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Case Report

Correlation Between the Acquisition of Resistance to Gemcitabine Therapy and the Expression of HuR in Pancreatic Ductal Adenocarcinoma: A Case Report

Atsushi Oba[1], Daisuke Ban[1], Atsushi Kudo[1], Susumu Kirimura[2], Hiromitsu Ito[1], Satoshi Matsumura[1], Yusuke Mitsunori[1], Arihiro Aihara[1], Takanori Ochiai[1], Shinji Tanaka[3], Minoru Tanabe[1]

[1]*Department of Hepatobiliary-Pancreatic Surgery, Graduate School of Medicine, Tokyo Medical and Dental University, Tokyo, Japan*

[2]*Department of Comprehensive Pathology, Graduate School of Medicine, Tokyo Medical and Dental University, Tokyo, Japan*

[3]*Department of Molecular Oncology, Graduate School of Medicine, Tokyo Medical and Dental University, Tokyo, Japan*

Recently, several studies have revealed the usefulness of biomarkers to predict the response to chemotherapy for pancreatic ductal adenocarcinoma (PDAC). Among them, human antigen R (HuR) is reported as a powerful marker for response to gemcitabine chemotherapy for PDAC. The present report describes a patient with PDAC who underwent gemcitabine therapy before resection and after recurrence, and HuR expression was examined at multiple stages. A 72-year-old man was diagnosed with locally advanced unresectable PDAC invading the common hepatic artery. After 9 cycles of gemcitabine treatment, a computed tomography (CT) scan demonstrated a partial response. He underwent distal pancreatectomy with portal vein resection. The pathologic assessment for response to the chemotherapy was grade Ib by Evans's criteria, and HuR expression was high. Serum carbohydrate antigen 19-9 (CA19-9) level rose rapidly at 4 months after the first resection. A CT scan and needle biopsy revealed a

Corresponding author: Daisuke Ban, MD, PhD, Department of Hepatobiliary-Pancreatic Surgery, Graduate School of Medicine, Tokyo Medical and Dental University; 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan.
Tel.: +81 3 5803 5928; Fax: +81 3 5803 0263; E-mail: d-ban.msrg@tmd.ac.jp

solitary recurrence in the abdominal wall, and HuR expression remained high. After 4 cycles of gemcitabine and S-1 combination therapy, a CT scan demonstrated a partial response, and serum CA19-9 decreased. However, after 2 additional cycles of the therapy, a CT scan demonstrated progressive disease, and serum CA19-9 increased slightly. By laparotomy, an abdominal wall recurrence and multiple peritoneal dissemination were found. HuR expression in the biopsy specimen obtained during the laparotomy was decreased. Although gemcitabine therapy was reinitiated, the disease progressed rapidly so the treatment was stopped. In this case, a correlation between the acquisition of resistance to gemcitabine therapy and change in HuR expression was demonstrated.

Key words: Pancreatic cancer – HuR – Gemcitabine

Pancreatic ductal adenocarcinoma (PDAC) is known for its aggressiveness and poor prognosis; it is the fourth leading cause of cancer-related death in both men and women.[1] PDAC is characterized by a high propensity for local invasion, distant metastasis, and limited response to chemotherapy.[2,3]

Gemcitabine is one of the current standard chemotherapies in both metastatic and adjuvant settings.[4–6] However, its effect is far from being acceptable. Tailor-made chemotherapy based on evaluation of biomarkers is one of the most important strategies for the improvement of the prognosis of patients with PDAC. Several studies have reported the utility of some biomarkers to predict the response to gemcitabine-based chemotherapy for PDAC.[7–9] Among them, human antigen R (HuR) is reported as a powerful marker for response to gemcitabine-based chemotherapy for PDAC. Thus far, no study has evaluated the response to gemcitabine by multiple assessments of the expression of a predictive biomarker in the same patient who received gemcitabine-based chemotherapy for PDAC.

Case Report

A 72-year-old man presented with exacerbation of diabetes mellitus at his local clinic and was diagnosed with locally advanced unresectable PDAC with invasion to the common hepatic artery. Clinical course and changes in serum carbohydrate antigen 19-9 (CA19-9) are shown in Fig. 1. The patient received 9 cycles of gemcitabine at 800 mg/m^2/d intravenously on days 1, 8, and 15 every 4 weeks. Computed tomography (CT) scans and positron emission tomography (PET) demonstrated a partial response (Fig. 2). The tumor decreased slightly in size, and the invasion to the common hepatic artery had been disappeared. Then, he visited our hospital for a consultation regarding the surgical treatment for the PDAC, and distal pancreatectomy with portal vein resection was subsequently performed.

Macroscopically, the tumor was located in the pancreatic body and was 1.2 cm in diameter. Invasion to the portal vein and the celiac axis, and metastasis to the regional lymph nodes were not detected. The microscopic examination revealed that some parts of the papillary adenocarcinoma had degenerated and was surrounded by fibrous tissue, which may have replaced the cancer cells that were killed by the chemotherapy. The existing cancer cells were approximately 0.7 cm in diameter. In total, 40% of the cancer cells were ablated, and pathologic assessment for response to the chemotherapy was grade Ib by Evans's criteria.[10] HuR expression in the tumor was high as assessed by immunohistochemistry of the resected specimen (Fig. 2).

We recommended adjuvant chemotherapy; however, the patient chose only follow-up without further treatment. Within 4 months after the first resection, CA19-9 level rose rapidly from 24 to 181.6 U/mL. CT and PET scans revealed a solitary recurrence in the abdominal wall. A specimen of the recurrent lesion obtained by needle biopsy was histopathologically diagnosed as an adenocarcinoma, and HuR expression was high (Fig. 3). The patient subsequently received gemcitabine and S-1 combination therapy (GS therapy); gemcitabine at 1000 mg/m^2/d was administered intravenously on days 1 and 8 every 3 weeks, and S-1 at 50 mg/m^2/d was given orally twice daily from days 1 to 14.

After 4 cycles of GS therapy, a CT scan demonstrated a partial response, and the level of

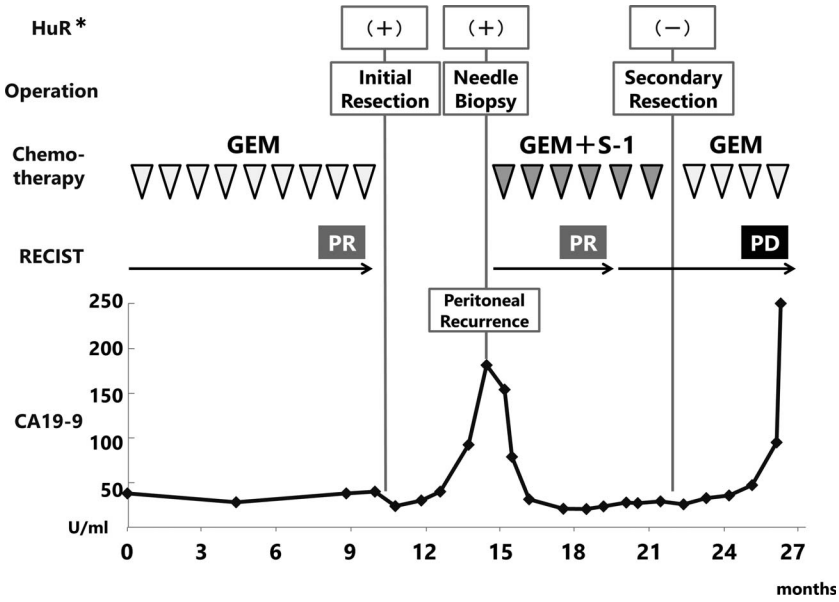

Fig. 1 Clinical course and changes in serum CA19-9. * Intensity of immunohistochemistry of HuR. PR, partial response; PD, progressive disease.

serum CA19-9 decreased to 20.7 U/mL. However, after 2 more cycles of GS therapy, a CT scan demonstrated progressive disease and serum CA19-9 slightly increased to 29.1 U/mL. One year after the first resection, the tumor no longer responded to the chemotherapy (Fig. 4). Thus, local resection of the solitary recurrence was planned. Unfortunately, we found that the abdominal wall recurrence had invaded into the mesenteric membrane and multiple peritoneal dissemination were found by laparotomy. HuR expression in a biopsy specimen of the abdominal wall recurrence obtained during laparotomy was low (Fig. 4). Although intravenous administration of gemcitabine at 800 mg/m^2/d on days 1, 8, and 15 every 4 weeks was reinitiated after the operation, the disease progressed rapidly which prompted the discontinuation of the therapy. In deference to his wishes, the patient was transferred to another hospital to receive hyperthermia therapy.

Discussion

PDAC is known for its aggressiveness and poor prognosis. Surgical resection is the only curative treatment option. Nevertheless, because of the late presentation of the disease, only 15% to 20% of patients are diagnosed early enough to be considered for potentially curative treatment.[11] Even after potentially curative surgery, the incidence of locoregional or distant recurrence is 80% or higher. Curability by surgery alone appears to be sharply limited.[12] Chemotherapy plays an important role as neoadjuvant, adjuvant, and palliative treatments. In recent years, despite a larger selection of treatment regimens for PDAC including FOLFIRINOX, nab-paclitaxel, and S-1 as well as gemcitabine, the

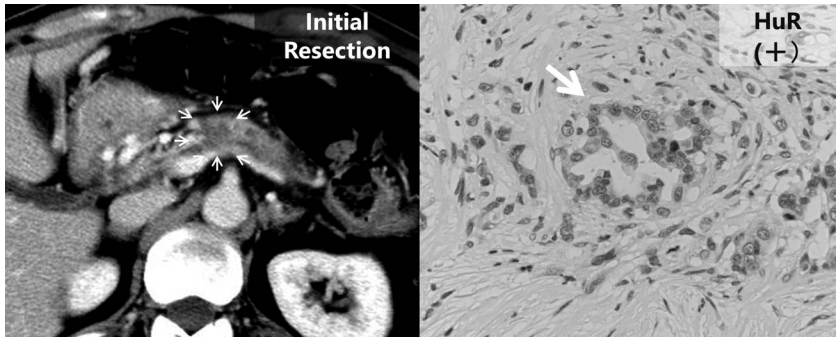

Fig. 2 A CT scan showed the primary PDAC in the pancreatic body before distal pancreatectomy with portal vein resection. The response to treatment was grade Ib by Evans's criteria, and both cytoplasmic and nuclear HuR stainings were strong.

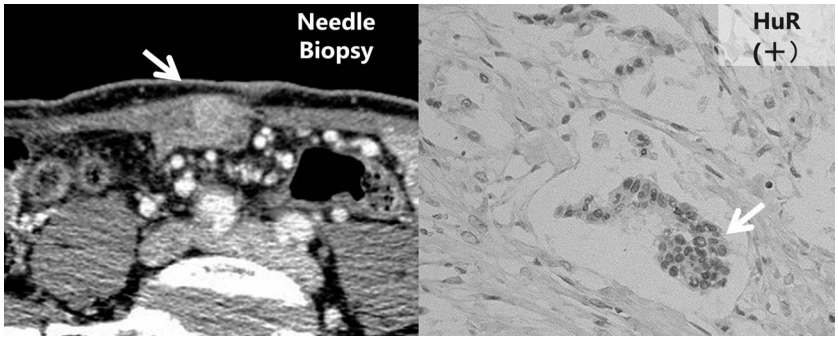

Fig. 3 A CT scan showed the solitary recurrence in the abdominal wall. The specimen obtained by needle biopsy was histopathologically diagnosed as an adenocarcinoma, and both cytoplasmic and nuclear HuR stainings were strong. This lesion responded to the initial 4 cycles of gemcitabine and S-1 combination therapy (GS therapy).

response is still far from satisfying.[4–6,13] Therefore, tailor-made chemotherapy based on evaluation of biomarkers is one of the most important strategies for the improvement of the clinical outcome and prognosis of patients with PDAC. To our knowledge, this is the first report that shows a correlation between the acquisition of resistance to gemcitabine therapy and the expression of HuR.

HuR, human equilibrative nucleoside transporter 1 (hENT1) and ribonucleotide reductase regulatory subunit M1 (RRM1) have been suggested as predictors of response to gemcitabine, which is one of the key drugs for PDAC.[7–9,11] The ubiquitous RNA-binding protein (RBP), HuR, is involved in the control of gene expression, mRNA stability and translation, and cellular response to internal and external signals.[14] Through its post-transcriptional effect by targeting mRNAs, HuR can alter the cellular response to proliferative, stress, apoptotic, differentiation, senescence, inflammatory, and immune signals.[11] Although HuR has never been reported to be mutated in cancer, it has been proposed to contribute to the tumorigenesis process.[15,16] High cytoplasmic expression of HuR correlates with high-grade malignancy in some cancers including breast, colon, and ovarian cancers.[17–19] Meanwhile, Costantino *et al* showed that HuR both targets and regulates the protein expression of deoxycytidine kinase (dCK), the key enzyme involved in metabolizing the prodrug gemcitabine into its active di- and triphosphate metabolites. They showed that HuR status was a predictive biomarker for response to gemcitabine in both cancer cell lines and clinical outcomes.[7,15]

In our case, gemcitabine had some efficacy for 9 months before the first resection, and HuR expression level in the resected specimen was high. Further, the abdominal wall recurrent lesion also responded to gemcitabine-based chemotherapy for 4 months, and HuR expression level in the biopsy specimen of the recurrent tumor was high as well. Subsequently, the lesion developed resistance to gemcitabine-based chemotherapy, and HuR expression level decreased. This progression of events shows that HuR expression is correlated to the efficacy of gemcitabine.

It is often observed clinically that a tumor that is thought to respond to chemotherapy is in fact nonresponsive and progressing.[20] On this point, it is very interesting that PDAC responded to gemcitabine, but acquired resistance to the chemotherapy, and HuR expression corresponded to this process. Thus, in terms of tailor-made chemotherapy, HuR expression could contribute to the selection of the

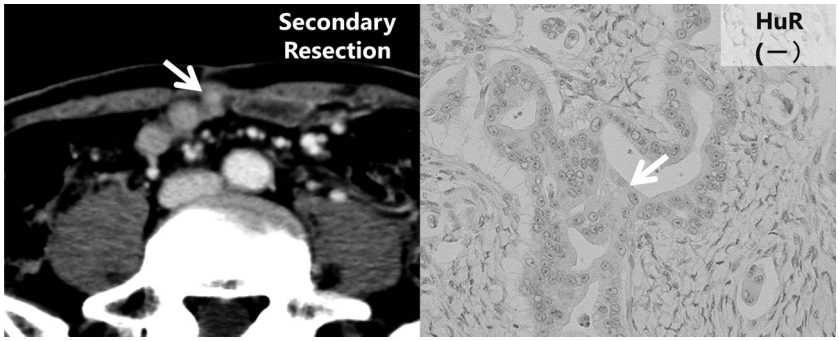

Fig. 4 After 2 additional cycles of GS therapy, the lesion progressed, and serum CA19-9 slightly increased. A CT scan showed the solitary recurrence before exploratory surgery. Both cytoplasmic and nuclear HuR stainings in the lesions obtained by biopsy during laparotomy were weak. Although gemcitabine therapy for multiple peritoneal dissemination was reinitiated, the disease progressed rapidly.

proper chemotherapy regimen for individual patients and facilitate the decision to change the treatment regimen in the case of acquisition of drug resistance.

In conclusion, we presented a case of PDAC that underwent gemcitabine therapy before resection and after recurrence, and HuR expression was examined at multiple stages. In this case, a correlation between the acquisition of resistance to gemcitabine therapy and change in HuR expression was demonstrated.

Acknowledgments

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References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *Cancer J Clin* 2011;**61**(2):69–90
2. Li D, Xie K, Wolff R, Abbruzzese JL. Pancreatic cancer. *Lancet* 2004;**363**(9414):1049–1057
3. Marechal R, Bachet JB, Mackey JR, Dalban C, Demetter P, Graham K *et al*. Levels of gemcitabine transport and metabolism proteins predict survival times of patients treated with gemcitabine for pancreatic adenocarcinoma. *Gastroenterology* 2012;**143**(3):664–674
4. Burris HA 3rd, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR *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**(6):2403–2413
5. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M *et al*. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013;**369**(18):1691–1703
6. Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y *et al*. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011;**364**(19):1817–1825
7. Costantino CL, Witkiewicz AK, Kuwano Y, Cozzitorto JA, Kennedy EP, Dasgupta A *et al*. The role of HuR in gemcitabine efficacy in pancreatic cancer: HuR up-regulates the expression of the gemcitabine metabolizing enzyme deoxycytidine kinase. *Cancer Res* 2009;**69**(11):4567–4572
8. Farrell JJ, Elsaleh H, Garcia M, Lai R, Ammar A, Regine WF *et al*. Human equilibrative nucleoside transporter 1 levels predict response to gemcitabine in patients with pancreatic cancer. *Gastroenterology* 2009;**136**(1):187–195
9. Akita H, Zheng Z, Takeda Y, Kim C, Kittaka N, Kobayashi S *et al*. Significance of RRM1 and ERCC1 expression in resectable pancreatic adenocarcinoma. *Oncogene* 2009;**28**(32):2903–2909
10. Evans DB, Rich TA, Byrd DR, Cleary KR, Connelly JH, Levin B *et al*. Preoperative chemoradiation and pancreaticoduodenectomy for adenocarcinoma of the pancreas. *Arch Surg* 1992;**127**(11):1335–1339
11. Lamarca A, Feliu J. Pancreatic biomarkers: could they be the answer? *World J Gastroenterol* 2014;**20**(24):7819–7829
12. Maeda A, Boku N, Fukutomi A, Kondo S, Kinoshita T, Nagino M *et al*. Randomized phase III trial of adjuvant chemotherapy with gemcitabine versus S-1 in patients with resected pancreatic cancer: Japan Adjuvant Study Group of Pancreatic Cancer (JASPAC-01). *Jpn J Clin Oncol* 2008;**38**(3):227–229
13. Ueno H, Ioka T, Ikeda M, Ohkawa S, Yanagimoto H, Boku N *et al*. Randomized phase III study of gemcitabine plus S-1, S-1 alone, or gemcitabine alone in patients with locally advanced and metastatic pancreatic cancer in Japan and Taiwan: GEST study. *J Clin Oncol* 2013;**31**(13):1640–1648
14. Srikantan S, Gorospe M. HuR function in disease. *Front Biosci* 2012;**17**:189–205
15. Richards NG, Rittenhouse DW, Freydin B, Cozzitorto JA, Grenda D, Rui H *et al*. HuR status is a powerful marker for prognosis and response to gemcitabine-based chemotherapy for resected pancreatic ductal adenocarcinoma patients. *Ann Surg* 2010;**252**(3):499–505
16. Silanes ILd, Lal A, Gorospe M. HuR: Post-transcriptional paths to malignancy. *RNA Biol* 2005;**2**(1):11–13
17. Heinonen M, Fagerholm R, Aaltonen K, Kilpivaara O, Aittomaki K, Blomqvist C *et al*. Prognostic role of HuR in hereditary breast cancer. *Clin Cancer Res* 2007;**13**(23):6959–6963
18. Yoo PS, Sullivan CA, Kiang S, Gao W, Uchio EM, Chung GG *et al*. Tissue microarray analysis of 560 patients with colorectal adenocarcinoma: high expression of HuR predicts poor survival. *Ann Surg Oncol* 2009;**16**(1):200–207
19. Denkert C, Weichert W, Pest S, Koch I, Licht D, Kobel M *et al*. Overexpression of the embryonic-lethal abnormal vision-like protein HuR in ovarian carcinoma is a prognostic factor and is associated with increased cyclooxygenase 2 expression. *Cancer Res* 2004;**64**(1):189–195
20. Oettle H. Progress in the knowledge and treatment of advanced pancreatic cancer: from benchside to bedside. *Cancer Treat Rev* 2014;**40**(9):1039–1047