Long-Term Survival of a Case of Anaplastic Carcinoma of the Pancreas Invading the Transverse Colon.

—A survey of the Japanese literature—

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Abstract

Pleomorphic giant cell carcinoma of the pancreas usually has a very poor prognosis with some investigators reporting a mean post-surgical survival time of just months. This poor post-surgical prognosis has led to the reappraisal of the use of surgical resection for pleomorphic carcinoma. Recently, this carcinoma is classified as a type of anaplastic ductal carcinoma by Japanese criteria 2002. We report the clinicopathological features of a case in which the patient has survived more than five years following surgical resection of a pancreatic pleomorphic giant cell carcinoma. A seventy-four years old Japanese man presented complained of an abdominal mass. The mass of pancreas head was 10 cm in diameter and had invaded the transverse colon. Pancreaticoduodenectomy combined with colectomy was performed. Histological and immunohistochemical studies led to a diagnosis of pleomorphic-type anaplastic carcinoma of the pancreas. For three years following surgery the patient received oral 5-Fluorouracil as adjuvant chemotherapy, and after five years the patient is still healthy without recurrence. A survey of the Japanese literature found about 45 cases of pleomorphic-type carcinoma. Although most cases survived for only months following surgery, six cases of one-year post-surgical survival and two cases of five-year post-surgical survival have been reported. We discuss herein factors of long time survival cases of pleomorphic carcinoma, focusing on the importance of proper diagnosis and classification for pleomorphic carcinoma.

Keyword

Pancreatic pleomorphic carcinoma, Pancreatic giant cell carcinoma, Pancreatic anaplastic carcinoma

Introduction

Pleomorphic giant cell carcinoma of the pancreas is a relatively rare disease and is classified as a type of anaplastic ductal carcinoma by recent Japanese criteria 2002. Some investigators have suggested reappraisal of surgical resection to treat this type of carcinoma due to poor prognosis¹, meaning other investigators have reported cases of long-term post-surgical survival². Classification of this carcinoma has changed multiple times both in Japan and in other countries, leading to possible discrepancies in findings. Older manuscripts may have included other types of cancer or osteoclastoid giant cell carcinoma³, while newer classifications have excluded giant cell carcinoma of osteoclastoid-type. Pure osteoclastoid giant cell carcinomas (tumor), even large-sized tumors, are frequently cured by surgical resection, while pleomorphic giant cell carcinomas have been characterized by extremely...
poor outcome. In the present report, we present a case of pleomorphic carcinoma of the pancreas that invaded the transverse colon and duodenum. We performed pancreaticoduodenectomy combined with transverse colectomy, in a patient who has survived for more than five years. A review of the Japanese literature for cases of giant cell carcinoma of the pancreas that were classified according to recent Japanese criteria found 45 cases. In 22 cases of macroscopically complete resection, six cases of one-year post-surgical survival and two cases of five-year post-surgical survival have been reported. The results of differential survival time in cases diagnosed as pleomorphic giant cell carcinoma in Japan, suggests misdiagnosis of osteoclastoid type or existence of a yet unclassified type of giant cell carcinoma. We present the clinicopathological features of our case, a survey of Japanese literature, and discuss the issue of diagnosis and classification of pleomorphic carcinoma.

Case

A seventy-four years old man experienced right upper abdominal pain for two months prior to visiting his family doctor for constipation. The doctor detected a large abdominal mass and sent him to our hospital. Upon physical examination a large mass was observed in the right upper quadrant of the abdomen. The mass had a smooth surface and was twice the size of an egg. Laboratory findings revealed leukocytosis (13000/mL), elevated serum CRP of 7.9 mg/mL, and high serum IAP of 1007 μg/mL. The serum CEA and CA19-9 were within normal limits. Abdominal computed tomography showed a round homogenous mass with a clear margin while contrast study showed a slight heterogenous mass (Figure 1). Abdominal magnetic resonance imaging (MRI) revealed a mass with low signal in T1 image and a relatively high signal in T2 image, MRI findings suggested duodenal invasion. Increased signal was obtained by dynamic MRI after injection of contrast medium, and on the basis of this data fibrosis was suspected (Figure 2). Color flow mapping ultrasonography revealed a large low echogenic mass with vascular structure. Celiac angiography revealed weak tumor blood supply from the gastroduodenal artery and encasement of the anterior superior pancreaticoduodenal artery (Figure 3). A superior mesenteric artery angiography revealed tumor blood supply from middle colic artery. Colonoscopic findings were an elevated lesion accompanied by ulceration and luminal stenosis, and a barium enema also revealed stenosis of transverse colon. Early gastric cancer was found in the antrum of the stomach by gastric endoscopy. From these results, we suspected leiomyosarcoma of transverse colon had invaded to the duodenum accompanied by early gastric cancer or other types of cancer.
Operative findings

A small amount of yellow ascites was noted. There were two egg-sized tumors in the pancreas head. This tumor was tightly affixed to the hepatic flexure of the colon, duodenum, and antrum of stomach. Although the invasion was close to the portal vein, it was possible to separate the tumor from the portal vein. No liver metastasis, peritoneal dissemination or swollen lymph nodes were found. The tumor was resected by pancreaticoduodenectomy accompanied with right hemicolectomy.

Pathological findings

Macroscopic findings revealed milky-colored mass originating from the pancreas with the tumor was seen to be growing in all directions (Figure 4). Under high magnification, the tumor had a relatively clear margin and was observed to compress the pancreatic tissues to the right upper side. Hematoxylin. Eosin. staining showed tumor cells to be large in size, and as well revealed the presence of unusual bizarre giant cells, a small number of which resembled osteoclastoid cells with basophilic cytoplasm (Figure 5). The nuclei of tumor cells were not uniform in size and were localized to the periphery of cells. Although duct-like structures of mononuclear tumor cells were observed in the periphery of the tumor, there were no obvious spindle cell patterns nor partial gland formation. Tumor cells were positive for epithelial membrane antigen (EMA) by immunohistochemical staining. Tumor cells were positive for cytokeratin (Figure 6), but negative for CD68. Giant cells were positive for vimentin (Figure 7). Although vimentin, a mesenchymal marker, was positive, the tumor was histologically diagnosed as pleomorphic-type anaplastic ductal carcinoma of the pancreas. Small early gastric cancer was found in the resected stomach.

Pathological diagnosis

Carcinoma of the pancreas head ph, 10×7×7 cm TS4, A anaplastic ductal carcinoma; Pleomorphic giant cell carcinoma medullary-type, INFα, ly0, v0, ne(+), mpd(−).

Figure 4. Macroscopic findings.

Figure 5. Hematoxylin Eosin staining (×20).

Figure 6. Immunostaining of cytokeratin (×40).

Figure 7. Immunostaining of vimentin (×40).
s(±), rp(−), ch(−), du(+), pv(−), a(−), pl(−), pw(−), bdw(−), ew(−)


Adenocarcinoma of stomach

A, IIb, 0.3×0.1 cm tubular adenocarcinoma; well-differentiated type with differentiated carcinoma focus, medullary-type INFα, sm, ly0, v0

After surgery, the patient was treated with oral 5-Fluorouracil adjuvant chemotherapy for three years. The patient has received follow-up care in our hospital since surgery, and is now in good health without recurrence for 5 years.

Discussion

Preoperative diagnosis of pleomorphic carcinoma of the pancreas is difficult because this tumor is multicentric. In ultrasounds, a mixed pattern of low and high echogenicity is often observed. The tumor has generally a low density in abdominal computed tomography, and is usually more hypervascular than pancreatic carcinoma. It was possible to differentiate pleomorphic carcinoma from adenocarcinoma, former is large in size, has a clear margin, and hypervascularity. Our preoperative diagnosis of our case was leiomyosarcoma.

The first case of pleomorphic carcinoma of the pancreas was reported by Sommers et al. in 1954. Several names (pleomorphic carcinoma, giant cell carcinoma, pleomorphic giant cell carcinoma, pleomorphic large cell carcinoma, pleomorphic giant cell tumor), and several categories (undifferentiated carcinoma, sarcomatoid carcinoma, anaplastic ductal carcinoma) have been employed to describe this type of carcinoma. Therefore, there is some confusion regarding classification of this neoplasm. Morohoshi and Kloppel divided pleomorphic carcinoma into giant cell-type, osteoclast-like cell-type, and small cell-type carcinoma. In 1984 Cubilla et al also classified pleomorphic carcinoma into giant cell carcinoma, osteoclastoid-type giant cell carcinoma, and unclassified carcinoma. In the Japanese classification (3rd Edition) of 1986, undifferentiated carcinoma of the pancreas was divided into pleomorphic-type including osteoclastoid-type, round cell-type, and spindle cell-type, but in 1993, the Japanese classification (4th Edition) reclassified undifferentiated carcinoma as anaplastic ductal carcinoma which includes giant cell-type, pleomorphic-type, spindle cell-type, and giant cell carcinoma of osteoclastoid-type. The literature of the last decade indicates that prognosis is better for osteoclastoid-type than for pleomorphic-type. In fact, the life expectancy is less than a year for patients with pleomorphic-type giant cell carcinoma, though with some cases of osteoclastoid-type long-term survival has been reported. Osteoclastoid-like giant cell carcinoma appears to be a different type of carcinoma, and for this reason, the latest General Rules for Cancer of the Pancreas (5th Edition 2002) edited by the Japan Pancreas Society classified anaplastic ductal carcinoma into giant cell-type, pleomorphic-type, and spindle cell-type, excluding giant cell carcinoma of the osteoclastoid-type from the classification. Giant cell carcinoma of osteoclastoid-type is defined in the new Japanese criteria as a carcinoma that predominantly contains giant macrophages or osteoclast-like giant cells. Likewise, the new AFIP (Armed Forces Institute of Pathology) also excludes giant cell carcinoma of osteoclastoid-type from the classification of anaplastic carcinomas. Because the histological appearance of these carcinomas is essentially pleomorphic, classification is changing. Table 1 shows changes of classification of pancreatic giant cell carcinoma in USA and Japan. Recently, immunohistochemistry has been employed in classifying and determining the origins of these giant cells. Deckard et al. reported the immunohistochemical distinction between tumors of osteoclastoid-type and pleomorphic-type, though they indicated that the distinction between these types is often not clear-cut. Kloppel et al reported that most tumors containing osteoclastoid-like cells contain pleomorphic cells and that pleomorphic-type tumors often include both types of cell. Lewardrowski et al or Watanabe et al as well described mixed tumors containing both osteoclastic and pleomorphic giant cells. The problem with current classification strategies is lack of classifications for tumors that contain both pleomorphic giant cells and osteoclastoid cells. Although our case contained small number of osteoclastoid-like cells, immunohistochemical and histological examination proved this tumor to be pleo-
morphic-type anaplastic carcinoma by the current Japanese criteria. Some old Japanese case reports of pleomorphic giant cell carcinoma include giant cell carcinoma of osteoclastoid type. Recent immuno-histochemical studies have revealed that pleomorphic giant cell carcinoma is a sarcomatous metaplasia of ductal adenocarcinoma that is from epithelial in origin. Conversely, the origin of osteoclastoid giant cell carcinoma has been debated, and both mesenchymal and epithelial origins have been reported. Although Ashizawa et al reported that osteoclastoid-like cells in pleomorphic giant cell carcinoma may be reactive histiocyte in origin, the origin of this cell remains unclear.

Treatment of pleomorphic carcinoma has essentially been surgical resection, though additional chemotherapy has also been employed. There has been a debate, however, even over the use of surgery in such cases, due to poor survival of patients following surgery. Yamaguchi et al. suggested that pleomorphic carcinoma of pancreas should not be a candidate for pancreatectomy due to its poor prognosis, whereas Solis et al. did not find pleomorphic feature of pancreatic neoplasms to be a contraindication for surgical resection. This difference in opinion over surgical resection for pleomorphic carcinoma of the pancreas may arise from the fact that this carcinoma is multifactorial or that osteoclastoid-type carcinoma cells are occasionally present. In 1979 Cubilla et al reported that the one year survival rate of true cases of pleomorphic carcinoma was 0%, and in 1980 Reyes et al reported a mean survival time of three months for pleomorphic giant cell carcinoma. However, almost of their cases were non-resected. In a recent review of 35 cases of anaplastic carcinoma of the pancreas, Peel et al. found that 29 of 35 patients died of disease (average 5.2 months after resection) while three patients were alive at last follow-up (average 94.0 months). Our own survey of the Japanese literature for 45 cases of pleomorphic-type carcinoma (excluding osteoclastoid-type) revealed that most cases died within a year and that only two cases achieved five-year survival (our case and the Kurihara case). Many cases appeared to have metastasized (26/45) so that the tumor could not be completely or nearly completely removed (23/45). Twenty-two cases received completely or nearly complete resection (“curative” resection by Japanese criteria) with or without combined surrounding organ and liver resection. These 22 cases had a mean age of 65 ± 8.1 years old (16 male and 6 female). These cases of diagnosed pleomorphic giant cell carcinoma could be split into a good outcome group and poor outcome group. Fourteen cases died despite “curative” resection, with a mean survival time of 4.9 months. Eight cases were reported to have survived without recurrence at the time of publication, each with survival time greater than a year (Table 1). Seven of the eight cases were male, and none of the cases had distant metastatic disease (2 regional lymph node metastasis). These discrepancies may be a confusion of different types of tumor or misdiagnosis. Tschang et al. revealed that pleomorphic giant cell carcinoma might be confused with melanoma, hepatocellular carcinoma, choriocarcinoma, pleomorphic liposarcoma, pleomorphic rhabdomyosarcoma, fibroxanthosarcoma, and giant cell carcinoma of the lung or thyroid. However, pathological reports for each case found in the Japanese literature revealed characteristics of pleomorphic giant cell carcinoma (bizarre pleomorphic mononucleated and multinucleated giant cell, noncohesive, sarcomatous growth etc).
large-sized carcinoma (case number 1, 2, 4 and 8) contained a small number of osteoclastoid-like cells, similar to the findings of our case. Deckard et al. reported good outcomes for cases of osteoclastoid-type containing no or few pleomorphic giant cells, thus the presence of these osteoclastoid-like cells may associate with a good outcome\[16\]. Jotsuka et al. also indicated that osteoclast formation was associated with longer survival\[31\]. Kurihara et al. reported long-term survival following resection of pleomorphic carcinoma of the pancreas with massive lymphocytic stromal infiltration (accompanied by lymphoepithelioma-like carcinoma)\[29\]. Their case (case number 6) is atypical and may be excluded from this survey. Yamamoto reported a resectable case (case number 7) of large pleomorphic giant cell carcinoma of the pancreas without recurrence for 1.5 years\[32\]. However, the Yamamoto case was negative for immunohistochemical markers of epithelial tissue.

We believe that the present classification still includes several types of tumor with different biological characteristics. If cases number 6 and 7 and small-sizes cases (numbers 3 and 5) are excluded, all remaining cases contain small numbers of osteoclastoid-like cells. In our investigation of the literature, we noted that large-sized pleomorphic carcinomas with foci of adenocarcinoma that do not contain osteoclastoid-like cell had very poor outcome and none of these patients achieved a surgical cure. Half of the cases of giant cell carcinoma are accompanied by adenocarcinoma\[13\]. The fact that our case did not have adenocarcinoma may have contributed to the good clinical outcome. Although our case does not have any of the typical pathological findings, like spindle cell pattern or gland like formation, we suggest that surgical treatment may be appropriate for carcinomas with favorable characteristics. For giant cell carcinoma of the pancreas their outcome is mixed, patients with osteoclastoid carcinomas have good outcomes whereas those with pleomorphic carcinomas have extremely poor outcomes. Therefore, careful differential diagnosis is needed for proper treatment. Further evaluation is needed for accurate pathological classification and appropriate treatment of this type of tumor.

**References**


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退形成膵管癌横行結腸浸潤の術後長期生存の1例
—本邦報告例の集計—

抄録

膵多形細胞型巨細胞癌は通常、非常に予後不良であり、その予後は数ヶ月と報告されていない。予後不良のため外科切除は避けられるべきであるとする意見もある。2002年の本邦取り扱い規約では退形成膵管癌に分類されるが、我々は術後5年無再発生存中の稀な症例を経験したので報告する。症例は74歳男性で腹部腫瘤を主訴として来院した。検査にて膵頭部に直径10 cmの腫瘤があり横行結腸に浸潤していた。横行結腸切除合併膵十二指腸切除を施行し、病理検査、免疫組織検査で膵多形細胞型巨細胞癌と診断された。術後補助化学療法として3年間、経口5FU葉を投与し、現在5年を経過するが再発を認めない。本邦文献の集計では45例の多形細胞型巨細胞癌の報告があり、ほとんどどの例が数ヶ月の予後であるが、6例が1年以上、内2例は5年以上の生存が報告されていた。多形細胞型巨細胞癌の診断と分類について生存例を含めて検討を加えた。

索引用語
膵多形細胞型巨細胞癌、膵巨細胞癌、退形成性膵管癌