Patients and methods

Study population

There were 189 patients initially enrolled in the register of the Japanese NHO Liver-Network Study and, of these, 174 were prospectively followed between 1995 and 2008 as a multicenter cohort study. All patients satisfied the 1999 revised criteria of the International Autoimmune Hepatitis Group (AIHG) for a diagnosis of definite (91 cases) or probable (83 cases) AIH [6]. Each patient had received conventional treatment, usually corticosteroid drugs, and some (66/174, 37.9%) had received ursodeoxycholic acid (UDCA). The study protocol was approved by the Ethics Committees of all involved institutes.

Clinical and histological assessments

Standard laboratory tests of liver inflammation and function were assessed at each examination and these follow-up data were collected at 1-year intervals.

Liver tissue from percutaneous biopsy specimens was available for the majority of the patients at the study entry (131/174, 75.3%) and at subsequent follow-up examination for some (38/174, 21.8%). The histological variables examined included degree of fibrosis (0, absent; 1, expansion of fibrosis to parenchyma; 2, portal-central or portal-portal bridging fibrosis; 3, presence of numerous fibrous septa; 4, multinodular cirrhosis). The histological diagnosis of cirrhosis required loss of normal lobular architecture, reconstruction of hepatic nodules, and the presence of regenerative nodules [7]. Anti-nuclear antibodies (ANA) and smooth muscle antibodies (SMA) were measured by indirect immunofluorescence, and cut-off titers were 1:40. In patients with risk factors for nonalcoholic fatty liver disease (NAFLD), a definite diagnosis of AIH was confirmed by the liver histological findings [8]. Differential diagnosis of primary biliary cirrhosis (PBC) was performed according to the diagnostic criteria as described previously [9].

Variables at study entry

Demographic and other characteristics of the 174 patients were recorded at the baseline assessment and included gender; age at diagnosis; duration of symptoms or other evidence of liver diseases; markers of infection with hepatitis viruses (HBV, HCV); alcohol intake; coexistence of other autoimmune diseases; serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, and bilirubin; platelet counts; and prothrombin time. Clinical relapse was defined as an increase of serum ALT levels to more than threefold the upper limit of the normal range (ULN) [10]. Data were collected and stored in a database.

Statistical analysis

For quantitative data, analysis was performed using the Mann–Whitney rank test for comparison of two independent groups. Differences in proportions were analyzed by Fisher's exact test when the number of subjects was <5, and the χ^2 test for 2 × 2 tables was used when the number of subjects was >5. Univariate and multivariate analyses were performed using the Cox proportional hazard model with SPSS software (Chicago, IL, USA). The p values for entering variables for the multivariate Cox proportional hazard model were <0.1.

Results

Baseline data at entry

Of the original 189 patients registered as having AIH, 15 were excluded from the analysis for the following reasons: an alternative diagnosis was made; medical records were incomplete; or they were lost to follow-up (Fig. 1). The remaining 174 patients were eligible for the study. Table 1 shows other demographic data for the cohort at entry. Data on autoantibodies were incomplete, in that data for SMA were lacking in 95 patients and data for ANA were lacking in 1 patient. Of the remaining patients, 144 of 173 (83.2%) had a positive test for ANA (>1:80) and 31 of 79 patients (39.2%) had a positive test for SMA (>1:80).

Development of cirrhosis

Among the 174 eligible patients, 21 (12.1%) had cirrhosis at the time of presentation, and among the remaining 153 patients without cirrhosis, 14 developed cirrhosis during follow-up (Fig. 1). For these 14 patients the time of progression to cirrhosis (mean ± standard deviation, SD) was 9.1 ± 4.4 years. Table 2 compares the clinical parameters of patients who did, or did not, develop cirrhosis during the follow-up period. Patients who developed cirrhosis were older at the onset of symptoms and had significantly lower levels of aminotransferases. The initial mean dose (± SD) of corticosteroid (prednisolone) was significantly lower in patients who developed cirrhosis compared with the dose in those who did not (13.9 ± 15.8 vs. 31.8 ± 8.5 mg/day). On time-dependent univariate analysis (Cox proportional hazard model), the development of cirrhosis was predictive by older age at onset (≥60 years, $p = 0.014$), being without steroid treatment ($p = 0.047$), and having lower serum ALT levels ($p = 0.007$) at presentation (Table 3).

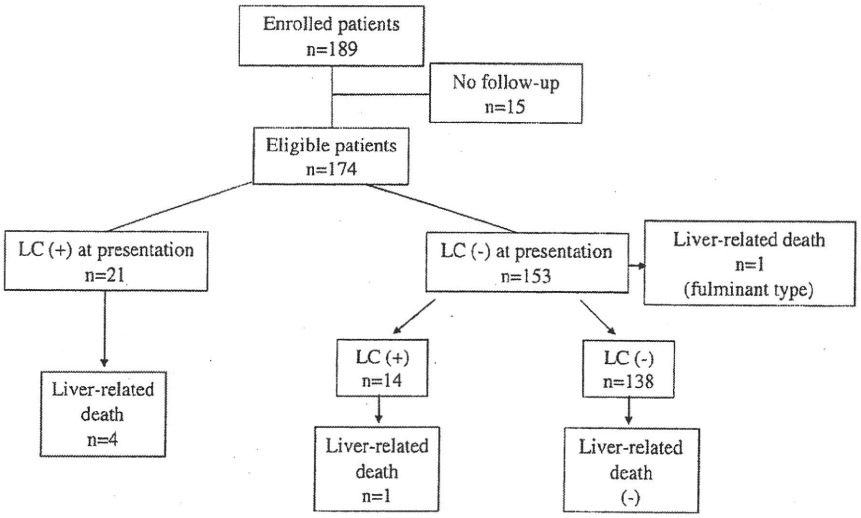

Fig. 1 Flow diagram of patient selection and clinical outcome of autoimmune hepatitis (AIH) patients in the present cohort study. *LC* Liver cirrhosis

Table 1 Baseline characteristics of autoimmune hepatitis (AIH) patients

	$n = 174$
Mean age (years)	
Age ≥60	89
Age <60	85
Gender (male/female)	16/158
Mean age at presentation (years)	56.7 ± 13.9 (16–84)
Other autoimmune diseases	45 (25.9%)
Mean follow-up (years)	8.0 ± 4.5 (0.1–21)
Baseline laboratory values	
AST (<40 IU/l)	396.83 ± 460.80 (29–2718)
ALT (<40 IU/l)	413.25 ± 427.05 (18–2020)
ALP (<112 IU/l)	443.16 ± 263.47 (112–2135)
Bilirubin (mg/ml)	4.08 ± 5.80 (0.27–31.8)
Albumin (3.5–5.0 g/l)	3.77 ± 0.61 (2.00–5.10)
IgG (500–1300 mg/dl)	2511.57 ± 904.80 (210.2–5199)
Platelets (15–40 × 10^4/μl)	18.70 ± 7.4 × 10^4 (2–42 × 10^4)
ANA+ (≥1:40)	144/173 (83.2%)
SMA+ (≥1:40)	31/79 (39.2%)
Cirrhosis at presentation	21 (12.1%)
Received treatment	
PSL alone	88 (50.6%)
PSL + UDCA	35 (20.1%)
PSL + Aza	2 (1.1%)
UDCA alone	31 (17.8%)
Relapse	47 (27.0%)

AST aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *ANA* anti-nuclear antibodies, *SMA* anti-smooth muscle antibodies, *PSL* prednisolone, *UDCA* ursodeoxycholic acid, *Aza* azathioprine

By multivariate Cox analysis, an older age at onset (≥60 years, hazard ratio 3.9, 95% confidence interval [CI] 1.1–14.3, $p = 0.039$) was associated independently with the risk of cirrhosis development (Table 4). Thus, the AIH patients with an older age at onset had a greater risk of developing cirrhosis. We also analyzed the association of serum ALT levels after 1 year of treatment and the progression of liver cirrhosis. However, we could not find any association between ALT levels after 1 year and the progression to liver cirrhosis (Table 5).

Finally, we assessed the clinical and histological features in all of the registered AIH patients, paying particular attention to the group of patients with AIH presenting at ≥60 years (Table 6). These 89 (51.0%) patients who developed AIH at age 60 years or more had a mean age of 67.6 years (range 60–84 years), whereas at the time of diagnosis the 85 younger patients had a mean age of 45.3 years (range 16–59 years). For the two groups, there were no significant differences in values for liver function tests, or frequencies of concomitant autoimmune diseases (24.7 vs. 27.1%). In patients who underwent liver biopsy, histological fibrosis scores (stage) were not significantly different between the older-onset and younger-onset AIH patients. Furthermore, in the whole cohort, there was no difference in the frequency of cirrhosis at presentation between older-onset and younger-onset patients.

Discussion

AIH is a chronic progressive liver disease caused by an autoimmune destruction of hepatic parenchymal cells. Essential clinical diagnostic criteria include histological interface hepatitis, hypergammaglobulinemia, and characteristic serum autoantibodies [1]. The precise pathogenic processes in AIH are uncertain. They likely depend on a genetic predisposition of the host leading to reactivity to particular self-antigens, which causes hepatic inflammation by presumed immune-cell-mediated cytotoxicity

Table 2 Baseline characteristics of AIH patients who developed cirrhosis

	Cirrhosis (+) $n = 14$	Cirrhosis (−) $n = 138$	p
Mean age (years)			
Age ≥60	11	65	0.025
Age <60	3	73	
Gender (male/female)	1/13	12/126	0.659
Mean age at presentation (years)	63.4 ± 8.9	56.0 ± 14.2 (16–84)	0.068
Other autoimmune diseases	3 (21.4%)	36 (26.1%)	0.494
Mean follow-up (years)	9.1 ± 4.4 (2–15)	7.6 ± 4.4 (0.8–21)	0.225
Baseline laboratory values			
AST (<40 IU/l)	144.00 ± 109.58 (48–459)	425.36 ± 480.24 (29–2718)	0.016
ALT (<40 IU/l)	158.50 ± 182.18 (30–613)	440.81 ± 423.49 (18–2020)	0.002
ALP (<112 IU/l)	554.50 ± 509.16 (181–2135)	441.59 ± 232.80 (112–1555)	0.927
Bilirubin (mg/ml)	2.76 ± 3.89 (0.6–15.8)	4.09 ± 5.88 (0.27–31.8)	0.964
Albumin (3.5–5.0 g/l)	3.49 ± 0.77 (2–4.6)	3.87 ± 0.54 (2.3–5.1)	0.113
IgG (500–1300 mg/dl)	2478.64 ± 696.67 (1490–3489)	2421.85 ± 874.18 (210.2–4891)	0.677
Platelets (15–40 × 10^4/μl)	14.7 ± 5.5 (2–23 × 10^4)	19.9 ± 6.9 (2–42 × 10^4)	0.013
ANA+ (≥1:40)	11/14 (78.6%)	117/138 (84.8%)	
SMA+ (≥1:40)	0/5	31/68 (45.6%)	
Received treatment			
Mean PSL mg/day (range)	13.92 ± 15.83 (0–40)	31.77 ± 85.53 (0–1000)	0.048
PSL ≥20 mg	6 (42.9%)	90 (65.7%)	
PSL alone	4 (28.6%)	74 (53.6%)	
PSL + UDCA	3 (21.4%)	25 (18.1%)	
PSL + Aza	0	2 (1.4%)	
UDCA alone	5 (35.7%)	23 (16.7%)	
Relapse	2 (16.7%)	37 (26.8%)	0.269
Liver biopsy specimen available at presentation	($n = 8$)	($n = 96$)	
Stage of fibrosis			
F0	2 (25.0%)	8 (8.3%)	
F1	2 (25.0%)	31 (32.3%)	
F2	2 (25.0%)	30 (31.3%)	
F3	2 (25.0%)	27 (28.1%)	
F4	0	0	

AST aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *ANA* anti-nuclear antibodies, *SMA* anti-smooth muscle antibodies, *PSL* prednisolone, *UDCA* ursodeoxycholic acid, *Aza* azathioprine

mechanisms [11]. Cytokines and adipokines play an important role in the progression of AIH [12, 13]. In the present study we assessed, in particular, determinants of the progression to liver cirrhosis in the Japanese NHO multi-center AIH cohort study. Our data demonstrated that onset in later life (≥60 years) was one independent risk factor for the development of liver cirrhosis.

It was reported earlier that older-onset AIH patients (≥60 years) had a higher frequency of cirrhosis at the time of presentation than younger-onset AIH patients (≤30 years), 33 vs. 10% [14]. However, in our study, the older-onset AIH patients (≥60 years) did not exhibit a greater degree of hepatic fibrosis at presentation compared with younger-onset AIH patients according to liver biopsy findings. However, our data do suggest that hepatic fibrosis progresses more extensively in older-onset AIH patients. Hepatic fibrosis is a dynamic and highly regulated process that has been shown to progress and regress [15]. Intrahepatic inflammation with the release of cytokines and participation of chemokines stimulates the transition of perivascular hepatic stellate cells into fibrogenic myofibroblasts, and these activated cells proliferate and synthesize fibrillar collagens and other matrix proteins [16]. Our findings suggest that aging in itself may potentiate these processes of fibrogenesis.

Table 3 Variables associated with increased risk factors for developing liver cirrhosis (univariate Cox proportional hazard model)

Characteristics	Subgroup	LC		HR (95% CI)	*p* value
		Yes ($n = 14$)	No ($n = 138$)		
Gender	Male	1 (7.1%)	12 (8.7%)	1.682 (0.209–13.556)	0.625
Age (years)	<50	2 (14.3%)	37 (26.8%)	0.476 (0.105–2.154)	0.335
	50–59	1 (7.1%)	36 (26.1%)	0.159 (0.021–1.233)	0.078
	≥60	11 (78.6%)	65 (47.1%)	4.965 (1.380–17.862)	0.014
Other autoimmune disease	(+)	3 (21.4%)	36 (26.1%)	0.672 (0.186–2.420)	0.543
ALT	<100	8 (57.1%)	30 (21.7%)	4.490 (1.508–13.369)	0.007
	100–500	4 (28.6%)	62 (44.9%)	0.496 (0.155–1.585)	0.237
	≥500	2 (14.3%)	46 (33.3%)	0.361 (0.080–1.623)	0.184
PSL	(−)	7 (50.0%)	37 (26.8%)	3.004 (1.016–8.879)	0.047
	1–19 mg/day	1 (7.1%)	11 (8.0%)	0.578 (0.075–4.460)	0.599
	20–39 mg/day	4 (28.6%)	47 (34.1%)	0.832 (0.260–2.665)	0.757
	≥40 mg/day	2 (14.3%)	43 (31.2%)	0.385 (0.085–1.737)	0.214
Relapse	(+)	2 (14.3%)	36 (26.1%)	0.437 (0.098–1.956)	0.279

ALT alanine aminotransferase, *LC* liver cirrhosis, *HR* hazard ratio, CI confidence interval, *PSL* prednisolone

Table 4 Multivariate analysis of predictive factors for cirrhosis in AIH patients (Cox proportional hazards model)

Variables	*p*	HR (95% CI)
Age ≥60 years	0.039	3.917 (1.074–14.290)
ALT <100	0.054	2.987 (0.979–9.108)
PSL (−)	0.174	2.160 (0.711–6.559)

ALT alanine aminotransferase, *PSL* prednisolone, *HR* hazard ratio

Previous studies have demonstrated that the suppression of inflammatory activity promotes the degradation of a fibrotic liver matrix. Miyake et al. [17] reported that an inability to maintain normal transaminase levels was an independent prognostic factor for the development of cirrhosis. In the present study, we did not find any association between the frequency of clinical relapses and progression to cirrhosis. Further large-scale studies will be needed to elucidate the links between the degree of remission and fibrogenesis in AIH.

Dufour et al. [4] reported in 1997 that, in a small number of AIH patients, fibrosis and even cirrhosis were reversible with appropriate treatments. These findings suggest that liver cirrhosis in AIH is reversible, likely due to reduced hepatic inflammatory activity in response to immunosuppressive treatments. Another interesting aspect of our study is that the initial steroid doses were lower in AIH patients who progressed to cirrhosis compared with the initial doses in those who did not. The immunological mechanism of liver injury in AIH is still not fully understood, but both cellular and humoral immune reactions appear to be involved in the liver inflammation [18]. Successful immunosuppressive treatments will arrest AIH progression to cirrhosis. Older patients have been shown to enter remission to a degree similar to that in younger patients, and treatment failure is less often during maintenance periods in the older patients. Therefore, the conventional combination regimen, prednisolone and azathioprine, can be recommended in older AIH patients with active hepatic inflammation in the presence or absence of advanced liver fibrosis.

Based on the results of the present study, we propose that one of the host-dependent factors, olderage at onset, determines the frequency of the progression of AIH to

Table 5 ALT levels 1year after the first treatment and progression to liver cirrhosis (univariate Cox proportional hazard model)

ALT levels (at 1 year)	LC		HR (95% CI)	*p* value
	Yes ($n = 10$)	No ($n = 120$)		
<×1 ULN	6 (60.0%)	78 (65.0%)	1.065 (0.296–3.831)	0.923
×1–×2 ULN	2 (20.0%)	28 (23.3%)	0.616 (0.130–2.915)	0.541
×2–×3 ULN	0	5 (4.2%)		
≥×3 ULN	2 (20.0%)	9 (7.5%)	2.195 (0.446–10.808)	0.334

ALT alanine aminotransferase, *LC* liver cirrhosis, *HR* hazard ratio, *ULN* upper limit of normal range

Table 6 Baseline characteristics of elderly-onset AIH patients

	Age ≥60 years $n = 89$	Age <60 years $n = 85$	p
Mean age at presentation (years)	67.63 ± 5.42 (60–84)	45.32 ± 10.67 (16–59)	
Gender (male/female)	9/80	7/78	0.668
Other autoimmune diseases	22 (24.7%)	23 (27.1%)	0.725
Mean follow-up (years)	7.1 ± 4.4 (0.1–21)	8.9 ± 4.5 (1–17)	0.010
Baseline laboratory values			
AST (<40 IU/l)	366.20 ± 431.64 (31–2718)	428.89 ± 492.57 (29–2350)	0.573
ALT (<40 IU/l)	355.29 ± 395.57 (18–1832)	473.93 ± 454.50 (22–2020)	0.046
ALP (<112 IU/l)	476.14 ± 310.91 (126–2135)	407.77 ± 198.53 (112–986)	0.205
Bilirubin (mg/ml)	3.52 ± 5.30 (0.3–28.4)	4.68 ± 6.30 (0.27–31.80)	0.580
Albumin (3.5–5.0 g/l)	3.61 ± 0.63 (2.0–4.9)	3.94 ± 0.55 (2.0–5.1)	0.000
IgG (500–1300 mg/dl)	2570.29 ± 865.76 (1051–4956)	2447.05 ± 952.43 (210–5199)	0.360
Platelets (15–40 × 10^4/μl)	16.5 ± 6.0 × 10^4 (2–29 × 10^4)	20.9 ± 8.1 × 10^4 (2–42 × 10^4)	0.000
ANA+ (≥1:40)	74/88	70/85	0.760
SMA+ (≥1:40)	11/37	20/42	0.104
Cirrhosis at presentation	12 (13.5%)	9 (10.6%)	0.558
Received treatment			
Mean PSL dose (mg/day)	33.57 ± 105.12 (0–1000)	25.54 ± 20.34 (0–60)	0.499
PSL alone	42 (47.2%)	46 (54.1%)	
PSL + UDCA	21 (23.6%)	14 (16.5%)	
PSL + Aza	1 (1.1%)	1 (1.2%)	
UDCA alone	17 (19.1%)	14 (16.5%)	
Relapse	25 (28.1%)	22 (25.9%)	
Histology			
Stage			
F0–F2	38/55	36/55	0.684
F3–F4	17/55	19/55	

AST aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *ANA* anti-nuclear antibodies, *SMA* anti-smooth muscle antibodies, *PSL* prednisolone, *UDCA* ursodeoxycholic acid, *Aza* azathioprine

cirrhosis. It has been shown that aging is associated with dysregulated cytokine function and decreased capacity for accurate DNA repair, both of which factors may promote the development of liver fibrosis [19, 20]. However, in autoimmune inflammation, the precise relationships between aging and the progression of liver fibrosis are yet to be determined, and further studies are needed.

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Appendix

The NHO-AIH Study Group consists of Kiyoshi Migita, Yuka Jiuchi, Seigo Abiru, Koji Yano, Atsumasa Komori, Hiroshi Yatsuhashi, Minoru Nakamura, Hiromi Ishibashi (NHO Nagasaki Medical Center), Yukio Watanabe, Yoko Nakamura (NHO Sagamihara National Hospital), Akira Saito (NHO Nishisaitama-chuo Hospital), Michiyasu Yagura (NHO Tokyo National Hospital), Hideo Morimoto (NHO Kanazawa Medical Center), Masaaki Shimada (NHO Nagoya Medical Center), Eiji Mita (NHO Osaka National Hospital), Taizo Hijioka (NHO Osaka Minami Medical Center), Haruhiro Yamashita (NHO Okayama Medical Center), Eiichi Takezaki (NHO Higashi Hiroshima Medical Center), Toyokichi Muro (NHO Oita Medical Center), Hironori Sakai (NHO Beppu Medical Center), and Makoto Nakamuta (NHO Kyusyu Medical Center).

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CASE REPORT

Poorly differentiated endocrine carcinoma of the pancreas responded to gemcitabine: Case report

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Abstract

Poorly differentiated endocrine carcinoma (PDEC) of the pancreas is a rare and aggressive tumor. First-line treatment is commonly a combination of etoposide and cisplatin, but there is no consensus regarding further treatment recommendations. In this report, we describe a case of pancreatic PDEC treated with gemcitabine as third-line chemotherapy. A 62-year-old man with pancreatic PDEC was administered etoposide plus cisplatin as first-line treatment; he then received irinotecan for tumor relapse. However, because irinotecan induced ileus in this patient, we chose gemcitabine as third-line chemotherapy. After two cycles of gemcitabine (1000 mg/m^2 on days 1, 8 and 15 every 4 wk), a partial tumor response was noted by computed tomography (approximately 68% reduction in tumor size). Our patient survived for 15 mo after diagnosis. This is a rare case of unresectable pancreatic PDEC, which showed a partial response to gemcitabine after the failure of two other regimens. Gemcitabine could be an effective treatment option for pancreatic PDEC that is resistant to other treatments.

Key words: Poorly differentiated endocrine carcinoma; Pancreatic endocrine tumor; Gemcitabine; Chemotherapy

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INTRODUCTION

Pancreatic endocrine tumors (PETs) are rare neoplasms with an annual incidence of less than 1 per 100 000 people[1-6]. These tumors account for less than 1%-2% of all pancreatic neoplasms[1,7]. Poorly differentiated endocrine

carcinoma (PDEC) of the pancreas is characterized by aggressive tumor biology and poor prognosis. The biological behavior of PDEC is similar to that of small-cell lung cancer (SCLC), and metastatic pancreatic PDECs are often treated with the chemotherapy regimens that are used to treat SCLC. The combination of etoposide and cisplatin has been widely used to treat pancreatic PDEC because no promising chemotherapy regimens have been reported for this disease. Effective second- or later-line chemotherapy is still uncertain. Gemcitabine is an active agent against untreated and recurrent SCLC. In this report, we describe a case of pancreatic PDEC treated with gemcitabine as third-line chemotherapy.

CASE REPORT

A 62-year-old man with Crohn's disease had previously received treatment at a different hospital. In July 2007, his serum carcinoembryonic antigen (CEA) level was found to be elevated. A contrast-enhanced computed tomography (CT) scan of the patient's abdomen showed a tumor in the head of the pancreas and enlarged para-aortic lymph nodes. In September 2007, he underwent exploratory laparotomy, during which peritoneal dissemination was observed, and hence, a biopsy of the para-aortic lymph nodes was conducted. Based on the histological findings, small cell carcinoma of the pancreas was diagnosed.

Because the tumor was unresectable at the time of diagnosis, the patient was treated with a combination of etoposide and cisplatin as first-line chemotherapy in October 2007. The chemotherapeutic response was deemed to be partial, until multiple bone metastases to the skull, vertebrae, and pelvis were detected using CT after five cycles of chemotherapy. The patient was next administered irinotecan monotherapy as second-line chemotherapy, which started in March 2008. Irinotecan was stopped after one cycle because ileus occurred. He was referred to our hospital for further treatment in July 2008.

The patient had no family history of cancer, and the results of a physical examination were unremarkable. The laboratory findings were hemoglobin 11.5 g/dL (normal 14.0-17.0 g/dL), γ-glutamyl transpeptidase 113 IU/L (normal, 10-47 IU/L), glucose 136 mg/dL (normal, 69-104 mg/dL), CEA 12.8 ng/mL (normal, < 4.0 ng/mL), carbohydrate antigen 19-9 14 U/mL (normal, < 37 U/mL), neuron-specific enolase (NSE) 36.2 ng/mL (normal, < 10.0 ng/mL), and pro-gastrin-releasing peptide (pro-GRP) 338 pg/mL (normal, < 46 pg/mL). A contrast-enhanced CT scan of his abdomen revealed a low-density mass, 7.5 cm in diameter, in the head of the pancreas, as well as enlarged para-aortic lymph nodes at the time of admission. The pancreatic tumor did not show contrast enhancement (Figure 1A). A CT scan of his chest did not show any primary or metastatic pulmonary tumors. We reviewed an excised biopsy specimen of a para-aortic lymph node obtained at the previous hospital. Histological examination of the specimen showed small to intermediate-sized cells with a high nuclear-cytoplasmic ratio and frequent mitosis, and partial necrosis. Immunohistochemical staining revealed that these cells were strongly positive for NSE, CD56, and keratin; weakly positive for chromogranin A; and negative for vimentin, leukocyte common antigen, S-100, and CD99 (Figure 2). On the basis of the pathological findings, the para-aortic lymphadenopathy was determined to be caused by metastasis of PDEC. Therefore, pancreatic PDEC with para-aortic lymph nodes and bone metastases was diagnosed.

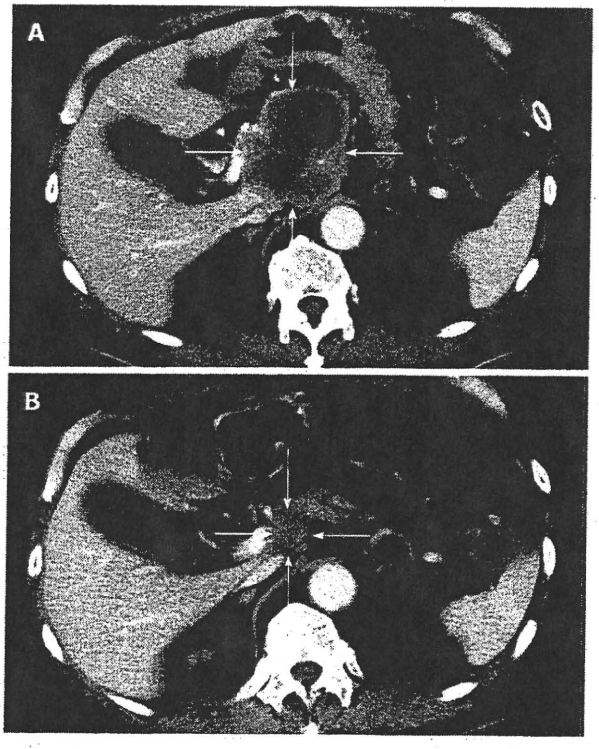

Figure 1 Contrast-enhanced computed tomography scan of the abdomen. A: There was a low-density mass, 7.5 cm in diameter, in the head of the pancreas at the time of admission. The pancreatic tumor (arrows) did not show contrast enhancement; B: A follow-up computed tomography scan showed that the pancreatic mass had reduced to 2.0 cm in diameter. The tumor (arrows) had markedly regressed 4 mo after starting chemotherapy with gemcitabine.

We chose gemcitabine as third-line chemotherapy. Starting in July 2008, the patient received 1000 mg/m^2 gemcitabine on days 1, 8 and 15 every 4 wk.

After two cycles of gemcitabine, a CT scan of his abdomen showed regression of the pancreatic tumor (from 7.5 cm to 2.4 cm in diameter), and his serum NSE and pro-GRP levels had decreased to within the normal range. The chemotherapeutic response was deemed to be a partial response. After four cycles of gemcitabine, an abdominal CT scan showed a pancreatic mass that was 2.0 cm in diameter (Figure 1B). In November 2008, after day 15 of the fifth cycle, the patient requested that the therapy be stopped because of general fatigue. He died of multiple organ failure in December 2008.

DISCUSSION

Pancreatic PDEC is a rare neoplasm. Recently, Bettini *et al*[8]

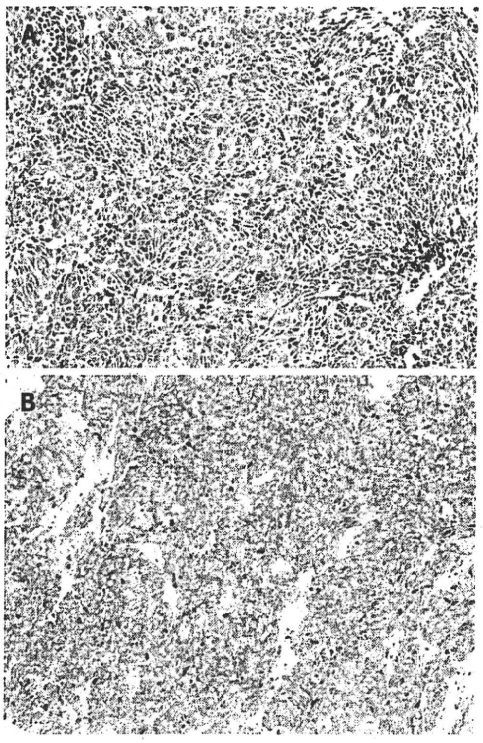

Figure 2 Histopathological findings. A: The excised para-aortic lymph node showed small to intermediate-sized cells with a high nuclear-cytoplasmic ratio. (HE stain, original magnification, × 200); B: Immunostaining for neuron-specific enolase was positive in the cytoplasm of many tumor cells (original magnification, × 200).

have reported that PDEC was diagnosed in 17 (9.4%) of 180 patients with non-functioning pancreatic endocrine tumors. PDEC is characterized by aggressive tumor biology and poor prognosis. Bettini *et al*[8] also have reported that all patients with PDEC died within 3.5 years after diagnosis (median, 11.8 mo), and that only 23.5% of the tumors were resectable at the time of diagnosis. Our patient survived for 15 mo after diagnosis. His survival time was longer than the median survival time that was reported by Bettini *et al*[8].

The standard treatment for advanced pancreatic PDEC has not yet been established. The initial approach to treatment of pancreatic PDEC is to attempt curative resection. However, liver and lymph node metastases are present in 32.5% and 59.5% of patients at the time of diagnosis[9]. Therefore, curative surgical resection cannot be achieved in most patients, and effective medical treatment to control metastatic lesions is urgently required. Systemic chemotherapy is proposed for patients with inoperable pancreatic PDEC, and adequate organ function and performance status; however, a standard chemotherapeutic regimen has not been established. In our patient, the tumor was inoperable owing to the presence of peritoneal dissemination and para-aortic lymph node metastases, and hence, systemic chemotherapy was administered to the patient.

The biological behavior of PDEC is similar to that of SCLC, and metastatic pancreatic PDECs are often treated with the same chemotherapy regimens that are used to treat SCLCs. Combination chemotherapy with etoposide and cisplatin, one of the standard regimens for SCLC, is commonly used to treat pancreatic PDEC.

Moertel *et al*[10] have reported that etoposide plus cisplatin produced good therapeutic results in patients with anaplastic neuroendocrine carcinoma (which has been defined as PDEC according to the recent WHO classification[11]), with an overall regression rate of 67% and a median regression duration of 8 mo [10]. Other investigators have reported similar results, with a median duration of response of 7-9 mo in patients with poorly differentiated endocrine tumors[12,13].

Since the report of Moertel *et al*[10], the combination of etoposide and cisplatin has been considered to be the reference treatment for PDEC; however, confirmatory studies have not been performed because of the rarity of PDEC. If this first-line chemotherapy fails to treat pancreatic PDEC, there is no consensus regarding further treatment recommendations. Irinotecan plus cisplatin is one of the standard regimens for extensive-stage SCLC[14]. In our case, the patient had been administered irinotecan monotherapy as second-line treatment before he was referred to our hospital. However, this therapy had been discontinued because ileus occurred after one cycle.

Several newer anticancer drugs, including paclitaxel[15], topotecan[16] and gemcitabine[17], have shown little activity as single agents against neuroendocrine tumors (NETs). Gemcitabine is a nucleoside analog with structural similarities to cytarabine and is widely used in the treatment of advanced pancreatic adenocarcinoma[18]. In a phase II trial of gemcitabine for the treatment of metastatic NETs, Kulke *et al*[17] have reported that, although the treatment was well tolerated, no radiological responses were observed, 65% of the patients (n = 18) experienced disease stabilization, and that the median overall survival was less than 1 year. However, their study included various histological subtypes of NETs, and only two of the 18 patients had poorly differentiated NETs. Thus, the efficacy of gemcitabine for poorly differentiated NET of the pancreas remains unclear.

Gemcitabine is an active agent against untreated and recurrent SCLC[19-21]. The response rate to gemcitabine was reported to be 27% in patients with previously untreated SCLC[19]. In patients with previously refractory or recurrent SCLC treated with at least one chemotherapeutic regimen, gemcitabine resulted in response rates of 6%-17%[20,21].

We believe that gemcitabine is a reasonable treatment option for pancreatic PDEC, and we chose gemcitabine as third-line chemotherapy. After two cycles of gemcitabine, the pancreatic tumor showed marked regression, which resulted in a partial response. Gemcitabine has shown good efficacy as third-line chemotherapy for refractory pancreatic PDEC. The prognosis of pancreatic PDEC is extremely poor because of its highly aggressive behavior, and hence, effective second- and later-line treatments are important for improving prognosis. In light of this, gem-

citabine could be an effective treatment option for pancreatic PDEC that is resistant to other treatment.

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