve diagnostic accuracy and early detection capabilities. Ultimately, we hope that ongoing research and exploration will lead to more effective treatment strategies and better prognoses for patients with pancreatic NECs and IPMN-B.

CASE PRESENTATION

Chief complaints

The patient, a 52-year-old female, developed skin and scleral jaundice without apparent cause on April 12, 2024, which gradually worsened and was accompanied by symptoms of abdominal distension.

History of present illness

However, there were no chills, fever, nausea, or vomiting symptoms during the illness. The patient had previously received treatment at a local hospital with no significant improvement. She presented to our hospital on April 26, 2024. The patient reported that her urine had darkened recently, and her feces had lightened in color. She had lost approximately 4 kg of weight in the past two weeks without significant changes in diet or activity level.

History of past illness

No history of exposure to infectious diseases such as hepatitis or tuberculosis. No history of drug allergies and no family history of similar liver or biliary diseases. There is no history of long-term alcohol consumption, and he denies any history of drug or substance abuse. The patient does not have occupational exposure to harmful chemicals in daily life.

Personal and family history

The patient had no history of chronic liver disease, biliary tract disease, or other significant medical conditions.

Physical examination

Physical examination revealed yellowing of the skin, mucous membranes, and sclera without significant skin itching. Abdominal palpation did not reveal tenderness or rebound tenderness, with mild hepatomegaly noted and no palpable mass below the rib cage. Further examination showed no signs of spider nevi, palmar erythema, or other chronic liver disease signs.

Laboratory examinations

Laboratory test results are as follows (Table 1): Total bilirubin (195.1 μmol/L, reference range: 5.1-25.6 μmol/L), direct bilirubin (178.0 μmol/L, reference range: 1.78-6.8 μmol/L), alanine aminotransferase (175 U/L, reference range: 0-40 U/L), aspartate aminotransferase (141 U/L, reference range: 0-40 U/L), carcinoembryonic antigen (CEA, 1.82 ng/mL, reference range: < 5.2 ng/mL), alpha-fetoprotein (AFP, 2.43 ng/mL, reference range: 0-7 ng/mL), carbohydrate antigen 19-9 (CA19-9, 25.5 U/mL, reference range: 0-34 U/mL), and CA-125 (10.50 U/mL, reference range: 0-35 U/mL).

Imaging examinations

For further treatment, the patient was admitted to our hospital. The results of auxiliary examinations are as follows (Figures 1-3). Abdominal enhanced computed tomography (CT) showed a lesion in the distal portion of the common bile duct, approximately 2.5 cm × 2.5 cm in size, accompanied by obstructive dilatation of the intrahepatic and extrahepatic bile ducts (Figure 1). Magnetic resonance cholangiopancreatography results showed a lesion in the pancreatic head region, approximately 2.7 cm × 2.7 cm in size, with unclear margins and involvement of the distal common bile duct, leading to dilatation of intrahepatic and extrahepatic bile ducts (Figure 2A and B).

FINAL DIAGNOSIS

In summary, considering the patient's clinical symptoms, auxiliary examination results, and laboratory findings, we preliminarily suspect that the patient may have obstructive jaundice caused by a space-occupying lesion in the pancreatic head area (such as pancreatic head cancer). Based on the above clinical data, the patient is generally in good condition and is considered suitable for surgery. We recommend surgical treatment to confirm the diagnosis. The specific details are as follows: (1) Anesthesia method: General anesthesia; (2) Surgical procedure: Initially performed laparoscopic pancreaticoduodenectomy, which was converted to open pancreaticoduodenectomy

during surgery; (3) Surgical scope: Enlarged gallbladder and dilated common bile duct observed during surgery, with the lesion located at the lower end of the common bile duct. No abnormal nodules were found on the liver surface or in the pelvic cavity. The tumor was completely excised during the surgery, and lymph nodes in groups 8 and 12 were cleared. The extent of surgical resection included the pancreatic head, duodenum, lower end of the common bile duct, and surrounding lymph nodes to ensure complete removal of the lesion and thorough lymph node clearance in the area; and (4) Duration of surgery: The surgery lasted approximately 6 hours.

TREATMENT

Specimens were sent for pathological examination after tumor resection during the operation, revealing (pancreatic) NECs (small cell NEC) with extensive necrosis. The tumor exhibited infiltrative growth beyond the pancreatic capsule, with evidence of neural infiltration and vascular cancer emboli involving the bile duct mucosa and surrounded by an increased amount of lymphoid tissue. An IPMN was observed in the ampulla of Vater and the bile duct, with areas of high-grade intraepithelial neoplasia. No tumor cells were detected at the ends of the common bile duct, pancreas, stomach, and small intestine (Figure 3). Examination of the specimens revealed the following pathology findings: No lymph node metastasis was identified (0/15), gallbladder neck region 0/2, pancreatic margin 0/3, ampulla of Vater 0-2, peripancreatic tissue 0/6, and lesser curvature of the stomach 0-2 (Figure 2C).

OUTCOME AND FOLLOW-UP

Follow-up content

Follow-up content included: (1) Clinical symptom assessment: Jaundice, bloating, and other symptoms have disappeared, with good dietary habits and stable weight. No new abdominal pain, nausea, vomiting, or other symptoms have been reported; (2) Imaging examinations: Regular abdominal ultrasound, CT, or magnetic resonance imaging (MRI) examinations are conducted to monitor for any recurrence or metastasis. Follow-

up checks are done every 3-6 months to detect any potential recurrence or metastasis promptly; (3) Laboratory tests: Regular monitoring of liver function tests and tumor markers (CEA, AFP, CA19-9, *etc.*). Examinations are conducted postoperatively at 1, 3, 6, and 12 months; and (4) Quality of life assessment: The patient's quality of life is evaluated using scales to assess daily activities, psychological status, *etc.* The World Health Organization Quality of Life Assessment or similar tools are utilized for the evaluation.

Follow-up time points

Follow-up time points included: (1) At 1 month postoperatively: The patient is experiencing no significant discomfort, the wound is healing well, appetite has returned to normal, and weight is stable. Imaging results (abdominal ultrasound) show good postoperative recovery with no signs of recurrence; (2) Three months postoperatively: Abdominal CT examination was performed, and no signs of recurrence were found. Liver function indicators (alanine aminotransferase, aspartate aminotransferase, and bilirubin) have returned to normal. The patient reported that daily life had not been affected; (3) Six months postoperatively: The patient's quality of life is good, with no recurrence of jaundice, and daily activities are not significantly affected. Regular checks show normal liver function, and tumor markers (CEA and CA19-9) are within normal ranges; and (4) Twelve months postoperatively: Follow-up imaging examination (MRI) and tumor marker testing showed no tumor recurrence or metastasis signs. The patient's weight remains stable, and quality of life is high. The relevant follow-up details and biomarker testing results are presented in Supplementary Table 1.

Postoperative outcome evaluation

The tumor was completely excised, along with thorough lymph node dissection. The patient recovered well postoperatively, with symptoms such as disappearing jaundice and significantly improving quality of life. There were no signs of tumor recurrence or metastasis during follow-up, and liver function and tumor markers were within normal

ranges. Overall, the surgical treatment showed significant effectiveness, with a high quality of life for the patient and a good long-term prognosis.

Regarding the surgical treatment plan and outcomes for pNENs combined with IPMN-B

During the surgical procedure for pNENs combined with IPMN-B, a meticulous exploration and assessment were conducted to select an appropriate extent of surgical resection to ensure complete removal of the lesion tissue while preserving normal pancreatic function. The surgical scope included the pancreatic head, affected pancreatic tissue, and corresponding lymph nodes. Regular postoperative follow-up was performed to monitor tumor recurrence and metastasis, assess the patient's quality of life, and evaluate functional recovery. Long-term follow-up results showed no obvious recurrence in the patient, indicating a good quality of life and the effectiveness of the surgical treatment plan.

Postoperative long-term management and support

Postoperative long-term management and support is as followed: (1) Nutritional support: During the postoperative recovery, provide a high-protein, high-calorie diet to promote wound healing and physical recovery; (2) Psychological support: Offer psychological counseling and support to help patients cope with the psychological stress of the surgery and recovery process; and (3) Rehabilitation training: Guide patients in moderate rehabilitation training to improve physical strength and enhance quality of life.

DISCUSSION

PNENs, as highly heterogeneous malignant tumors, have been increasing in incidence annually. Due to their endocrine characteristics, they are prone to misdiagnosis and missed diagnosis, leading to delays in early treatment for patients. Therefore, early diagnosis and treatment of pNENs are crucial. Regarding early diagnosis, the focus is

mainly on immunomarkers and imaging examinations. Research has shown that international serum chromogranin A is currently the preferred circulating biomarker for neuroendocrine tumors, providing an important basis for clinical diagnosis, treatment assessment, prognosis, and follow-up[16]. Domestic studies have also indicated that neuron-specific enolase can be used as one of the diagnostic and prognostic indicators for NECs, but due to its limitations, it is difficult to use as the primary diagnostic marker[17,18].

Although the research on these biomarkers is still in its early stages, with low clinical popularity and susceptibility to multiple factors, it is difficult for them to become the frontline testing indicators for pNENs. Imaging examinations remain the main means of clinically diagnosing pNENs, including routine imaging examinations and functional imaging examinations: (1) Multi-slice spiral CT examination: CT plain scan can clearly show the location, size, range, relationship with surrounding tissues, and metastasis of the tumor. Enhanced CT can clearly show the blood supply characteristics of the tumor, providing evidence for benign or malignant judgment. However, CT has a low detection rate for early small lesions and carries the risk of ionizing radiation[19]; (2) MRI examination: MRI can detect early tiny lesions and is often used as a supplementary examination after enhanced CT, with no risk of ionizing radiation[20]; (3) Positron emission tomography-computed tomography (PET-CT): Studies have shown that the sensitivity and specificity of 68Ga-labeled somatostatin receptor imaging can reach 93% and 95%, respectively, making a significant contribution to the diagnosis and individualized treatment of the disease[21]. However, it is easily influenced by factors such as inflammation, leading to false positives, and requires comprehensive clinical consideration. By reflecting the tumor's glucose metabolism, 18F-fluorodeoxyglucose PET-CT can distinguish between benign and malignant tumors and holds diagnostic value for NECs[22].

In this case, to evaluate the biliary tract condition and differentiate other biliary obstructions, magnetic resonance cholangiopancreatography was performed initially, revealing dilation of the lower bile duct and a mass in the pancreatic head region.

Subsequent enhanced CT examination highly suggested a malignant tumor. CT and MRI have become the preferred clinical diagnostic imaging modalities for pNENs, playing an important role in detecting early tumors. Treatment after diagnosis is equally important, with surgery always being the primary treatment method for pNENs. Early detection and curative surgery are crucial in patient survival time and quality of life[16]. In addition, interferon, targeted drugs, peptide receptor radionuclide therapy, and immunotherapy can also serve as adjuvant therapy before or after surgery.

IPMN-B is a relatively rare and unique type of tumor with some heterogeneity and the possibility of malignant transformation. In this case, postoperative pathology indicated the presence of local carcinoma. The pathogenesis of this disease is still not clear, with many believing it is associated with various factors such as biliary tract infections, liver fluke infestations, and intrahepatic bile duct stones[23,24], while others suggest a link to abnormalities in *K-ras* gene mutations and *p53* gene expression[25]. Agostini *et al*[26] conducted DNA-targeted sequencing on a Visium exploratory cohort sample and found that all high-grade IPMNs showed *p53* mutations, thereby confirming to some extent the association between IPMN-B and *p53* gene mutations. Similarly, the key focus for this disease is early diagnosis and treatment. Laboratory tests and imaging examinations are also utilized to diagnose this disease. Unlike in the case of biomarkers that are not clearly defined, laboratory tests often rely on parameters such as alkaline phosphatase, gamma-glutamyl transferase, and tumor markers in the blood such as CA19-9 and CEA. However, conditions like obstructive jaundice caused by common bile duct stones, pancreatic head cancer, and primary tumors in the intestines can also elevate these markers, leading to a variety of differential diagnoses. Therefore, these markers cannot be definitive indicators for diagnosing this disease. In terms of imaging, in addition to routine examinations like ultrasound, CT scans, and MRIs, ERCP is commonly used in clinical practice. Through duodenoscopy, copious mucoid secretions from the papilla and mucus and lesions in the bile duct can be observed. ERCP allows for concurrent histopathological examination of lesions, making it an important diagnostic tool for this disease and considered an indispensable examination in clinical

practice[27]. As for the treatment of this disease, the current preferred option is still surgical treatment, especially in cases where patients have not shown malignancy or metastasis. It is vital to undergo curative resection early. Unfortunately, due to the difficulty in early diagnosis and the low diagnostic rate, the possibility of early curative surgery is reduced. A new type of treatment, photodynamic therapy (PDT), is gradually being used to treat IPMN-B. Its effects mainly include directly killing tumor cells, damaging tumor blood vessels, and inducing inflammation to activate the immune response, significantly improving patients' survival rates. Numerous studies have shown that patients who undergo PDT in combination have a significantly prolonged survival period compared to those who do not undergo PDT[28-31]. Additionally, for elderly patients who have already developed malignancy or metastasis leading to obstructive jaundice, to improve their quality of life and alleviate suffering, ultrasound-guided percutaneous transhepatic cholangiodrainage and endoscopic placement of biliary stents under duodenoscopy, as well as radiofrequency ablation of tumor tissue, can be performed to relieve biliary obstruction and alleviate symptoms of jaundice.

We conducted a comprehensive review of articles published from 2010 to 2024 by searching the PubMed database using the search terms "pancreatic neuroendocrine tumors" and "cases". As shown in Table 2, we summarized the clinical manifestations, diagnostic methods, treatments, and prognosis of patients in the 11 most relevant articles on this topic. We have conducted an in-depth discussion on the following aspects.

Diagnostic methods

The diagnosis of pNENs typically involves a variety of imaging techniques such as CT scans, MRI, PET scans, and endoscopic ultrasound-guided fine-needle aspiration. These technologies are crucial for determining the tumor's location, extent, and potential metastasis. For example, Mihalache *et al*[32] diagnosed 18 patients with pNENs using CT, MRI, PET, and endoscopic ultrasound-guided fine-needle aspiration, emphasizing the importance of comprehensive imaging examinations for accurate diagnosis.

Similarly, Shiba *et al*[33] confirmed the effectiveness of CT, MRI, and PET in diagnosing 100 patients with pNENs. These imaging techniques not only help confirm the presence of the tumor but also provide crucial information about the tumor's size, morphology, and extent of infiltration, aiding in formulating appropriate treatment plans.

Additionally, the pathological classification is essential for determining the grade and potential malignancy of the tumor. Feola *et al*[32] highlighted the role of pathological classification in assessing 148 cases of sporadic gastroenteropancreatic NENs. Histopathological features, including mitotic count and Ki-67 index, are crucial for tumor grading and prognosis. Through these pathological markers, a more accurate prediction of the tumor's biological behavior and the patient's prognosis can be made, leading to more personalized treatment strategies (Figure 4) below.

Treatment plan

Surgery is the primary method for treating pNENs and offers a potential chance for cure. The scope of surgical intervention varies based on the tumor's size, location, and metastasis. Studies have reported cases of tumor excisions and pancreatic resections, with some cases requiring splenectomy or hepatic metastasis resection[32]. Research also indicates that the reported five-year survival rates demonstrate the effectiveness of surgical resection, with a survival rate of 91% for neuroendocrine tumor G1 and 69% for neuroendocrine tumor G2[33]. These data suggest that early and comprehensive surgical intervention significantly improves long-term survival rates for pNENs patients.

Furthermore, as Nappo *et al*[34] discussed, laparoscopic surgery reflects advancements in minimally invasive procedures, reducing patient recovery time and surgical complications. The application of minimally invasive surgical techniques decreases postoperative pain and hospitalization time and reduces the risk of surgical-related complications, enhancing the quality of life for patients. Adjuvant therapies, including somatostatin analogs, interferon therapy, and radiation therapy, are crucial for managing metastatic and recurrent pNENs. A research team documented a case of a

non-functional, well-differentiated pNEN patient with liver and bone metastasis who achieved good long-term survival outcomes using these therapies[35]. The use of adjuvant therapy expands the treatment options for pNENs and provides additional therapeutic choices for patients who cannot undergo complete tumor resection through surgery.

Prognosis and follow-up

The prognosis of pNENs is closely associated with tumor grading, staging at the time of diagnosis, and the effectiveness of surgical resection. For instance, in most cases reported in studies, there were no instances of local or distant recurrence, emphasizing the curative potential of appropriate surgical intervention. Studies have also highlighted significant differences in survival rates among different tumor grades, with a particularly poor prognosis for NECs[36]. These studies indicate that accurate staging and grading are crucial for developing effective treatment plans, and prognosis varies significantly among different tumor types. An early and accurate diagnosis significantly influences treatment outcomes. Research has shown that incidentally discovered pancreatic lesions underscore the potential for early intervention and improved prognosis[37]. Early diagnosis allows for effective treatment before the tumor has spread extensively, thereby enhancing patient survival rates and quality of life. In some cases, the management of pancreatic tumors in children and adolescents requires customized approaches. Research teams have analyzed the clinical characteristics of pancreatic tumors in patients under 21 years old, emphasizing the need for specific surgical strategies in this population[38]. Due to the physiological characteristics and growth needs of children and adolescents, treatment strategies need to be more cautious and individualized to minimize the impact on normal growth and development. For mixed neuroendocrine-non-neuroendocrine tumors, such as reported by the In Park *et al*[35], comprehensive diagnostic workup and thorough surgical procedures are necessary to manage complex pathology and improve patient prognosis[38]. The heterogeneity of these tumors increases the complexity of diagnosis

and treatment, necessitating interdisciplinary teamwork to develop optimal treatment plans.

In conclusion, pNENs and IPMN-B share commonalities, such as atypical clinical presentations, inadequate early diagnosis, and surgery as the main treatment approach. The early symptoms of pNENs and IPMN-B are often subtle, making them prone to being overlooked or misdiagnosed. It presents a significant challenge for clinicians in the diagnosis, especially when the tumor has not caused significant symptoms or presented clear radiological features, making early diagnosis even more difficult. The coexistence of these two tumors is extremely rare. In this case, postoperative pathological examination confirmed the coexistence of pNENs and IPMN-B, with localized carcinoma identified in the bile duct tissues. Notably, despite abnormal liver function, routine tumor markers (CEA, AFP, CA19-9, *etc.*) levels were not significantly elevated. This phenomenon may be related to the complex growth pattern of mixed neuroendocrine-non-NENs. Mixed neuroendocrine-non-NENs has a unique histological structure, where the composite growth of its two components may interfere with the secretion of tumor markers. Additionally, the intraductal growth characteristic of the neuroendocrine lesions may cause localized pathology without significantly altering marker levels[39]. Moreover, a high degree of tumor differentiation or a smaller tumor size may also limit the release of tumor markers[40]. These characteristics highlight the limitations of relying solely on tumor markers for diagnosis. A comprehensive evaluation combining imaging examinations, histopathological analysis, and immunohistochemical testing is essential to improve diagnostic accuracy and reduce the risk of misdiagnosis or missed diagnosis.

Fortunately, before the tumors metastasized, the patient underwent curative surgical resection, providing valuable time for prognosis. The case's complexity emphasizes the need for a more comprehensive and detailed diagnostic approach in clinical practice. Particularly in patients with multifocal lesions or complex medical histories, vigilance for the possibility of multiple tumors is crucial. This case also highlights that incomplete consideration during the diagnostic process, failure to complete relevant immunological

examinations, and PET-CT scans may result in inadequate early diagnosis and treatment delays. PET-CT, as a highly sensitive and specific imaging examination method, is of significant importance in the early detection and evaluation of tumors, while immunological examinations can provide more information about the nature and characteristics of the tumor, aiding in the development of precise treatment strategies. Therefore, improving these diagnostic procedures is crucial in enhancing early diagnosis rates and guiding subsequent treatments. Early diagnosis and curative surgical treatment are essential for prolonging patient life, improving quality of life, and enhancing prognosis. Early detection and intervention can effectively control tumor progression and prevent metastasis and spread, significantly increasing long-term survival rates for patients. It is worth noting that cases where pNENs and IPMN-B coexist have not been reported in the literature, and the rarity of this occurrence has raised discussions regarding whether there is a connection or causal relationship between the two. There is insufficient evidence to suggest a clear association or causal relationship between these two tumors, but the potential cannot be ruled out. Future research should focus on investigating the comorbid mechanisms of the two and understanding if there are common pathogenic factors or molecular pathways.

In this context, recommendations for the early diagnosis and treatment of coexisting pNENs and IPMN-B are proposed as follows: (1) Increase clinical vigilance: For patients with nonspecific symptoms but abnormal findings on imaging studies, consider various possible diagnoses, including the possibility of coexistence; (2) Utilize a comprehensive diagnostic approach: Combine CT, MRI, PET-CT, and immunological examinations to enhance the accuracy of early diagnosis; (3) Personalized treatment plans: Based on each patient's specific situation, develop personalized surgical and adjuvant treatment plans to ensure comprehensive and effective treatment; (4) Enhance multidisciplinary collaboration: Collaborate with oncology, surgery, radiology, pathology, and other multidisciplinary teams to formulate the best treatment strategies; and (5) Maintain continuous follow-up and monitoring: Conduct long-term follow-up and monitoring of treated patients to promptly detect and manage potential recurrence or new lesions.

Implementing the above strategies is expected to significantly improve the early diagnosis rates and treatment outcomes of patients with coexisting pNENs and IPMN-B, providing a better prognosis and quality of life for patients. Future research should continue to delve into the mechanisms of occurrence and treatment strategies for these two tumors, further refine clinical management, and enhance patient outcomes.

CONCLUSION

This case report describes the first documented coexistence of pNENs with biliary IPMN-B, highlighting the challenges of diagnosing and managing such rare combinations. Through comprehensive diagnostic evaluations, including imaging, histopathological analysis, and immunohistochemical staining, the accurate identification of dual tumors was achieved, enabling successful curative surgical treatment. The postoperative outcomes demonstrated significant improvements in quality of life, with no signs of recurrence during follow-up. This case underscores the importance of a multidisciplinary approach to diagnosing and treating rare tumor combinations and provides new insights into clinical management and potential molecular mechanisms. Future research should further investigate the pathophysiological and molecular associations between these tumor types to refine diagnostic strategies and optimize treatment outcomes.

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