INTRODUCTION

Pancreatic cancer remains one of the most lethal malignancies, with a five-year survival rate of approximately 10%.\(^1\) Most patients with pancreatic cancer are diagnosed at advanced stage because they have nonspecific symptoms and there is no effective screening tool for pancreatic cancer.\(^2\) As cytotoxic chemotherapy has been developed, the survival rate of pancreatic cancer has been improved.\(^3,4\) Targeted therapy and immunotherapy has also contributed to improved survival of pancreatic cancer.\(^5\) Despite several therapeutic advancements, pancreatic cancer remains challenging to treat, prompting active research on the tumor microenvironment.\(^6\) Analysis of the tumor microenvironment is expected to improve diagnostic and therapeutic strategies.\(^7,8\)

Keywords: Pancreatic cancer; Long-term survivor; Tumor microenvironment; Single-cell gene expression analysis
microenvironment, which is closely related to treatment resistance. Single-cell ribonucleic acid transcriptome analysis, in particular, has been instrumental in deepening our comprehension of the tumor microenvironment. Here, we present a case of metastatic pancreatic cancer patient with five-year survival and discuss the results of single-cell transcriptome analysis performed on pancreatic cancer tissues obtained at the initial diagnosis and after disease progression.

CASE

A 61-year-old women visited a local hospital with epigastric and back pain that began two months ago. Abdominopelvic computed tomography (CT) was performed and suggested pancreas head cancer (Fig. 1A). The patient was referred to our institution for further evaluation and treatment of pancreatic cancer. The patient had medical history of diabetes mellitus and hypertension. The patient was never smoker. The patient had abdominal pain on systemic examination. Physical examination revealed no specific findings. On initial laboratory results, complete blood count revealed that white blood cell count of 6,320/µL, hemoglobin of 12.5 g/dL and platelet count of 265,000/µL. On chemistry analysis, alkaline phosphatase level was elevated at 146 IU/L. Total bilirubin, aspartate transaminase, alanine transaminase was 0.4 mg/dL, 15 U/L and 15 U/L, respectively. Tumor marker of carcinoembryonic antigen and carbohydrate antigen 19-9 was elevated at 185.48 ng/mL and 269.44 U/mL, respectively.

Pancreas magnetic resonance imaging with magnetic resonance cholangiopancreatography revealed a focal ill-defined delayed enhancing lesion in pancreas head with abrupt cut off and dilatation of biliary tree and pancreatic duct with combined pancreatitis (Fig. 1B). F-18 fluorodeoxyglucose (F-18 FDG) positron emission tomography-CT (PET-CT) showed a hypermetabolic mass involving the head of pancreas suggesting pancreatic cancer and osteolytic bone lesions with hypermetabolism in the bilateral iliac bones suggesting bone metastases (Fig. 2). Endoscopic ultrasound-guided fine needle core biopsy at pancreas head mass was performed and pathologic result was moderately differentiated ductal adenocarcinoma (Fig. 3). The final diagnosis was pancreatic cancer with bone metastasis.

Initial treatment plan was to administer chemotherapy consisting of oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX). After nine cycles of FOLFIRINOX chemotherapy, follow-up study of F-18 FDG PET-CT showed near complete metabolic response of the primary malignant tumor involving pancreas head (Fig. 4). After sixty-one cycles of FOLFIRINOX chemotherapy over 50 months, F-18 FDG PET-CT showed an interval increase in the metabolic activity and size of the mass in the head of the pancreas (Fig. 5). Chemotherapy was switched to the combination of gemcitabine and nab-paclitaxel as the second
line of chemotherapy. After two cycles of second line chemotherapy, abdominal and chest CT scans showed that increase in extent of pancreas head cancer with newly developed peritoneal carcinomatosis and newly noted multiple nodules in both lungs, probably metastasis (Fig. 6). Third-line chemotherapy of combination of 5-fluorouracil/leucovorin and nanoliposomal irinotecan was administered in total fourteen cycles until the progression of pancreatic cancer. After ten cycles of third-line chemotherapy, which was 57 months post-diagnosis, endoscopic ultrasound-guided fine needle core biopsy was performed to identify potential targets for further treatment. Although fourth-line TS-1 chemotherapy was initiated after disease progression following third-line chemotherapy, the patient passed away about two weeks later.

DISCUSSION

The prognosis of metastatic pancreatic cancer is still poor, with a median survival of less than one year. However, in this case, the...
patient showed a favorable response to FOLFIRINOX, surviving five years, with nearly four of those years on FOLFIRINOX alone. FOLFIRINOX is a platinum-based chemotherapy regimen known to present a superior treatment response when there is a mutation in DNA damage repair genes.11,12 The ataxia telangiectasia mutated gene is one of the most commonly mutated DNA damage repair genes. In the germline mutation test of this patient, the rs779004090 single nucleotide polymorphism was identified in the ataxia telangiectasia mutated gene, which may have contributed to this patient’s superior response to FOLFIRINOX regimen.

As the tumor progressed, single-cell transcriptome analysis of the tissue obtained at 57 months after diagnosis revealed significant changes in the tumor immune microenvironment compared to tissues obtained at the time of diagnosis. Specifically, there was an increase in CD69+ T-cells and CD68+ lymphocyte-activation gene 3+ T-cells, which are involved in immune-suppression, and a decrease in killer cell lectin-like receptor subfamily F member 1+ natural killer cells, which are involved in identifying and destroying cancer cells.13-16 This pattern of change in immune cells is similar to the immunosuppressive microenvironment of pancreatic cancer with liver metastasis, as reported in a recent study of single-cell transcriptome analysis involving 21 pancreatic cancer patients.9

This indicates that an immunosuppressive microenvironment was formed in this patient as the cancer progressed, and such changes in the tumor microenvironment may have contributed to the progression of the cancer. Further studies on changes in the tumor microenvironment during the progression of pancreatic cancer, as demonstrated in this case, are necessary to gain a deeper understanding of the mechanisms of pancreatic cancer progression.

요 약

췌장암은 전반 시점에 진행된 상태인 경우가 많으며, 이때 항암화학요법이 주요 치료법으로 사용된다. 지난 10여 년간 새로운 항암화학요법의 도입으로 전체 생존 기간이 연장되었음에도 진행된 쌍장암의 중앙 생존 기간은 여전히 1년 미만이다. 그러나 임상현장에서는 때때로 진행된 쌍장암 환자 중 장기 생존자를 경험하게 되며, 이러한 사례를 분석하면 쌍장암에 대한 이해를 높이고 치료 방침 개선에 중요한

Conflicts of Interest

The authors have no conflicts to disclose.

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REFERENCES