Shinshu Med J, 64(2) : 79～83, 2016

Complete Response of Advanced Invasive Mucinous Adenocarcinoma of the Lung with Gemcitabine and Pemetrexed

Kentaro MIURA* and Ryoichi KONDO

Department of Thoracic Surgery, National Hospital Organization Matsumoto Medical Center

In 2011, mucinous bronchioloalveolar carcinoma was reclassified as invasive mucinous adenocarcinoma, mucinous adenocarcinoma in situ, and mucinous minimally invasive adenocarcinoma. A part of the invasive mucinous adenocarcinoma of the lung differentiates to gastric mucous cells, and we term this type of carcinoma gastric-like invasive mucinous adenocarcinoma. However, treatment approaches have not yet been established.

An 84-year-old Japanese male visited our hospital because of multiple consolidations and ground-glass opacity on his chest computed tomography. Surgical biopsy of the right lung ground-glass opacity was performed, and it was diagnosed as gastric-like invasive mucinous adenocarcinoma by immunohistochemical analysis. Treatment with gemcitabine and pemetrexed was quite effective, and the radiologic response was complete. We suggest that it is meaningful to determine whether the diagnosis of gastric-like invasive mucinous adenocarcinoma is correct because this may indicate a favourable response to the anticancer drug gemcitabine. *Shinshu Med J 64 : 79—83, 2016*

(Received for publication July 23, 2015 ; accepted in revised form December 16, 2015)

Key words : ground-glass opacity, invasive mucinous adenocarcinoma, gemcitabine, pemetrexed

Abbreviations : IMA, invasive mucinous adenocarcinoma ; CT, computed tomography ; GGO, ground-glass opacity ; NSCLC, non-small cell lung carcinoma

I Introduction

In 2011, mucinous bronchioloalveolar carcinoma was reclassified as invasive mucinous adenocarcinoma (IMA), mucinous adenocarcinoma in situ, or mucinous minimally invasive adenocarcinoma[1]. It is said that the response rate of advanced IMA to chemotherapy is lower than that of other non-small cell lung carcinomas (NSCLC)[2]. Conversely, an IMA part of the lung appears to differentiate into gastric mucous cells[3] ; we term this type of carcinoma gastric-like IMA. However, its features and approach to therapy have not yet been clearly defined. We report a case of advanced gastric-like IMA, which demonstrated a complete response to treatment with gemcitabine and pemeterexed.

II Case presentation

An 84-year-old Japanese male visited our hospital because of multiple consolidations and ground-glass opacity (GGO) on his chest computed tomography (CT). He was a former smoker, and his past medical histories comprised pancreatic cancer (**Fig. 1**) and adenoma of the colon for which surgical resection was done approximately 2 years previously. The largest lesion existed on the left upper lung lobe, which was considered the main tumor, and some consolidations and GGOs were located at the bilateral pulmonary lesion on his chest CT (**Fig. 2**). Bronchoscopic examination was performed ; however, it only detected inflammatory cells, and the

* Corresponding author : Kentaro Miura
Department of Thoracic Surgery, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto, Nagano 390-8621, Japan
E-mail : kmiura@shinshu-u.ac.jp

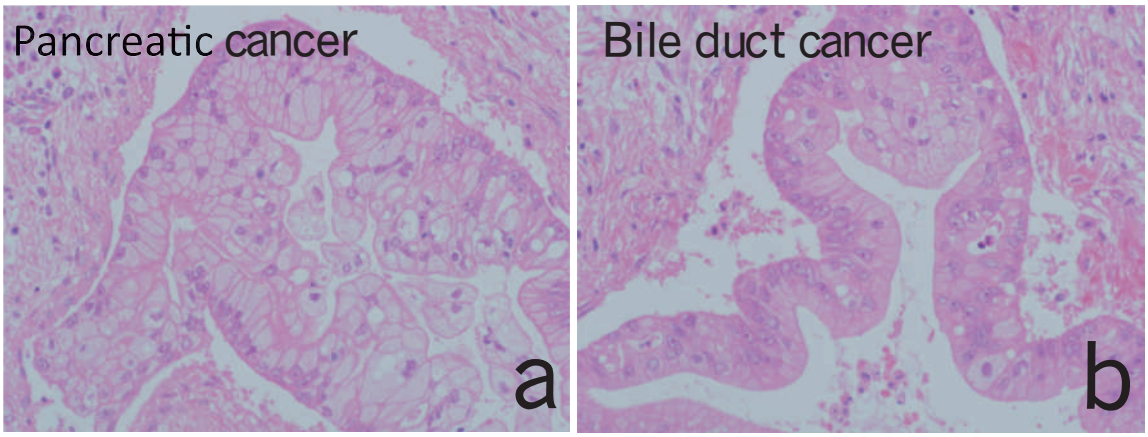

Fig. 1 Histopathological findings of pancreatic and bile duct cancers.
Pancreatic (a) and bile duct cancers (b) (Hematoxylin and eosin staining) are shown. These were mucus-producing tumors ; however, the malignancy grade was higher in these cancers than in lung cancer.

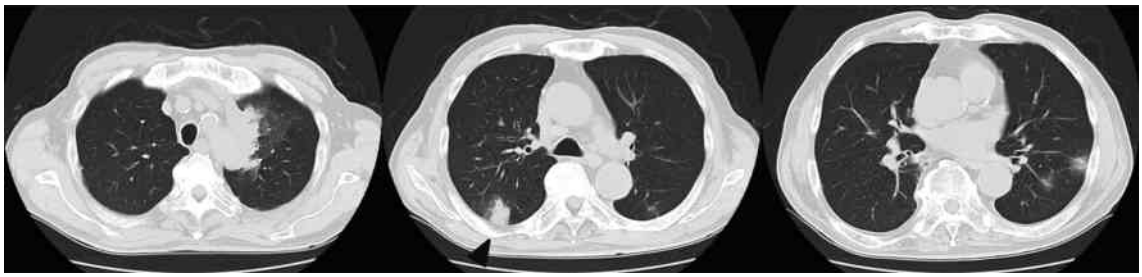

Fig. 2 High-resolution computed tomography of the lung at the time of initial visit.
There were multiple GGOs and consolidations in the bilateral lungs. The main tumor existed at the left upper lobe. The lung biopsy was taken for the right upper lobe (S2 segment) via video-assisted thoracoscopic surgery (arrowhead).

diagnosis was not correct. To confirm the diagnosis, we performed surgical partial resection of the right lung GGO lesion via video-assisted thoracoscopic surgery (**Fig. 2**).

The histopathological findings revealed the existence of low-grade atypical cells filled with mucin in their cytoplasm along with the surface of alveolar wall, and it demonstrated aerogenous dissemination by hematoxylin and eosin staining (**Fig. 3**). An immunohistochemical analysis was positive for alcian blue-periodic-acid Schiff stain (AB/PAS) and mucin-6 (MUC6) and was slightly positive for thyroid transcription factor-1 (TTF-1) (**Fig. 3**). Although metastatic lung tumor was considered, it was diagnosed as primary lung cancer because it revealed aerogenous dissemination and its malignancy grade was lower than pancreatic cancer. These facts indicated organoid differentiation to the gastric pyloric mucosa, and we diagnosed this as gastric-like IMA, stage IV (cT4N0M1a). In genetic screening, epidermal growth factor receptor mutations, anaplastic lymphoma kinase rearrangements, and Kirsten rat sarcoma mutations were not recognized.

The administration of the oral fluoropyrimidine anticancer agent, TS-1 (50 mg/day, Taiho Pharmaceutical, Tokyo, Japan) was immediately initiated. However, a chest CT done 3 months after TS-1 administration revealed a progressive course of disease, and its effect was not satisfactory (**Fig. 4a**). In addition, blood tests revealed abnormal hepatic function. Abdominal CT showed dilation of the bile duct ; he was diagnosed with bile duct cancer by endoscopic biopsy (**Fig. 1**), and a stent was placed in the bile duct. For the treatment of both the lung and bile duct cancers, we chose gemcitabine (GEMZAR, Eli Lilly and Company, Indianapolis, USA) and

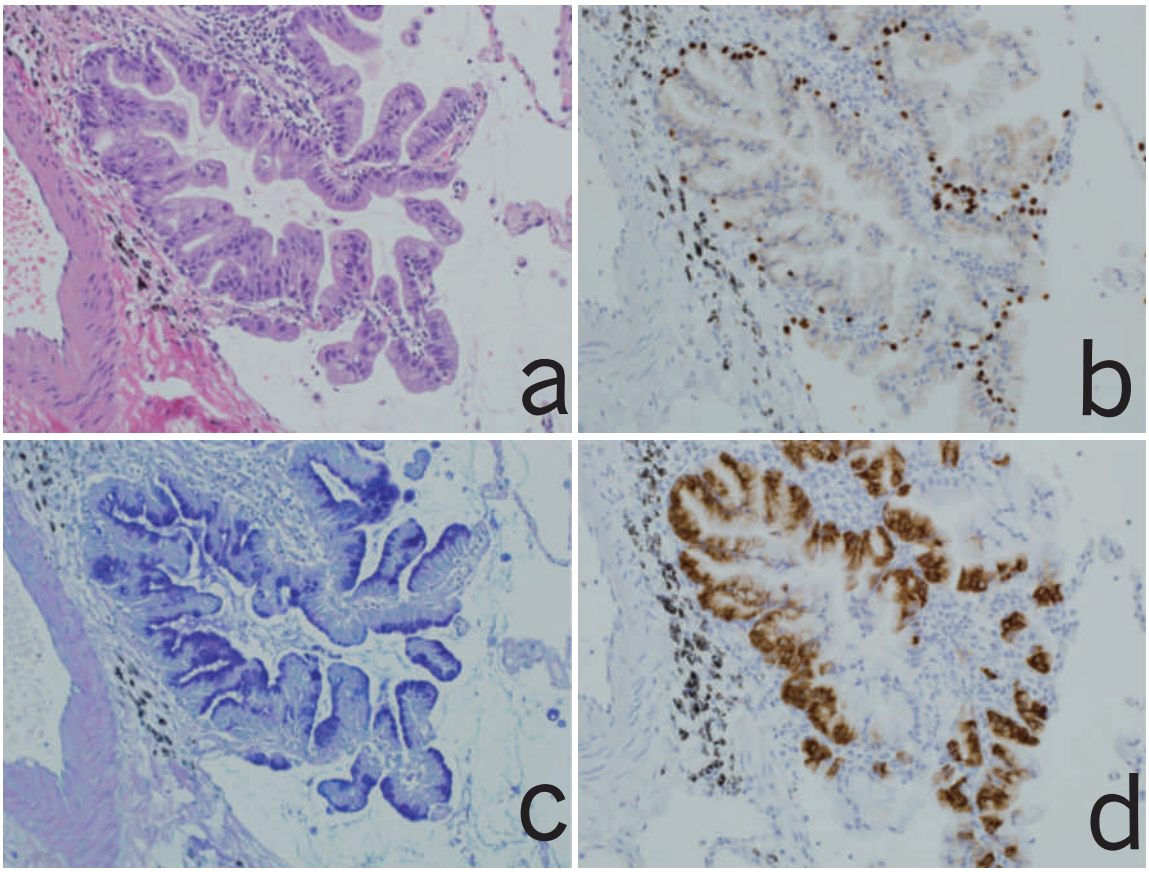

Fig. 3 Histopathological findings of lung cancer.
Hematoxylin and eosin staining revealed the existence of low-grade atypical cells filled with mucin in their cytoplasm along with the surface of alveolar wall, and it demonstrated aerogenous dissemination (a). An immunohistochemical analysis was slightly positive for TTF-1 (b) and positive for AB-PAS (c) and MUC6 (d).

pemetrexed (Alimta, Eli Lilly and Company, Indianapolis, USA) as the new chemotherapy regimen in expectation of beneficial effects on both IMA and bile duct cancer. The doses for gemcitabine (1,200 mg/m^2 × 0.7 dose on day 1), and pemetrexed (500 mg/m^2 × 0.7 dose day 1), administered over 28-day cycles, were chosen in consideration of his age. Furthermore, he was administered folic acid and vitamin B supplements. The radiologic response was complete after 10 cycles without side effects. Lesions were replaced by cavities (**Fig. 4b**). In addition, as the bile duct cancer had not worsened in a CT scan, it was considered that this combination of drugs was effective against bile duct cancer. The chemotherapy is ongoing, and he is alive without recurrence of cancer.

Ⅲ Discussion

It is reported that a part of IMA shows organoid differentiation mimicking gastric pyloric mucosa[3]. It is diagnosed by immunostaining, which is positive for gastric surface mucous cell-type or gastric gland mucous cell-type mucins[3]. This IMA type is said to exist in approximately 60 % of all IMA. In this case, AB/PAS and MUC6 stainings were positive. This concept was advocated first by Honda et al but remains relatively unknown. We term this type of IMA as gastric-like IMA. The treatment for gastric-like IMA has not been established, and clinical features have not been clearly delineated. It may be important to check whether gastric-like IMA or non-gastric-like IMA is an accurate term or not. The clinical features of gastric-like IMA have not yet been defined, and its differences from

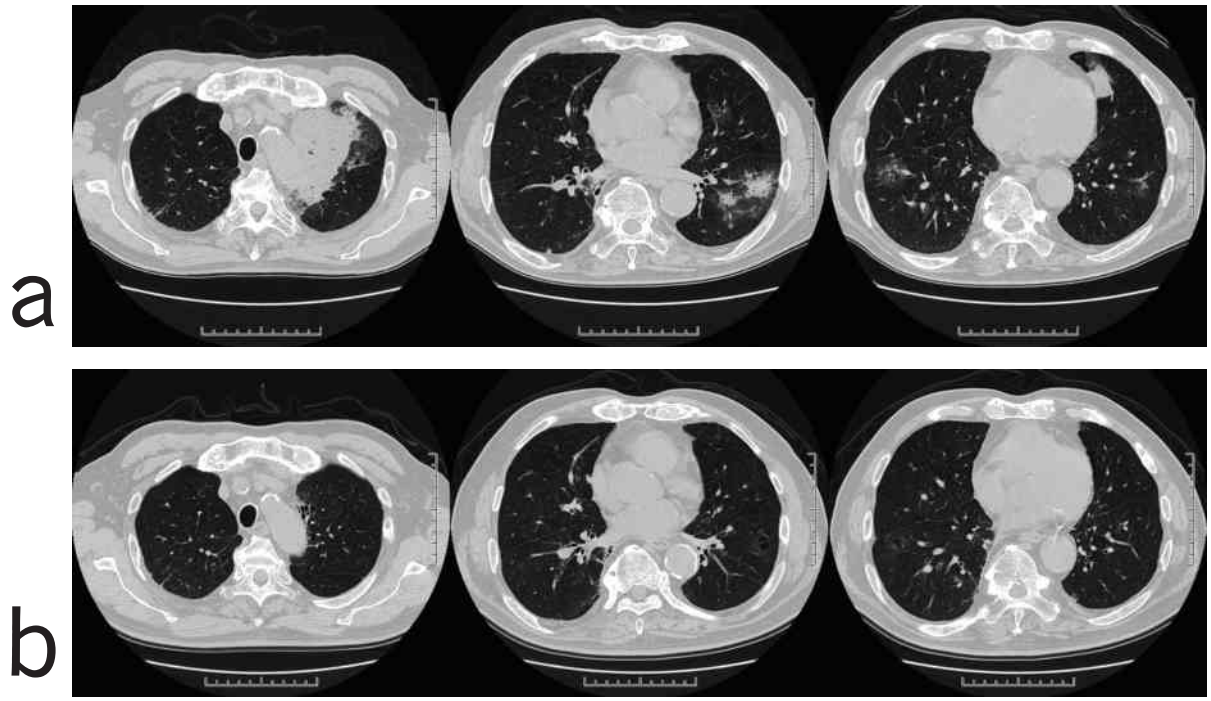

Fig. 4 The changes before and after treatment with gemcitabine and pemetrexed.
TS-1 was not effective, and the lesions of GGOs and consolidations had grown compared with those at the initial visit (a). After treatment with gemcitabine and pemetrexed, the lesions of GGOs and consolidations almost completely disappeared, and these lesions were replaced by cavities (b).

other non-gastric-like IMAs have not been clarified.

There was a review regarding gemcitabine and pemetrexed therapy for advanced NSCLC[4]. They administered gemcitabine 1,250 mg/m² on days 1 and 8 and pemetrexed 500 mg/m² on day 8. Median survival was 10.4-11.6 months, and overall response rate was 8.7 %-44.1 %. It appears to be rare to demonstrate the complete response that was observed in our case.

Alternatively, gemcitabine is often used for carcinomas of the biliary duct and pancreas. It is said that most of the biliary duct and pancreas carcinomas produce ectopic phenotypic expression of gastric mucins[5]. Therefore, because our case appeared to be a gastric-like carcinoma, gemcitabine might be effective.

However, in this case, the possibility of pemeterexed effectiveness should not be ruled out. Yamakawa et al. reported two cases of advanced IMA that indicated favorable responses using cisplatin, pemetrexed, and bavacizumab[6]. Some cases of IMA have been reported as having favorable responses using pemeterexed[7)-9)]; however, these reports do not specify whether IMA was gastric-like or not. There are no reports about the use of chemotherapy in the treatment of gastric-like IMA. We experienced some cases of advanced gastric-like IMA in which pemetrexed and other drugs without gemcitabine were administered; however, all of them revealed a progressive course of the disease. It appears that gemcitabine may be a key drug for gastric-like IMA.

Ⅳ Conclusions

The combination of gemcitabine and pemetrexed was effective in the treatment of advanced gastric-like IMA. Gastric-like IMA has not yet been recognized and focused on, and its clinical features and significance have not been clarified. However, we suggest that it is beneficial to examine whether IMA is gastric-like or not because it may indicate a favorable response to gemcitabine. We hope to investigate more cases of gastric-like IMA and clarify its clinical and pathological features.

COI

The authors declare that they have no competing interests.

Acknowledgments

We would like to special by thank Dr. Keiko Ishii (Department of Diagnostic Pathology, Okaya Municipal Hospital, Japan) for assistance with the pathological diagnosis.

References

1) Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger K, Yatabe Y, Powell CA, Beer D, Riely G, Garg K, Austin JH, Rusch VW, Hirsch FR, Jett J, Yang PC, Gould M : International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society : international multidisciplinary classification of lung adenocarcinoma : executive summary. Proc Am Thorac Soc 8 : 381–385, 2011
2) Kris MG, Giaccone G, Davies A, Fukuoka M, Garfield DH, Jassem J, Quoix EA, Sandler AB, Scagliotti GV, Van Meerbeeck JP, West H : Systemic therapy of bronchioloalveolar carcinoma : results of the first IASLC/ASCO consensus conference on bronchioloalveolar carcinoma. J Thorac Oncol 1 : S32–36, 2006
3) Honda T, Ota H, Ishii K, Nakamura N, Kubo K, Katsuyama T : Mucinous bronchioloalveolar carcinoma with organoid differentiation simulating the pyloric mucosa of the stomach : clinicopathologic, histochemical, and immunohistochemical analysis. Am J Clin Pathol 109 : 423–430, 1988
4) Monnerat C, Le Chevalier T : Review of the pemetrexed and gemcitabine combination in patients with advanced-stage non-small cell lung cancer. Ann Oncol 17 : 86–90, 2006
5) Matsuzawa K, Akamatsu K, Katsuyama T : Mucin histochemistry of pancreatic duct cell carcinoma, with special reference to organoid differentiation simulating gastric pyloric mucosa. Hum Pathol 23 : 925–933, 1992
6) Yamakawa H, Takayanagi N, Ishiguro T, Kagiyama N, Shimizu Y, Sugita Y : A favorable response to cisplatin, pemetrexed and bevacizumab in two cases of invasive mucinous adenocarcinoma formerly known as pneumonic-type mucinous bronchioloalveolar carcinoma. Intern Med 52 : 2781–2784, 2013
7) Morichika D, Miyahara N, Hotta K, Okamoto Y, Minami D, Irie M, Tanimoto Y, Kanehiro A, Tanimoto M, Kiura K : Invasive mucinous adenocarcinoma mimicking organizing pneumonia associated with Mycobacterium fortuitum infection. Intern Med 53 : 2795–2799, 2014
8) Garfield DH, Franklin W : Dramatic response to pemetrexed in a patient with pneumonic-type mucinous bronchioloalveolar carcinoma. J Thorac Oncol 6 : 397–398, 2011
9) Manson GV, Ma PC : Response to pemetrexed chemotherapy in lung adenocarcinoma-bronchioloalveolar carcinoma insensitive to erlotinib." Clin Lung Cancer 11 : 57–60, 2010

(2015. 7. 23 received ; 2015. 12. 16 accepted)