



# Pancreatic follicular lymphoma: a report of two cases and literature review

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## Abstract

Primary pancreatic lymphomas are extremely rare, accounting for 0.1–0.5% of malignant lymphomas and about 0.2% of primary pancreatic tumors. They occur most commonly in the pancreatic head of elderly males, with diffuse large B-cell lymphoma being the most common subtype. Primary pancreatic follicular lymphoma is the most commonly reported primary pancreatic indolent lymphoma, accounting for 9–14% of primary pancreatic lymphomas. We report two cases of primary pancreatic follicular lymphoma treated with obinutuzumab, a second-generation humanized anti-CD20 monoclonal antibody, and bendamustine. One was diagnosed by endoscopic ultrasound-guided fine-needle aspiration, while the other required laparoscopic lymph node sampling to reach a diagnosis. Both achieved complete response with induction therapy and opted for maintenance therapy with obinutuzumab. We also conducted a literature review of primary pancreatic follicular lymphoma cases reported over the last 30 years.

**Keywords** Malignant lymphoma · Endoscopic ultrasound-guided fine-needle aspiration · Monoclonal antibody · Pancreas

## Introduction

Primary pancreatic lymphomas (PPL) are extremely rare, accounting for 0.1–0.5% of malignant lymphomas and about 0.2% of primary pancreatic tumors [1–3]. They occur most commonly in the pancreatic head of elderly males, with diffuse large B-cell lymphoma being the most common subtype [4]. The diagnosis of PPL can be made if lymphoma is mainly localized in the pancreas, even if there is peripheral lymph node involvement or distant spread [5]. Primary pancreatic follicular lymphoma (PPFL) is the most commonly

reported indolent PPL, with up to 31 reports over the last 30 years [2, 4, 6–18]. PPFL accounts for 9–14% of PPLs [17–19].

PPFL presents difficulties in diagnosis. The differential diagnosis may include neuroendocrine neoplasms, autoimmune pancreatitis and, most importantly, pancreatic ductal adenocarcinoma [14, 16]. Diagnostic accuracy of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) in PPFL may be suboptimal [11]. It is therefore not unusual for PPFLs to be diagnosed only after surgical resection [15, 16, 18].

As treatment of follicular lymphoma is not dictated by origin, standard regimens can be used for extranodal disease, including PPFL. Treatment outcomes in PPFL have not been elucidated, owing to its rarity. While obinutuzumab-based regimens have come to be accepted as first-line therapy in advanced follicular lymphoma with high tumor burden [20], its safety and efficacy in PPFL have not been reported. We report two cases of successful diagnosis and treatment of PPFL and review the English literature on PPFL.

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## Case reports

### Case 1

An asymptomatic 67-year-old man was referred for multiple masses in the pancreatic head discovered on screening abdominal ultrasound. He was also receiving treatment for hypertension and dyslipidemia, which were well-controlled with medications. He had no family history of malignancies. Physical examination was unremarkable. Laboratory tests revealed an increase in soluble interleukin-2 receptor to 623 U/mL (reference range 145–519 U/mL); all other results including immunoglobulin G4 (IgG4), carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) were within the normal range. The hepatitis B panel was negative.

Computed tomography (CT) with contrast revealed a slowly-enhancing 4 cm mass in the pancreatic head. Multiple mildly enlarged lymph nodes in the hepatoduodenal ligament and mesentery were also observed, with no clear vascular invasion. There was no biliary or pancreatic duct dilatation or signs of chronic pancreatitis (Fig. 1a). Magnetic resonance imaging (MRI) with contrast revealed a heterogeneous pancreatic mass and mesenteric lymphadenopathy with abnormal diffusion restriction. 18F-fluorodeoxyglucose positron emission tomography (FDG-PET)/CT showed increased uptake in the pancreatic head (maximum Standardized Uptake Value (SUVmax): 6.7) and para-aortic lymph nodes (SUVmax: 2.9) (Fig. 1b). A mass with SUVmax of 9.1 was also noted in the right lobe of thyroid.

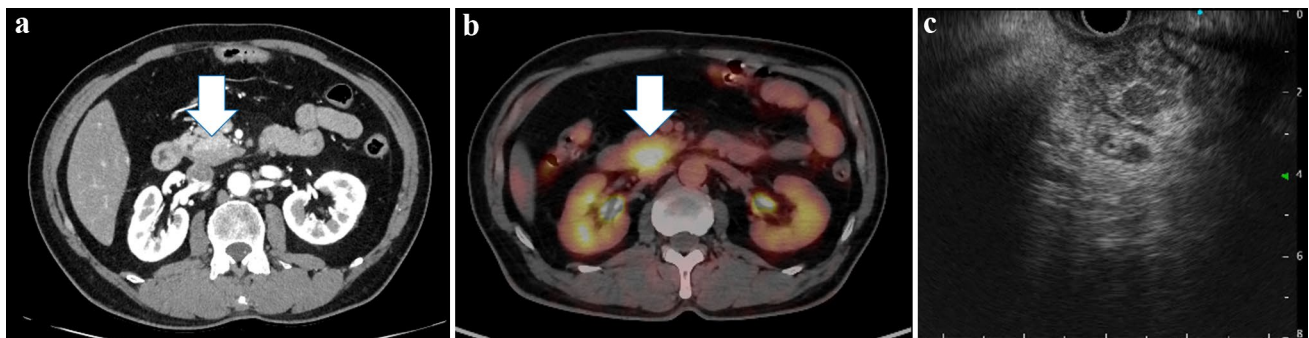
EUS revealed a 36 × 34 mm heterogeneous, multi-nodular mass in the pancreatic head near the inferior duodenal angle (Fig. 1c). Borders were relatively clearly delineated. Significant blood flow was confirmed on Doppler EUS. Contrast-enhanced EUS showed early enhancement similar to the adjacent normal pancreas, which was not typical

for adenocarcinoma but not as strongly enhanced as may be expected for neuroendocrine neoplasms or autoimmune pancreatitis. Multiple slightly enlarged lymph nodes were also noted. IgG4-related pancreatitis was believed to be the leading differential, while pancreatic cancer and malignant lymphoma could not be ruled out.

EUS-FNA was performed using a 22-gauge fine-needle biopsy needle (Acquire, Boston Scientific, Marlborough, MA, USA). Two passes were made using the slow-pull technique with 20 strokes per pass, achieving an adequate specimen for pathological diagnosis. Histological evaluation of the specimen revealed a dense, monotonous proliferation of atypical lymphocytes. Immunohistochemistry was consistent with Grade 1–2 follicular lymphoma: CD5–, CD10+, CD20+, BCL2+, BCL6+, MUM1– (Fig. 2). Ki-67 labeling index was less than 1%, indicating low proliferative activity. Only a few plasma cells were positive for IgG4 staining.

Esophagogastroduodenoscopy and colonoscopy were unremarkable. Bone marrow aspiration was negative for malignancy. As a result, the patient was diagnosed with PPFL with low tumor burden, Grade 1–2, Lugano classification stage IIE, with a Follicular Lymphoma International Prognostic Index (FLIPI) of 1 (age): low risk, assuming that the thyroidal lesion was not lymphoma. If the thyroid was involved, the diagnosis would be Lugano classification stage IIIE, with a FLIPI of 2 (age, stage): intermediate risk.

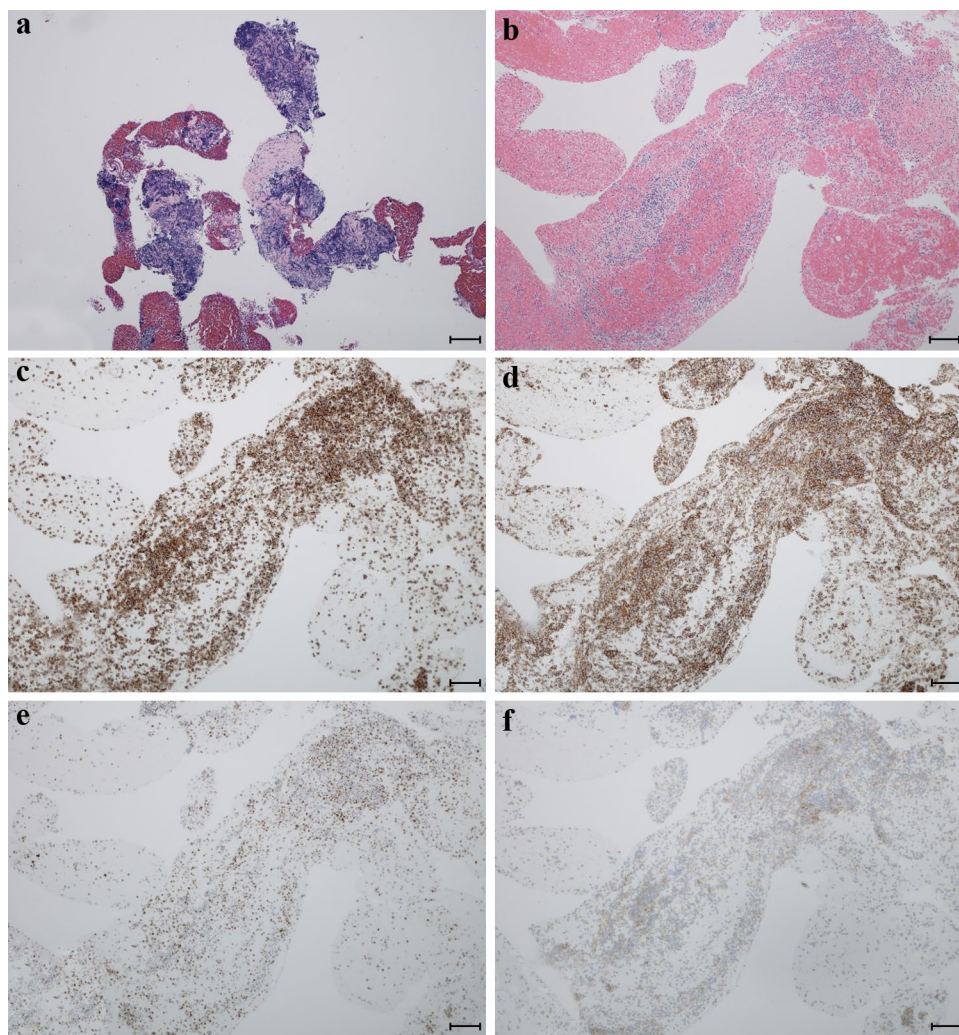
Despite the low tumor volume, the multiple pancreatic masses posed a high risk of biliary obstruction. There was also a possibility that the lymphoma was already at an advanced stage, as it could not be determined at the time whether the thyroid was involved or not. Informed consent was therefore obtained for treatment with obinutuzumab and bendamustine (GB). Six cycles of GB led to complete response with minimal adverse effects. As the thyroid mass remained unchanged, we determined that it was a separate clinical entity from the lymphoma. Surgical resection was



**Fig. 1** a Computed tomography (CT) with contrast revealed a slowly-enhancing 4 cm mass in the pancreatic head (arrow). b 18F-fluorodeoxyglucose positron emission tomography/CT revealed increased uptake (arrow) in the pancreatic head (maximum Standardized

Uptake Value: 6.7). c Endoscopic ultrasound revealed a 36 × 34 mm clearly delineated, heterogeneous, multi-nodular mass in the pancreatic head

**Fig. 2** Histological evaluation of the endoscopic ultrasound-guided fine-needle aspiration specimen. **a** Hematoxylin and eosin staining with low-power (scale bar: 200  $\mu$ m) and **b** high-power (scale bar: 100  $\mu$ m) magnifications revealed a dense, monotonous proliferation of atypical lymphocytes. Immunohistochemistry was positive for **c** CD20, **d** BCL2, **e** BCL6, and **f** CD10 (scale bars: 100  $\mu$ m)



performed. Pathology was consistent with follicular thyroid cancer. Thus, the initial Lugano classification staging was determined to be stage IIIe in retrospect. Maintenance obinutuzumab monotherapy was commenced thereafter, with no adverse effects other than one episode of neutropenia unaccompanied by fever. The patient remains in complete response 15 months after starting induction therapy.

## Case 2

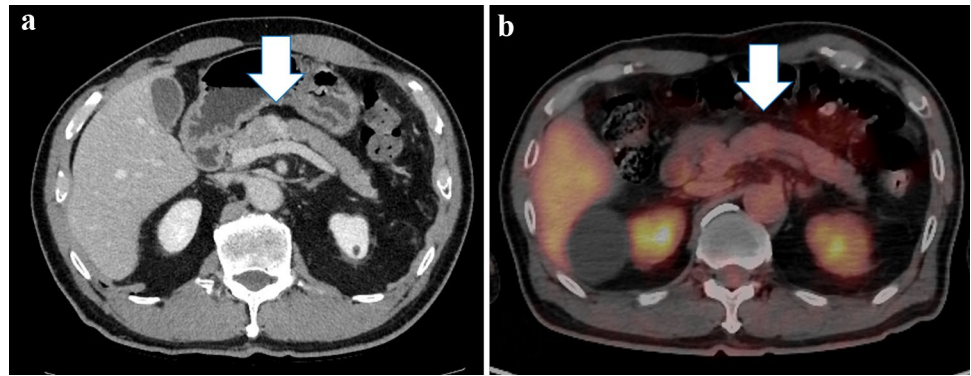
An asymptomatic 70-year-old man was referred for a pancreatic mass noted on screening abdominal ultrasound. He had a history of hypertension and cataract surgery. He had no family history of malignancies. Physical examination and laboratory tests including soluble interleukin-2 receptor, IgG4, CEA, and CA 19-9 were unremarkable. The hepatitis B panel was negative. CT with contrast revealed a slowly-enhancing mass in the pancreatic body and mildly enlarged mesenteric lymph nodes (Fig. 3a). FDG-PET/CT revealed minimally increased uptake (Fig. 3b).

EUS revealed a 15 × 11 mm heterogeneous, clearly delineated hypoechoic mass in the pancreatic body with no dilation of the distal pancreatic duct. EUS-FNA was performed using a 22-gauge fine-needle biopsy needle (Acquire, Boston Scientific) (Fig. 4a). Two passes were made with suction and two passes were made using the slow-pull technique, with 20 strokes for each pass. Histological evaluation of the specimen revealed a monotonous proliferation of atypical lymphocytes without follicular architecture (Fig. 5a). Immunohistochemistry revealed that these cells were positive for BCL2, marginally positive for BCL6 and negative for CD10, but were indeterminate for lymphoma (Fig. 5b–d).

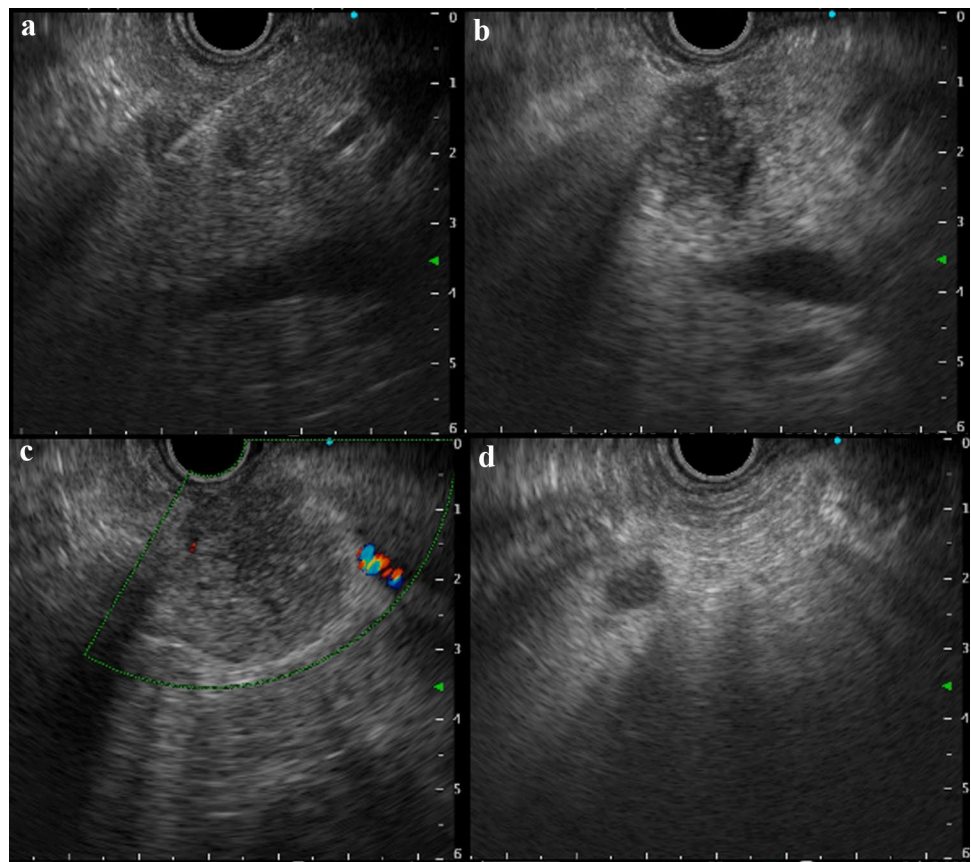
EUS-FNA was repeated after 3 months, when the lesion had grown to 16 × 14 mm (Fig. 4b). This time, four passes were made with a 20-gauge EchoTip ProCore needle (Cook Medical, Bloomington, IN, USA). The same inconclusive findings were obtained, with negative immunohistochemical staining for CD10. Another 3 months later, the pancreatic body mass had grown to 28 mm and a new, similar mass had appeared in the pancreatic tail (Fig. 4c, d). EUS-FNA



**Fig. 3** **a** Initial computed tomography (CT) with contrast revealed a vaguely enhancing mass in the pancreatic body (arrow). **b** 18F-fluorodeoxyglucose positron emission tomography/CT revealed slightly increased uptake (arrow) in the pancreatic body



**Fig. 4** **a** First endoscopic ultrasound-guided fine-needle aspiration of a 15 × 11 mm heterogeneous, clearly delineated hypoechoic mass in the pancreatic body. **b** The mass had grown to 16 × 14 mm 3 months later. **c** The mass had grown to 28 mm another 3 months later. **d** A new, similar mass appeared in the pancreatic tail



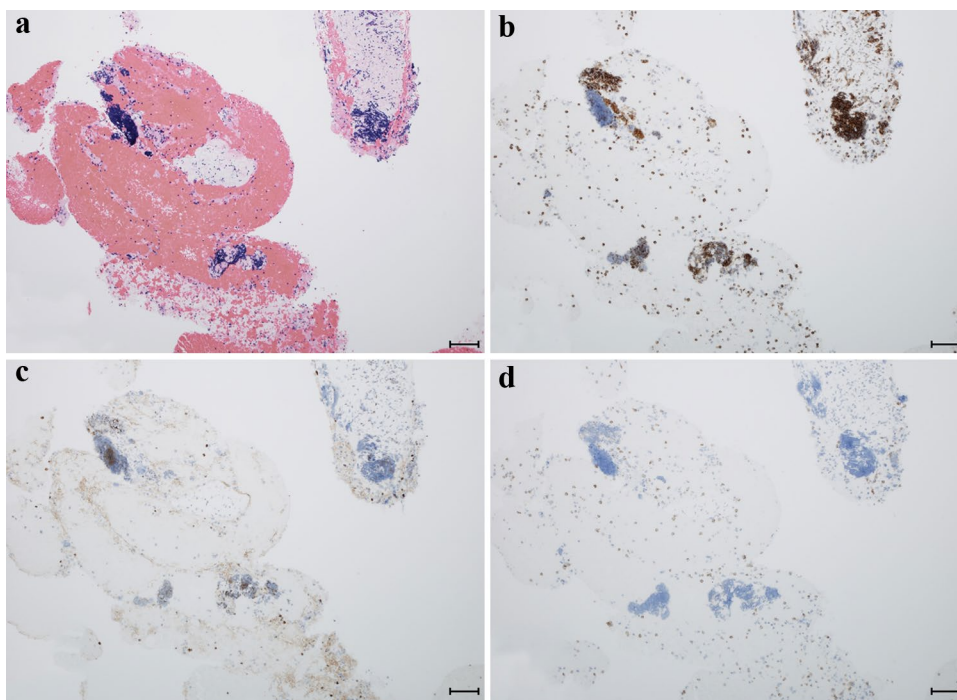
was repeated for both the pancreatic body mass and the new pancreatic tail mass, but a definite diagnosis could not be reached.

FDG-PET/CT taken after the third EUS-FNA session revealed increased uptake in the pancreas (SUVmax: 4.1) as well as abdominal, lower esophageal, and left supraclavicular lymph nodes. Consent for laparoscopic lymph node sampling was obtained and performed without complications. An abdominal lymph node measuring 21 mm was obtained. Histological evaluation revealed medium-sized atypical lymphocytes forming uniform and densely packed follicles. Immunohistochemistry was consistent with Grade 1–2

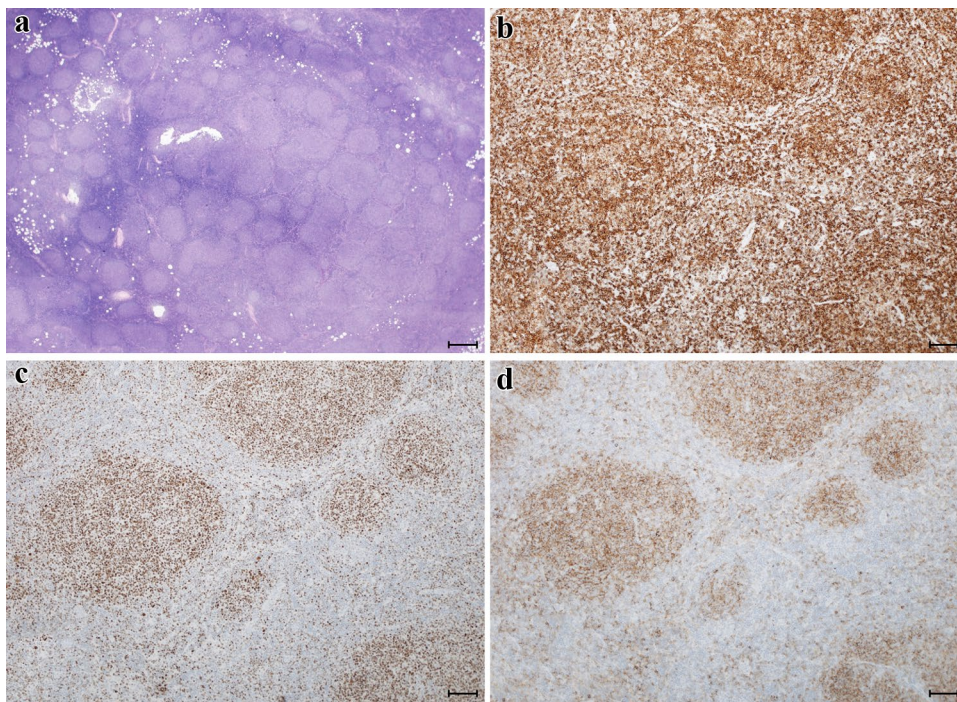
follicular lymphoma: CD5–, CD10+, CD20+. BCL2+, BCL6+, MUM1– (Fig. 6). Ki-67 labeling index was approximately 30%. Flow cytometry also revealed a B-cell neoplasm (CD19+, CD20+, CD10 dim+) with lambda light chain restriction. Bone marrow aspiration was negative for malignancy. As a result, the patient was diagnosed with PPFL with low tumor burden, Grade 1–2, Lugano classification stage IIIIE, FLIPI of 2 (age, stage): intermediate risk.

Although the tumor burden was low, the disease had progressed relatively quickly over a period of 6 months. Informed consent was therefore obtained for treatment with GB. Six cycles of GB led to complete response with

**Fig. 5** Histological evaluation of the first endoscopic ultrasound-guided fine-needle aspiration specimen (scale bars: 100  $\mu$ m). **a** Hematoxylin and eosin stain revealed a dense, monotonous proliferation of atypical lymphocytes. Immunohistochemistry was positive for **b** BCL2, **c** marginally positive for BCL6, and **d** negative for CD10



**Fig. 6** Histological evaluation of the surgically resected lymph node. **a** Hematoxylin and eosin stain revealed medium-sized atypical lymphocytes forming uniform and densely packed follicles (scale bar: 1 mm). Immunohistochemistry was positive for **b** BCL2, **c** BCL6, and **d** CD10 (scale bars: 100  $\mu$ m)



minimal adverse effects, which included one episode of Grade 3 neutropenia without fever. Although the patient opted for maintenance therapy, treatment was suspended 4 months later as the patient wished to receive the Severe Acute Respiratory Syndrome Coronavirus 2 vaccine [21].

## Discussion

Lymphoma in the pancreas can take two forms: direct invasion from adjacent peripancreatic lymph nodes and,



much less commonly, PPL. About 30% of patients with extranodal non-Hodgkin's lymphoma have pancreatic involvement [7]. On the other hand, the diagnosis of PPL can be made if lymphoma is mainly localized in the pancreas, even if there is peripheral lymph node involvement or distant spread [5]. The distinction between the two is therefore unclear. While both of our cases meet the criteria for PPFL, we cannot completely rule out the possibility that the lesions observed in Cases 1 and 2 arose from peripancreatic lymph nodes in the hepatoduodenal ligament and mesentery, respectively. Further research is required to determine differences in clinical characteristics and outcomes between the two entities.

Across the two largest PPL studies, the mean age at diagnosis was 57–63 years and 55–56% were male [4, 19]. Most presented as large masses (mean 79–81 mm). About 72% were located in the pancreatic head [4] while 10% presented as diffuse lesions [19]. Jaundice was observed in 33–47% [4, 19]. While 84% were diagnosed as early-stage disease, 67% were unresectable and 50% had lymphadenopathy [19]. Complete response was achieved with chemotherapy alone in 75% of cases. Endoscopic biopsy led to the diagnosis in 7–36% of cases, although it was unstated whether this involved EUS-FNA of the pancreatic lesion or endoscopic biopsies of duodenal invasion [4, 19].

Based on a review of the English literature over the last 30 years, we summarized the 33 reports of PPFL including our two cases in Table 1 [2, 4, 6–18]. Eighty percent of cases were male, with a median age of 67 years (range 51–82 years). While pancreatic head was involved in 87% of cases and median size was 70 mm (range 15–140 mm), jaundice was observed in only 25% of cases. Our cases represent the two smallest lesions reported to date and are the first cases to present with multiple pancreatic lesions. Excluding Case 2, all were discovered as Stage IE–IIE disease. While these characteristics are similar to PPL in general, PPFL may be more likely to affect males and less likely cause obstructive jaundice.

While imaging findings in PPL generally involve large, homogenous, hypovascular masses in the pancreatic head without pancreatic duct obstruction, differentiation from pancreatic ductal adenocarcinoma may be difficult [22]. EUS-FNA has become a standard diagnostic procedure for pancreatic masses, which may include suspected PPLs. According to one report, EUS-FNA of enlarged lymph nodes allowed for accurate diagnosis and classification of lymphomas in 88% of cases [23]. However, diagnostic yield of EUS-FNA for PPL remains low despite generally presenting as large masses [11]. In addition, EUS-FNA specimens cannot retain the follicular architecture which would aid in the diagnosis of PPFL.

While we successfully reached a diagnosis in Case 1 after a single EUS-FNA session, Case 2 could not be diagnosed

despite obtaining satisfactory samples in 16 EUS-FNA passes during three different sessions over a course of 6 months. Diagnosis could not be reached in Case 2 despite using both Menghini needles and Franseen needles, both of which have high diagnostic yield [24, 25]. Repeated CD10 negativity was the key factor precluding the diagnosis of PPFL. Interestingly, the same phenomenon was observed in one previous report: EUS-FNA revealed CD19-positivity but CT-guided FNA was required to confirm CD10 expression [11]. Another report failed to reach the diagnosis despite performing EUS-FNA on the pancreatic lesion as well as multiple lymph nodes [14]. EUS-FNA was avoided in two other cases due to intervening vessels and hypervascularity, respectively [15, 16]. Laparoscopic lymph node sampling should be considered in cases like these, where a definite diagnosis cannot be reached (1) on immunohistochemical grounds despite obtaining adequate FNA samples, (2) after multiple EUS-FNA attempts, or (3) because EUS-FNA cannot be performed safely.

In summary, EUS-FNA successfully diagnosed PPFL in only three of eight cases (38%) where EUS-FNA was considered and in three of six cases (50%) where EUS-FNA was actually performed. Difficulties in pathological diagnoses with EUS-FNA specimens have also been reported in diffuse large B-cell lymphoma: two cases reached a diagnosis only after the second EUS-FNA session and one case failed to reach a conclusive diagnosis despite finding atypical lymphocytes [26, 27]. According to one report, a higher number of EUS-FNA passes was required to diagnose PPFL compared to other PPLs [11].

The National Comprehensive Cancer Network Guidelines suggest anti-CD20 monoclonal antibody treatment with or without chemotherapy as an option for Grade 1–2 follicular lymphoma cases of all stages [28]. Watchful waiting is also an acceptable option for asymptomatic disease or when the tumor burden is low [29, 30]. Obinutuzumab, a new type II, glycoengineered, humanized anti-CD20 monoclonal antibody, demonstrated longer progression-free survival over rituximab and is now accepted as a part of standard first-line regimens for follicular lymphoma [20], including extranodal disease. Although its use in PFL has not been reported, we selected obinutuzumab-based regimens for our two cases based on the reported progression-free survival as well as the acceptable adverse events profile. Both patients also opted for maintenance obinutuzumab when suggested as an option to reduce relapse risk.

All reported PPFL cases in the literature were treated aggressively with surgery, chemotherapy, and/or radiotherapy except for one case when the patient refused treatment (and died of disease 6 years later) and another diagnosed only after autopsy [4, 10]. Surgery may be selected when pre-operative diagnosis is inconclusive, for fear of possible pancreatic adenocarcinoma. Physicians may also be

**Table 1** Reports of primary pancreatic follicular lymphoma

Author	Year	Ref	n	Age	Sex	Location	Size (cm)	Symptoms	Stage (Lugano)	Diagnostic method	EUS-FNA passes	Failed methods	Treatment	Outcome
Prayer	1992	[5]	4 <sup>a</sup>	N/A	N/A	N/A	6–12	N/A	N/A	Surgery or biopsy	–	–	N/A	N/A
Behrns	1994	[6]	3 <sup>b</sup>	N/A	N/A	N/A	8–12	N/A	IE	Surgery	–	–	Biliary bypass, gastroenterostomy	Survived
				N/A	N/A	N/A	8–12	N/A	IE	Surgical biopsy	–	–	Radiation	Survived
				N/A	N/A	N/A	8–12	N/A	IIE	Surgery	–	–	Gastroenterostomy, chemoradiotherapy	Survived
Bouvet	1998	[7]	1	72	M	Head	5	Fatigue	IE	Surgical biopsy	–	–	Chemotherapy (CHOP-bleomycin), radiation	CR
Koniaris	2000	[8]	1	63	M	Head	NA	None	IIE	Surgery (PD)	–	–	Surgery (PD)	CR
Nishimura	2001	[9]	2	63	M	Head	NA	Fatigue	IE	Surgery	–	–	Surgery, chemotherapy	CR
Volmar	2004	[10]	3	78	M	Head	5.4	Pain	IE	Autopsy	–	–	None	Died of disease
				51	M	Head	14	N/A	N/A	EUS-FNA	8	CT-FNA US-FNA	N/A	N/A
				57	F	Head	4.3	N/A	N/A	EUS-FNA, CT-FNA	1	–	N/A	N/A
Grimison	2006	[11]	1	56	M	Head	5	Dyspepsia, weight loss	IIE	CT-FNA	6	EUS-FNA	N/A	N/A
				58	M	Head	8	Pain	IIE	Laparotomy	–	–	Radiation, chemotherapy (CVP, rituximab)	CR
Malin	2010	[2]	2 <sup>c</sup>	N/A	N/A	N/A	N/A	N/A	N/A	N/A	–	–	Surgery, radiation	CR
				73	F	Head	6	Jaundice	IIE	CT-FNA	–	EUS-FNA (pancreas and lymph nodes)	Chemotherapy (R-CHOP)	N/A

**Table 1** (continued)

Author	Year	Ref	n	Age	Sex	Location	Size (cm)	Symptoms	Stage (Lugano)	Diagnostic method	EUS-FNA passes	Failed methods	Treatment	Outcome
Alexander	2011	[14]	1	61	M	Head	5	Jaundice, fatigue, weight loss	IIE	Surgery (PD)	–	EUS-FNA (not attempted due to intervening vessels)	Surgery, chemotherapy (R-CHOP 6 cycles)	CR
Shirai	2015	[15]	1	71	F	Body	5	Pain	IIE	Surgery (DP)	–	EUS-FNA (not attempted due to hyper-vascularity)	Surgery, chemotherapy	N/A
Boninsegna <sup>d</sup>	2018	[16]	5	N/A	N/A	N/A	N/A	N/A	N/A	N/A	–	N/A	N/A	N/A
Sallapan	2018	[17]	1	75	M	Head	5	Jaundice	IIE	Surgery (PD)	–	–	N/A	N/A
Facchinelli <sup>d</sup>	2020	[4]	4	N/A	N/A	N/A	N/A	N/A	N/A	Surgery (1)	–	–	Surgery (1), Chemotherapy (BR, 2), None (1)	N/A
Our cases	2021	2	67	M	Head (multiple)	4	None	IIE	EUS-FNA	2	–	–	Chemotherapy (GB, G maintenance)	CR
			70	M	Body, tail (multiple)	1.5	None	IIIE	Laparoscopy	4, 4, 8	EUS-FNA	EUS-FNA	Chemotherapy (GB, G maintenance)	CR

CR complete response, CT-FNA computed tomography-guided fine-needle aspiration, DP distal pancreatectomy, EUS-FNA Endoscopic ultrasound-guided fine-needle aspiration, G obinutuzumab, GB obinutuzumab/bendamustine, PD pancreaticoduodenectomy, US-FNA ultrasound-guided fine-needle aspiration

<sup>a</sup>Three cases of centrocytic/centroblastic lymphoma and one case of centrocytic lymphoma based on the Kiel classification

<sup>b</sup>Two cases of follicular mixed cell lymphoma and one case of follicular large cell lymphoma

<sup>c</sup>One other case included in the report (excluded from this analysis) was diffuse large B-cell lymphoma with a focus of follicular lymphoma, grade 3

<sup>d</sup>Possible overlap due to overlap in reporting institutions



reluctant to leave PPFLs untreated as most occur in the pancreatic head, posing the risk of obstructive jaundice. Complete response has been reported in all cases treated by surgery, chemotherapy, radiotherapy, and combinations of these alternatives. While the literature appears to favor treatment over watchful waiting, the optimal approach remains unclear. Combination therapy used in some previous reports may be excessive treatment. It should also be noted that long-term follow-up is required as follicular lymphoma can relapse after an extended period of maintained response [31].

In conclusion, we report two cases of PPFL treated successfully with obinutuzumab and bendamustine induction therapy and maintained on obinutuzumab monotherapy. Pancreatectomy may be avoidable in advanced or multiple PPFL if a pre-operative diagnosis can be reached. Laparoscopic lymph node sampling may be beneficial when a diagnosis cannot be reached despite obtaining a satisfactory EUS-FNA specimen. Our literature review suggests a favorable prognosis after surgery, chemotherapy, and/or radiotherapy.

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## Declarations

**Conflict of interest** Takeshi Okamoto, Takashi Sasaki, Noriko Nishimura, Manabu Takamatsu, Chinatsu Mori, Takafumi Mie, Takaaki Furukawa, Yuto Yamada, Tsuyoshi Takeda, Akiyoshi Kasuga, Masato Matsuyama, Masato Ozaka, Dai Maruyama, and Naoki Sasahira declare that they have no conflict of interest.

**Human Rights** This study does not include any data about human subjects.

**Informed Consent** Informed consent was obtained from all patients for the publication of this case report.

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