Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.5499-20
Intern Med 60: 251-257, 2021
http://internmed.jp

【 CASE REPORT 】

Secondary Minimal Change Disease Due to Pancreatic Cancer Improved by Chemotherapy

Sakue Masuda[1], Kazuya Koizumi[1], Hidekazu Moriya[2], Takashi Nishino[1], Haruki Uojima[3], Tomohiko Tazawa[1], Karen Kimura[1], Junichi Tasaki[1], Chikamasa Ichita[1], Akiko Sasaki[1], Makoto Kako[1], Sumi Hidaka[2] and Madoka Kudo[4]

Abstract:
We herein describe an 82-year-old patient who presented with proteinuria and systemic edema. He was diagnosed with minimal change disease (MCD) and was found to have stage III pancreatic cancer. He could not undergo surgical resection due to invasion to the celiac artery and he was thus treated with chemotherapy. After a month of chemotherapy, his proteinuria improved to a normal level. After two months of chemotherapy, computed tomography indicated a partial response to the therapy. MCD can occur as paraneoplastic syndrome in patients with malignant disease, and chemotherapy can be effective for MCD associated with paraneoplastic syndrome.

Key words: minimal change disease, proteinuria, pancreatic cancer, nab-Paclitaxel, chemoradiotherapy

(Intern Med 60: 251-257, 2021)
(DOI: 10.2169/internalmedicine.5499-20)

Introduction

In adults, minimal change disease (MCD) represents approximately 10-15% of patients with idiopathic nephrotic syndrome (1, 2). Secondary MCD is associated with neoplasia, drug use (e.g., non-steroidal anti-inflammatory drugs), infections, and atopy superimposed on another renal diseases. However, MCD is an uncommon occurrence associated with malignant tumors (3). Lymphoma are among the most frequently reported neoplastic processes associated with MCD (3), and a few solid tumors with MCD have been reported, especially with thymoma, renal cell carcinoma, colorectal carcinoma, and lung carcinoma (4). However, only two cases of pancreatic cancer (PC) associated with MCD have been previously reported (5, 6).

The complications of nephrotic syndrome include increased susceptibility to infections due to urinary loss of immunoglobulins, an increased frequency of thromboembolic events due to urinary loss of antithrombotic factors, and increased frequency of acute kidney injury (7-11). The prognosis for secondary MCD is generally favorable because the remission rate for prednisolone in MCD is high and the relapse rate is low (10, 12). However, when MCD is secondary to paraneoplastic syndrome, the relapse rate for prednisolone in MCD is high (13). The relationship between the treatment of the malignant lesion and the prognosis of MCD has been reported; for example, Hodgkin's disease associated with MCD that is refractory to chemotherapy has very adverse prognoses (3), and mesotheliomas with MCD are associated with a poor prognoses (14). Therefore, aggressive therapy for cancer is preferable in patients with cancer-associated MCD. However, there have beenfew reports about the treatment for MCD associated with PC. We herein report a rare case of MCD associated with PC that was effectively treated with chemotherapy for both PC and MCD.

Case Report

An 82-year-old man presented with a 2-month history of

[1]Department of Gastroenterology Medicine Center, Shonan Kamakura General Hospital, Japan, [2]Department of Nephrology, Shonan Kamakura General Hospital, Japan, [3]Department of Gastroenterology, Internal Medicine, Kitasato University School of Medicine, Japan and [4]Department of Pathology, Shonan Kamakura General Hospital, Japan
Received: June 5, 2020; Accepted: July 29, 2020; Advance Publication by J-STAGE: September 19, 2020
Correspondence to Dr. Sakue Masuda, sakue.masuda@tokushukai.jp

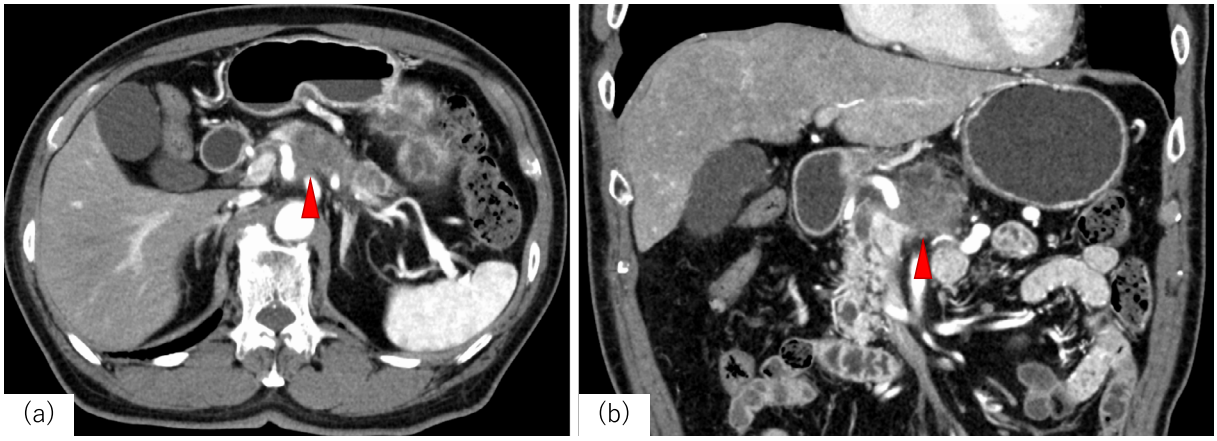

Figure 1. CT findings on admission. (a, b) Computed tomography on admission revealed a pancreatic tumor (red arrow) which invaded the celiac and common hepatic arteries.

upper abdominal pain and a 2-week history of bilateral lower limb edema. He had a history of hyperuricemia, and he had received allopurinol treatment. He had no history of smoking. Computed tomography (CT) revealed a pancreatic tumor measuring 3 cm in diameter which had invaded the celiac artery (Fig. 1a, b). Among the serum tumor markers, carbohydrate antigen 19-9, Duke pancreatic monoclonal antigen type 2 (DUPAN-2), and s-pancreas antigen-1 (SPan-1) were elevated to 772 U/mL (normal range: <37 U/mL), 1,600 or more U/mL (normal range: <150 U/mL) and 824 U/mL (normal range: <30 U/mL), respectively; carcinoembryonic antigen was within the normal limits. Tests for hepatitis B virus surface antigens and for antibodies to hepatitis C virus were negative. The following laboratory tests were normal level: Immunoglobulins IgG, IgA, and IgM; complement proteins C3 and C4; antinuclear antibody; rheumatoid factor; and antineutrophil cytoplasmic antibodies. Serum protein electrophoresis was normal. Serum creatinine was 1.05 mg/dL. A urine protein-to-creatinine ratio was high: 6.94 g/gCr (per gram of creatinine) and a 24-hour urine specimen contained 7.46 g of protein. The urine protein selectivity index was low (0.08). He was found to have a reduced serum albumin level of 2.9 g/dL and total protein level of 5.7 g/dL. The total cholesterol level was normal. Renal ultrasonography showed no abnormal findings. (Table 1)

We performed a renal biopsy and endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) for a pancreatic tumor (Fig. 2). The specimen obtained by EUS-FNA revealed a well-differentiated adenocarcinoma (Fig. 3). Renal biopsy specimens showed minor glomerular abnormalities on light microscopy (Fig. 4a, b) and negative staining on immunofluorescence microscopy against IgG, IgA, IgM, and carbohydrate antigen 19-9. Electron microscopy showed diffuse foot process effacement without electron-dense deposits (Fig. 4c). Therefore, he was diagnosed with pancreatic cancer and nephrotic syndrome due to MCD. The patient was classified as stage III (T4N0M0) in accordance with the Union for International Cancer Control 7th edition.

He was started on angiotensin receptor blocker (ARB); however, ARB treatment was interrupted after one month due to a low blood pressure and totter. In the ARB period, proteinuria remained at a high level with the urine protein-to-creatinine ratio fluctuating from 6.94 to 2.02 to 8.94 to 3.89 g/gCr. After a second opinion, he was started on definitive treatment with chemotherapy (gemcitabine+nab-paclitaxel: GnP) (gemcitabine 1,800 mg; nab-paclitaxel 226 mg). Just before the start of GnP treatment, the serum creatinine was 1.89 mg/dL, serum albumin was 1.7 g/dL, and the urine protein-to-creatinine ratio was 3.89 g/gCr. He was not administered steroids, except for the small amount of dexamethasone (6.6 mg per dose, three times per month) included in the GnP regimen, or any other immunosuppressive agents. His proteinuria improved to the normal level one month after the start of chemotherapy. Because of grade 3 neutropenia based on the common terminology criteria for adverse events version 4.0 (CTCAE ver. 4.0), he required a dose reduction of the GnP therapy (gemcitabine 1,400 mg; nab-paclitaxel 174 mg) during cycles 2 to 5. Because of exertional dyspnea and peripheral neuropathy, he required a two-dose reduction of the GnP therapy (gemcitabine 1,100 mg; nab-paclitaxel 135 mg) during cycles 6 and 7. A follow-up CT performed 2 months after the start of GnP therapy showed a partial response. A follow-up CT performed 6 months after the start of GnP therapy (Fig. 5) showed no further change. The serum level of carbohydrate antigen 19-9 decreased to near-normal levels by 5 months (Fig. 6). However, due to advanced general fatigue, we changed the GnP therapy to chemoradiotherapy [tegafur/gimeracil/oteracil (S-1) + radiation at 50.4 Gy in 28 fractions] (S-1 120 mg). A follow-up CT performed after the completion of chemoradiotherapy showed stable disease (Fig. 7). He was then started on S-1 monotherapy with a two-dose reduction (S-1 80 mg) due to general fatigue and appetite loss. A follow-up CT performed 6 months after the start of S-1 monotherapy showed stable disease (Fig. 8). At 20

Table 1. Blood Test and Urinalysis.

WBC	4,700 /μL
Hb	13.0 g/dL
Ht	37.6 %
MCV	91.0 fL
PLT	162,000 /μL
PT-INR	1.00
APTT	30.2 s
T-BIL	0.3 mg/dL
AST	28 U/L
ALT	15 U/L
LDH	211 U/L
γGTP	15 U/L
ALP	2.9 U/L
TP	5.7 g/dL
ALB	2.9 g/dL
T-chol	196 mg/dL
HbA1c	5.8 %
BUN	16.2 mg/dL
CRE	1.05 mg/dL
Na	139 mEq/L
K	4.3 mEq/L
Cl	105 mEq/L
Ca	8.5 mg/dL
CRP	0.023 mg/dL
CA19-9	772 U/mL
DUPAN-2	>1,600 U/mL
SPan-1	824 U/mL
CEA	4.5 ng/mL
HBs antigens	(-)
HBs antibody	(-)
HCV antibody	(-)
IgG	656 mg/dL
IgA	242 mg/dL
IgM	56 mg/dL
C3	95 mg/dL
C4	25 mg/dL
RF	2.69 U/mL
PR3-ANCA	0.1 U/mL
MPO-ANCA	0.1 U/mL
Serum protein electrophoresis	Normal
A urine protein-to-creatinine ratio	6.94 g/gCr
a 24-hour urine specimen	7.46 g
The urine protein selectivity index	0.08

T-chol: total cholesterol, DUPAN-2: Duke pancreatic monoclonal antigen type 2, SPan-1: s-pancreas antigen-1, CA19-9: carbohydrate antigen 19-9, CEA: carcinoembryonic antigen, HBs antigens: tests for hepatitis B virus surface antigens, HCV antibodies: antibodies to hepatitis C virus, Ig: immunoglobulins, C3 and C4: complement proteins C3 and C4, RF: rheumatoid factor, ANCA: antineutrophil cytoplasmic antibodies

months after the start of GnP therapy, the patient was in complete remission for MCD.

Discussion

Glomerular disease in malignancies has been recognized for decades. Membranous nephropathy is the most common glomerular pathology. MCD has been associated with Hodgkin's lymphoma as well as other hematological malignancies; however, in two large studies on 1,700 Hodgkin's disease patients, only 0.4% of them had MCD (15, 16). MCD has rarely been associated with carcinomas such as thymoma, renal cell carcinoma, colorectal carcinoma, and lung carcinoma (3, 4). We searched for case reports of minimal change nephrotic syndrome patients with malignancy through PubMed using "minimal change nephrotic syndrome," "pancreatic adenocarcinoma," or "pancreatic cancer" as queries; only two cases were found (5, 6). The main characteristics of these patients and our case are shown in Table 2. The ages of the patients ranged from 67-82 years. The proteinuria level was in the nephrotic range in all patients (>3.5 g/day or urine test 4+). The creatinine level was high in our patient, but the other cases had no records. Although our patient received chemotherapy, others received no treatment for the malignant tumor. One case was administered a corticosteroid for MCD (5). Although the prognoses of pancreatic cancer with MCD were unclear in the previous reports, a long-term survival was obtained in our case using chemotherapy and chemoradiotherapy.

Acute renal failure in the setting of MCD has been well described. In one study, it occurred in 25% of adult MCD patients and 4% of cases that required dialysis (10). In our case, the serum creatinine level was elevated at 1.89 mg/dL before the start of the GnP treatment, and it normalized during the therapy for the malignant tumor.

Nakayama et al. suggested the possible role of the inflammatory cytokines such as tumor necrosis factor-α in MCD preceding Hodgkin lymphoma (17). Inflammatory responses induced by Th2-related cytokines such as interleukin-13 might be important for development of MCD in patients with Hodgkin lymphoma (18). Although the cause of MCD with solid tumors has not yet been identified, cytokines, chemokines, other related factors produced by tumor cells, and general inflammation caused by tumors may be implicated (14).

A diagnosis of paraneoplastic nephrotic syndrome can be considered if the following criteria are present: 1) no evidence of any other etiology, 2) nephrotic syndrome develops 6 months before or after a cancer diagnosis, 3) cancer treatment is associated with a decrease in proteinuria, and 4) cancer relapse is associated with an increase in proteinuria (19). Since the first three criteria were fulfilled in our patient, we considered that the MCD was therefore related to PC.

The currently accepted treatment of MCD in adults is prednisolone at 1 mg/kg per day for 16 weeks (10). The remission rate is 80-90%, and immunosuppressive agents such as cyclophosphamide, cyclosporine, or tacrolimus are rarely

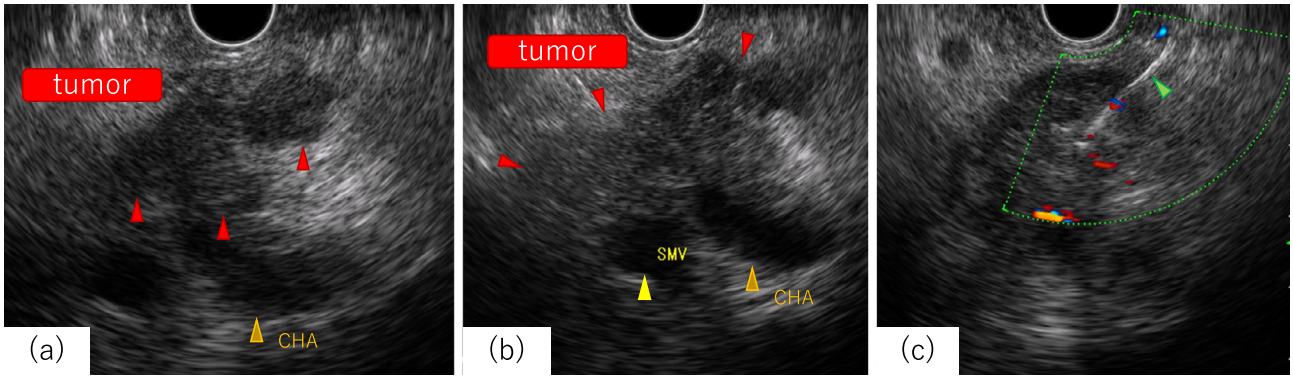

Figure 2. **Endoscopic ultrasound. (a, b) A pancreatic tumor (red arrowhead) is observed to have invaded the superior mesenteric vein (yellow arrowhead) and common hepatic artery (orange arrowhead). (c) Endoscopic ultrasound-guided fine needle aspiration with aspiration needle via the gastric wall (green arrowhead).**

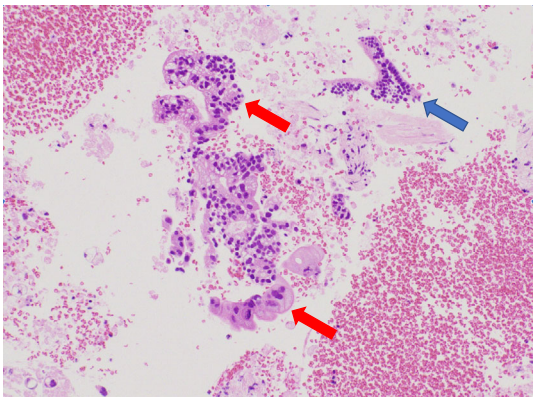

Figure 3. **Pathology of pancreatic cancer (×400). Normal pancreatic duct cells (blue arrow), Adenocarcinoma cells (red arrow).**

necessary (12). However, when MCD is secondary to a paraneoplastic syndrome, the treatment of neoplasia should be considered (20). Kofman et al. reported that 18 of 13,992 cases of non-Hodgkin lymphoma showed MCD, and that relapse of MCD occurred more frequently in patients treated only by steroids (77.8%) than those receiving combined therapy with steroids and other chemotherapeutic agents (25%) (13). Just before GnP, the urine protein-to-creatinine ratio was 3.89 g/gCr in our case. The prognosis of MCD associated with neoplasia was poor. Moreover, for the remission of MCD with steroid treatment without chemotherapy, the relapse rate is high (3, 14). Thus, it was considered that the complete remission of MCD was difficult, regardless of chemotherapy. Since the effects of steroids may be insufficient (13), we considered that chemotherapy was more important than steroid therapy for MCD associated with a malignant tumor. Moreover, diuretics improved the bilateral lower limb edema in our case. Thus, chemotherapy was administered first, but steroids were planned to be introduced if the improvement of nephrotic syndrome was poor. In our case, since the GnP was effective for nephrotic syndrome, steroids were therefore not administered.

The criteria considered as remission are as follows: resolution of edema, normalization of serum albumin (≥3.5 g/dL), and marked reduction in proteinuria. In adults, a complete remission is less than 0.3 g/day proteinuria, and a partial remission is less than 3.5 g/day proteinuria and a 50% reduction (21). To achieve proteinuria reduction normally requires several months of treatment in adults. In idiopathic MCD, the probability of remission is approximately 30% after 4 weeks and 80% after 16 weeks of steroid therapy (10, 22, 23). The criterion considered as relapse in adults is the recurrence of massive proteinuria (≥3.5 g/day) (21). In our case, a partial remission was achieved after 2 weeks of GnP therapy, and a complete remission was achieved after 5 weeks. Although the GnP regimen included a small amount of dexamethasone, it was very low compared to an MCD therapeutic dose. In addition, even though relapse of MCD occurred in 77.8% in patients with malignant diseases treated only by steroid (13), there was no relapse of MCD after switching to the TS-1 regimen in which steroids were not included in our case. Therefore, we considered that the GnP therapy was effective for both the pancreatic cancer and for the MCD.

In summary, we herein presented a rare case of MCD associated with pancreatic cancer treated with GnP therapy. Since the prognosis of MCD associated with a malignant tumor is a poor outcome in cases in which the therapy for the malignant tumor is not effective, it is considered that aggressive therapy for the malignant tumor is preferable in patients with malignancy-associated MCD.

The patient gave her informed consent for inclusion in the study.

The authors state that they have no Conflict of Interest (COI).

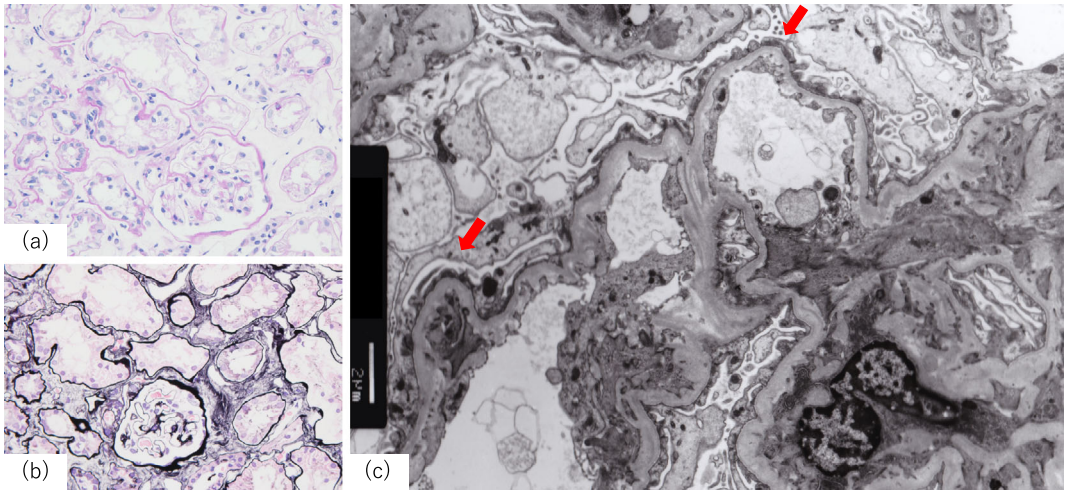

Figure 4. **Pathology of the renal biopsy. (a) PAS staining (b) PAM staining (×400). A renal biopsy shows a minor glomerular abnormality on light microscopy. (c) Electron microscopy (×5,000) shows diffuse foot process effacement without any electron dense deposits (red arrow). PAM: periodic acid-methenamine silver, PAS: periodic acid-Schiff**

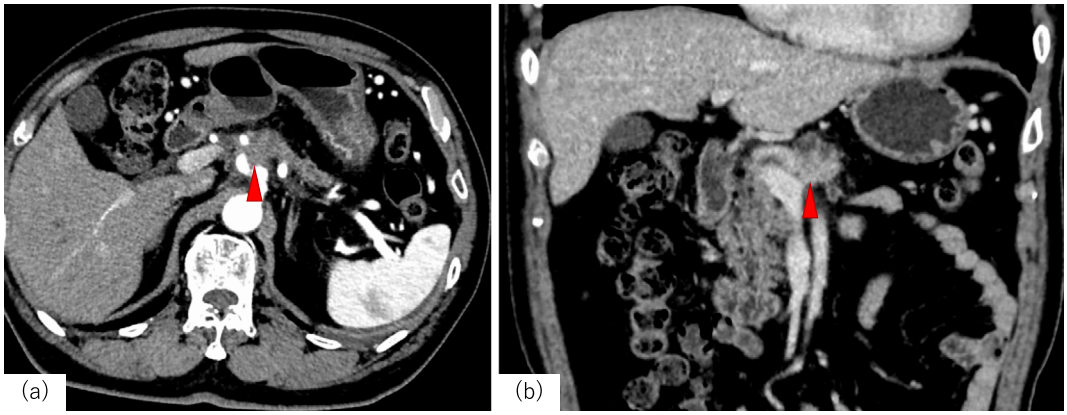

Figure 5. **Computed tomography 6 months after the start of GnP. (a, b) pancreatic cancer (red arrowhead). GnP: gemcitabine+nab-paclitaxel**

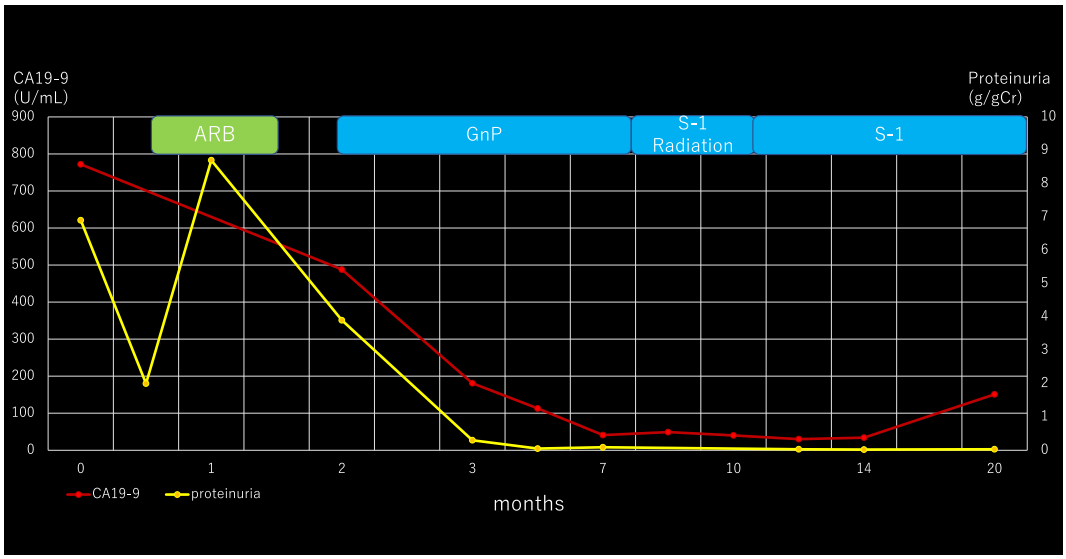

Figure 6. **Changes in proteinuria and CA19-9. The yellow line shows the proteinuria level. ARB was not effective. However, it normalized one month after GnP. The red line shows the CA19-9 level. It decreased accompanied by proteinuria. ARB: angiotensin receptor blocker, CA19-9: carbohydrate antigen 19-9, GnP: gemcitabine+nab-paclitaxel, S-1: tegafur/gimeracil/oteracil**

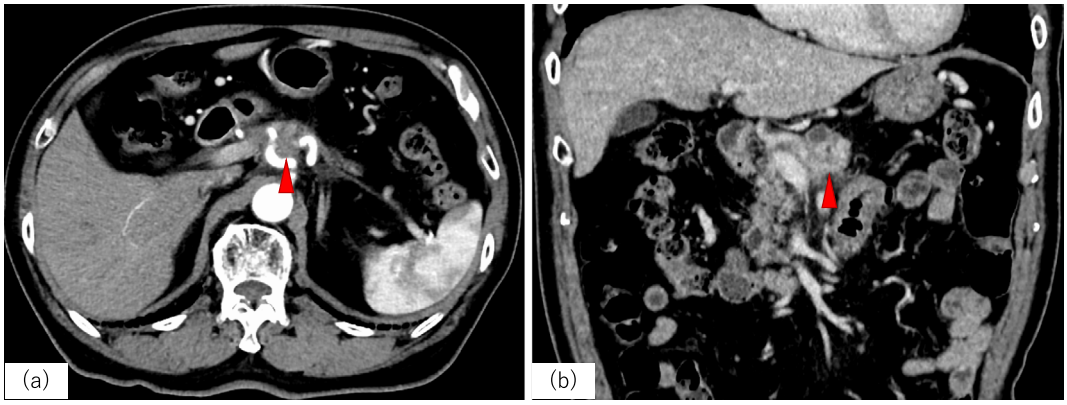

Figure 7. **Computed tomography 2 months after switch of S-1+radiation therapy. (a, b) pancreatic cancer (red arrowhead). S-1: tegafur/gimeracil/oteracil**

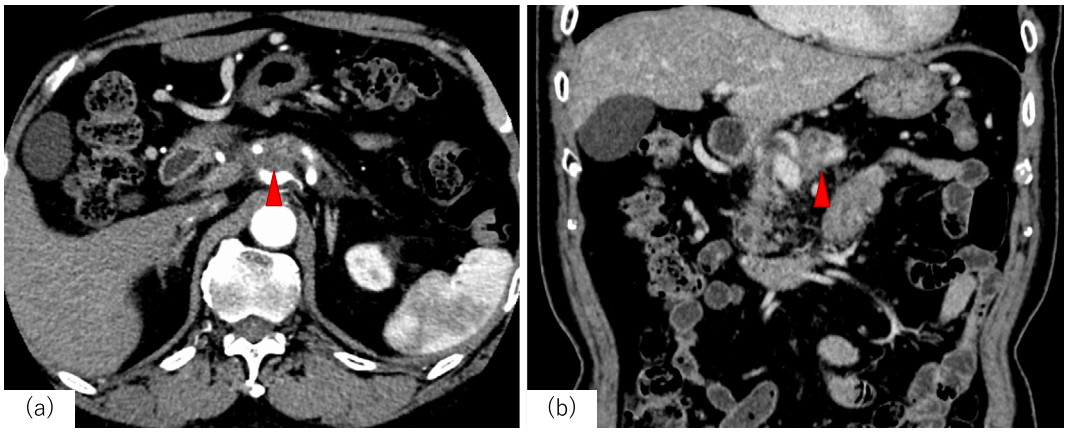

Figure 8. **Computed tomography 6 months after switch of S-1. (a, b) pancreatic cancer (red arrowhead). S-1: tegafur/gimeracil/oteracil**

Table 2. **The Characteristics of the Patients with Minimal Change Disease (MCD) Associated with Pancreatic Cancer.**

Reference	Age/ sex	Creatinine level (mg/dL)	Proteinuria (g/day)	malignat tumor	Therapy for MCD	Therapy for malignant tumor	Evaluate the response to treatment for tumor	Proteinuria after treatment (g/day)	course of MCD	Prognosis (from MCD diagnosis)	adverse event
our case	82/ M	1.89	6.94	Pancreatic carcinoma	×	chemo-therapy	effective	0.01	no recurrent	survived (24 mo)	
[5]	67/ M	NR	>3.5	Pancreatic carcinoma	Prednizolone	×	NR	<0.15	NR	died (8 mo)	infection (pneumonia, liver abscess)
[6]	68/ M	NR	NR (urine test 4+)	Pancreatic carcinoma, Thymoma	×	×	NR	NR	NR	died (3 days)	

NR: no record, M: man, mo: month

References

1. Nachman PH, Jennette JC, Falk RJ. Primary glomerular disease. In: The Kidney. 8th ed. Brenner BM, Ed. Saunders Elsevier, Philadelphia, 2008: 987-1066.
2. Cameron JS. The nephrotic syndrome and its complications. Am J Kidney Dis **10**: 157-171, 1987.
3. Glassock RJ. Secondary minimal change disease. Nephrol Dial Transplant **18**: vi52-vi58, 2003.
4. Jhaveri KD, Shah HH, Calderon K, Campenot ES, Radhakrishnan J. Glomerular diseases seen with cancer and chemotherapy: a narrative review. Kidney Int **84**: 34-44, 2013.
5. Whelan TV, Hirszel P. Minimal-change nephropathy associated with pancreatic carcinoma. Arch Intern Med **148**: 975-976, 1988.
6. Hirokawa M, Moriya T, Manabe T. Minimal change renal disease

associated with thymoma and pancreatic carcinoma. Acta Pathol **36**: 1075-1081, 1986.

7. Avner ED, Harmon WE, Niaudet P, Yoshikawa N, Emma F, Goldstein SL. Idiopathic nephrotic syndrome in children: clinical aspects. In: Pediatric Nephrology. 7th ed. Springer, Berlin, 2016: 2730.

8. Lewis JB, Neilson EG. Glomerular diseases. In: Harrison's Online [Internet]. 18th ed. Longo DL, Fauci AS, Kasper DL, et al., Eds. McGraw-Hill, New York, 2012. Available from: https://www.sohail university.edu.pk/wp-content/uploads/2018/12/Harrisons-Manual-of-Medicine-18th-Edition.pdf

9. Shalhoub RJ. Pathogenesis of lipid nephrosis: a disorder of T-cell function. Lancet **2**: 556-560, 1974.

10. Waldman M, Crew RJ, Valeri A, et al. Adult minimal-change disease: clinical characteristics, treatment, and outcomes. Clin J Am Soc Nephrol **2**: 445-453, 2007.

11. Kerlin BA, Ayoob R, Smoyer WE. Epidemiology and pathophysiology of nephrotic syndrome-associated thromboembolic disease. Clin J Am Soc Nephrol **7**: 513-520, 2012.

12. Hogan J, Radhakrishman J. The treatment of minimal change disease in adults. J Am Soc Nephrol **24**: 702-711, 2013.

13. Kofman T, Zhang SY, Copie-Bergman C, et al. Minimal change nephrotic syndrome associated with non-Hodgkin lymphoid disorders: a retrospective study of 18 cases. Medicine (Baltimore) **93**: 350-358, 2014.

14. Li JY, Yong TY, Kuss BJ, Klebe S, Kotasek D, Barbara JA. Malignant pleural mesothelioma with associated minimal change disease and acute renal failure. Renal Failure **32**: 1012-1115, 2010.

15. Plager J, Stutzman L. Acute nephrotic syndrome as a manifestation of active Hodgkin's disease. Am J Med **50**: 56-66, 1971.

16. Kramer P, Sizoo W, Twiss EE. Nephrotic syndrome in Hodgkin's disease. Neth J Med **24**: 114-119, 1981.

17. Nakayama S, Yokote T, Kobayashi K, et al. Minimal-change nephrotic syndrome preceding Hodgkin lymphoma by 5 years with expression of tumor necrosis factor alpha in Hodgkin-Reed-Sternberg cells. Hum Pathol **41**: 1196-1199, 2010.

18. Audard V, Larousserie F, Grimbert P, et al. Minimal change nephrotic syndrome and classical Hodgkin's lymphoma: report of 21 cases and review of the literature. Kidney Int **69**: 2251-2260, 2006.

19. Burstein DM, Korbet SM, Schwartz MM. Membranous glomerulonephritis and malignancy. Am J Kidney Dis **9**: 23-26, 1993.

20. Yildiz H, Andreea SI, Hoton D, Yombi JC. Minimal change disease associated with malignant pleural mesothelioma: case report and review of literature. BMJ Case Rep **2016**: bcr2016217958, 2016.

21. Vivarelli M, Massella L, Ruggiero B, Emma F. Minimal change disease. Clin J Am Soc Nephrol **12**: 332-345, 2017.

22. Vivarelli M, Moscaritolo E, Tsalkidis A, Massella L, Emma F. Time for initial response to steroids is a major prognostic factor in idiopathic nephrotic syndrome. J Pediatr **156**: 965-971, 2010.

23. Chen CL, Fang HC, Chou KJ, et al. Increased endothelin 1 expression in adult-onset minimal change nephropathy with acute renal failure. Am J Kidney Dis **45**: 818-825, 2005.