Case report

Simultaneous occurrence of pancreatic mixed acinar-ductal adenocarcinoma and primary follicular lymphoma of the duodenum, accompanied by increased number of IgG4 plasma cells in tumor-free parenchyma as concomitant IgG4-related disease or reaction to tumor? A case report

Branislava Ranković[1], Clara Limbaeck-Stokin[2], Mihajlo Đokić[3], Dragoje Stanisavljević[3], Metka Volavšek[1]

[1]Institute of Pathology, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia
[2]Imperial College Healthcare NHS Trust, Department of Histopathology, Charing Cross Hospital, London, United Kingdom
[3]Clinical Department of Abdominal Surgery, University Clinical Center Ljubljana, Ljubljana, Slovenia

Mixed acinar-ductal carcinoma is rare among pancreatic cancers, as is duodenal involvement in follicular lymphoma (FL). Although usually a systemic disease, primary FL of the duodenum occurs, with superficial involvement of the intestinal wall and low risk of progression.
We report on a unique case of mixed ductal-acinar carcinoma of the pancreatic head accompanied by low-grade duodenal FL and autoimmune pancreatitis-like changes in adjacent pancreatic parenchyma.
To our knowledge this is the first report of concomitant pancreatic mixed acinar-ductal carcinoma and duodenal FL. Clinico-pathological features of this unusual case, possible relationship between the entities and differential diagnosis are discussed.

Key words: mixed ductal-acinar carcinoma, follicular lymphoma, autoimmune pancreatitis, IgG4, pancreas, duodenum.

Introduction

Although originally described already in the 18th century by Giovanni Battista Morgagni, pancreatic cancer remains one of the deadliest malignant tumors [1]. It usually affects elderly male patients and is most frequently located in the pancreatic head. Due to its silent clinical course, patients usually present at late disease stages. Histologically, the vast majority are ductal adenocarcinomas, while acinar cell carcinoma represents less than 2% of all pancreatic cancers. More common in males, they clinically present with non-specific abdominal symptoms [2, 3]. Mixed neoplasms, such as acinar-neuroendocrine or acinar-ductal adenocarcinoma, have been described, as well as even less frequent mixed acinar-neuroendocrine-ductal adenocarcinoma [2, 4].

Gastrointestinal (GIT) non-Hodgkin lymphomas (NHL) are the most common among primary extra-nodal lymphomas [5]. They constitute a heterogeneous group of tumors with different clinical and pathological features and predominant gastric and small intestine involvement [5].

Autoimmune pancreatitis (AIP) is a rather novel clinical entity. It was introduced by Yoshida *et al*. in

1995 and is subdivided into two groups with quite different characteristics: AIP I-IgG4 related disease and AIP II [6].

Here we describe a unique case of mixed acinar cell carcinoma and ductal adenocarcinoma of the head of the pancreas accompanied by primary follicular lymphoma (FL) of the duodenum as well as histological changes suggestive of IgG4-related disease in the surrounding pancreatic parenchyma.

Case presentation

Clinical history

A 63-year-old man was admitted to the Clinical Department of Gastroenterology from the emergency room. He had not been feeling well for two months, had squeezing pain in the upper abdomen and reported to have lost 15 kg in weight. Clinically, jaundice, acholic stool and darker urine were observed. Elevated blood levels of direct and indirect bilirubin, ALP, AST, ALT, GGT and the tumor marker S-CA 19-9 were detected. Urine bilirubin was elevated as well.

Abdominal ultrasound showed dilatation of the gallbladder, choledochal and intrahepatic ducts. While biliary stenting was unsuccessful, ERCP revealed an elevated and disfigured papilla Vateri which was biopsied (biopsy A).

Abdominal CT, performed at the Clinical Department of Abdominal Surgery where the patient was transferred for further treatment, showed a mass in the pancreatic head, measuring 4.5 × 4 × 3.8 cm (Fig. 1) growing in close vicinity of the portal vein and truncus coeliacus. Both the main bile duct and main pancreatic duct were obstructed with retrograde dilatation. The patient was operated 5 days after ERCP. Frozen section of suspicious mesenteric lymph nodes was performed during surgery (biopsy B). Subsequently, the Whipple procedure was performed with resection of the superior mesenteric vein and end-to-end anastomosis (biopsy C).

The postoperative period was uneventful and the patient was released into home care on postoperative day 8. He was additionally treated for pancreatic carcinoma with chemotherapy (gemcitabine), and his clinical status up to now is stable. Systemic progression of lymphoma has not been noted. The last abdominal CT, performed 10 months after the Whipple procedure, revealed only (post-operative?) sclerotic changes of the peripancreatic tissue.

Methods

All biopsies were analyzed at the Institute of Pathology, Faculty of Medicine, Ljubljana. Formalin-fixed and paraffin-embedded tissue sections were stained with hematoxylin and eosin (HE), as was the sample obtained for frozen section. Immunohistochemical analysis was performed on fully automated immunostainer Ventana XT apparatus (Ventana Medical Systems Inc., USA). The following primary antibodies were used: CK7 (Dako); Bcl2 (Dako); Bcl6 (Ventana); CD10 (Novocastra); CD20 (Dako); Cyclin D1 (Neo Markers); Synaptophysin (Cell Marque);

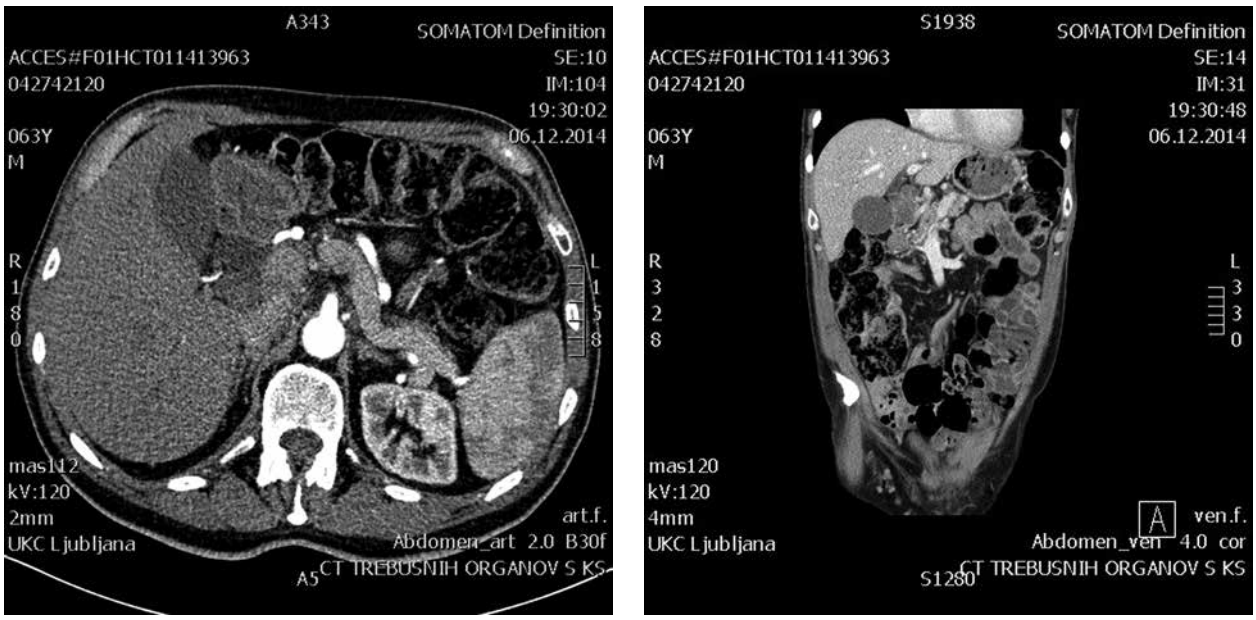

Fig. 1. CT scan before operation: gall bladder, extrahepatic bile duct as well as main pancreatic duct are dilated. Obstruction is caused by tumor formation in the pancreatic head. It is impossible to discriminate between cancer of the pancreatic head growing into papilla and cancer of papilla Vateri spreading into the head of the pancreas. Ingrowth of tumor into the descending and horizontal part of the duodenum is suspected, as well tumor deposits in the lymph node in front of the tumor

Chromogranin A (Dako); CEA (Dako); MUC1 (Cell Marque); IgG; IgG4 (The Binding site).

Morphology

Endoscopic samples of papilla Vateri (biopsy A) showed duodenal mucosa with partial preservation of villi and rather superficial infiltration with lymphoid infiltrates showing follicular growth pattern. Closely packed follicles showed little variation in size and shape and were predominantly seen in lamina propria. The majority of follicular cells were small, with scanty cytoplasm and no visible nucleoli (centrocytes), admixed with a few (< 15 per hpf) larger cells with vesicular nuclei and two to three peripherally located nucleoli (centroblasts), positive for CD20, Bcl2 (Fig. 2A, B), Bcl6 and CD10, and negative for cyclin D1, with a proliferation index (Ki-67) of approximately 15%. Morphology and immunohistochemical profile were diagnostic for low grade FL with a follicular growth pattern. Clinical workup was suggested to exclude possible systemic involvement by FL. The same morphology was observed in the duodenal mucosa of the resected specimen.

One of two lymph nodes which were sent for frozen sections (biopsy B) was infiltrated with moderately differentiated ductal adenocarcinoma.

Resection specimen after Whipple procedure (biopsy C) showed a poorly demarcated tumor of the pancreatic head with obvious infiltration of peripancreatic fat, measuring 4.5 cm in the greatest diameter. On the cut surface, the tumor was firm, yellow grey, and poorly demarcated from the surrounding tissue. Polypoid elevations of duodenal mucosa were observed at several locations including papilla Vateri, measuring up to 2 cm. Common bile duct stenosis was observed in the ampullary region. The gallbladder was macroscopically normal.

On histology the pancreatic tumor was composed of solid sheets, lobules, interconnecting trabeculae, as well as glandular structures, accompanied by a moderate amount of desmoplastic stroma (Fig. 3A). Tumor cells in solid areas were uniform, with eosinophilic cytoplasm, round nuclei and small nucleoli. PAS and PAS/diastase revealed some intracytoplasmic granules (Figs. 3A-C). Cells of the glandular regions were more pleomorphic with prominent nucleoli (Fig. 3D). The tumor cells were diffusely positive for CK7 and negative for synaptophysin and chromogranin A. The ductal component was additionally positive for CEA and MUC1. The final diagnosis of the tumor (with the Ki-67 index varying between 20 and 40%) was mixed acinar and ductal adenocarcinoma. Tumor infiltrated peripancreatic tissue and showed massive lymphovascular and perineural invasion with metastases in 14/26 lymph nodes (pT3N1).

Pancreatic tumor-free parenchyma was atrophic, with periductal concentric fibrosis, lymphoplasmacytic infiltrate and venulitis (Figs. 4A-D). Staining for IgG and IgG4 with subsequent counting of positive cells on four high power fields (HPF) revealed approximately 28 IgG4 plasma cells per HPF, with an IgG4/IgG ratio of 35%.

Discussion

Mixed tumors, acinar-endocrine or acinar-ductal carcinomas are rare. To justify a diagnosis of mixed tumor, the second component must constitute at least 25% of the tumor cell population [3, 4]. Although most acinar cell carcinomas are positive for cytokeratin, in order to support the acinic/acinar cell differentiation either immunohistochemistry for trypsin or PAS/PASD stains should be performed. In our case, the predominant component was acinic cell carcinoma, which constituted approximately 70% of the tumor. Follicular lymphoma (FL) is a neoplasm composed of follicle center B cells and one of the most common subtypes of NHL. However, in

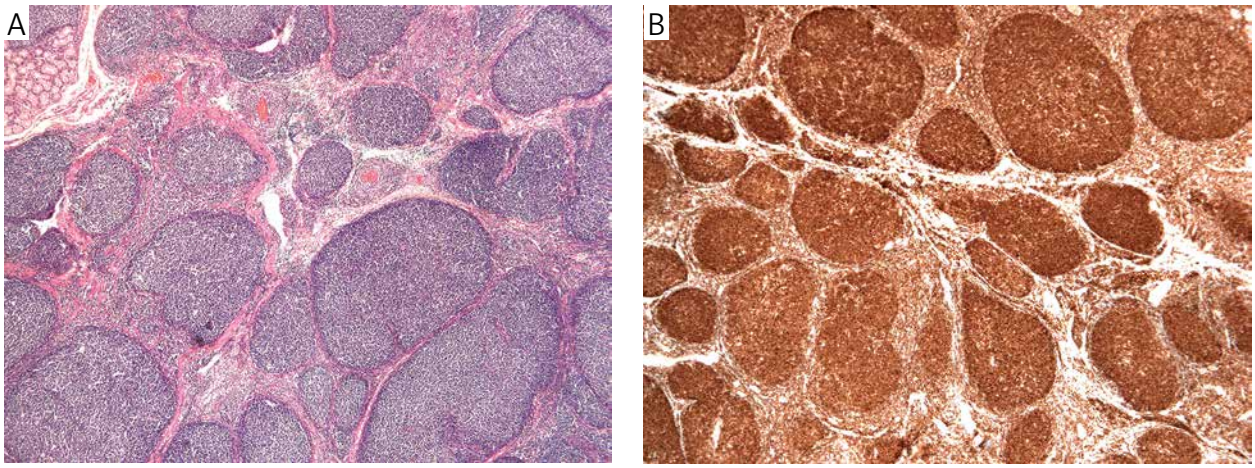

Fig. 2. Follicular lymphoma. A) Closely packed lymphoid nodules infiltrating duodenal mucosa (Brunner glands in upper left corner) (HE, original magnification 10×). B) Neoplastic follicles are diffusely positive for Bcl2 (Bcl2, original magnification 10×)

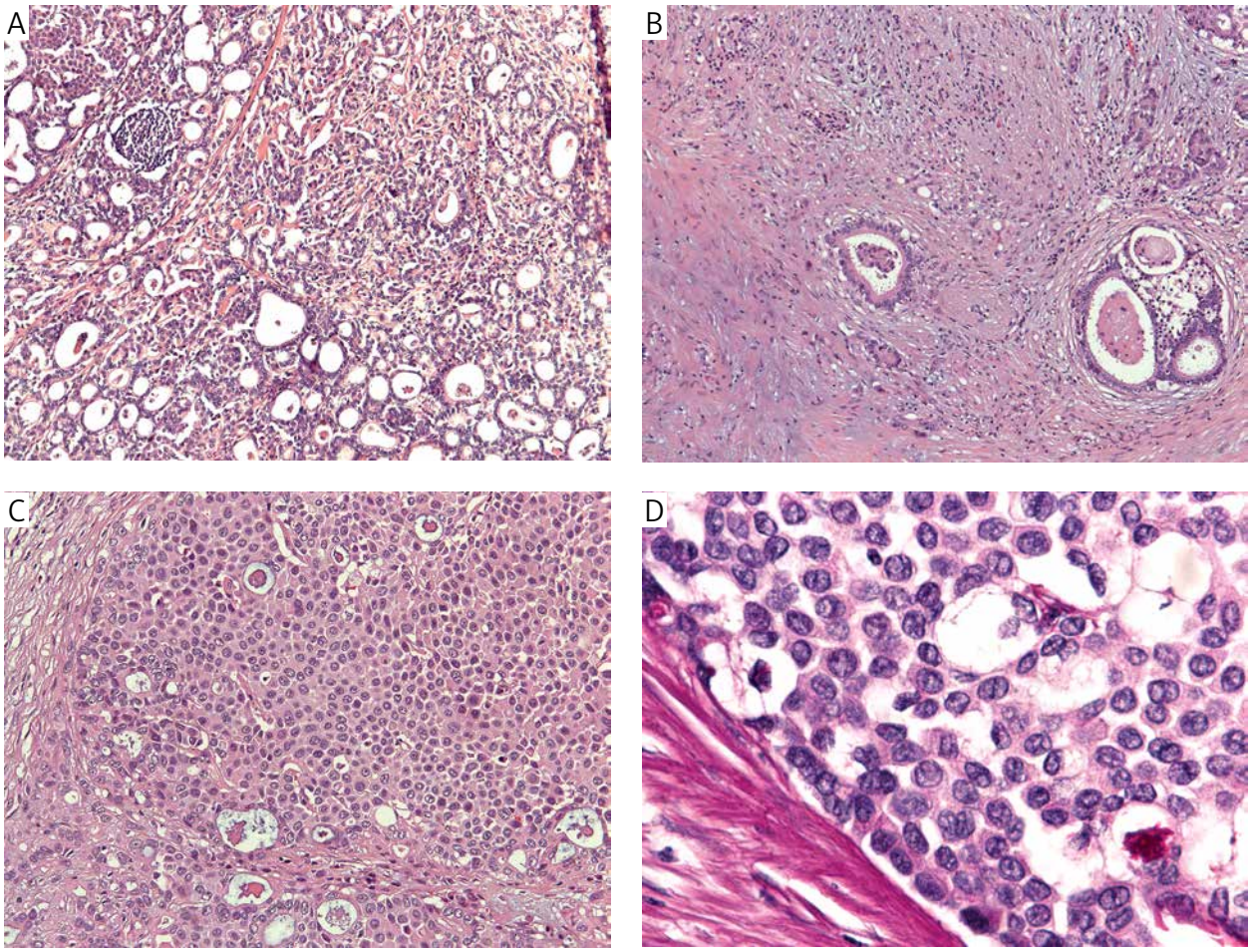

Fig. 3. Mixed acinar/ductal adenocarcinoma. A) Solid sheets and cords (acinar carcinoma) combined with glandular structures (ductal carcinoma) (HE, original magnification 10×). B) Desmoplastic stromal reaction (HE, original magnification 10×). C) Uniform acinar tumor cells with eosinophilic cytoplasm, round nuclei and small nucleoli (HE, original magnification 20×). D) PAS/PAS diastase positive intra-cytoplasmic granules in some of the tumor cells (PAS/PASD, original magnification 40×)

extra-nodal sites, FL is among the rarest, with a reported incidence of only 1-3.6% of GIT lymphomas [7, 8]. The majority of primary GIT lymphomas are represented by extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) and diffuse large B cell lymphoma. Duodenal FL is a rare entity, with only a few reported cases [7, 8, 9]. This particular subtype of FL is now being recognized as a clinicopathologic entity, and should appear in the updated WHO classification as duodenal type FL. As in our patient, most duodenal FL arise near the papilla Vateri, manifesting as a slight polypoid elevation, usually having indolent course. Patients are asymptomatic in most cases and FL is diagnosed incidentally [9]. Histological diagnosis of a GIT lymphoma from a small biopsy sample may be difficult. However, initial biopsy of the papilla Vateri in our case was sufficient and corresponded to the morphology observed in the resection samples. Systemic involvement has been excluded. The two tumors were separated by normal parenchyma, lymphoma was rather superficial – infiltrating submucosa of the duodenal wall, while pancreatic carcinoma was focally infiltrating the muscularis propria of the duodenum and peripancreatic fat.

A possible relationship between duodenal FL and pancreatic carcinoma tumorigenesis is uncertain. According to some authors, several factors may lead to the tumorigenesis of collisional tumors: (i) a carcinogenic agent can affect multiple targets at the same time; (ii) the decrease of the systemic and local immune defense system after the development of the tumor facilitates the occurrence of another tumor; and (iii) dysfunction of the tumor suppressor mutated gene leads to inadequate repair of a gene mutation, which could result in formation of multiple tumors [10]. Constant irritation of the duodenal mucosa by bile and pancreatic juice with a superimposed bacterial infection may also lead to mucosal damage and induce cell proliferation activity and multiple gene mutations, which could explain duodenal predilection for neoplasms [10, 11]. Hypothetically these factors could also be stimuli for FL and mixed pancreatic carcinoma in our case.

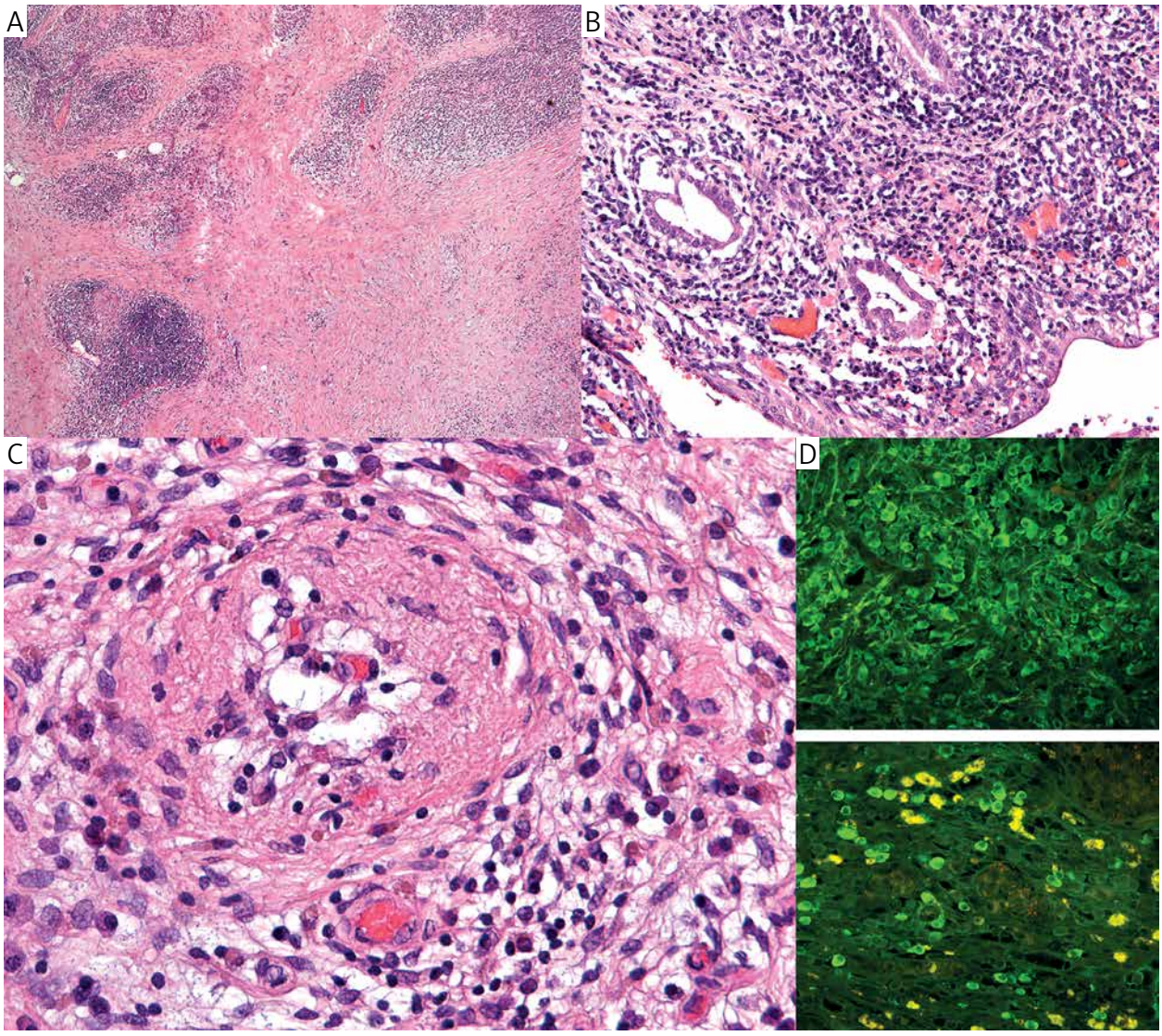

Fig. 4. Pancreatic tumor-free parenchyma. A) Fibrosis and atrophy of acinar structures accompanied by moderate inflammatory infiltrate (HE, original magnification 10×) B) Moderate periductal lymphoplasmacytic infiltrate (HE, original magnification 40×). C) Mild vasculitis (HE, original magnification 40×). D) Approximately 28 IgG4 plasma cells per high power field, IgG4/IgG ratio 30% (immunofluorescence for IgG and IgG4, original magnification 40×)

Although histological changes in surrounding parenchyma – fibrosis and dense inflammatory infiltrate – are usually seen in peritumoral tissue, the elevated number of IgG4 plasma cells raised the suspicion of concomitant IgG4 related disease, in our case type I autoimmune pancreatitis (AIP). Although pancreatitis associated with hypergammaglobulinemia was reported already in 1961, in 1995 AIP was first described as a benign autoimmune disease [6, 12]. The underlying pathophysiology of AIP is still unclear. AIP consists of two distinct clinical and pathological entities. As both subtypes can mimic a malignant process, the diagnosis of AIP requires adequate clinical and pathological evaluation [13]. AIP type I is included in the spectrum of IgG4-related disease. The diagnosis of this fibroinflammatory disease with a heterogeneous clinical picture is based on the clinical presentation and typical histological changes, such as lymphoplasmacytic infiltrate, fibrosis (at least focally arranged in a storiform pattern), obliterative phlebitis and an elevated number of IgG4 plasma cells which is defined by the Consensus statement (30 cells per high power field for pancreas biopsy and 50 for resections; the proposed IgG4-to-IgG ratio is more than 40%) [14, 15, 16, 17, 18]. IgG4 related disease can affect different organs and usually manifests as a tumorous mass in the affected organ [19]. However, many inflammatory conditions (gastrointestinal, skin) and malignant neoplasms may be accompanied by an increased number of IgG4 positive plasma cells. In such cases the infiltrate is usually patchy and there are no other histological features typical for IgG4 RD. Concerning consensus criteria, our case is borderline, and we assume that fibrosis,

inflammatory infiltrate and phlebitis are part of the complex morphological changes due to nearby carcinoma. We had no information about involvement of other organs or serum IgG4 levels. Those changes are likely to be found in the vicinity of the tumor tissue and might represent a diagnostic pitfall. Nevertheless, the diagnosis of AIP demands a more complex clinical and histological approach, and since the histological findings and IgG4/IgG ratio as well as elevated number of IgG4 plasma cells are borderline, we cannot confirm or exclude AIP type I as a potential concomitant disease. In any case, the possible pathogenetic mechanisms of: (i) carcinoma and/or lymphoma inducing chronic inflammation with an increased number of IgG4 plasma cells, or (ii) AIP facilitating cancer growth, are considered. The relation between malignant neoplasms and IgG4-related disease is still unclear. According to the literature, immunoglobulin G4 plays a role in the tumor pathogenesis; therefore the patients with IgG4-related disease might be at higher risk for developing carcinomas and NHL [20].

And last, but not least important, in cases of simultaneous tumors occurring in the same region, insufficient biopsy samples could lead to inappropriate diagnosis. In our case the first biopsy showed only infiltration of low grade FL of the duodenal mucosa; a second biopsy taken from peritumoral tissue with fibrosis and elevated number of IgG4 plasma cells would lead to misdiagnosis of AIP – a radiological and clinical mimicker of carcinoma; therefore carcinoma would be overlooked. In such cases a good correlation between the clinicians, radiologist and pathologist is of greatest importance.

In conclusion, this is the first case of a mixed acinar cell and ductal adenocarcinoma of the pancreas accompanied by primary duodenal FL. Accompanying chronic pancreatitis of the peritumoral tissue as well as moderate lymphoplasmacytic infiltrate of the stomach, duodenum and gallbladder together with an elevated number of IgG4 plasma cells raise the idea of possible preexisting IgG4-related disease, which we assume might have been involved in cancer and lymphoma development.

The authors declare no conflict of interest.

References

1. Hruban RH, Klimstra DS. Adenocarcinoma of the pancreas. Semin Diagn Pathol 2014; 31: 443-451.
2. Klimstra DS, Klopel G, Morohoshi T, et al. WHO classification of tumours of the digestive system. In: Bosman FTJ, Lakhani SR, Ohgaki H, et al. (eds). WHO Classification of tumours, 4th ed. International Agency for Research on Cancer, Lyon 2010; 280-337.
3. Wood LD, Klimstra DS. Pathology and genetics of pancreatic neoplasms with acinar differentiation. Semin Diagn Pathol 2014; 31: 491-497.
4. Stelow EB, Shaco-Levy R, Bao F, et al. Pancreatic acinar cell carcinoma with prominent ductal differentiation: mixed acinar ductal carcinoma and mixed acinar endocrine ductal carcinoma. Am J Surg Pathol 2010; 34: 510-518.
5. Yamamoto S, Nakase H, Yamashita K, et al. Gastrointestinal follicular lymphoma: review of the literature. J Gastroenterol 2010; 45: 370-388.
6. Yoshida K, Toki F, Takeuchi T, et al. Chronic pancreatitis caused by an autoimmune abnormality. Proposal of the concept of autoimmune pancreatitis. Dig Dis Sci 1995; 40: 1561-1568.
7. Sentani K, Maeshima AM, Nomoto J, et al. Folicular lymphoma of the duodenum: A clinicopathologic analysis of 26 cases. Jpn J Clin Oncol 2008; 38: 547-552.
8. Otter R, Bieger R, Kluin PM, et al. Primary gastrointestinal non-Hodgkin's lymphoma in a population based registry. Br J Cancer 1989; 60: 745-750.
9. Yoshino T, Miyake K, Ichimura K, et al. Increased incidence of folicular lymphoma in the duodenum. Am J Surg Pathol 2000; 24: 688-693.
10. Niu GM, Jin DY, Ji Y, et al. Survival analysis of pancreatic and periampullary collision cancers. J Dig Dis 2010; 11: 231-236.
11. Suzuki S, Tanioka F, Inaba K, et al. A Rare Collision Tumor Composed of Follicular Lymphoma and Adenocarcinoma in the Ampulla of Vater: A Case Report. Case Rep Pathol 2014; 2014: 530727.
12. Sarles H, Sarles JC, Muratore R, et al. Chronic inflammatory sclerosis of the pancreas - an autonomous pancreatic disease? Am J Dig Dis 1961; 6: 688-698.
13. Okazaki K, Tomiyama T, Mitsuyama T, et al. Diagnosis and classification of autoimmune pancreatitis. Autoimmun Rev 2014; 13: 451-458.
14. Desphande V, Zen Y, Chan JK, et al. Consensus statement on the pathology of IgG4-related disease. Mod Pathol 2012; 25: 1181-1192.
15. Morse B, Centeno B, Vignesh S. Autoimmune pancreatitis: Updated concepts of a chaleging diagnosis. Am J Med 2014; 127: 1010.e1-1010.e9.
16. Kamisava T, Takuma K, Egawa N, et al. Autoimmune pancreatitis and the IgG4-related sclerosing disease. Nat Rev Gastroenterol Hepatol 2010; 7: 401-409.
17. Dhall D, Suriawinata AA, Tang LH, et al. Use of immunohistochemistry for IgG4 in the distinction of autoimmune pancreatitis from peritumoral pancreatitis. Hum Pathol 2010; 41: 643-652.
18. Runowska M, Majewski D, Puszczewicz M. Retroperitoneal fibrosis – the state-of-the-art. Reumatol 2016; 54: 156-263.
19. Oles K, Szczepanski W, Skladzien J, et al. IgG4- related inflammatory orbital pseudotumors – a retrospective case series. Folia Neuropathol 2015; 53: 111-120.
20. Yamamoto M, Takahashi H, Tabeya T, et al. Risk of malignancies in IgG4-related disease. Mod Rheumatol 2012; 22: 414-418.

Address for correspondence

Metka Volavšek, MD, PhD
Institute of Pathology, Faculty of Medicine
University of Ljubljana
Korytkova 2
1000 Ljubljana, Slovenia
Tel. +386-1-5437148
Fax +386-1-5437101
e-mail: metka.volavsek@mf.uni-lj.si