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Case Report

Favorable Response After Gemcitabine-Radiotherapy for Invasive Pancreatic Intraductal Papillary Mucinous Neoplasm: A Case Report

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The efficacy of chemoradiotherapy for invasive pancreatic ductal carcinoma derived from an intraductal papillary mucinous neoplasm (IPMN) has not been established. The subject of the present report was a 53-year-old man admitted for the treatment of IPMN. The tumor, located in the pancreatic body, was of the mixed type of IPMN, and it involved the branch duct, where it was 38 mm in diameter, and the main duct, where it was 6 mm in diameter. Distal pancreatectomy was performed and the postoperative course was uneventful; however, histopathologic diagnosis revealed invasive ductal carcinoma with a positive surgical margin in the pancreatic duct. Although total pancreatectomy was recommended, chemoradiotherapy (50.4-Gy irradiation and gemcitabine) was preferred by the patient. At 9-month follow up, computed tomography and magnetic resonance imaging showed a cystic mass at the surgical margin of the pancreas. Endoscopic ultrasonography showed a 44-mm cystic lesion with nodules in the remnant pancreas, on the basis of which he underwent total pancreatectomy. Pathologic examination of the resected specimen revealed absence of the epithelium at the surgical margin of the main pancreatic duct, and malignant cells were not detected.

Key words: Pancreatic cancer – Intraductal papillary mucinous neoplasm – Chemoradiotherapy

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Intraductal papillary mucinous neoplasms (IPMNs) of the pancreas are generally characterized by the proliferation of mucinous epithelium with varying degrees of ductal and cystic dilatation.[1,2] With advances in noninvasive imaging, such as transabdominal and endoscopic ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI), this tumor is now being diagnosed with increasing frequency.[3–6] It is made up of intraductal components with varying degrees of cytoarchitectural atypia from adenoma, through borderline to carcinoma in situ and invasive carcinoma. Moreover, there are 3 types of IPMN: main pancreatic duct type, branched duct type, and mixed type, the last of these being a combination of the first two.[7]

A surgical strategy for IPMN is well established.[8] However, the efficacy of chemoradiotherapy for invasive IPMN remains unclear, even though its effectiveness against unresectable ductal carcinoma of the pancreas has been demonstrated.[9,10] This case report presents a patient with invasive IPMN who responded favorably to chemoradiotherapy.

Case Report

A 53-year-old man was admitted for investigation and treatment of a tumor in the pancreatic body, which had been detected on ultrasonography by a general practitioner. MRI revealed a cystic mass in the body of the pancreas, and magnetic resonance cholangiopancreatography demonstrated a 38-mm mass in a branch of the pancreatic duct and a 6-mm mass in the main pancreatic duct (Fig. 1). Laboratory data showed slight elevation of the serum amylase level (188 U/L), but the other values were within normal limits, including the tumor markers CEA, CA19-9, DUPAN-2, and Span-1. We diagnosed mixed-type IPMN and performed distal pancreatectomy. The patient had an uneventful postoperative course, but histopathologic examination revealed invasive ductal adenocarcinoma with an involved resection margin (Fig. 2). Malignant cells were recognized in the pancreatic duct of resected margin, partially, and lymphatic vessel invasion and lymph node metastasis were not recognized. We recommended total pancreatectomy; however, the patient chose the option of chemoradiotherapy with 50.4-Gy/28-fraction/5.6-week 3-dimensional conformal radiotherapy treatment and consecutive gemcitabine (1000 mg/m^2). As radiotherapy, the stump of the pancreas and prophylactic para-aortic

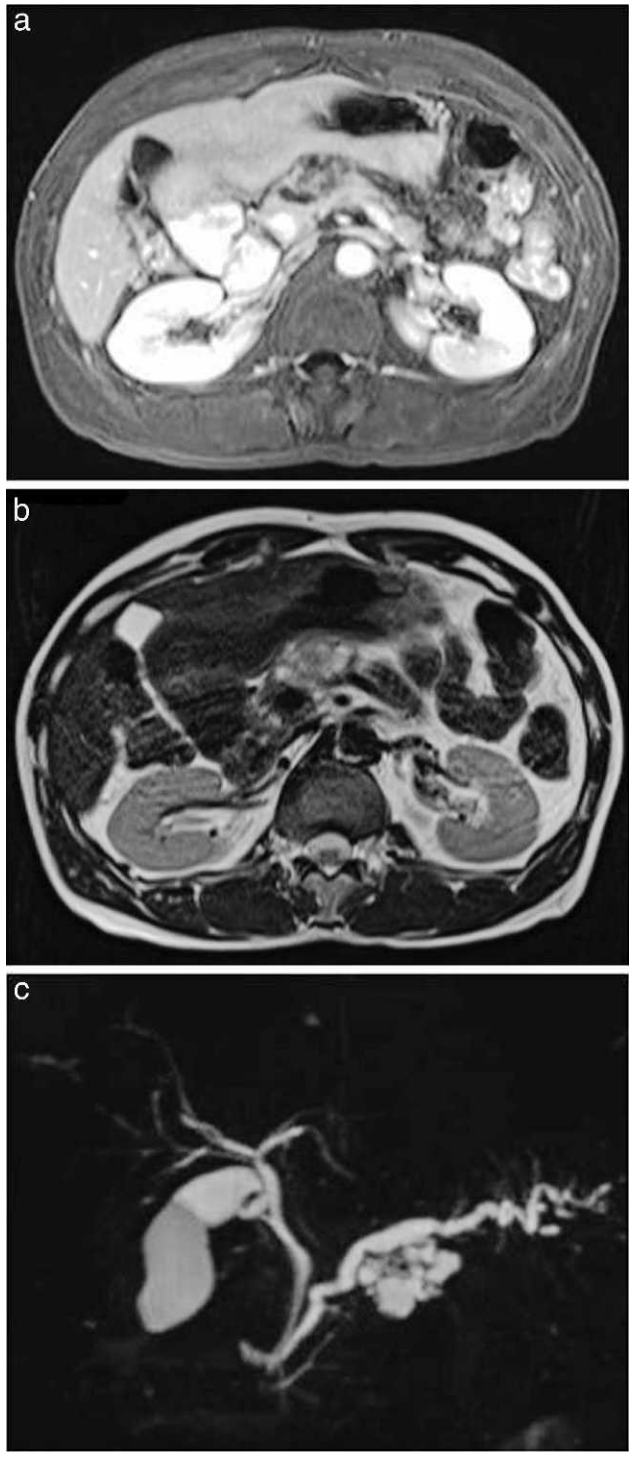

Fig. 1 MRI showed a mass in the body of the pancreas, and papillary projections are also visible (a and b). Magnetic resonance cholangiopancreatography (MRCP) revealed a combined type of IPMN (c).

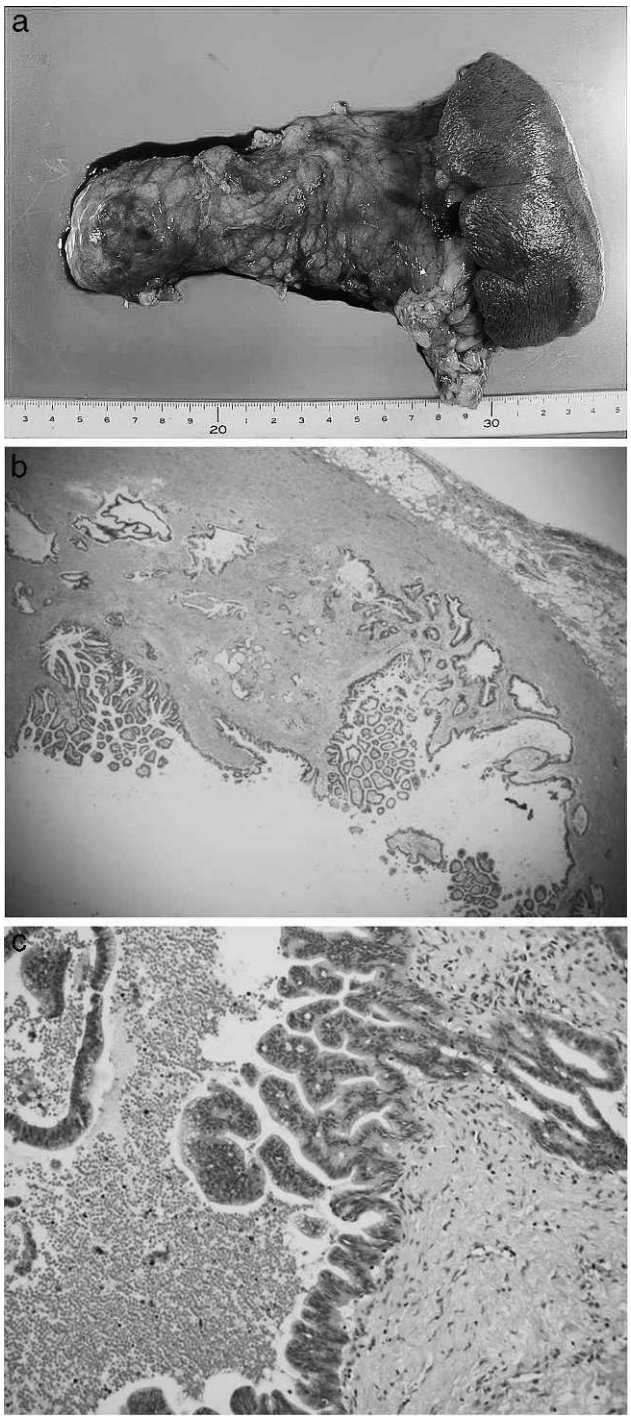

Fig. 2 Resected body and tail of the pancreas and the spleen (a). Histologic examination revealed a margin positive for invasive IPMN (b and c).

lymph nodes from the celiac trunk to the left renal vein were included in the fields. An MRI scan done 9 months postoperatively revealed a cystic mass at the surgical margin of the pancreas (Fig. 3), but enhanced CT did not detect any lymph node or distant metastases. After endoscopic ultrasonography showed a 44-mm cystic lesion in the remnant pancreas containing nodules (Fig. 4), total pancreatectomy was performed. Pathologic examination revealed desolation of the epithelium in the main pancreatic ductal stump, and neither malignant cells nor IPMN cells were recognized (Fig. 5). The cystic lesions were cicatrix tissue, and the nodules were composed of fibrin formation and foam cells. The patient's postoperative course was uneventful, and he is still alive at 3 years and 4 months from the time of total pancreatectomy without obvious evidence of recurrence.

Discussion

IPMNs of the pancreas are a relatively new entity, having been initially described by Ohashi *et al*[11] as recently as 1982. However, the incidence of these mucin-producing epithelial tumors of the exocrine pancreas is increasing.[11] IPMNs can be subdivided into main duct, branch duct, and mixed (combined) types, depending on whether the lesion is located in the main pancreatic duct or the side branch.[12,13] There are significant differences in the prevalence of cancer between main duct IPMNs and branch duct IPMNs, ranging from 57% to 92% and 6% to 46%, respectively.[5,14–18] Therefore, the classification of IPMNs has substantial value in determining the management strategy for this neoplasm. It was recently reported that one of the acceptable predictive signs of malignancy for branch duct IPMNs is a size greater than 30 mm plus the presence of mural nodules or protruding lesions in dilated branch ducts,[18–21] whereas surgical treatment is recommended for main duct variants.

IPMN ranges in atypia from benign adenoma to pancreatic ductal adenocarcinoma. Pancreatic ductal adenocarcinoma arising in the setting of an IPMN appears to have a different natural history and molecular pathogenesis than ductal adenocarcinoma arising from pancreatic intraepithelial neoplasia.[3,22–25] Moreover, in relation to the concept of transformation from benign to invasive carcinoma, previous studies have shown a progression in time, ranging from 5 to 7 years.[3,5]

The extent of resection for IPMN is controversial, and much of this controversy lies in the status of the resected margin. A negative transection margin is a reasonable guide to determine the extent of resection, but it does not guarantee that IPMN will not develop in the pancreatic remnant.[3,5] Several inves-

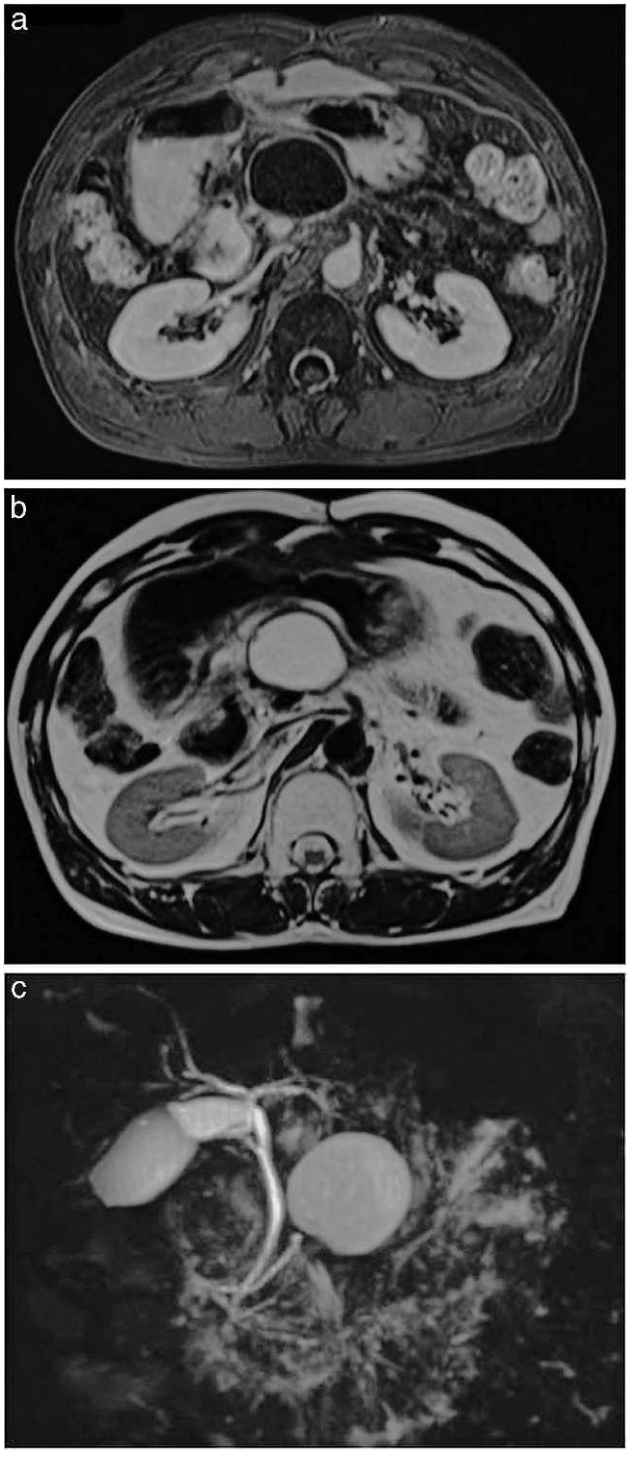

Fig. 3 MRI showed a cystic mass in the surgical margin 9 months postoperatively. The capsule of the cystic mass was enhanced and its contents were seen as low intensity on the T1-weighted image (a) and high intensity on the T2-weighted image (b and c).

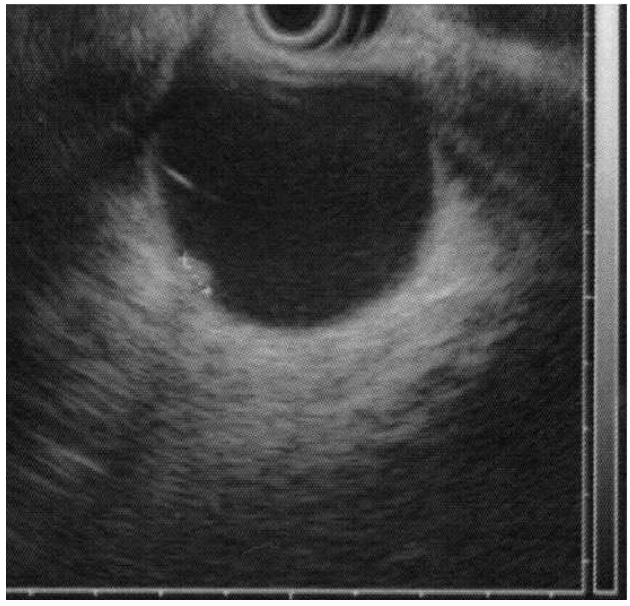

Fig. 4 Endoscopic ultrasonography showed a 44-mm cystic lesion in the remnant pancreas, with nodules.

tigators advocate total pancreatectomy to avoid the risk of noninvasive or invasive carcinoma developing in the remnant pancreas, but this often results in severe metabolic consequences.[26] In the present case, because the surgical margin of the main pancreatic duct was not seen to be dilated intraoperatively, intraoperative frozen section of the pancreatic margin was not done; however, histologic examination subsequently revealed a positive surgical margin. Previously, frozen section of all IPMNs was not done in our institution, but since this experience, intraoperative frozen section for main duct variant and combined variants is now the rule. Concerning the margin status of invasive IPMN, the Johns Hopkins group studied the correlation between margin status and survival, and it concluded that margin status was associated with outcome for invasive IPMNs.[3] Therefore, after the confirmation of a positive surgical margin, we recommended total pancreatectomy of the remnant pancreas as the first choice, and chemoradiotherapy as the second. Whereas chemoradiotherapy has been demonstrated to prolong the survival of patients with pancreatic ductal adenocarcinoma from pancreatic intraepithelial neoplasia,[27,28] it is unclear whether it improves the survival of patients with invasive IPMN. Swartz *et al*[29] concluded that adjuvant chemoradiotherapy was effective after pancreatic resection for invasive carcinoma associated with IPMN, but details on the malignant status were

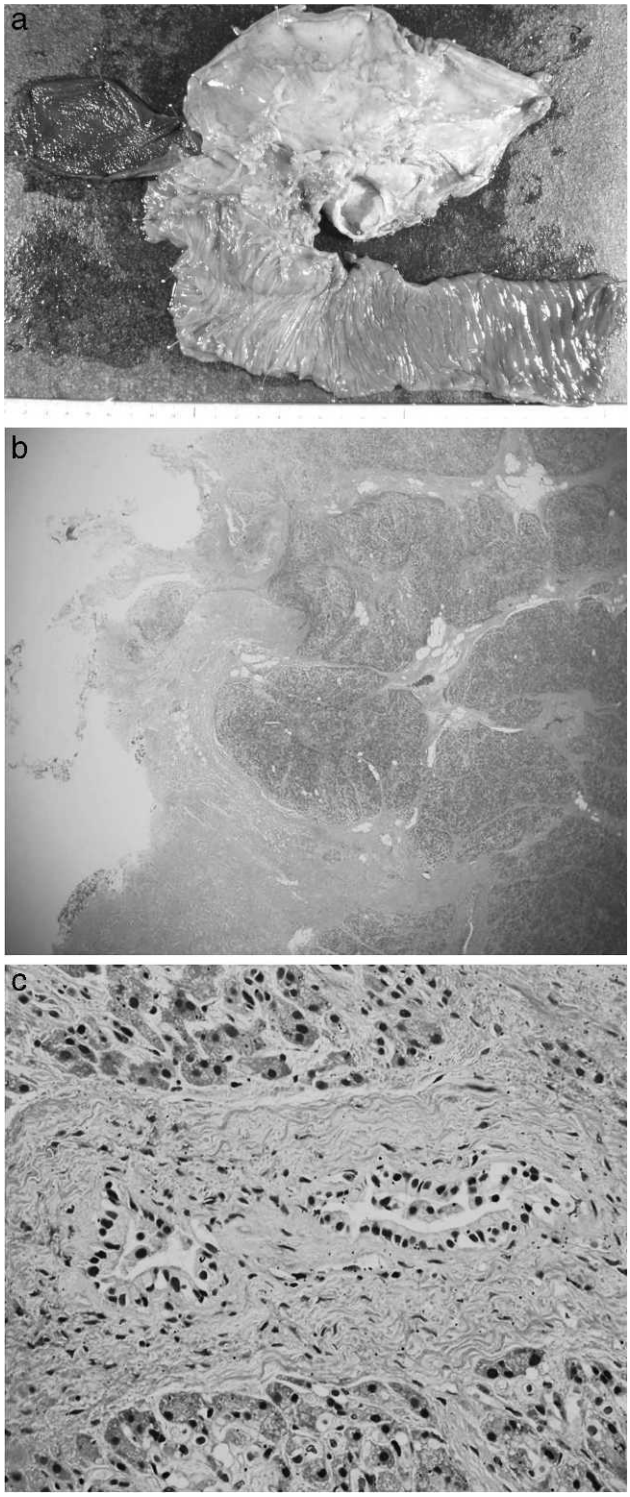

Fig. 5 Surgical specimen of the remnant total pancreatectomy (a). Microscopic examination revealed no epithelium at the surgical margin of the main pancreatic duct and no malignant cells (b and c).

unclear. Hence, the patient was given chemoradiotherapy, and the follow-up imaging examinations revealed a cystic mass with nodules at the surgical margin of pancreatic remnant at 9 months after the first distal pancreatectomy. This cystic mass was interpreted as recurrent disease with unfavorable response to chemoradiotherapy. Subsequently, total pancreatectomy was done, removing the pancreatic remnant. However, histologic examination of the removed pancreatic remnant confirmed that it was cancer-free, suggesting that the chemoradiotherapy had been effective against the invasive pancreatic ductal carcinoma derived from IPMN.

In conclusion, gemcitabine-based chemoradiotherapy could be effective for malignant IPMN with positive margins, especially for high-risk patients, who are unable to undergo total pancreatectomy.

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