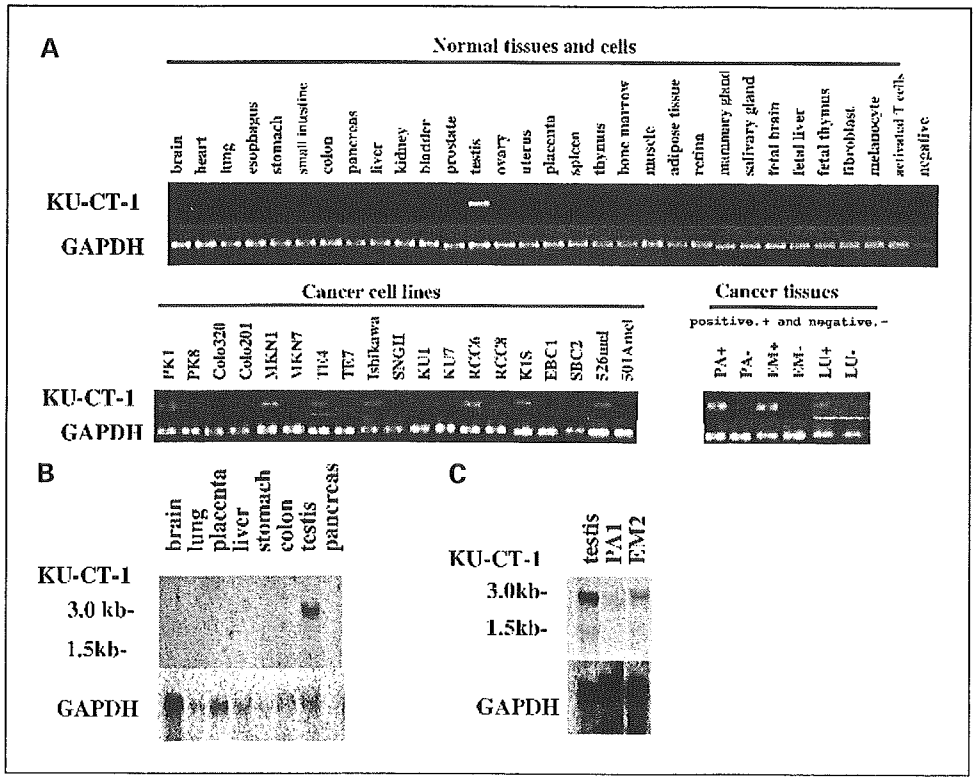

Fig. 1. KU-CT-1 is a cancer testis antigen that is frequently expressed in pancreatic and endometrial cancers. *A*, expression of KU-CT-1 (TW3) in various cancer cell lines, cancer tissues, and normal testis evaluated by reverse transcription-PCR analysis. Thirty cycles of PCR were done with total RNAs obtained from various cancer cell lines, cultured noncancer cells, and cancer and normal tissues. PA, pancreatic cancer tissue; EM, endometrial cancer tissue; LU, lung cancer tissue. Northern blot hybridization was done in normal tissues (*B*) and cancer tissues (*C*). A main 3.0-kb band and a faint 1.5-kb band were observed in normal testis, pancreatic cancer (PA1), and endometrial cancer tissues (EM2).

phosphorylation sites, and two tyrosine kinase phosphorylation sites. The additional COOH-terminal sequence of KU-CT-1L contained two Armadillo/β-catenin-like repeats, three N-glycosylation sites, two cyclic AMP-dependent and cyclic GMP-dependent protein kinase phosphorylation sites, nine protein kinase C phosphorylation sites, 10 casein kinase phosphorylation sites, and two tyrosine kinase phosphorylation sites.

Table 2. Frequency of KU-CT-1 mRNA expression in various cancer cell lines and tissues

Tumor type	Positive/total	
	Cell lines	Tissues
Pancreatic cancer	2/8 (25%)	3/9 (33%)
Colon cancer	0/7 (0%)	0/21 (0%)
Stomach cancer	2/5 (40%)	0/6 (0%)
Esophagus cancer	4/15 (27%)	ND
Endometrial cancer	4/7 (57%)	7/11 (64%)
Bladder cancer	0/5 (0%)	ND
Renal cell cancer	6/10 (60%)	1/8 (13%)
Prostate cancer	1/4 (25%)	ND
Breast cancer	0/2 (0%)	ND
Lung cancer	7/12 (58%)	9/24 (38%)
Hematological malignancy	1/5 (20%)	ND
Melanoma	1/11 (9%)	0/13 (0%)

NOTE: The results were obtained using 30 cycles of PCR.
Abbreviation: ND, not determined.

Immunogenicity of KU-CT-1 in patients with various cancers. The immunogenicity of KU-CT-1 was evaluated by screening for serum IgG antibody in patients with various cancers, using a phage plaque assay. The IgG antibody specific for KU-CT-1 was detected in sera from 3 of 20 pancreatic cancer patients, 2 of 12 endometrial cancer patients, 1 of 18 colon cancer patients, 1 of 10 prostate cancer patients, and 1 of 30 healthy individuals but was not detected in sera from nine esophageal cancer patients, 18 bladder cancer patients, 14 renal cell cancer patients, 22 melanoma patients, and seven pancreatitis patients (Table 3). To confirm the specificity of the antigen recognition, we further evaluated the IgG recognition of KU-CT-1 using an immunoprecipitation assay with a partial KU-CT-1 protein (448 amino acids of KU-CT-1S plus 36 amino acids in KU-CT-1L) produced by *in vitro* transcription/translation. Sera from patients who were antibody positive by the phage assay (three with pancreatic cancers, one with endometrial cancer, and one with prostate cancer) were also positive in the immunoprecipitation assay, whereas sera from two pancreatic-cancer patients and one healthy donor (HE17) who were antibody negative in the phage assay and one healthy donor who was antibody positive in the phage assay (HE27) were all negative in the immunoprecipitation assay (Fig. 3). Therefore, the results obtained in the phage plaque assay were consistent with those obtained in the immunoprecipitation assay, except in one healthy donor. The correlation between expression of KU-CT-1 and positive IgG was not evaluated, because of a lack of availability of paired samples, and this requires investigation in a future study. Nonetheless, the results indicate that KU-CT-1 was specifically recognized by sera from various cancer patients but not by sera from healthy individuals, indicating that KU-CT-1 is an immunogenic tumor antigen in cancer patients.

Discussion

Early diagnosis and treatment of pancreatic cancer with conventional therapeutics is difficult, and new diagnostic and therapeutic methods are needed. Previous immunotherapy trials on patients with pancreatic cancer, including immunization with a mutated K-ras peptide along with granulocyte macrophage colony-stimulating factor administration, immunization with granulocyte macrophage colony-stimulating factor–transduced allogeneic pancreatic cancer cell lines along with adjuvant radiation, and chemotherapy following surgical excision have shown possible antitumor effects with detection of immune responses to tumor antigens (7, 17). However, detailed analysis of immune responses in pancreatic cancer for improvement of immunotherapy has not been done, partly because of the small number of tumor antigens available for the measurement of immune responses. Several pancreatic cancer antigens, including MUC-1, K-ras, HER-2/*neu*, and p53, have been reported, and the SEREX method has been used to identify hsp105, which is overexpressed in various cancers, including pancreatic cancer (18), and coactosin-like protein (CLP). CLP is ubiquitously expressed in normal tissues, but in induced HLA-A2-restricted, tumor-reactive CTLs, CLP(104-113) peptide–specific CTL activity was induced in three of five pancreatic cancer patients and in one of seven healthy donors, and a CLP-specific IgG antibody was detected in the sera of all seven cancer patients tested but not in nine healthy donors (19).

In this study, we isolated a novel cancer testis antigen KU-CT-1 by screening a testis cDNA library with serum from a patient with pancreatic ductal adenocarcinoma. Use of the testis cDNA library seems to be effective for isolation of cancer testis antigens by SEREX, because other cancer testis antigens (SSX2, SCP-1, and CAGE) have previously been isolated with sera from patients with melanoma, renal cell carcinoma, and gastric cancer, respectively. Using reverse transcription-PCR analysis, Kubuschok et al. reported the expression of 10 cancer testis antigens in pancreatic cancer: SCP-1, NY-ESO-1, SSX-1, SSX-2, SSX-4, GAGE, MAGE-3, MAGE-4, CT-7, and CT-8 (14). SSX-4 was expressed in 8 of 10 pancreatic cancer cell lines, and SCP-1 and GAGE were expressed in 29 and 13 of 61 pancreatic cancer tissues, respectively. Other studies evaluating the expression of cancer testis antigens indicate relatively rare expression of NY-ESO-1, CTp11, MMA-1, XAGE1b, and HCA587 in pancreatic cancers (9–13). Because KU-CT-1 was expressed in 3 of 9 pancreatic cancer tissues (33%), it represents an additional cancer testis antigen that is expressed in pancreatic cancers. Furthermore, KU-CT-1 was shown to be immunogenic in multiple patients with pancreatic cancers, indicating possible use of KU-CT-1 for diagnosis and immunotherapy in patients with pancreatic cancers. In addition, KU-CT-1 was found to express even more frequently in endometrial cancers (7 of 11 patients, 64%) and lung cancers (9 of 24 patients 38%) and was immunogenic in some of these patients, indicating that it may also be useful for immunotherapy in patients with endometrial cancer and lung cancers.

The *KU-CT-1* gene consists of 20 exons and is located on chromosome 10p12. It is transcribed to give two splice variants

Table 3. The presence of an IgG antibody specific for KU-CT-1 in sera from various cancer patients

Subject	Positive/total
Pancreatic cancer	3/20
Colon cancer	1/18
Esophageal cancer	0/9
Endometrial cancer	2/12
Bladder cancer	0/18
Renal cell cancer	0/14
Prostate cancer	1/10
Melanoma	0/22
Pancreatitis	0/7
Healthy individual	1/30

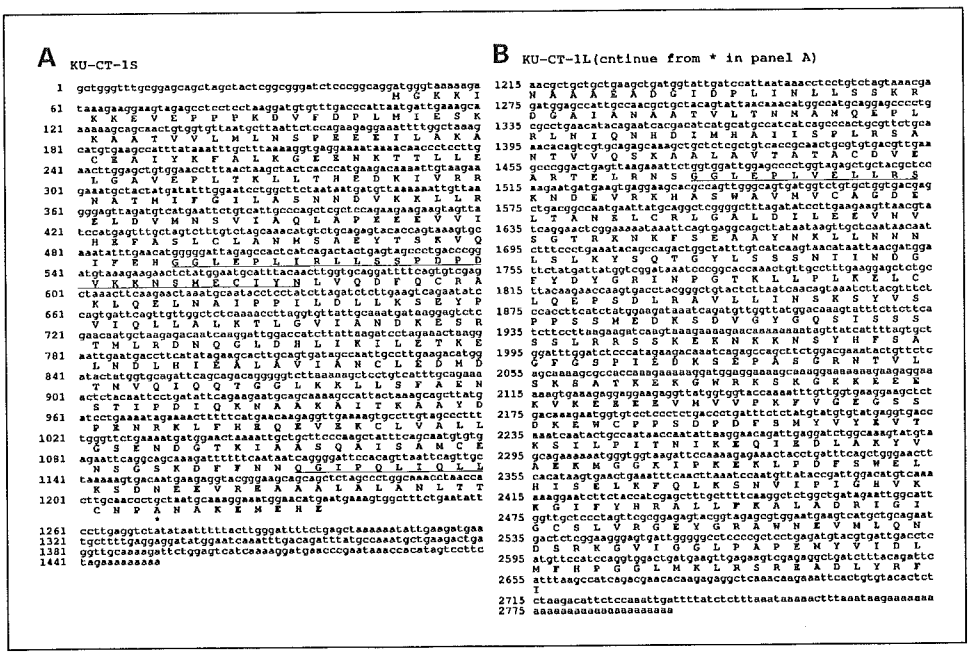

Fig. 2. Nucleotide and amino acid sequences of KU-CT-1S and KU-CT-1L. *A*, nucleotide and amino acid sequences of KU-CT-1S. *B*, nucleotide and amino acid sequences of KU-CT-1L. KU-CT-1L and KU-CT-1S share the same sequence from 1 to 1,214 at the NH_2 terminus. *, position 1,214 (*A*). KU-CT-1 contains 20 exons and is localized in chromosome 10p12. KU-CT-1S contains 11 of these exons (exons 1-11), and KU-CT-1L contains 19 exons (lacking exon 11). Armadillo/β-catenin-like repeat sequences are underlined.

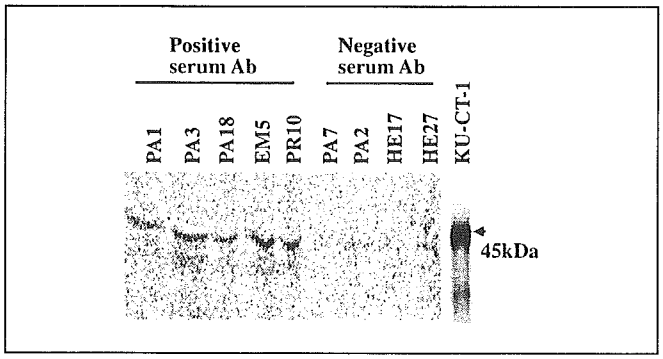

Fig. 3. Detection of a serum IgG antibody (*Ab*) specific for *in vitro* transcribed/translated KU-CT-1 by immunoprecipitation assay. [^{35}S]methionine-labeled *in vitro* translated KU-CT-1 proteins were immunoprecipitated from sera. Anti-KU-CT-1 IgG antibody was detected as a band of ~45 kDa in sera from patients who had anti-KU-CT-1 IgG in the phage plaque assay, as shown in Table 3. PA, pancreatic ductal adenocarcinoma; EM, endometrial cancer; PR, prostate cancer; HE, healthy individuals.

of 1.5 and 2.8 kb, which encode for proteins of 397 amino acids (KU-CT-1S) and 872 amino acids (KU-CT-1L), respectively. Northern blot analysis indicated that KU-CT-1L is the major product, and the expression pattern of the splice variants was similar between normal testis tissue and various cancers. The function of KU-CT-1 remains unknown with regard to oncogenesis and cancer progression. KU-CT-1L does not possess a transmembrane domain and has four Armadillo/β-catenin-like repeats that are typically present in cytoplasmic proteins, including β-catenin, adenomatous polyposis coli (*APC*) gene, and a melanoma antigen KU-MEL-1 (20). It is assumed that three of the Armadillo/β-catenin-like repeats make one positively charged helix that allows interaction with other proteins. The functions of two cancer testis antigens are reported. SCP-1 is involved in the pairing of homologous chromosomes, an essential step for the generation of haploid cells in meiosis I (21), and MAGE-A1 binds to SKIP, inhibiting the activity of a SKIP-interacting transactivator, and recruits HDACs, thereby acting as a potent transcriptional repressor (22). Thus, the regulation of transcription by MAGE-A1 may be involved in the oncogenesis and tumor progression of cancer cells. Several cancer testis antigens, including SSX, NY-ESO-1, and N-RAGE, were reported to be expressed in mesenchymal stem cells and down-regulated after differentiation (23), suggesting possible expression of cancer testis antigens in cancer stem cells. Therefore, further investigations are necessary for the functional role of KU-CT-1 in the formation of malignant phenotype of cancer cells and its expression in cancer stem cells as well.

Serum IgG specific for KU-CT-1 was detected in patients with pancreatic cancer and endometrial cancer, in which KU-CT-1 is frequently expressed. Correlation between the expression of KU-CT-1 and the presence of IgG was not studied because paired samples were not available. However, the presence of an IgG antibody against KU-CT-1 in multiple patients suggests that KU-CT-1 activated CD4$^+$ helper T cells (Th) in patients with these cancers, suggesting that KU-CT-1 may at least be useful as a CD4$^+$ helper T-cell antigen for immunotherapy in patients with these cancers and particularly in patients with antibody-positive serum. In addition, many SEREX-derived antigens have been shown to induce CD8$^+$ CTLs (24–28), and a positive correlation was observed between positive serum IgG antibody and induction of CD8$^+$ CTLs against a cancer testis antigen, NY-ESO-1 (24, 29). Therefore, KU-CT-1 may be a useful target for immunotherapy in patients with pancreatic cancers and endometrial cancers.

In summary, screening of a testis cDNA library with serum from a patient with pancreatic cancer led to identification of a novel cancer testis antigen, KU-CT-1, which was frequently expressed in pancreatic cancer, lung cancer, and endometrial cancer and was immunogenic in some of these patients. These results indicate that KU-CT-1 may be useful diagnostically and in immunotherapy for patient with these cancers.

Acknowledgments

We thank Dr. Katsuaki Dan for expert technical advice and Keiko Uchiyama and Sinobu Noji for technical assistance.

References

1. Kawakami Y, Okada T, Akada M. Development of immunotherapy for pancreatic cancer. Pancreas 2004; 28:320–5.
2. Kawakami Y, Fujita T, Matsuzaki Y, et al. Identification of human tumor antigens and its implications for diagnosis and treatment of cancer. Cancer Sci 2004;95: 784–91.
3. Lan MS, Batra SK, Qi WN, Metzgar RS, Hollingsworth MA. Cloning and sequencing of a human pancreatic tumor mucin cDNA. J Biol Chem 1990;265:15294–9.
4. Almoguera C, Shibata D, Forrester K, Martin J, Arnheim N, Perucho M. Most human carcinomas of the exocrine pancreas contain mutant c-K-ras genes. Cell 1988;53:549–54.
5. Peiper M, Goedegebuure PS, Linehan DC, Ganguly E, Douville CC, Eberlein TJ. The HER2/*neu*-derived peptide p654-662 is a tumor-associated antigen in human pancreatic cancer recognized by cytotoxic T lymphocytes. Eur J Immunol 1997;27: 1115–23.
6. Casey G, Yamanaka Y, Friess H, et al. p53 mutations are common in pancreatic cancer and are absent in chronic pancreatitis. Cancer Lett 1993;69: 151–60.
7. Gjertsen MK, Buanes T, Rosseland AR, et al. Intradermal ras peptide vaccination with granulocyte-macrophage colony-stimulating factor as adjuvant: clinical and immunological responses in patients with pancreatic adenocarcinoma. Int J Cancer 2001;92: 441–50.
8. Takahashi K, Shichijo S, Noguchi M, Hirohata M, Itoh K. Identification of MAGE-1 and MAGE-4 proteins in spermatogonia and primary spermatocytes of testis. Cancer Res 1995;55:3478–82.
9. Chen YT, Scanlan MJ, Sahin U, et al. A testicular antigen aberrantly expressed in human cancers detected by autologous antibody screening. Proc Natl Acad Sci U S A 1997;94:1914–8.
10. Zendman AJ, Cornelissen IM, Weidle UH, Ruiter DJ, van Muijen GN. CTp11, a novel member of the family of human cancer/testis antigens. Cancer Res 1999; 59:6223–9.
11. de Wit NJ, Weidle UH, Ruiter DJ, van Muijen GN. Expression profiling of MMA-1a and splice variant MMA-1b: new cancer/testis antigens identified in human melanoma. Int J Cancer 2002;98:547–53.
12. Zendman AJ, van Kraats AA, den Hollander AI, Weidle UH, Ruiter DJ, van Muijen GN. Characterization of XAGE-1b, a short major transcript of cancer/testis-associated gene XAGE-1, induced in melanoma metastasis. Int J Cancer 2002;97:195–204.
13. Wang Y, Han KJ, Pang XW, et al. Large scale identification of human hepatocellular carcinoma-associated antigens by autoantibodies. J Immunol 2002;169: 1102–9.
14. Kubuschok B, Xie X, Jesnowski R, et al. Expression of cancer testis antigens in pancreatic carcinoma cell lines, pancreatic adenocarcinoma and chronic pancreatitis. Int J Cancer 2004;109:568–75.
15. Zendman AJ, Ruiter DJ, Van Muijen GN. Cancer/testis-associated genes: identification, expression profile, and putative function. J Cell Physiol 2003; 194:272–88.
16. Ishikawa T, Fujita T, Suzuki Y, et al. Tumor-specific immunological recognition of frameshift-mutated peptides in colon cancer with microsatellite instability. Cancer Res 2003;63:5564–72.
17. Jaffee EM, Hruban RH, Biedrzycki B, et al. Novel allogeneic granulocyte-macrophage colony-stimulating factor-secreting tumor vaccine for pancreatic cancer: a phase I trial of safety and immune activation. J Clin Oncol 2001;19:145–56.

18. Nakatsura T, Senju S, Yamada K, Jotsuka T, Ogawa M, Nishimura Y. Gene cloning of immunogenic antigens overexpressed in pancreatic cancer. Biochem Biophys Res Commun 2001;281:936–44.
19. Nakatsura T, Senju S, Ito M, Nishimura Y, Itoh K. Cellular and humoral immune responses to a human pancreatic cancer antigen, coactosin-like protein, originally defined by the SEREX method. Eur J Immunol 2002;32:826–36.
20. Kiniwa Y, Fujita T, Akada M, et al. Tumor antigens isolated from a patient with vitiligo and T-cell-infiltrated melanoma. Cancer Res 2001;61:7900–7.
21. Tureci O, Sahin U, Zwick C, Koslowski M, Seitz G, Pfreundschuh M. Identification of a meiosis-specific protein as a member of the class of cancer/testis antigens. Proc Natl Acad Sci U S A 1998;95:5211–6.
22. Laduron S, Deplus R, Zhou S, et al. MAGE-A1 interacts with adaptor SKIP and the deacetylase HDAC1 to repress transcription. Nucleic Acids Res 2004;32:4340–50.
23. Cronwright G, Le Blanc K, Gotherstrom C, Darcy P, Ehnman M, Brodin B. Cancer/testis antigen expression in human mesenchymal stem cells: down-regulation of SSX impairs cell migration and matrix metalloproteinase 2 expression. Cancer Res 2005;65:2207–15.
24. Tureci O, Sahin U, Schobert I, et al. The SSX-2 gene, which is involved in the t(X;18) translocation of synovial sarcomas, codes for the human tumor antigen HOM-MEL-40. Cancer Res 1996;56:4766–72.
25. Coulie PG, Karanikas V, Colau D, et al. A monoclonal cytolytic T-lymphocyte response observed in a melanoma patient vaccinated with a tumor-specific antigenic peptide encoded by gene MAGE-3. Proc Natl Acad Sci U S A 2001;98:10290–5.
26. Jager E, Stockert E, Zidianakis Z, et al. Humoral immune responses of cancer patients against "cancer-testis" antigen NY-ESO-1: correlation with clinical events. Int J Cancer 1999;84:506–10.
27. Jager D, Stockert E, Jager E, et al. Serological cloning of a melanocyte rab guanosine 5'-triphosphate-binding protein and a chromosome condensation protein from a melanoma complementary DNA library. Cancer Res 2000;60:3584–91.
28. Ito K, Fujita T, Akada M, et al. Identification of bladder cancer antigens recognized by IgG antibodies of a patient with metastatic bladder cancer. Int J Cancer 2004;108:712–24.
29. Gnjatic S, Jager E, Chen W, et al. CD8(+) T cell responses against a dominant cryptic HLA-A2 epitope after NY-ESO-1 peptide immunization of cancer patients. Proc Natl Acad Sci U S A 2002;99:11813–8.

J Hepatobiliary Pancreat Surg (2005) 12:336–340
DOI 10.1007/s00534-005-0994-z

Journal of HBP Surgery

Image-diagnostic features of mature cystic teratomas of the pancreas: report on two cases difficult to diagnose preoperatively

Makoto Seki[1], Eiji Ninomiya[2], Akiko Aruga[3], Keiko Yamada[3], Rintaro Koga[1], Akio Saiura[1], Junji Yamamoto[1], Toshiharu Yamaguchi[1], Koichi Takano[4], Rikiya Fujita[4], Keiko Sasaki[5], and Yo Kato[5]

[1]Department of Surgery, Cancer Institute of the JFCR, 3-10-6 Ariake, Koto-ku, Tokyo 135-8550, Japan
[2]Kasumigaseki-Building Clinic, Tokyo, Japan
[3]Department of Radiology, Cancer Institute of the JFCR, Tokyo, Japan
[4]Department of Internal Medicine, Cancer Institute of the JFCR, Tokyo, Japan
[5]Department of Pathology, Cancer Institute of the JFCR, Tokyo, Japan

Abstract
This report documents the findings of two rare cases of mature cystic teratoma of the pancreas. Although they could not be diagnosed preoperatively, our retrospective report suggests that the combined diagnosis of ultrasonography (US), enhanced computed tomography (CT), and magnetic resonance cholangiopancreatography (MRCP) might allow differentiation from other cystic lesions such as mucinous cystic tumors (MCTs) and intraductal papillary–mucinous tumors (IPMTs). Since the cystic teratomas were both filled with keratinous and sebaceous material, they were echogenic, appearing as solid masses on US. Enhanced CT showed their cystic nature, with values slightly higher than water, and MRCP revealed defects of internal signals.

Key words Mature cystic teratoma of the pancreas · Dermoid cyst of the pancreas · Image diagnosis

Introduction

Mature cystic teratomas of the pancreas (dermoid cyst) are extremely uncommon. To our knowledge, only 16 cases[1–16] have hitherto been reported in the literature. Although current imaging modalities are very useful for the preoperative diagnosis of pancreatic cysts, the findings are sometimes inconclusive, and we recently experienced two cases of mature cystic teratoma of the pancreas for which correct diagnoses could not be made preoperatively. We retrospectively found both to be filled with keratinous and sebaceous materials, which were responsible for the characteristic computed tomography (CT) and echo values. This article documents the image characteristics of our two cases to aid future differential diagnosis of mature cystic teratomas of the pancreas.

Offprint requests to: M. Seki
Received: February 16, 2005 / Accepted: April 15, 2005

Case reports

Case 1

The patient was a plump 57-year-old man, status postcoronarial stenting for myocardial infarction, who had no abdominal complaints. Ultrasonography (US) showed a well-defined, hypoechogenic mass of the pancreatic body, demonstrating remarkable, ventral and superior extrapancreatic extension. The mass measured 5.9 × 4.1 × 4.1 cm (Fig. 1A). Enhanced computed tomography (CT) showed a low-attenuation, multilocular, cystic lesion arising from the body of the pancreas and extending ventrally and superiorly (Fig. 1B). The CT value of the mass was +31.4 Hounsfield units (HU), which is slightly higher than that of water. Magnetic resonance cholangiopancreatography (MRCP) showed only a small water-intensity area (Fig. 1C). Our preoperative diagnosis was a serous cystadenoma or an epidermoid cyst of the pancreas.

Laparotomy was performed on March 10, 2004, and a multilocular cystic mass was found originating in the body of the pancreas, protruding beyond the upper border, and abutting the celiac axis without encasement or invasion. The mass was locally excised with a rim of normal pancreas. Macroscopically, the cyst, measuring 55 × 37 × 33 mm, was encapsulated by a thin cyst wall and filled with finely granular, yellowish white, keratinous and sebaceous material (Fig. 1D). Histologically, the cyst wall was lined by mature stratified squamous epithelium surrounded by lymphoid tissue containing a few germinal centers, with small sebaceous glands (Fig. 1E). A few isolated groups of goblet cells with brush borders were also apparent on the surface of the squamous epithelial lining.

Case 2

The patient was an obese 60-year-old woman, who had a well-defined cystic lesion of the pancreatic body

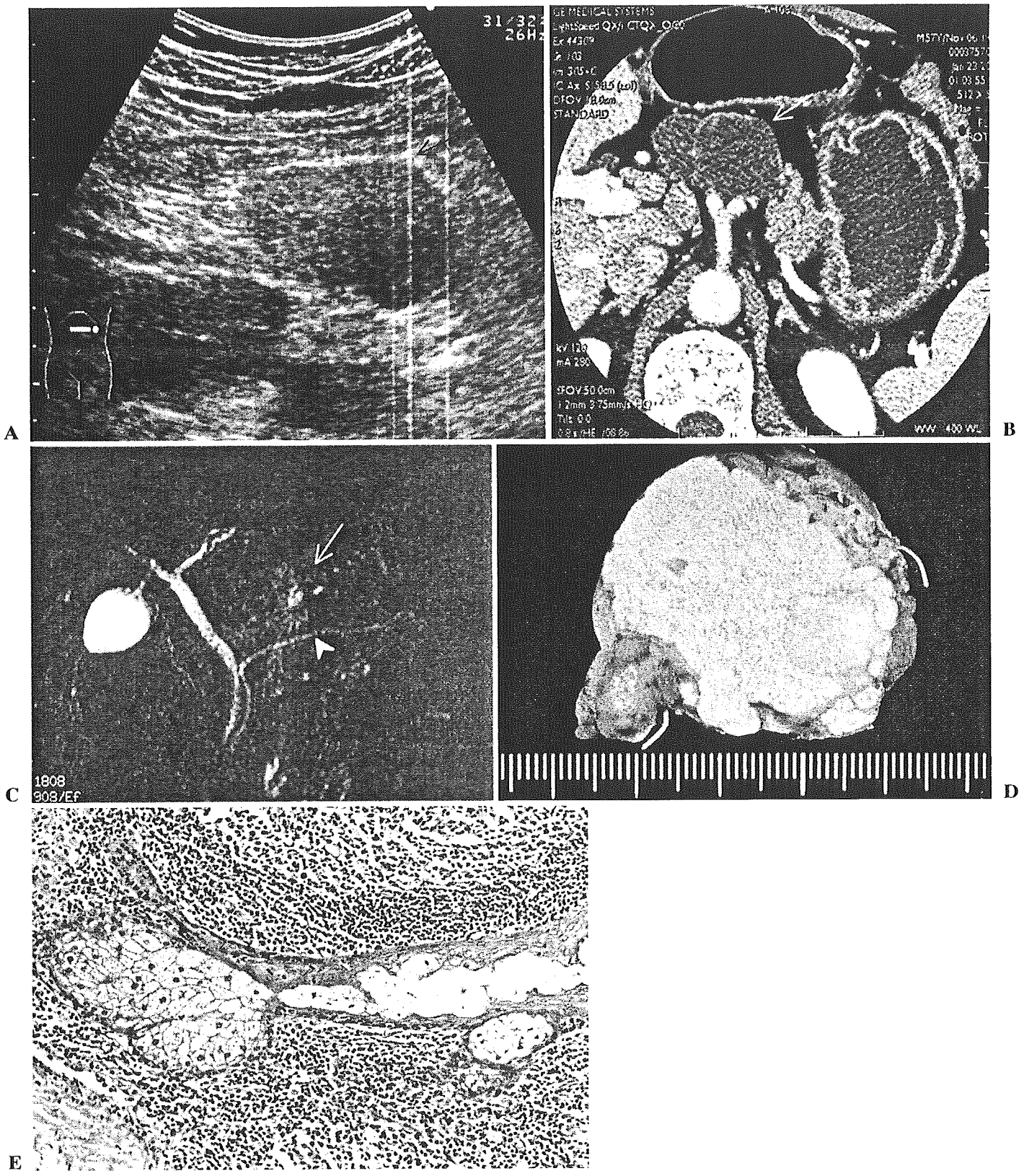

Fig. 1. A Ultrasonograph (US) showing a well-defined, hypoechogenic mass of the pancreatic body, measuring 5.9 × 4.1 × 4.1 cm (*arrow*). **B** An enhanced computed tomograph (CT) showing a low-attenuation, multilocular, cystic mass arising from the body of the pancreas and extending ventrally and superiorly (*arrow*). **C** Magnetic resonance cholangiopancreatography (MRCP) shows a small water-intensity area (*arrow*) cranial to the main pancreatic duct (*arrowhead*). **D** Macroscopic view of the cut surface of the tumor. The cyst is encapsulated by a thin cyst wall and filled with finely granular, yellowish white, keratinous, and sebaceous material. **E** Microscopic, high-power view of the tumor reveals that the cyst wall is lined by mature stratified squamous epithelium, surrounded by lymphoid tissue containing a few germinal centers, accompanied by small sebaceous glands (H&E ×200)

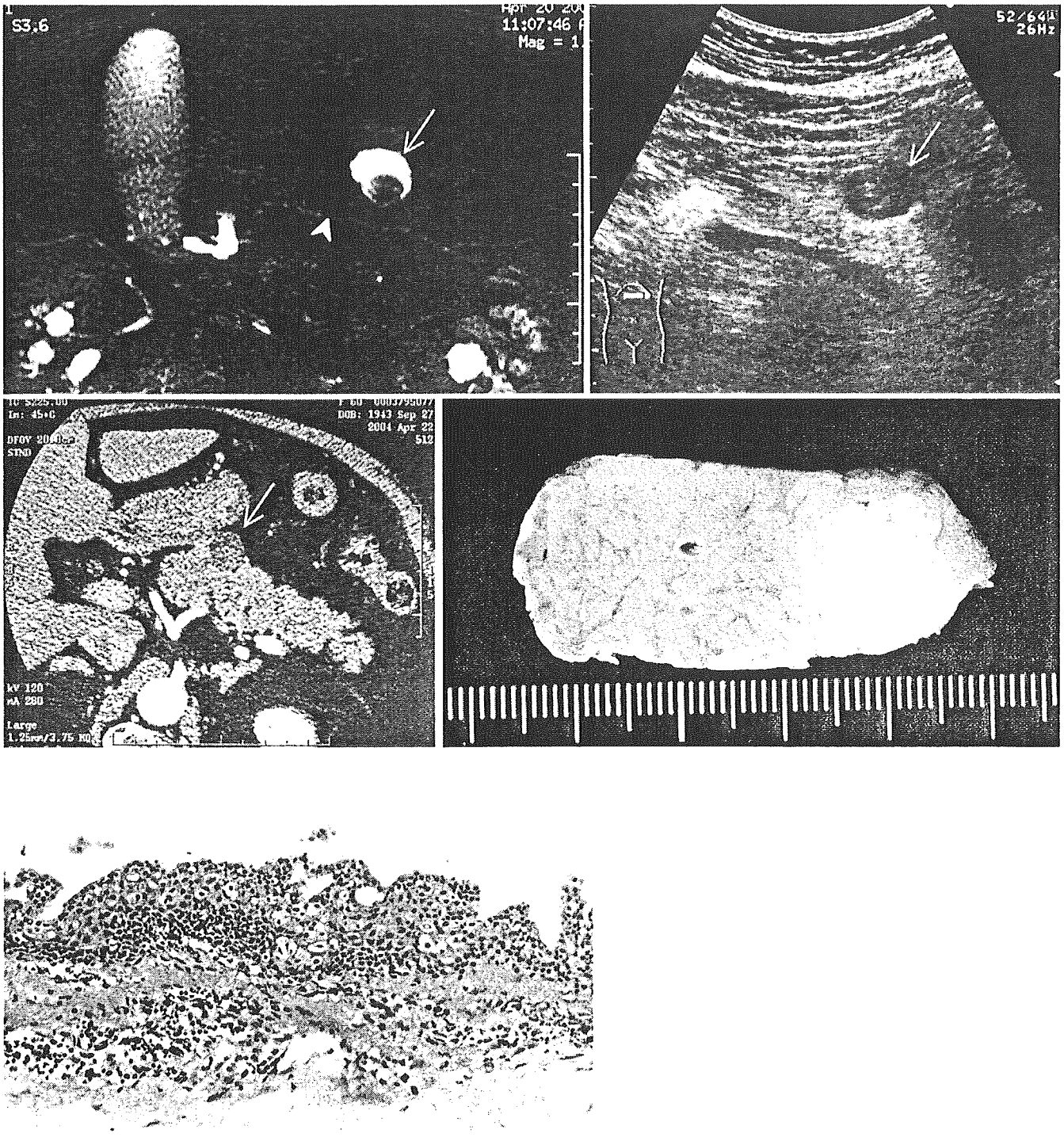

Fig. 2. **A** MRCP showing a filling defect in the cystic lesion (*arrow*) near the main pancreatic duct (*arrowhead*). **B** US showing a well-defined, hypoechogenic mass (*arrow*), measuring 22 × 19 × 14 mm, in the body of the pancreas. **C** Enhanced CT showing a round, low-attenuation mass in the body of the pancreas (*arrow*). **D** Macroscopic view of the cut surface of the tumor in the pancreas. The cyst is encapsulated by a thin wall and filled with finely granular, milky-white, keratinous, and sebaceous material. **E** Microscopic, high-power view of the tumor reveals that the cyst wall shows several layers of squamoid cells in which mature sebaceous cells or lobules are apparent in many places (H&E ×200)

discovered by abdominal US 2 years previously. She had no abdominal complaints, but MRCP had recently revealed a filling defect in the cystic lesion (Fig. 2A). US showed a well-defined, hypoechogenic mass (Fig. 2B), 22 × 19 × 14 mm in size, featuring a heterogeneous internal echo, 14 × 12 mm in size. Enhanced CT demonstrated a low-attenuation mass in the body of the pancreas (Fig. 2C), whose CT value was 36.9 HU. Our preoperative diagnosis was an intraductal papillary–mucinous tumor of the pancreas without mucin-hypersecretion.

Laparotomy was performed on May 19, 2004, a small cystic mass was found in the body of the pancreas and so middle pancreatectomy was performed. Macroscopically, the cyst measuring 21 × 22 × 15 mm was encapsulated by a thin wall and filled with finely granular, milky-white, keratinous and sebaceous material (Fig. 2D). Histologically, the wall demonstrated a corrugated appearance and was composed of single basaloid cells with several internal layers of squamoid cells, in which mature sebaceous cells or lobules were apparent in many places (Fig. 2E).

Discussion

Cystic teratomas are rare neoplasms of germ cell origin, which most often occur in the ovaries, testes, cranium, brain, mediastinum, retroperitoneum, omentum, and bladder. The pancreas is extremely rare as a primary site, and to our knowledge only 16 cases have been reported in the literature.

Differential diagnosis from lymphoepithelial cysts (LECs) and epidermoid cystic pancreatic lesions lined by squamous epithelium[16–20] may be difficult, and these are slightly more common than cystic teratomas. In particular, LECs are also round to ovoid in shape and filled with keratinous and sebaceous material,[18,19] so that preoperative differentiation is rather hard radiologically or cytologically.

It has been considered difficult to diagnose cystic teratomas originating from the pancreas because of their rare nature, but Assawamatiyanont and King[6] and Jacobs and Dinsmore[13] have previously pointed out that they are visualized as predominantly echogenic masses with US. With CT, they are commonly loculated or nonloculated cystic masses with a thin capsule, but Jacobs and Dinsmore[13] described a finding of tissue with a density similar to that of fat with some nodular regions of soft-tissue attenuation. Although we also could not uneqivocally diagnose the present two cases preoperatively, from this retrospective study it would appear that combined US, enhanced CT, and MRCP might make it possible to differentiate cystic teratomas from other cystic lesions such as mucinous cystic tumors (MCTs), serous cystic tumors, intraductal papillary–mucinous tumors (IPMTs), solid-pseudopapillary tumors, and pseudocysts of the pancreas. Since they are filled with keratinous and sebaceous material, they appear echogenic by US, they are cystic with enhanced CT, and demonstrate internal defects with MRCP.

Mature cystic teratomas may occur at any site within the pancreas.[7,13,15] Histopathologically, the cyst walls of mature cystic teratomas are lined by stratified keratinizing squamous epithelium,[12,21] often accompanied by mucin-producing ciliated columnar epithelium,[12] and allow differentiation from LECs with or without sebaceous glands or hair shafts in the main cyst wall. The second case in this report has close similarities to steatocystoma multiplex or dermoid cyst of the skin.[22,23]

Basically, if apt diagnoses were made, mature cystic teratomas do not need to be resected because they are benign, although a small percentage of them may develop into malignant forms.[14] If they cause a mass effect, or if the possibility of MCTs or IPMTs is undeniable, they should be totally resected. External drainage and marsupialization has failed in the past because of the development of chronic draining fistulas.[2]

Acknowledgment. The authors thank Prof. Akio Yanagisawa, Department of Pathology, Kyoto Prefectural School of Medicine, Kyoto, Japan, for his invaluable advice.

References

1. Kerr AA. Cysts and pseudocysts of the pancreas. Surg Gynecol Obstet 1918;27:40–4.
2. Dennis WA. Dermoid cyst of the pancreas. Surg Clin N Am 1923;3:1319–22.
3. DeCourcy JL. Dermoid cyst of pancreas. Ann Surg 1943;118:394–5.
4. Iovchec II. Suppurative dermoid cyst of the pancreas. Vestn Khir 1972;108:124.
5. Pomosov DV, Shpit'ko FS, Volianiuk MA. Dermoid cyst of the pancreas in a child. Vestn Khir 1973;110:92–3.
6. Assawamatiyanont S, King AD Jr. Dermoid cyst of the pancreas. Am Surg 1977;43:503–4.
7. Lazaro Da Silva A, Moreno M Jr. Surgery of pancreatic dermoid cyst with ligature of superior mesenteric vein. Arch Gastroenterol 1984;21:183–6.
8. Bowen B, Ros PR, McCarthy MJ, Olmsted WW, Hjermstad BM. Gastrointestinal teratomas: CT and US appearance with pathologic correlation. Radiology 1987;162:431–3.
9. Mester M, Trajber HJ, Compton CC, de Camargo HAS Jr, de Almeida C, Hoover HC Jr. Cystic teratomas of the pancreas. Arch Surg 1990;125:1215–8.
10. Vermeulen BJM, Widgren S, Gur V, Meyer P, Iselin C, Rohner A. Dermoid cyst of the pancreas. Gastroenterol Clin Biol 1990; 14:1023–5.
11. Jentschura D, Bohrer MH, Geiger G. Pankreasnahe Dermoidcyste. Chirurg 1990;61:548–9.
12. Markovsky V, Russin VL. Fine-needle aspiration of dermoid cyst of the pancreas: a case report. Diagn Cytopathol 1993;9:66–9.

13. Jacobs JE, Dinsmore BJ. Mature cystic teratoma of the pancreas: sonographic and CT findings. AJR 1993;160:523–4.
14. Iacono C, Zamboni G, Di Marcello R, Zicari M, Maran M, Montresor E et al. Dermoid cyst of the head of the pancreas. Int J Pancreatol 1993;14:269–73.
15. Fernandez-Cebrian JM, Carda P, Morales V, Galindo J. Dermoid cyst of the pancreas: a rare cystic neoplasm. Hepato-Gastroenterology 1998;45:1874–6.
16. Adsay NV, Hasteh F, Cheng JD, Klimstra DS. Squamous-lined cysts of the pancreas: lymphoepithelial cysts, dermoid cysts (teratomas), and accessory-splenic epidermoid cysts. Seminars Diagn Pathol 2000;17:56–65.
17. Tateyama H, Tada T, Murase T, Fujitake S, Eimoto T. Lymphoepithelial cyst and epidermoid cyst of the accessory spleen in the pancreas. Mod Pathol 1998;11:1171–7.
18. Mandavilli SR, Port J, Ali SZ. Lymphoepithelial cyst (LEC) of the pancreas: cytomorphology and differential diagnosis on fine-needle aspiration (FNA). Diagn Cytopathol 1999;20:371–4.
19. Liu J, Shin HJC, Rubenchic I, Lang E, Lahoti S, Staerkel GA. Cytologic features of lymphoepithelial cyst of the pancreas: two preoperatively diagnosed cases based on fine-needle aspiration. Diagn Cytopathol 1999;21:346–50.
20. Furukawa T, Ohhashi K, Toda N, Kurimoto K, Hibino K, Nitta Y, et al. Epidermoid cyst derived from an accessory spleen in the pancreas (in Japanese). Suizo (Pancreas) 1996;11:304–10.
21. Cubilla AL, Fitzgerald PJ. Tumors of exocrine pancres. In: Atlas of tumor pathology. 2nd series. Fascicle 19. Washington, DC: Armed Forces Institute of Pathology; 1984. p. 53–9.
22. Murphy GF, Elder DE. Non-melanocytic tumors of the skin. In: Atlas of tumor pathology. 3rd series. Fascicle 1. Washington, DC: Armed Forces Institute of Pathology; 1991. p. 131–2.
23. Kirkham N. Tumors and cysts of the epidermis. In: Elder DE, Elenitsas R, Jaworsky C, Johnson B (eds) Lever's histopathology of the skin. New York: Lippincott-Raven; 1997. p. 697–9.

Int J Clin Oncol (2005) 10:97–102
DOI 10.1007/s10147-004-0481-6

REVIEW ARTICLE

Junji Yamamoto · Akio Saiura · Rintaro Koga
Makoto Seki · Masashi Ueno · Masatoshi Oya
Kaoru Azekura · Yasuyuki Seto · Shigekazu Ohyama
Satoshi Fukunaga · Toshiharu Yamaguchi
Norihiro Kokudo · Masatoshi Makuuchi · Tetsuichiro Muto

Surgical treatment for metastatic malignancies. Nonanatomical resection of liver metastasis: indications and outcomes

Received: January 31, 2005

Key words Colorectal cancer · Liver metastasis · Surgery · Survival · Surgical margin

Introduction

Surgical resection represents the only radical treatment for liver metastases from colorectal cancer, and has been investigated at many centers.[1–31] Prospective comparative studies are needed to more accurately verify the advantages of resection. However, now that surgical resection is considered to have a certain survival benefit and other treatment modalities show a low likelihood of cure, the studies that are actually being conducted should be those comparing surgical resection with non-surgical treatment in patients for whom surgical resection is of some limited use.

Surgeons express differing opinions regarding the selection of resection procedures (anatomical hepatectomy vs nonanatomical limited hepatectomy) and the extent of surgical margins. The present report discusses the findings of a literature review focusing on these contentious issues.

Indications for surgical resection of colorectal liver metastases

Surgical resection is indicated in patients with metastatic liver cancer if the preoperative and intraoperative diagnoses indicate that the tumor mass can be safely and completely resected. The safety of liver resection depends on: (1) functional hepatic reserve after resection; and (2) the degree of difficulty of the surgical procedure. These factors are, in turn, determined by the location of the tumor(s) within the liver and the extent of liver involvement. Hepatic reserve is evaluated by estimating anticipated residual liver volume and function based on liver function tests, and imaging information obtained using computed tomography or other methods. Hepatic reserve does not often limit the indications for resection, because liver metastasis usually occurs in normal livers. In patients who require extensive resection of uninvolved sections of liver (e.g., extended right hepatectomy plus partial resection of the left liver and trisegmentectomy plus partial resection of the remaining segments), the risk of postoperative liver failure due to massive parenchymal loss can be reduced by performing portal vein embolization of the area to be resected, rather than one-stage hepatectomy.[32–34]

The degree of difficulty of liver resection is determined by the relationship between the tumor and the hilar hepatoportal region, inferior vena cava, and major hepatic veins. As both liver resection itself and vascular reconstruction can now be performed safely, few patients are considered to have "nonresectable" disease as a result of tumor characteristics (tumor diameter, distribution, and location), other than the number of metastases. Liver resection combined with resection and reconstruction of the hepatic veins and inferior vena cava should also be performed whenever possible if complete resection can be achieved.[35,36] Even if the tumor has infiltrated the confluence of the hepatic veins and inferior vena cava, complete resection can be achieved by resecting and reconstructing the main hepatic vein.[37]

Previously, the conditions that were considered to preclude resection in patients with colorectal liver metastasis comprised: (1) liver metastases that cannot be completely resected; (2) regional hepatic lymph nodes positive for metastasis; and (3) extrahepatic remote metastases.[38] However, now that liver resection can be performed extremely safely, indications for surgical resection are expanding in some areas. For example, relatively good outcomes have been reported even in patients with pulmonary metastasis if liver resection is also performed, provided that the pulmo-

J. Yamamoto (✉) · A. Saiura · R. Koga · M. Seki · M. Ueno · M. Oya · K. Azekura · Y. Seto · S. Ohyama · S. Fukunaga · T. Yamaguchi · T. Muto
Department of Surgery, Cancer Institute Hospital, 3-10-6 Ariake, Koto-ku, Tokyo 135-8550, Japan
Tel. +81-3-3520-0111; Fax +81-3-3570-0343
e-mail: jyamamoto@jfcr.or.jp

N. Kokudo · M. Makuuchi
Hepatobiliary Pancreatic Surgery Division, Graduate School of Medicine, University of Tokyo, Tokyo, Japan

nary metastases are completely resectable.[39-41] Clinicians must recognize that failing to operate on patients with completely resectable localized metastases overlooks those patients who may be curable.

Outcomes after surgical resection of colorectal liver metastases

Surgical outcomes in the main studies of resection for colorectal liver metastases are shown in Table 1. Operative mortality in recent studies was 0–3%, and the 3-, 5-, and 10-year survival rates after surgery were 31%–57%, 16%–51%, and 19%–28%, respectively. Overseas studies also included a recent study that reported a 5-year survival rate exceeding 50%.[31] Establishment of patient selection criteria and improvements in resection techniques were thought to have contributed to this result. The breakdown of data on patients who have undergone resection is important. In most European and American studies, 50% or more of patients had tumors with a maximum diameter of more than 5 cm. In contrast, only around 30% of patients in Japanese studies had tumors of this size. Conversely, around 40% of patients in Japanese studies displayed multiple bilobar disease, compared to only about 10%–30% in overseas studies. Patients with four or more metastases comprised less than 10% of subjects in European and American studies, contrasting sharply with the 23% in Japanese studies. These differences suggest variations in patient selection criteria based on resection techniques.

Factors influencing surgical outcome

Direct comparison of factors affecting surgical outcome after resection of colorectal liver metastases is difficult, as the factors included in analysis differ from study to study (Table 2). Little divergence of opinion is seen with regard to the following as prognostic factors: (1) stage of the primary disease; (2) number of metastases (<4 vs ≥ 4); (3) status of surgical margins (positive vs negative); (4) metastasis to hepatic regional lymph nodes; (5) extrahepatic disease; and (6) satellite nodules. The following have been reported as special prognostic factors based on pathological examinations of resected specimens: (1) tumor pseudocapsule; (2) macroscopic invasion of the bile duct; (3) intrahepatic vascular invasion;[42] (4) lymphatic duct invasion;[43] and (5) islands of entrapped liver cells in metastases.[44] In contrast, evaluations of the following differ depending on the study: (1) time of diagnosis of liver metastasis (synchronous vs metachronous); (2) intrahepatic distribution of metastases (unilobar vs bilobar); (3) resection procedure (nonanatomical resection vs anatomical resection); and (4) extent of surgical margin (≥ 10 mm vs <10 mm). Obtaining uniform results would, presumably, be difficult because the criteria used to select patients for resection differ from study to study, and numerous factors are involved in the prognosis of metastatic liver cancer, due to a complex pathology that includes the primary tumor.

Liver resection procedures

Hepatocellular carcinoma is well-known to display a high affinity for the portal vein, and shows a transportal pattern of spread.[45] If colorectal liver metastases show marked secondary intrahepatic spread, the resection procedure used should be in accordance with the pattern of spread. Our review showed that, in colorectal liver metastases, both the number of metastases and invasion of the portal vein by metastases were indicators of poor postoperative outcome, but that the two indicators were unrelated. Multiple liver metastases thus appear to occur not as a result of intrahepatic metastasis by invasion of the portal vein, but, rather, as a result of the formation of multiple metastases from the outset.[29] Accordingly, surgical treatment of liver metastasis does not require close adherence to a systematic approach based on anatomy of the portal tract. Instead, limited hepatectomy is generally used, so that complete resection can be achieved in as many patients as possible.[29,42,46] Using intraoperative ultrasonography, tumors are resected so as to maximize the sparing of uninvolved liver parenchyma and achieve tumor-free surgical margins. If patients display multiple metastases in one hemiliver and hemihepatectomy or segmentectomy appears considerably easier than individually resecting tumors by limited resection, hemihepatectomy or segmentectomy will be used. In overseas studies, major anatomical resections such as hemihepatectomy represent the basic procedure used, as shown in Table 1.

Surgical margins

When considering surgical margins, a distinction needs to be made between "whether tumor involvement is present at the surgical margin" and "whether the surgical margin is 10 mm or more, or less than 10 mm". Postoperative outcome is known to be appreciably worse in patients with tumor involvement of the surgical margin, as has already been shown. The involvement of the surgical margin by the tumor would increase the likelihood of microscopic residual disease; thus, why this should be avoided wherever possible is easy to understand. However, the effects of the extent of surgical margins on postoperative outcome are not as clear. Some studies have found that postoperative outcomes differ depending on whether the surgical margin was 10 mm or more, or less than 10 mm,[10,47,48] whereas others have identified no such differences.[29,49] Our review showed that postoperative survival rates tended to be lower in patients with surgical margins of 10 mm or more than in patients with surgical margins of less than 10 mm on univariate analysis. However, the extent of surgical margins does not represent an independent prognostic factor on multivariate analysis. Extent of surgical margins has been shown to be

Table 1. Studies of outcome after surgical resection of colorectal liver metastases

Authors (year)	Number of patients who underwent resection (number of patients who underwent radical resection)	3-Year survival rate (%)	5-Year survival rate (%)	50% Survival period	Recurrence rate (%)	Hepatic recurrence rate (%)	Metastases ≥4 (%)	Solitary: Multiple unilobar: Multiple bilobar	Surgical or in-hospital mortality (%)
Adson et al.[6] (1980)	34	41							5.9
Morrow et al.[7] (1982)[a]	64		34						20
Rajpal et al.[8] (1982)	34			31.3 Months					11.8
Fortner et al.[9] (1984)	65	57							7
Adson et al.[10] (1984)	141		25						2
August et al.[11] (1985)	33		53 (4-year survival rate)	38 Months					0
Petrelli et al.[12] (1985)	36			22 Months					14 (5/36)
Bozzetti et al.[13] (1986)	45		36		62	36	–	26:14:5	NA
Gennari et al.[14] (1986)	48	53		30 Months	46	31	–	26:15:7	2.1
Butler et al.[15] (1986)	62	50	34		61	32	–	42:13:7	9.7
Iwatsuki et al.[16] (1986)	60 (60)	53	45		48	30	12	–	0
Ekberg et al.[17] (1986)	72	30	16	22 Months	78	65	19	34:18:16	5.6
Nordlinger et al.[18] (1987)	80	40.5	24.9		64	43	–	44:19:17	5
Holm et al.[20] (1989)	35	31			74	66	0	11:16:8	0
Scheele et al.[21] (1990)	226 (183)		38		61	43		105:40:28	5 (12/226)
Doci et al.[22] (1991)	107 (100)		30		69	41	–	58:28:14	5
Rosen et al.[23] (1992)	280	47	25	2.8 Years	–	–	–	–	3.6
Nakamura et al.[24] (1992)	31		45		61	48	19	–	3
Sugihara et al.[25] (1993)	159 (109)	57.2 (Curative resection)	47.9 (Curative resection)		60	32		51:16:40	1
Gayowski et al.[26] (1994)	204	43	32		72	72	–	91:33:80	0
Jatzko et al.[27] (1995)	66		29.6		73	38	–	39:13:14	4.5
Yamamoto et al.[29] (1999)	96	61	51	–	–	–	23	39:17:40	0
Minagawa et al.[30] (2000)	235	51	38	3.1 Years	77	–	23	110:36:99	0
Choti et al.[31] (2002)	226	57	40	46 Months	80	–	9	141:32:53	1

[a] Includes primary tumors other than colorectal cancer
NA, not available

Table 2. Factors affecting surgical outcome after resection of colorectal liver metastases

	Sex	Age (years)	Preoperative CEA value	Synchronous vs metachronous	Disease-free interval	Site of primary tumor	Stage of primary tumor	Size of metastatic tumor(s)
Positivity rate (%)	20	10	33	38	0	10	50	20
Ekberg[17] (1986)	×	×		×		×	×	×
Registry of Hepatic Metastases[19] (1988)		(≧70 vs <70	×	○			○	×
Holm[20] (1989)	○			×		×	×	×
Scheele[21] (1990)	×	×		○		×	○	△
Sugihara[25] (1993)			×	○		×	×	×
Gayouski[26] (1994)	○	×		×		×	○	×
Jatzko[27] (1995)	×	×		×		×	○	×
Nordlinger[18] (1987)	×	×				○	○	○
Beckerts (1997)	×	×		○			×	
Jaeck (1997)			×		×		○	×
Jamison (1997)						×		×
Jenkins (1997)	×	×		○		×		
Rees[45] (1997)				×			×	○
Yasui (1997)								
Cady[46] (1998)			○		×		×	×
Elias (1998)								
Yamamoto[29] (1999)	×	×		×				×
Minagawa[30] (2000)	×	×	×	×	×	×	○	×
Choti[31] (2002)			○	×	×		×	×

○, Significant; ×, not significant; △, not determined significant

related to number of metastases.[29] When removing tumors that require multiple resections, surgical margins will more often have to be less than 10 mm to ensure sufficient residual liver volume. While some studies have reported a higher frequency of micrometastases in the liver parenchyma within 10 mm of the tumor margin,[28] these are in the minority, and satellite configurations such as that seen with fungating intrahepatic cholangiocarcinoma are rarely seen with colorectal liver metastases. Kokudo et al.[50] conducted a detailed study of micrometastases around resected liver metastases, using K-*ras* and *p53* mutations as genetic markers. Micrometastases in the liver parenchyma were seen in 2% of specimens, while metastases via the portal tract were seen in 14.3%. All micrometastases were within close proximity (≤5 mm) of the tumor. They proposed a surgical margin of 2 mm as the minimum requirement for colorectal liver metastases, and stated that margins of less than 2 mm carried a risk of margin-related recurrence of approximately 6%.

Specifying the extent of surgical margins as a requirement for resection is undesirable, as this limits the number of patients for whom resection is indicated. For example, the requirement that a surgical margin of 10 mm or more is the necessary condition for curative resection would exclude numerous patients with multiple bilobar liver metastases. When choosing suitable procedures for liver resection, a degree of flexibility is useful, and surgical margins of 10 mm should be used only as a guiding principle. This allows resection to be safely performed in a large number of patients. In a relatively recent paper, by Cady et al.,[46] ability to ensure surgical margins of 10 mm was considered a condition for resection, but this criterion would markedly lower the resection rate. A comparison of studies conducted in Europe and the United States with those conducted in Japan shows distinct differences in the indications for patients with multiple bipolar disease and patients with multiple disease with four or more metastases (Table 1). The extent of surgical margins that can be ensured should not be made a condition for liver resection, as the extent of surgical margins should be determined as a balance between the number of metastases, locations of metastases within the liver, and the resection procedure.

Conclusions

The present article has discussed resection of colorectal liver metastases based on a review of the literature. Although the response rate for nonsurgical treatment of colorectal liver metastases has increased, such treatment is frequently not curative. To reiterate, the goal of treatment should be to completely remove tumors by resection whenever possible. The treatment of first choice for resectable colorectal liver metastases is surgical resection, and surgical margins should be sufficient to safely achieve complete resection.

Acknowledgments This work was supported in part by Grants-in-Aid for Basic Science Research from the Ministry of Education, Culture, Sports, Science, and Technology.

Number of metastatic tumor(s) Solitary/ Multiple	Number of metastatic tumor(s) Multiple; ≧4 vs <4	Unilobar/ Bilobar distribution	Satellite metastases	Resection procedure	Surgical margin Positive/ Negative	Surgical margin ≧10mm or <10mm	Extrahepatic metastasis	Hepatic lymph node metastasis	Perioperative blood transfusion
53	75	7	100	36	100	50	55	100	0
○	○	×	○	×	○	○	○		
○	○	×		○		○	×	○	
△		×		×	○				
×	×	×	○	○	○	○	×		
×	×			×	○				
○	○	○		○	○	×	○	○	×
○	○	×		○		×			
○		×		×	○				
				×	Incomplete resection				
×		×		×	○				
×		×				×	○	○	
×				×	Incomplete resection		○		
×		×			○				
×				○			×	○	
○		×				○			
					○	○	×		
○	○	×			○	×			
○	○	×		×		×	×	○	
×		×		×	○				×

References

1. Brunschwig A (1963) Hepatic lobectomy for metastatic cancer. Cancer 16:277–282
2. Woodington GF, Waugh JM (1963) Results of resection of metastatic tumors of the liver. Am J Surg 105:24–29
3. Flanagan L, Foster JH (1967) Hepatic resection for metastatic cancer. Am J Surg 113:551–557
4. Attiyeh FF, Wanebo HJ, Stearns MW (1978) Hepatic resection for metastasis from colorectal cancer. Dis Colon Rectum 21:160–162
5. Wanebo HJ, Semoglou C, Attiyeh F, et al. (1978) Surgical management of patients with primary operable colorectal cancer and synchronous liver metastases. Am J Surg 135:81–85
6. Adson MA, Van Heerden JA (1980) Major hepatic resection for metastatic colorectal cancer. Ann Surg 191:576–583
7. Morrow CE, Grage TB, Sutherland DER, et al. (1982) Hepatic resection for secondary neoplasms. Surgery 92:610–614
8. Rajpal S, Dasmahapatra KS, Ledesma E, et al. (1982) Extensive resections of isolated metastases from carcinoma of the colon and rectum. Surg Gynecol Obstet 155:813–816
9. Fortner JG, Silva JS, Golbey RB, et al. (1984) Multivariate analysis of a personal series of 247 consecutive patients with liver metastases from colorectal cancer. I. Treatment by hepatic resection. Ann Surg 199:306–315
10. Adson MA, Van Heerden JA, Adson MH, et al. (1984) Resection of hepatic metastases from colorectal cancer. Arch Surg 119:647–651
11. August DA, Sugarbaker PH, Ottow RT, et al. (1985) Hepatic resection of colorectal metastases. Influence of clinical factors and adjuvant intraperitoneal 5-fluorouracil via Tenckhoff catheter on survival. Ann Surg 201:210–218
12. Petrelli NJ, Nambisan RN, Herrera L, et al. (1985) Hepatic resection for isolated metastasis from colorectal carcinoma. Am J Surg 149:205–209
13. Bozzetti F, Bignami P, Morabito A, et al. (1986) Patterns of failure following surgical resection of colorectal cancer liver metastases. Rationale for multimodal approach. Ann Surg 205: 264–270
14. Gennari L, Doci R, Bozzetti F, et al. (1986) Surgical treatment of hepatic metastases from colorectal cancer. Ann Surg 203:49–54
15. Butler J, Attiyeh FF, Daly JM (1986) Hepatic resection for metastases of the colon and rectum. Surg Gynecol Obstet 162:109–113
16. Iwatsuki S, Esquivel CO, Gordon RD, et al. (1986) Liver resection for metastatic colorectal cancer. Surgery 100:804–809
17. Ekberg H, Tranberg KG, Andersson R, et al. (1986) Determinants of survival in liver resection for colorectal secondaries. Br J Surg 73:727–731
18. Nordlinger B, Parc R, Delva E, et al. (1987) Hepatic resection for colorectal liver metastases. Influence on survival of preoperative factors and surgery for recurrence in 80 patients. Ann Surg 205:256–263
19. Registry of Hepatic Metastases (1988) Resection of the liver for colorectal carcinoma metastases: a multi-institutional study of indication for resection. Surgery 103:278–288
20. Holm A, Bradley E, Aldrete JS (1989) Hepatic resection of metastasis from colorectal carcinoma. Morbidity, mortality and pattern of recurrence. Ann Surg 209:428–434
21. Scheele J, Stangl R, Altendorf-Hoffmann A (1990) Hepatic metastases from colorectal carcinoma: impact of surgical resection on the natural history. Br J Surg 77:1241–1246
22. Doci R, Gennari L, Bignami P, et al. (1991) One hundred patients with hepatic metastases from colorectal cancer treated by resection: analysis of prognostic determinants. Br J Surg 78:797–801
23. Rosen CB, Nagorney DM, Taswell HF, et al. (1992) Perioperative blood transfusion and determinants of survival after liver resection for metastatic colorectal carcinoma. Ann Surg 216:493–505
24. Nakamura S, Yokoi Y, Suzuki S, et al. (1992) Results of extensive surgery for liver metastases in colorectal carcinoma. Br J Surg 79:35–38
25. Sugihara K, Hojo K, Moriya Y, et al. (1993) Pattern of recurrence after hepatic resection for colorectal metastases. Br J Surg 80:1032–1035

26. Gayowski TJ, Iwatsuki S, Madariage JR, et al. (1994) Experience in hepatic resection for metastatic colorectal cancer: analysis of clinical and pathologic risk factors. Surgery 116:703–711
27. Jatzko GR, Losborg PH, Stettner HM, et al. (1995) Hepatic resection for metastases from colorectal carcinoma – a survival analysis. Eur J Cancer 31A:41–46
28. Shirabe K, Takenaka K, Gion T, et al. (1997) Analysis of prognostic risk factors in hepatic resection for metastatic colorectal carcinoma with special reference to the surgical margin. Br J Surg 84:1077–1080
29. Yamamoto J, Shimada K, Kosuge T, et al. (1999) Factors influencing suvival of patients undergoing hepatectomy for colorectal metastasis. Br J Surg 86:332–337
30. Minagawa M, Makuuchi M, Torzilli G, et al. (2000) Extension of the frontiers of surgical indications in the treatment of liver metastases from colorectal cancer: long-term results. Ann Surg 231: 487–499
31. Choti MA, Sitzmann JV, Tiburi MF, et al. (2002) Trends in long-term survival following liver resection for hepatic colorectal metastases. Ann Surg 235:759–766
32. Makuuchi M, Thai BL, Takayasu K, et al. (1990) Preoperative portal embolization to increase safety of major hepatectomy for hilar bile duct carcinoma: a preliminary report. Surgery 107:521–527
33. Kawasaki S, Makuuchi M, Kakazu T, et al. (1994) Resection for multiple metastatic liver tumors after portal embolization. Surgery 115:674–677
34. Nagino M, Nimura Y, Kamiya J, et al. (1995) Changes in hepatic lobe volume in biliary tract cancer patients after right portal vein embolization. Hepatology 21:434–439
35. Takayama T, Nakatsuka T, Yamamoto J, et al. (1996) Reconstruction of a single remnant hepatic vein. Br J Surg 83:762–763
36. Sakamoto Y, Yamamoto J, Kosuge T, et al. (2004) Extended left hepatectomy by severing all major hepatic veins with reconstruction of the right hepatic vein. Surg Today 34:482–484
37. Hughes K, Scheele J, Sugarbaker PH (1989) Surgery for colorectal cancer metastatic to the liver. Optimizing the results of treatment. Surg Clin North Am 69:339–359
38. Murata S, Moriya Y, Akasu T, et al. (1998) Resection of both hepatic and pulmonary metastases in patients with colorectal carcinoma. Cancer 83:1086–1093
39. Robinson BJ, Rice TW, Strong SA, et al. (1999) Is resection of pulmonary and hepatic metastases warranted in patients with colorectal cancer? J Thorac Cardiovasc Surg 117:66–75; discussion 75–76
40. Lehnert T, Knaebel HP, Duck M, et al. (1999) Sequential hepatic and pulmonary resections for metastatic colorectal cancer. Br J Surg 86:241–243
41. Yamamoto J, Sugihara K, Kosuge T, et al. (1995) Pathologic support for limited hepatectomy in the treatment of liver metastases from colorectal cancer. Ann Surg 221:74–78
42. Sasaki A, Aramaki M, Kawano K, et al. (2002) Prognostic significance of intrahepatic lymphatic invasion in patients with hepatic resection due to metastases from colorectal carcinoma. Cancer 95:105–111
43. Koike M, Yasui K, Torii A, et al. (2000) Prognostic significance of entrapped liver cells in hepatic metastases from colorectal cancer. Ann Surg 232:653–657
44. Kokudo N, Tada K, Seki M, et al. (2001) Anatomical major resection versus nonanatomical limited resection for liver metastases from colorectal carcinoma. Am J Surg 181:153–159
45. Rees M, Plant G, Bygrave S (1997) Late results justify resection for multiple hepatic metastases from colorectal cancer. Br J Surg 84: 1136–1140
46. Cady B, Jenkins RL, Steele GD Jr, et al. (1998) Surgical margin in hepatic resection for colorectal metastasis: a critical and improvable determinant of outcome. Ann Surg 227:566–571
47. Sano K, Makuuchi M, Miki K, et al. (2002) Evaluation of hepatic venous congestion: proposed indication criteria for hepatic vein reconstruction. Ann Surg 236:241–247
48. Maema A, Imamura H, Takayama T, et al. (2002) Impaired volume regeneration of split livers with partial venous disruption: a latent problem in partial liver transplantation. Transplantation 73:765–769
49. Hughes KS, Simon R, Songhorabodi S, et al. (1986) Resection of the liver for colorectal carcinoma metastases: a multi-institutional study of patterns of recurrence. Surgery 100:278–284
50. Kokudo N, Miki Y, Sugai S, et al. (2002) Genetic and histological assessment of surgical margins in resected liver metastases from colorectal carcinoma: minimum surgical margins for successful resection. Arch Surg 137:833–840

Inflammatory Myofibroblastic Tumor (Inflammatory Fibrosarcoma) of the Pancreas: A Case Report

Yuta Nakamura[1], Kazuo Inui[1], Junji Yoshino[1], Takamasa Tokoro[2], Luis Sabater[2] Shin Takeda[2], Katsuya Yamashita[2], Osamu Okochi[2], Akimasa Nakao[2]

[1]Department of Internal Medicine, Second Teaching Hospital, Fujita Health University School of Medicine and [2]Department of Surgery II, Nagoya University School of Medicine, Japan

Corresponding Author: Akimasa Nakao, Department of Surgery II

Nagoya University School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, 466-8550, Japan

Tel: +81 52 744 2232, Fax: +81 52 744 2255, E-mail: nakaoaki@med.nagoya-u.ac.jp

SUMMARY

Inflammatory myofibroblastic tumors (inflammatory fibrosarcomas) of the pancreas are extremely rare. We report a 29-year-old woman who underwent pancreatoduodenectomy for a 6-cm tumor of the pancreas head causing obstructive jaundice. Tumor involvement was local, without apparent metastasis. The tumor was composed of proliferating fibroblastic/or myofibroblast-like spindle cells and aggregates of chronic inflammatory cells in a fibromyxoid matrix. Immunohistochemical examination demonstrated reactivity only to vimentin. This tumor has often been found in the peritoneal cavity, the retroperitoneum, or the pelvic cavity, but only very rarely in the pancreas.

KEY WORDS: Inflammatory myofibroblastic tumor; Inflammatory fibrosarcoma; Pancreas

ABBREVIATIONS: Inflammatory Myofibroblastic Tumor (IMT); Inflammatory Fibrosarcoma (IFS); α-Smooth Muscle Actin (α-SMA)

INTRODUCTION

Most tumors originating in the pancreas are epithelial tumors, with soft tissue tumors being uncommon. In general, histopathologic criteria for diagnosis soft tissue tumors have been reexamined in recent years, and new disease categories including inflammatory myofibroblastic tumor (IMT) and inflammatory fibrosarcoma (IFS) have been proposed (1-3). This is a report of a very rare occurrence of IMT in the pancreas of a young woman.

CASE REPORT

A 29-year-old woman consulted a private hospital because of nausea and upper abdominal pain. Ultrasonography disclosed a mass in the head of the pancreas. She was referred to our hospital and admitted on February 27, 2001. Jaundice and pallor were observed. A firm mass was palpable in the upper abdomen. Blood analyses showed a typical obstructive jaundice pattern with a total bilirubin concentration of 3.8mg/dL, and mild anemia with a hemoglobin value of 10.2g/dL.

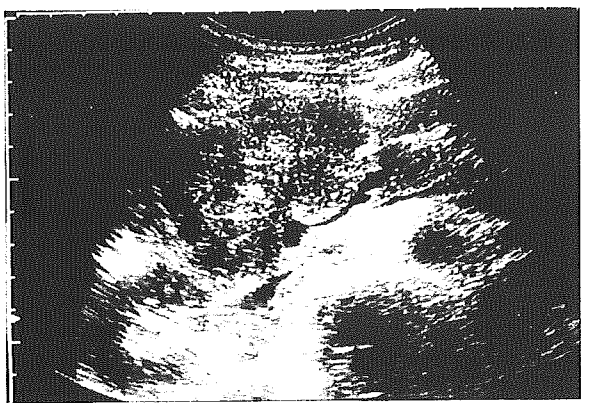

FIGURE 1 Abdominal Ultrasonography showing a heterogeneous, 6-cm solid mass in the head of the pancreas.

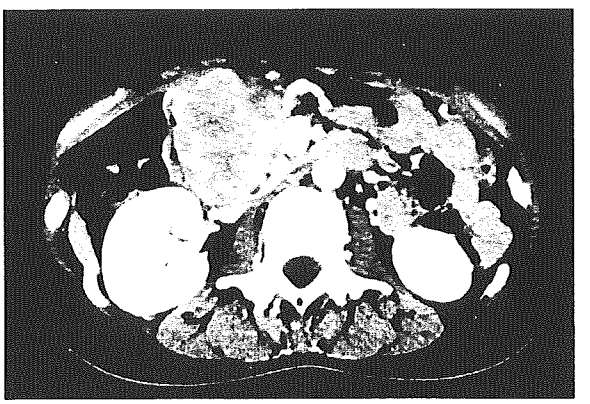

FIGURE 2 Abdominal computed tomography with contrast administration demonstrates a heterogeneously enhancing solid mass compressing the duodenum.

Abdominal ultrasonography demonstrated a heterogeneous solid mass 6cm in diameter in the pancreatic head, as well as dilation of the biliary duct and main pancreatic duct (**Figure 1**). Computed tomography with intravenous contrast administration showed heterogeneous enhancement of the mass; neither metastasis to the liver nor lymphadenopathy was seen

Hepato-Gastroenterology 2005; 52:625-628

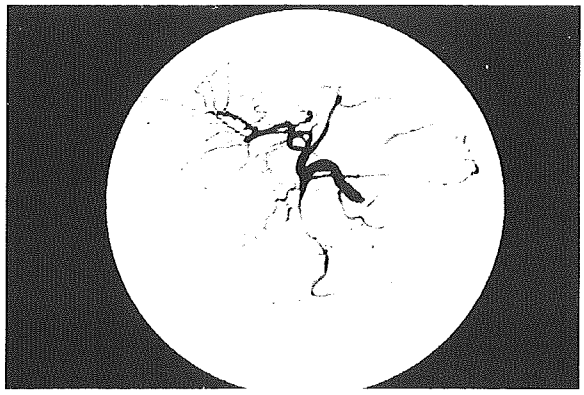

FIGURE 3 Angiography reveals a bilateral narrowing of the gastroduodenal arteries and extension and displacement of the posterior superior and anterior superior pancreaticoduodenal arteries.

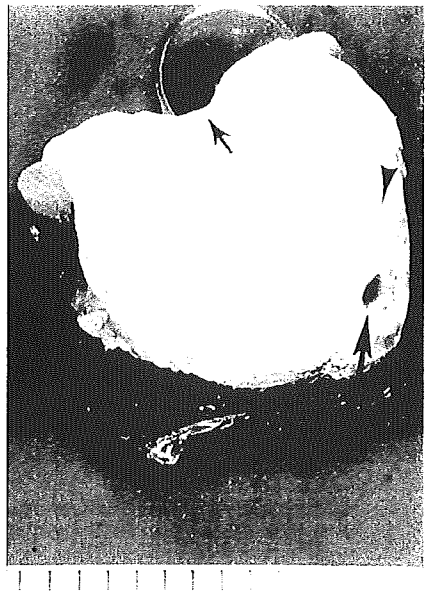

FIGURE 4 Macroscopically the tumor is a 6x5-cm solid, grayish white mass that is relatively well circumscribed. Encasement of the common bile duct (arrowhead) and dilation of the main pancreatic duct (arrow) can be observed as well as tumor growth toward the duodenum (small arrow).

(Figure 2). To treat obstructive jaundice, percutaneous transhepatic bile duct drainage was performed on the day of admission. Selective angiography indicated narrowing of the gastroduodenal artery and extension and displacement of the posterior superior and anterior superior pancreaticoduodenal arteries **(Figure 3)**. Upper gastrointestinal endoscopy revealed duodenal ulceration, but no tumor could be demonstrated in biopsy specimens. From the various findings we suspected a solid pseudopapillary tumor with no cystic component.

Materials

The patient underwent abdominal exploration through a upper midline skin incision in the Department of Surgery II of Nagoya University Hospital. A large tumor was observed in the head of the pancreas and seemed to invade into the first portion of the duodenum. Pancreatoduodenectomy and lymphadenectomy were carried out. Gross examination of the resected specimen revealed a grayish white, solid mass measuring 6x5cm. While relatively well circumscribed the mass encased the common bile duct and extended toward the adjacent duodenum **(Figure 4)**.

Results

Microscopically the tumor represented a proliferation of fibroblastic/or myofibroblast-like spindle cells, often admixed with cells resembling atypical ganglion cells. Individual and clustered chronic inflammatory cells were scattered in a fibromyxoid matrix **(Figures 5 and 6)**. The tumor cells rather diffusely permeated into adjacent pancreatic tissue **(Figure 7)**. No mitotic figures could be demonstrated in 50 consecutive high-power fields (x400). No resected lymph nodes contained metastases.

Immunohistochemical analyses demonstrated strong cytoplasmic labeling for vimentin, but no reactivity for desmine, α-smooth muscle actin (α-SMA), CD34, cytokeratin, or S-100 protein. Expression of the c-kit protein was not detected.

On the basis of histologic pattern, cellular morphology, and immunohistochemical staining, the final pathologic diagnosis was low-grade malignant inflammatory myofibroblastic tumor (inflammatory fibrosarcoma).

The postoperative course was uneventful, and the patient was discharged on postoperative day 28. No

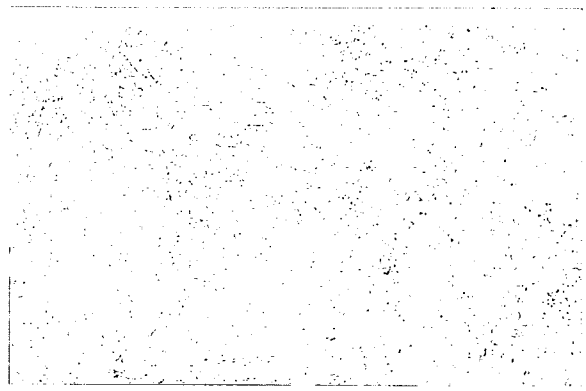

FIGURE 5 Microscopically, spindle cells are compactly arranged in a fascicular pattern. Chronic inflammatory cells also are noted (hematoxylin and eosin; original magnification, x40).

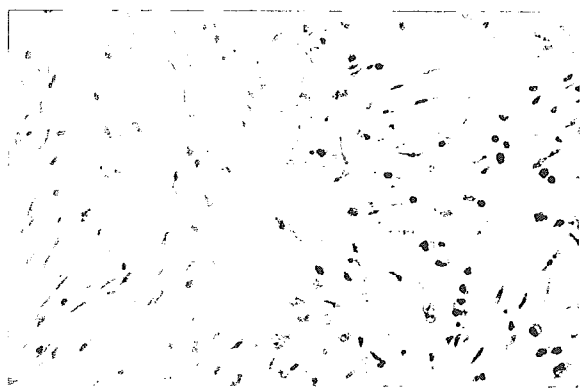

FIGURE 6 The tumor shows a proliferation of fibroblastic/or myofibroblast-like spindle cells in a fibromyxoid matrix (hematoxylin and eosin; original magnification, x400).

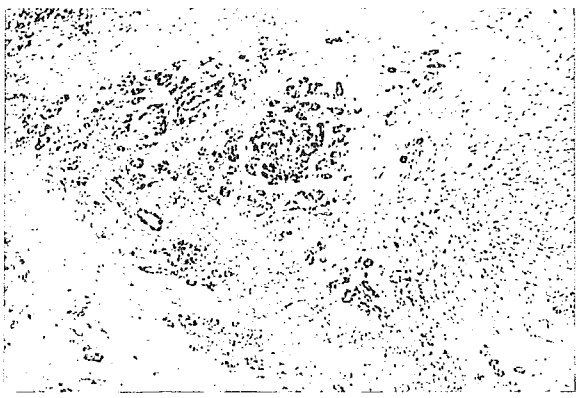

FIGURE 7 The tumor cells diffusely invade the pancreas (hematoxylin and eosin; original magnification, x100).

recurrence has been observed in one year.

DISCUSSION

Disease concepts relating to fibrous tumors have been reexamined in recent years. New categories including inflammatory myofibroblastic tumor (IMT) and inflammatory fibrosarcoma (IFS) have been proposed (1-5). The lesions are characterized by proliferation of myofibroblasts and the presence of inflammatory cells. The term IMT was suggested by Pettinato *et al.* (1) based on the finding that myofibroblasts constituted the major component of the lesions in their study of 20 "inflammatory pseudotumors" of the lung: Coffin *et al.* (2) subsequently reported 84 extrapulmonary cases of this tumor in detail. IMT often is seen in children and young adults (mean age, 9 yr), and can occur at any site. In most cases (73% of 61), the tumor has been found in the peritoneal cavity, retroperitoneum, or pelvic cavity. Tumor size averaged 6.4cm (range, 1 to 17). IMTs located in the peritoneal cavity tended to be large. No tumors among the 84 cases reported by Coffin *et al.* (2) originated in the pancreas. Systemic manifestations, such as fever, weight loss, and anemia have been reported to occur in 15 to 30% of cases of this tumor. Our IMT patient was a young adult (age, 29) who had a 6-cm tumor of the pancreas that was associated with obstructive jaundice and mild anemia, and showed the reported characteristics of IMT (2).

Histopathologically, IMTs exhibit morphologic characteristics. Myofibroblasts or fibroblasts assume a spindle shape and grow densely within myxoid matrix in a fascicular or storiforni arrangement. Various inflammatory cells, including lymphocytes and plasma cells, are interposed (2). The number of mitoses observed varies from case to case, but atypical mitoses have not been reported (2). Based on these features, our patient's tumor was diagnosed as IMT.

The category of IMT remains associated with difficulties in diagnostic classification. First, some investigators favor an earlier term, "inflammatory pseudotumors", but that diagnosis should be limited to inflammatory tissue reactions and not be applied to true neoplasms (6). According to Coffin *et al.* (2), IMTs are characterized by local invasion, vascular invasion, metastasis, and multifocal onset. Invasion of surrounding pancreatic tissue and the duodenal wall was seen in our case, indicating that the lesion was neoplastic.

Another nosological problem with IMT is differentiation from IFS, which first was reported in 1991 by Meis and Enzinger (3) as an invasive tumor with greater atypia of constituent fibroblasts or myofibroblasts than is seen in IMT. More aggressive behavior is seen, including higher incidences of recurrence and death (3). Apart from such atypia, no morphologic factors that determine the biologic properties of these two tumors have been suggested. Indeed, IFS and IMT have been speculated to be two lesions occupying the same spectrum, with reported cases of IMT probably including some low-grade examples of IFS. Some degree of cellular atypia was noted in our case, but we could not make a clear distinction between IFS and IMT.

When our patient's tumor was examined immunohistochemically, only vimentin was stained; antibodies against SMA and desmin produced no staining. Depending on the various cytoskeletal phenotypes of the constituent myofibroblasts, combinations of cells can exist that express only vimentin (7). Coffin *et al.* (4) reported vimentin staining in 98% of IMT (112/114) and an SMA staining in 82% (94/114). Their results are reasonably consistent with a diagnosis of the present tumor as IMT.

Non-epithelial tumors originating in the pancreas are very rare; of these, leiomyosarcoma has shown the highest incidence in reports to date (8-10). Granulocytic sarcoma (11,12), malignant fibrous histocytoma (13,14), nerve sheath tumor (15), liposarcoma (16), and fibrosarcoma (17), also have been reported. Our literature search revealed no previous reports of truly neoplastic IMT or IFS originating in the pancreas, although a case reported by Owen *et al.* (18) as a spindle-cell stromal tumor showed invasion by spindle-shaped cells, contained inflammatory cells, and immunostained for vimentin, suggesting a resemblance to the tumor in our patient.

ACKNOWLEDGEMENT

The author is indebted to Hiroshi Hashimoto MD, Department of Pathology, University of Occupational and Environmental Health, Japan, and Yoshimune Horibe MD, Department of Pathology, Fujita Health University Second Hospital, for their valuable comments concerning histopathologic diagnosis.

REFERENCES

1 **Pettinato G, Manivel JC, DeRosa N, Dehner LP:** Inflammatory myofibroblastic tumor (plasma cell granuloma); Clinicopathologic study of 20 cases with immunohistochemical and ultrastructural observation. Am J Clin Pathol 1990; 94:538-546.

2 **Coffin CM, Watterson J, Priest JR, Dehner LP:** Extra-

pulmonary inflammatory myofibroblastic tumor (inflammatory pseudotumor); A clinicopathologic and immunohistochemical study of 84 cases. Am J Surg Pathol 1995; 19:859-872.

3 **Meis JM, Enzinger FM:** Inflammatory fibrosarcoma of the mesentery and retroperitoneum; A tumor closely simulating inflammatory pseudotumor. Am J Surg Pathol 1991; 15:1146-1156.

4 **Coffin CM, Humphrey PA, Dehner LP:** Extrapulmonary Inflammatory myofibroblastic tumor; A clinical and pathological survey. Semin Diagn Pathol 1998; 15:85-101.

5 **Mentzel T, Dry S, Katenkamp D, Fletcher CDM:** Low-grade myofibroblastic sarcoma; Analysis of 18 cases in the spectrum of myofibroblastic tumors. Am J Surg Pathol 1998; 22:1228-1238.

6 **Meis-Kindblom JM, Kjellstrom C, Kindblom L-G:** Inflammatory fibrosarcoma: Update, reappraisal, and perspective on its place in the spectrum of inflammatory myofibroblastic tumors. Semin Diagn Pathol 1998; 15:133-143.

7 **Schurch W, Seemayer TA, Gabbiani G:** Myofibroblast. In: Sternberg SS (Ed.). Histology for pathologists. Second Edition. Philadelphia: Lippincott-Raven, 1997; pp. 129-166.

8 **Zalatnai A, Kovacs M, Flautner L, Sipos B, Sarkady E, Bocsi J:** Pancreatic leiomyosarcoma; Case report with immunohistochemical and flow cytometric studies. Virchows Arch 1998; 432:469-472.

9 **Ferlan-Marolt V, Vladislav P, Alojz P:** Pancreatic leiomyosarcoma; Clinicopathohistological presentation of a rare tumor. Hepatogastroenterology 2000; 47:556-559.

10 **Nesi G, Pantalone D, Ragionieri I, Amorosi A:** Primary leiomyosarcoma of the pancreas; A case report and review the literature. Arch Pathol Lab Med 2001; 125:152-155.

11 **King DJ, Ewen SWB, Sewell HF, Ewen SWB, Dawson AA:** Obstructive Jaundice; An unusual presentation of granulocytic sarcoma. Cancer 1987; 60:114-117.

12 **Ravandi-Kashani F, Estey E, Cortes J, Medeiros LJ, Giles FJ:** Granulocystic sarcoma of the pancreas; A report of two cases and literature review. Clin Lab Haem 1999; 21:219-224.

13 **Allen KB, Skandalakis LJ, Brown BC, Gray SW Skandalakis J:** Malignant fibrous histocytoma of the pancreas. Am Surg 1990; 56:364-368.

14 **Bastian D, Ramaswamy A, Barth PJ, Gerdes B, Ernst M, Bartsch D:** Malignant fibrous histocytoma of the pancreas; A case report with genetic analysis. Cancer 1999; 85:2352-2358.

15 **Pereira-Lima L, Kalil AN, Furian MB:** Pancreatic stromal tumor of nerve sheath origin treated by pancreatoduodenectomy. HPB Surg 1991; 4:165-169.

16 **Elliott TE, Albertazzi VJ, Danto LA:** Pancreatic liposarcoma; Case report with review of retroperitoneal liposarcomas. Cancer 1980; 45:1720-1723.

17 **Brooke WS, Maxwell JG:** Primary sarcoma of the pancreas; Eight year survival after pancreatoduodenectomy. Am J Surg 1966; 112:657-661.

18 **Owen CH, Madden JF, Clavien P-A:** Spindle cell stromal tumor of the pancreas: Treatment by pancreatoduodenectomy. Surgery 1997; 122:105-111.

Para-aortic lymph node metastasis in carcinoma of the head of the pancreas

Mitsuru Sakai, MD, Akimasa Nakao, MD, Tetsuya Kaneko, MD, Shin Takeda, MD, Soichiro Inoue, MD, Yasuhiro Kodera, MD, Shuji Nomoto, MD, Naohito Kanazumi, MD, *and* **Hiroyuki Sugimoto, MD,**
Nagoya, Japan

Background. *Metastasis to para-aortic lymph nodes often occurs in pancreatic head cancer, but factors that predict it are not well known.*
Methods. *Using histopathologic data of 178 patients who underwent extended lymph node dissection for pancreatic head cancer, we analyzed the distribution of metastases to lymph node groups classified in detail and attempted to identify the lymph node groups that have a strong relation with metastasis to para-aortic lymph nodes.*
Results. *A high incidence of lymph node metastasis was found in para-aortic lymph nodes (No. 16, 19%) as well as in regional lymph nodes, such as those on the posterior aspect of the pancreas head (No. 13, 47%), on the anterior surface of the pancreas head (No. 17, 29%), along the superior mesenteric artery (No. 14, 28%), and along the hepatoduodenal ligament (No. 12, 19%). Statistical analysis showed that metastases to para-aortic lymph nodes had a strong correlation with metastases to Nos. 12, 13, 14, and 17 lymph nodes. Para-aortic lymph node metastases were seldom observed among the patients who had no metastases to Nos.13, 14, and 17 lymph nodes.*
Conclusions. *Examination of Nos. 13, 14, and 17 lymph nodes may be useful to predict the involvement of para-aortic lymph nodes. (Surgery 2005;137:606-11.)*

From the Department of Surgery II, Nagoya University School of Medicine

PANCREATIC CANCER remains a disease with a dismal outcome despite continuous efforts to improve its survival rate. Systemic resection of lymph nodes has been performed in various cancer types in an attempt to improve survival in patients who have node metastases; long-term survivors among those with node metastases may serve as proof of the benefits achieved from such a procedure. Extending the range of node dissection may, in theory, increase the chance for cure, but the survival benefit of extended lymphadenectomy for gastric carcinoma, for instance, has not been proven clearly in prospective randomized trials.[1] The issue of adequate extent of lymphadenectomy for pancreatic cancer also is currently a matter of controversy.[2] Para-aortic lymph nodes usually are outside the range of resection in the standard surgical treatment for pancreatic cancer. Metastases to the para-aortic lymph nodes, however, are observed commonly among patients with carcinoma of the head of the pancreas.[3-6] The true indication for systematic resection of these lymph nodes is undetermined currently.

Since 1981 we have performed isolated pancreatectomy with extended lymphadenectomy that includes systematic dissection of the para-aortic lymph nodes, in addition to the standard range of lymph nodes, and coresection of the portal vein using a catheter bypass procedure.[3,7-9] As a result, a relatively large body of cumulative data from a single institution on the lymph node involvement of cancer of the head of the pancreas has enabled us to conduct a retrospective analysis. On the basis of these data, we analyzed the distribution of metastases to lymph node groups classified in detail and attempted to identify the "junctional lymph nodes" to para-aortic lymph nodes. The concept of "junctional lymph nodes" has been advocated recently in an attempt to choose between limited and more extensive lymphadenectomy.[10] In this view, cancer cells are considered to spread to distant lymph nodes via the junctional lymph nodes, the examination of which allows the surgeon to decide whether to stop the dissection of lymph nodes there or to proceed to more extensive lymphadenectomy. According to our

Accepted for publication February 23, 2005.

Reprint requests: Akimasa Nakao, MD, Department of Surgery II, Nagoya University School of Medicine, Tsurumai-cho 65, Showa-ku, Nagoya 466-8550, Japan. E-mail: nakaoaki@med.nagoya-u.ac.jp.

0039-6060/$ - see front matter

doi:10.1016/j.surg.2005.02.009