

## CASE REPORT

# Familial Pancreatic Cancer at Elderly Siblings in Japan

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### ABSTRACT

Two female siblings aged 87 and 90 years were clinically diagnosed as pancreatic cancer by abdominal ultrasonography and abdominal contrast-enhanced CT. Pancreatic cancer of these patients was confirmed during the autopsy. Both patients shared risk factors of pancreatic cancer; old age, diabetes, and passive smoking. Strong family history of pancreatic cancer was found in these two patients as their father and younger brother were also suffering from this cancer. The present study seems to report two eldest cases of familial pancreatic cancer in siblings.

**Keywords:** Cancer risk, Elderly siblings, Familial pancreatic cancer.

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### INTRODUCTION

Familial pancreatic cancer (FPC) is defined as at least two first-degree relatives with pancreatic cancer (PC) that does not meet the criteria of other hereditary cancer syndromes. Japan initiated a nationwide FPC registry in 2014 and it seems that younger onset is common in FPC.<sup>1</sup> This age-related phenomenon has also been supported by FPC from other countries.<sup>2,3</sup> However, we experienced two cases of FPC in siblings aged 87 years and 90 years. The PC of these two patients was also confirmed at autopsy as well. They also had a direct family history of pancreatic cancer as their father and brother also suffered from same cancer.

### CASE REPORTS

#### Case 1

An 87-year-old Japanese female with complaints of abdominal pain and constipation was admitted to our hospital in March 2016. She had been suffering from type 2 diabetes mellitus for almost forty years and had Hashimoto's disease. She did not require insulin but was on oral antidiabetics and thyroid replacement therapy. There has been no history of drinking alcohol or smoking cigarettes. However, her husband was a heavy smoker. She was 153 cm tall, and her body weight was 44.8 kg with body mass index (BMI) of 19.1 kg/m<sup>2</sup>. Her abdomen was flat and soft. She had a dull tenderness in her right lower abdomen. She was not jaundiced. Main laboratory findings on admission revealed as follows: HbA1c 8.2%, free T4 1.13 ng/dL, thyroid stimulating hormone (TSH) 4.19 μU/mL, carcinoembryonic antigen (CEA) 4.7 ng/mL, carbohydrate associated antigen 19-9 (CA19-9) 200.6U/mL, s-pancreas antigen-1 67.9 U/mL. Contrast-enhanced CT showed an oval-shaped hypovascular tumor in the pancreatic body (diameter of 32 mm along with multiple nodules in the peritoneum). The final diagnosis was PC complicated with peritoneal dissemination (cT4, cNx, cM1, stage IV). She was under palliative care until she died 2 months later. The gross appearance of the abdomen at autopsy revealed hemorrhagic ascites, a cluster formation with adhesion by adjacent abdominal organs and tissues (Fig. 1), and dissemination of multiple white nodules in the peritoneum. Microscopic picture of the pancreas revealed a proliferation of cancer cells and abundant fibrosis. The final pathological diagnosis was well-poor differentiated adenocarcinoma of the PC (Fig. 2).

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**Conflict of interest:** None

#### Case 2

A 90-year-old Japanese female patient (elder sister of Case 1) was hospitalized to our hospital with epigastric pain and anorexia in June 2016. She had a 40-year history of type 2 diabetes, and she was on oral antidiabetics but never required insulin. She also had Hashimoto's disease, but thyroid replacement was discontinued after normalization of thyroid hormone profiles in sera. She denied smoking tobacco or drinking alcohol. However, her husband was a heavy smoker. She was 149 cm tall and her body weight was 48 kg (BMI 21.6 kg/m<sup>2</sup>). Physical status on admission was stable

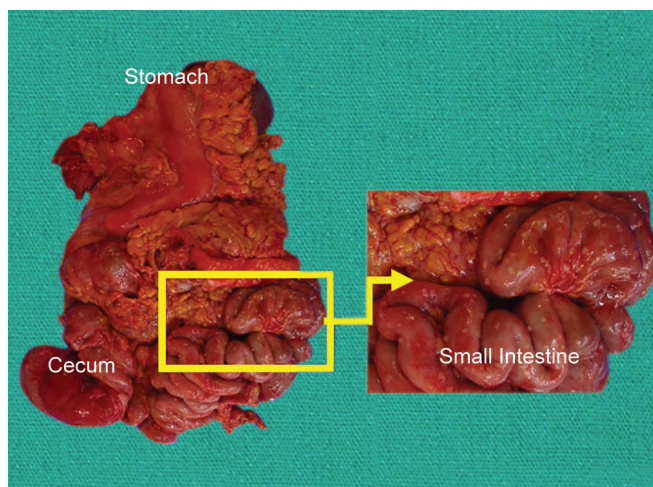


Fig. 1: Gross appearance of abdomen (Case 1)

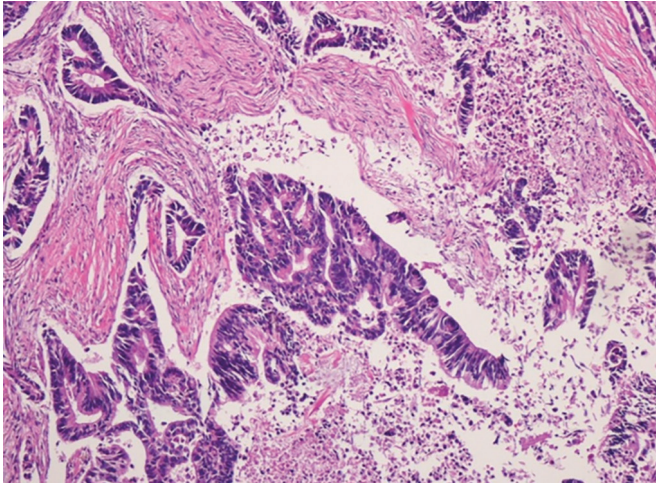


Fig. 2: Microscopic picture of pancreatic cancer (case 1)

except tenderness in her upper abdomen. She was not jaundiced. She did not have hepatomegaly or splenomegaly, and there was no palpable mass in the abdomen. Main laboratory findings on admission revealed as follows: HbA1c 6.5%, free T4 1.15 ng/dL, TSH 0.96  $\mu$ U/mL, thyroglobulin 77.10 ng/mL, thyroglobulin antibody 592.1 IU/mL, thyroid stimulating antibody 105%, thyroid peroxidase antibody 10.4 IU/mL, TSH receptor antibody 0.5 IU/mL, CEA 5.8 ng/mL, CA19-9 80.9 U/mL. Contrast-enhanced CT and PET-CT revealed a tumor in the head of the pancreas at the diameter of 26 mm. The final diagnosis was locally advanced PC (cT4, N0, M0, stage III). She initially received chemoradiation therapy, but she finally chose palliative care alone. Although metallic stent was placed in the duodenum for duodenal stenosis followed by biliary stenting for obstructive jaundice, she eventually died 15 months after initial diagnosis. On autopsy, the gross appearance of the abdomen revealed some metastatic nodules in the liver (Fig. 3). Carcinoma arising from pancreatic head invaded into the duodenum and lower bile duct with respective stents remaining. The hemorrhagic change was found in gastrointestinal tracts and uterus presumably caused by disseminated intravascular coagulation. Microscopically the main tumor was diagnosed as well differentiated tubular adenocarcinoma with a component of papillary adenocarcinoma and mucinous carcinoma (Fig. 4).

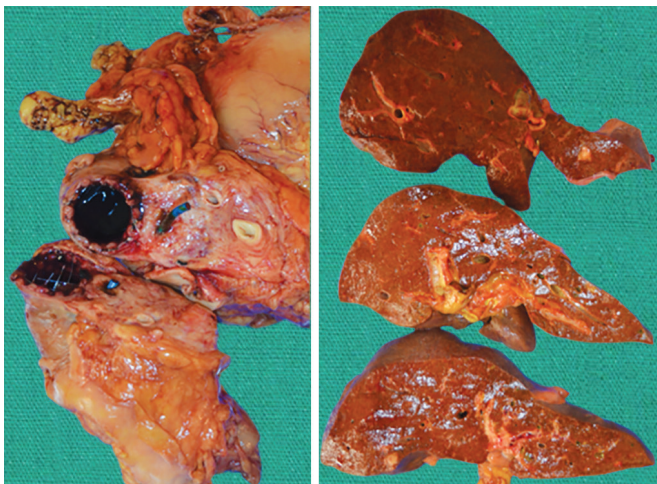


Fig. 3: Gross appearance of abdomen (case 2)

With regards to the familial tree of these two present cases, these two patients were a sibling. There were four patients with PC within the first-degree family (sisters, young brother, and father) (Flowchart 1). Notably, various cancers, breast cancer, were included in this family. Of note, eight family members of the family had been suffering from diabetes.

**DISCUSSION**

PC is currently the 4th leading cause of cancer death in Japan following colon cancer, lung cancer, and stomach cancer.<sup>4</sup> Incidence of PC is also increasing, ranked the 7th among various malignancies, and approximately 30,000 patients with PC are newly diagnosed annually.<sup>4</sup> Although the true etiology of PC is not well defined, the risk factors of PC are known, i.e., age, diabetes, smoking, alcohol consumption, and family history.<sup>4</sup> The peak onset of PC is in the 6th and 7th decades of life. However, the onset of hereditary malignant tumors, hereditary non-polyposis colorectal cancer and multiple endocrine neoplasia type 1 for instance, is significantly younger than sporadic malignant tumors.<sup>1,2</sup> As for FPC, there are reports to show the younger onset in comparison to sporadic PC.<sup>3-5</sup>

In this regard, the presented two sister cases of FPC with very advanced age (90 and 87 years old) are unique. There are reports regarding onset age among FPC, some dating back to the 70s. However, to the best of our knowledge even after extensive literature research, there is no report of FPC age above 80 years.<sup>3,4,6-14</sup> There are two possible underlying reasons to explain about elderly patients with FPC. One possibility is the acquisition of new unique genome in these siblings.<sup>15,16</sup> The other is incidental cases with sporadic PC due to the accumulation of various risk factors, such as longstanding diabetes and passive smoking alike the present sibling cases. At present, clinical and genetic data of patients with FPC are piling up worldwide including Japan.<sup>17-19</sup> Accumulation of PC is usually due to environmental exposure to carcinogenetic factors and genetic factors associated with PC, presumably stronger in FPC.<sup>19</sup> Therefore, PC would develop in a young age if the members of FPC are exposed to multiple environmental risk factors.<sup>20</sup> The environmental exposures, i.e., longstanding diabetes and passive smoking are important in the development of sporadic PC and FPC.<sup>21</sup> As shown in Flowchart 1, four patients in this family suffered from PC, two males, and two females. Two male patients with PC died younger than the present sisters, father and younger brother at the age of 52 and

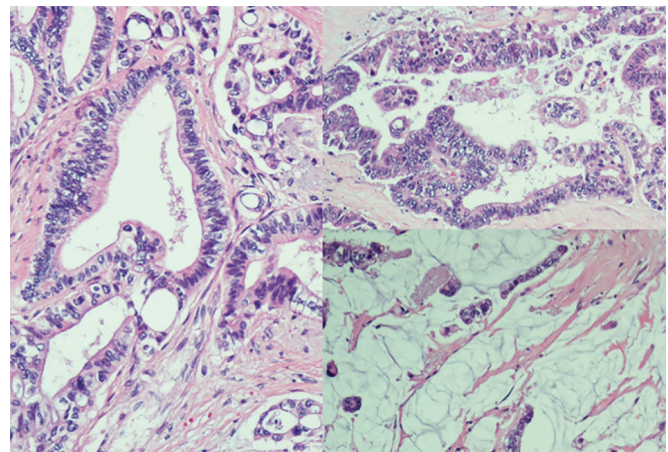
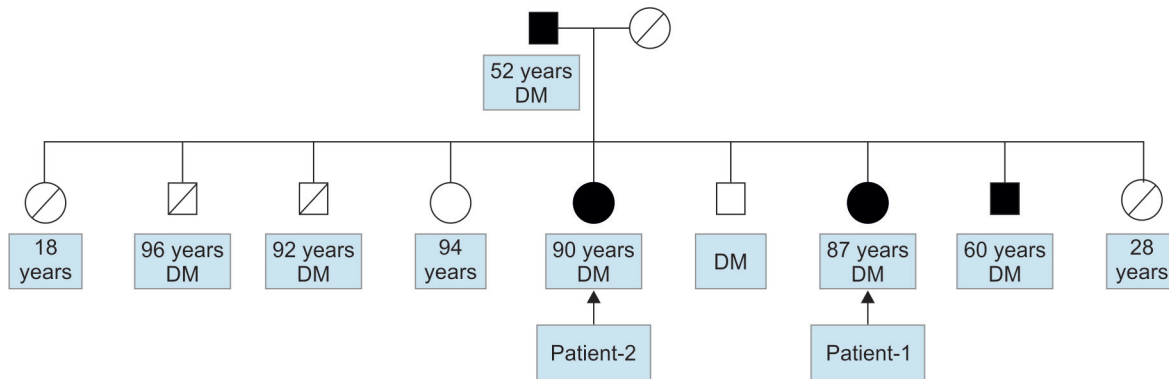


Fig. 4: Microscopic picture of pancreatic cancer (case 2)

Flowchart 1: Familial tree in two siblings of FPC



50, respectively. Although odd index about gender and age risk factors of PC are not larger than other risk factors including family history, smoking, and obesity, recent new research data from Japan demonstrated a crucial role of dedifferentiation-associated epigenetic regulations in the initiation of pancreatic cancers.<sup>22</sup> At any rate, the present case report would contribute to provide new unique subject on the research area on FPC, for example, the elucidation of risk factors of very elderly PC patients between FPC and sporadic PC.

Both patients had Hashimoto's disease. There are reports suggesting an increased risk for extrathyroidal cancers in thyroid diseases: breast, colon, melanoma, hematologic malignancies, uterus, kidney, and ovary.<sup>23</sup> Grave's disease and high thyroid hormone level in sera, especially T3 levels, were linked to breast cancer incidence.<sup>24</sup> However, there is no report showing its association between PC and thyroid diseases including Hashimoto's diseases. Since Hashimoto's disease is a relatively common disease as such there might be no relationship with PC. However, we may hypothesize that Hashimoto's disease delayed the onset of PC in the sisters. This should be addressed in the future.

In summary, the eldest sibling cases of FPC ever reported. The further genetic and epigenetic analysis would give us an answer to understand the underlying pathogenesis of FPC.<sup>25</sup> In the meantime, it is essential we collect the clinical data and preserve the materials of DNA from many cases with FPC.<sup>26</sup> It is expected that the present report should provide a new research project of FPC.

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