

Autoimmune Pancreatitis with Response to Chemoradiation Therapy

Hiroyuki Matsubayashi¹, Noriaki Hasuike¹, Yusuke Onozawa², Hideyuki Kanemoto³, Hiroyuki Ono¹, Ralph H. Hruban⁴

Division of 1) Endoscopy; 2) GI-Oncology; 3) Hepato-biliary-pancreatic Surgery, Shizuoka Cancer Center, Suntogun, Shizuoka, Japan; 4) Department of Pathology, The Sol Goldman Pancreatic Cancer Research Center, Johns Hopkins University, Baltimore, MD, USA

Abstract

Autoimmune pancreatitis (AIP) sometimes mimics pancreatic cancer, and is rarely resected under this misdiagnosis. However, there is no report in the literature regarding a case of AIP, which was misdiagnosed as an inoperative stage of pancreatic cancer and which received systemic chemotherapy with or without radiation. We report a 59-year-old man with a mass-forming lesion at the pancreatic head involving the common hepatic artery and portal vein, initially diagnosed as locally advanced pancreatic cancer and treated with chemoradiation therapy. After a month of continuous infusion of low dose 5-fluorouracil with concurrent local radiation (50.4 Gy), the pancreatic lesion diminished in size. However, the pancreatic body gradually enlarged and a capsule-like limb appeared in the following year. Serological markers and endoscopic retrograde cholangiopancreatography were compatible with those of AIP. No neoplastic tissue was identified on the fine needle aspiration biopsy of the pancreas. The pancreatic lesion responded well to steroid therapy and the patient remained in remission for one year after the withdrawal of steroids. Similar to pancreatic cancer, this current case of AIP responded to chemoradiation. Both serological and histological examinations were essential for images equivocal for either locally advanced pancreatic cancer or AIP.

Key words

Autoimmune pancreatitis – pancreatic cancer – diagnosis – chemoradiation – response.

Introduction

Autoimmune pancreatitis (AIP), one of a family of IgG4-related sclerosing inflammatory diseases, is characterized by a duct-centric mixed inflammatory cell infiltrate and associated venulitis. The diagnosis of AIP is sometimes difficult, and AIP is occasionally surgically resected because it so closely mimics pancreatic cancer (PC) [1, 2]. Diffusely swollen pancreas with capsule-like limb is typical of AIP; however, AIP also produces a focal pancreatic lesion [3-5]. Some cases of focal-type AIP, even those that are relatively small may involve larger arteries [3] and veins [3, 6]. This vascular involvement on imaging appears to correspond to the histologic finding of obliterative phlebitis [6, 7]. IgG4-related sclerosing disease may also produce an inflammatory pseudotumor of the liver. These lesions histologically consist of IgG4-positive plasma cells in a mixed inflammatory background with associated fibrosis [8] and appear as cancer metastases on clinical imaging [9]. Hence, AIP may mimic both early and advanced pancreatobiliary cancer.

Low dose 5-fluorouracil (5-FU) with concurrent radiation [10] was the standard treatment for patients with locally advanced PC [11], prior to the introduction of gemcitabine [12]. When given in this way, 5-FU acts as a S-phase-specific radiosensitizer, which is related to cell synchronization and altered DNA repair with a different effect on the tumor cells and normal cells [13]. However, the effect of this therapy on autoimmune conditions is not well known. We report a case of AIP, which was misdiagnosed as pancreatic cancer and which responded to chemoradiation therapy.

Case Report

A 59-year-old man was referred to Shizuoka Cancer Center for the surgical evaluation of a pancreatic head mass. The patient's medical history was not remarkable except for atrial fibrillation and hypertension. His father had a history of laryngeal cancer and his brother of pancreatic cancer. Abdominal computed tomography (CT) revealed a slightly low-dense mass lesion in the head of pancreas, accompanied with a dilated upstream main pancreatic duct (MPD). The

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Address for correspondence:

Hiroyuki Matsubayashi, M.D, Ph.D
Chief of Pancreaticobiliary Endoscopy
Division of Endoscopy
Shizuoka Cancer Center
Shizuoka 411-8777
Japan
Email: h.matsubayashi@scchr.jp

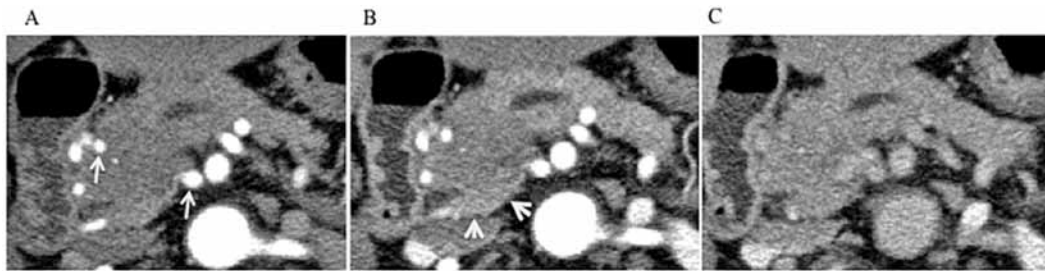


Fig 1. A. The pancreatic head is swollen and ill enhanced by computed tomography (CT). The common hepatic artery appears to be involved by the lesion (small arrows) (30 seconds after the venous injection of contrast medium). B. The portal vein is attached to the posterior side of the pancreatic head lesion (arrow head) (48 seconds). C. Enhancement of the head lesion is recovered and is almost the same as the pancreatic body at 120 seconds.

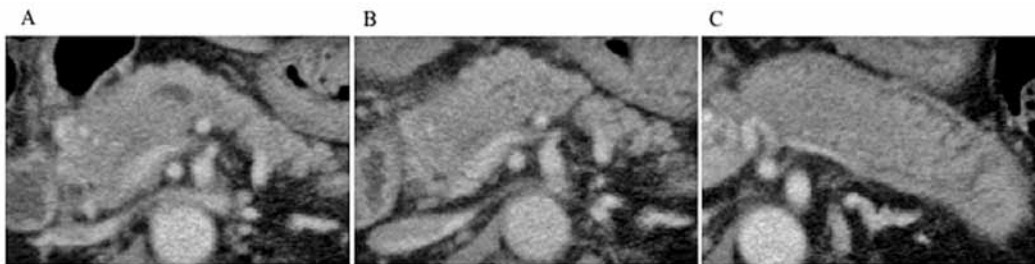


Fig 2. A. Enhanced CT (120 seconds) evidences a lesion of the pancreatic head resolved soon after the radiation therapy. B. After three months, dilatation of the upstream pancreatic duct disappeared. C. Typical capsule-like limb appeared one year after the initiation of chemoradiation.

common hepatic artery was involved by the mass and the portal vein was attached irregularly at the posterior margin of the lesion (Fig. 1). An ultrasonogram confirmed these findings. Although the patient's serum bilirubin level was slightly increased (1.3 mg/dl), the other blood tests were within the normal range, including hepatobiliary enzymes, glucose, and tumor markers (CEA and CA19-9). With the involvement of large size of vessels, the patient was clinically diagnosed with locally advanced pancreatic head cancer without biopsy confirmation of the diagnosis. Surgery was not indicated because of the involvement of the common hepatic artery and he underwent systemic chemotherapy, which included low dose 5-fluorouracil (5-FU) (2500 mg/week) with concurrent local radiation (1.8 Gy x 28 times, total 50.4 Gy). Steroids were not included in the regimen. After the completion of radiation therapy, CT demonstrated that the pancreatic lesion decreased significantly in size (Fig. 2A). As the assumption was that the carcinoma was sensitive to the regimen, low-dose 5-FU therapy was continued. Three months after starting chemotherapy, the upstream dilatation of the MPD had resolved (Fig. 2B). After nine months, the pancreatic body was noted to have gradually enlarged and a capsule-like limb was clearly apparent at one year (Fig. 2C). The lesion in the pancreatic head remained in remission for two years and the diagnosis of pancreatic cancer was then questioned. Serum IgG and IgG4 levels were found to be elevated (1857 mg/dl and 295 mg/dl, respectively), although serum autoantibody was normal including antinuclear antibody, rheumatoid arthritis particle agglutination, anti-Sjögren's syndrome-A, anti-Sjögren's



Fig 3. Endoscopic ultrasonogram (EUS) demonstrated enlarged, low-echoic, pancreatic body. Patchy high echogenicity was recognized within the pancreatic parenchyma. Bold low-echoic streak was visible (small arrow), corresponding to the capsule-like limb on CT.

syndrome-B and anti-DNA antibody. By endoscopic ultrasonogram (EUS), enlarged pancreatic parenchyma revealed a lobular low-echoic pattern (Fig. 3). The papilla of the Vater was unremarkable with duodenoscopic observation. Endoscopic retrograde cholangiography (ERC) showed a smooth-margined compression of the lower bile duct (Fig. 4A), and intraductal ultrasonogram showed a thickened biliary wall at the stricture (Fig. 4B). Pancreatography

demonstrated stenosis of the pancreatic duct in the head of the pancreas (Fig. 4C) and narrowing at the upstream duct (Fig. 4D). Forceps biopsies from the narrowed portion of pancreatobiliary ducts and papilla of the Vater and EUS-guided fine needle aspiration biopsy (FNAB) (22-gauge, EchoTip®, Cook, U.S.A.) from the head and body were obtained and all were negative for a tumor (Fig. 5). Within these samples, typical histological findings of AIP/lymphoplasmacytic sclerosing pancreatitis (LPSP) or idiopathic duct-centric pancreatitis (IDCP) [7] were not recognized even with IgG4 immunostaining. By fulfilling two of three major conditions (images and serology) of the Japanese criteria (2006) [5], his diagnosis was revised as AIP, and steroid therapy was started with 40 mg of prednisolone. Remission of AIP was recognized by clinical images as early as two weeks after the steroid therapy was initiated. Five months after the steroids were started, a second ERCP was performed and the stricture of the pancreatobiliary duct was found to be significantly improved. Steroids were withdrawn after two years, and to date, the patient's disease has not returned. The patient has also not developed any chronic complications such as attacks of pancreatitis, pancreatic stone formation, or dysfunction of exocrine and endocrine systems of the pancreas.

Discussion

This is the first reported case of AIP misdiagnosed as unresectable pancreatic cancer (PC) which responded to chemoradiation. Autoimmune pancreatitis can clinically mimic pancreatobiliary cancer [3, 9] and is even occasionally resected [1, 2]. Since the establishment of diagnostic criteria, many patients are now spared surgery [14]. The current case was first seen in the autumn of 2005, half a year before the first case of AIP was diagnosed in our institution (April of 2006). Lack of familiarity with the disease entity and its varied radiologic appearances made the diagnosis difficult. The lesion in the pancreatic head was not typical for AIP, i.e., not sausage-like, without capsule-like limb, with dilatation of the upstream pancreatic duct. However, in retrospective CT observation, the enhancement pattern of the lesion should have provided a clue to the diagnosis. The enhancement in the initial phase (30s) was weak (Fig. 1A), but increased in the late phase (120s) (Fig. 1C). These findings are not typical of PC and should raise the question of AIP in the differential diagnosis [15]. In this current case, the initial misdiagnosis might have been avoided if the physicians in charge of the patient's care had been aware of these findings and the importance of serological and histological examinations. As we have previously reported a case of PC that mimicked AIP not only radiographically (diffuse swelling of the pancreas) but also serologically (elevated serum IgG4 and positive anti-DNA antibody) [16], we recommend both studies in difficult cases. Endoscopic ultrasonogram guided fine needle aspiration biopsy (EUS-FNAB) can be performed in the tertiary hospitals and can be useful in excluding PC. In the case of PC, sensitivity of perampulla access for obtaining cancerous cells is 66% [17] at most; however, the sensitivity

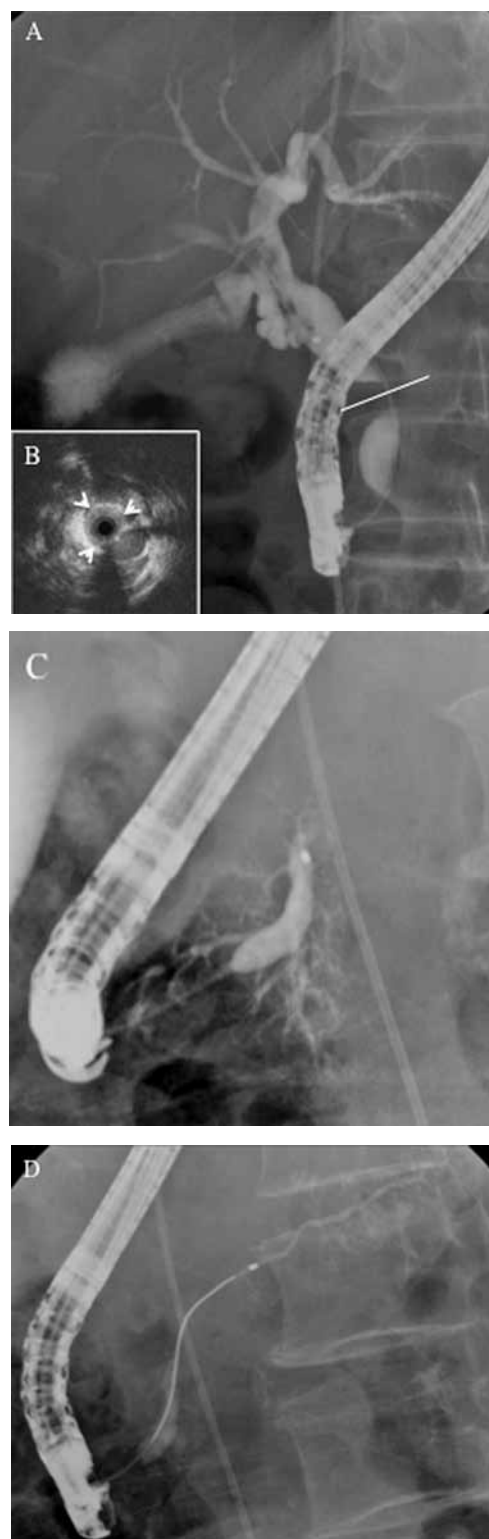


Fig 4. A. Endoscopic retrograde cholangiogram (ERC) showed a stenosis of the lower bile duct with smooth margin. B. Intraductal ultrasonogram (IDUS) at the stenotic site (white line) demonstrated the thickening of the biliary wall (arrow head). C. Pancreatogram revealed the stenosis of the main pancreatic duct at the head, although deep cannulation was possible. D. Upstream pancreatic duct was irregularly narrowed.

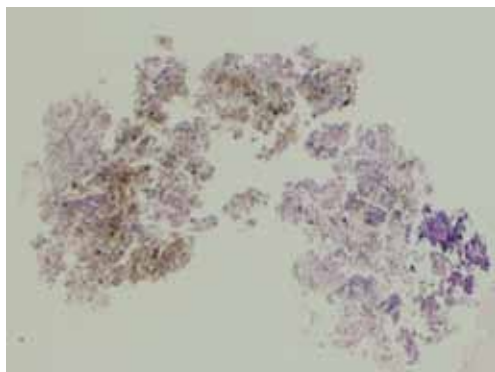


Fig 5. A fragment of the sample obtained by EUS-FNA using 22-gauge needle was remarkable for degenerative and inflamed tissue with hemosiderin precipitation. Neither lymphoplasmacytic aggregation or cancer cells were recognized (H&E, x40).

of EUS-FNAB is significantly higher: 82% [18] ~ 93% [19]. Autoimmune pancreatitis mostly produces larger lesions, so the clinician can usually easily target and obtain tissues by EUS-FNAB using a 22-gauge needle. If a definitive diagnosis still can not be established, a steroid trial is an another option [3, 20].

Chemoradiation is used to treat a variety of human malignancies. For locally advanced pancreatic cancer, low-dose 5-FU coupled with focal irradiation was a standard therapy before the introduction of gemcitabine. Le Scodan et al [21] reported that 50% of the locally advanced pancreatic cancer patients successfully resected after neoadjuvant chemoradiation (5-FU + cisplatin + 50 Gy of irradiation) demonstrated severe (>80%) degenerative cancer cells in the resected materials. However, no report is available on how autoimmune lesions, such as AIP, react to chemoradiation. In this current case, the patient's pancreatic head lesion responded to chemoradiation. The FNAB from this patient revealed some degenerative pancreatic parenchymal tissue with hemosiderin precipitation, which is not seen in the usual specimens of AIP. It is interesting to speculate that these findings were caused by chemoradiation, but we cannot rule out the possibility that they were secondary to the MPD stricture [22]. While the response of this patient's AIP was temporally linked to the chemoradiation therapy, we cannot rule out the possibility that the two were not causally related. It is also possible that this patient simply had a spontaneous remission, because as many as ~40% of AIP are minimized without steroid treatment [23].

We reported a case of AIP which responded to chemoradiation. This case highlights not only the difficulties that can arise in distinguishing between pancreatic cancer and AIP, but it is, we believe, relatively unique in that the patient was treated with chemoradiation. For the differentiation between locally advanced pancreatic cancer and AIP, both serological and histological examinations are essential.

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Conflict of interest

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References

1. Servais A, Pestieau SR, Detry O, et al. Autoimmune pancreatitis mimicking cancer of the head of pancreas: report of two cases. *Acta Gastroenterol Belg* 2001;64:227-230.
2. Gardner TB, Levy MJ, Takahashi N, Smyrk TC, Chari ST. Misdiagnosis of autoimmune pancreatitis: a caution to clinicians. *Am J Gastroenterol* 2009;104:1620-1623.
3. Matsubayashi H, Imai K, Kusumoto K, Ono H. Suspected autoimmune pancreatitis-An indication for steroid treatment? *Dig Liver Dis* 2010;45:525-526.
4. Matsubayashi H, Tomita H, Sugiura T, et al. Autoimmune pancreatitis without a response to steroid therapy: a case which met criteria after withdrawal of steroid. *Intern Med* 2009;48:2087-2091.
5. Okazaki K, Uchida K, Matsushita M, Takaoka M. How to diagnose autoimmune pancreatitis by the revised Japanese clinical criteria. *J Gastroenterol* 2007;42 Suppl 18:32-38.
6. Kobayashi G, Fujita N, Noda Y, et al. Lymphoplasmacytic sclerosing pancreatitis forming a localized mass: a variant form of autoimmune pancreatitis. *J Gastroenterol* 2007;42:650-656.
7. Notohara K, Burgart LJ, Yadav D, Chari S, Smyrk TC. Idiopathic chronic pancreatitis with periductal lymphoplasmacytic infiltration: clinicopathologic features of 35 cases. *Am J Surg Pathol* 2003;27:1119-1127.
8. Zen Y, Harada K, Sasaki M, et al. IgG4-related sclerosing cholangitis with and without hepatic inflammatory pseudotumor, and sclerosing pancreatitis-associated sclerosing cholangitis: do they belong to a spectrum of sclerosing pancreatitis? *Am J Surg Pathol* 2004;28:1193-1203.
9. Matsubayashi H, Furukawa H, Uesaka K, Sasaki K, Ono H, Hruban RH. Autoimmune pancreatitis accompanied with cholecystitis, periaortitis and pseudotumors of the liver. *Case Rep Gastroenterol* 2008;1:155-161.
10. Taira K, Boku N, Fukutomi A, et al. Results of a retrospective analysis of gemcitabine as a second-line treatment after chemoradiotherapy and maintenance chemotherapy using 5-fluorouracil in patients with locally advanced pancreatic cancer. *J Gastroenterol* 2008;43:875-880.
11. Okusaka T, Ito Y, Furuse J, et al. Current status of chemoradiotherapy for locally advanced pancreatic cancer in Japan. *Int J Clin Oncol* 2008;13:127-131.
12. Burris HA 3rd, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997;15:2403-2413.
13. Kinsella TJ. Radiosensitization and cell kinetics: clinical implications for S-phase-specific radiosensitizers. *Semin Oncol* 1992;19:41-47.
14. Japan Pancreatic Society. Diagnostic criteria for autoimmune pancreatitis by the Japan Pancreas Society. *J Jpn Panc Soc* 2002;17:587.
15. Kamisawa T, Imai M, Yui Chen P, et al. Strategy for differentiating autoimmune pancreatitis from pancreatic cancer. *Pancreas* 2008;37:e62-67.
16. Matsubayashi H, Matsunaga K, Uesaka K, et al. A case of pancreatic carcinoma with suspected autoimmune pancreatitis. *Clin J Gastroenterol* 2009;2:59-63.
17. Uchida N, Kamada H, Tsutsui K, et al. Utility of pancreatic duct brushing for diagnosis of pancreatic carcinoma. *J Gastroenterol* 2007;42:657-662.

18. Takahashi K, Yamao K, Okubo K, et al. Differential diagnosis of pancreatic cancer and focal pancreatitis by using EUS-guided FNA. *Gastrointest Endosc* 2005;61:76-79.
19. Wakatsuki T, Irisawa A, Bhutani MS, et al. Comparative study of diagnostic value of cytologic sampling by endoscopic ultrasonography-guided fine-needle aspiration and that by endoscopic retrograde pancreatography for the management of pancreatic mass without biliary stricture. *J Gastroenterol Hepatol* 2005;20:1707-1711.
20. Moon SH, Kim MH, Park DH, et al. Is a 2-week steroid trial after initial negative investigation for malignancy useful in differentiating autoimmune pancreatitis from pancreatic cancer? A prospective outcome study. *Gut* 2008;57: 1704-1712.
21. Le Scodan R, Mornex F, Girard N et al. Preoperative chemoradiation in potentially resectable pancreatic adenocarcinoma: feasibility, treatment effect evaluation and prognostic factors, analysis of the SFRO-FFCD 9704 trial and literature review. *Ann Oncol* 2009; 20: 1387-1396.
22. Ohara H, Nakazawa T, Sano H, et al. Systemic extrapancreatic lesions associated with autoimmune pancreatitis. *Pancreas* 2005;31:232-237.
23. Kubota K, Iida H, Fujisawa T, et al. Clinical factors predictive of spontaneous remission or relapse in cases of autoimmune pancreatitis. *Gastrointest Endosc* 2007;66:1142-1151.