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Surgical Approach to Tumor Recurrence and Metastatic Lesions of the Liver in a Patient with Malignant Endocrine Tumors of the Pancreas: Case Report

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Running head: Malignant endocrine tumor

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Abstract

We describe herein a 72-year-old woman with tumor recurrence in the residual pancreas and metastasis to the liver following a pylorus-preserving pancreatoduodenectomy for multiple endocrine tumors in the head of the pancreas. Abdominal ultrasonography performed 7 years after the initial surgery detected new lesions in the residual pancreas and liver. After recurrence of endocrine tumors of the pancreas and metastasis to the liver were diagnosed, the lesions were successfully resected by total pancreatectomy with distal gastrectomy and both lateral segmentectomy and partial resection of segment 8. Genetic analysis using a blood specimen showed that this patient carried multiple endocrine neoplasia type 1 (MEN1) gene mutation. One year after the second resection, the patient remains in good health using insulin and has not shown any sign of recurrence. This case report describes successful surgical resection for recurrence and metastasis of malignant endocrine tumors in a patient with MEN1 gene mutation.

Introduction

The majority of clinically relevant pancreatic endocrine tumors (PETs) are functional. Nonfunctioning PETs (NPETs) with endocrine differentiation in the absence of clinical symptoms are found in 15-30% of surgical cases, and are associated with signs of an expanding mass (1, 2). Patients with PETs have a remarkably better postoperative prognosis than those with adenocarcinoma of the pancreas (3,4). Evidence of malignancy of PETs is gross invasion of adjacent organs, metastases to regional lymph nodes, liver, and other distant sites, or blood vessel invasion (1). Surgical resection of PETs is generally beneficial in achieving long survival (3).

In patients with multiple endocrine neoplasia type 1 (MEN1), however, the pancreas is involved in 80 to 100% of cases including gastrinoma, insulinoma and NPETs (1). MEN1 is an autosomal dominant genetic disorder associated with germline mutations in the recently identified MEN1 suppressor gene on chromosome 11q (5). A standardized surgical approach and algorithm for decision-making in patients with MEN1 have previously been reported (6, 7). We describe herein a patient with MEN1 gene mutation who developed recurrent tumor and metastatic lesions of the liver that were successfully resected by total pancreatectomy with distal gastrectomy combined with lateral

segmentectomy and partial resection of the liver.

Case report

A 72-year-old female was admitted to Asahikawa Kousei Hospital for the treatment of asymptomatic pancreatic lesions in July 1995. Familial history included a sister who had died of adenocarcinoma of the pancreas, but there was no history of pancreatic disease in her parents or children. Computed tomography (CT) showed two enhanced lesions (each 2 cm in diameter) at the head of the pancreas (**Fig. 1**). Endoscopic retrograde pancreatography (ERP) did not demonstrate any abnormal findings of the main pancreatic duct and we could not detect elevated levels of insulin, glucagon or gastrin in the serum. We diagnosed NPETs of the head of the pancreas and performed pylorus-preserving pancreatoduodenectomy (PPPD) using Suzuki's reconstruction. Macroscopically, tumors were located separately in the head of the pancreas (**Fig. 2a**). Pathological findings showed two neoplastic lesions without blood vessel invasion (**Fig. 2b**) that were immunohistochemically stained for pancreatic polypeptide (PP) (**Fig. 2c**), and other hyperplastic islet cells.

Seven years after PPPD, the patient demonstrated new lesions of the pancreas and metastatic tumors of the liver on abdominal ultrasonography despite the continued absence of any clinical symptoms.

CT showed enhanced lesions located separately in the body and tail of the pancreas (**Fig. 3a and 3b**), and in segment (S) 3 (5 cm in diameter) and S 8 (2 cm in diameter) of the liver (**Fig. 3c**). Additionally we detected three small solid lesions of the thyroid and one lesion (5 mm in diameter) of the right-lower parathyroid gland but we could not detect any lesions of the pituitary gland or adrenal glands. On hormonal examination, her serum PP level was high (31,000 pg/ml), parathyroid hormone was slightly high (900 pg/ml), and growth hormone was normal (0.92 ng/ml). Calcium level in the serum was slightly high (5.2 mEq/l). We successfully performed ERP that showed slight deviation of the main pancreatic duct. Recurrence of PETs in the residual pancreas and metastasis to the liver were diagnosed, and resection of the pancreas and metastatic lesions were performed after obtaining informed consent from the patient. Pathological findings showed two separate neoplastic lesions in the pancreas. The tumor in the tail had infiltrated the surrounding tissue with blood vessel invasion and showed a few mitoses per high-power field (**Fig. 4a and 4b**). Islet cell adenomas and hyperplastic islet cells were also detected. There was single metastasis to a lymph node adjacent to the pancreas. These cells were immunohistochemically PP-positive (**Fig. 4c**) and some were stained for insulin (**Fig. 4d**) or glucagon. In addition, some of them were

chromogranin-positive but none were stained for p53 protein. After the second operation, we investigated the existence of MEN1 gene mutation. Genomic DNA was isolated from a blood specimen and amplified for the MEN1 gene by polymerase chain reaction (8). Direct sequencing of the DNA product demonstrated one germline mutation, 1460+1 del14insCT. Based on genetic analysis and clinical evidence, we diagnosed this patient as a case of MEN1. One year after the second resection, the patient is in good health using insulin without any sign of recurrence.

Discussion

Despite the general impression that PETs grow slowly and the performance status of patients is usually well maintained, some reports describe that some patients with NPETs do not survive 5 years after the first diagnosis (6). In a recent retrospective report, there was no correlation between the size of the primary PETs and the incidence of regional or distant metastasis (9). A surgical approach to patients with resectable PETs is beneficial to long-term survival (3,4). Innovative treatment strategies including chemotherapy and interventional treatment are needed for patients with locally advanced or nonresectable PETs. In the present case, we followed the patient once a year, and detected recurrence and metastasis of NPETs 7 years after the initial surgery. Long-term followup is thus required for patients with multiple NPETs after diagnosis.

Understanding the natural history of PETs in patients with MEN1 is important for clinical management. Because PETs are the most common MEN1-related cause of death, an aggressive surgical approach before malignant spread appears justified (7, 9). In the present case, the diagnosis of MEN1 was not established by clinical evidence at the second operation. Because pathological findings in the resected pancreas showed multiple lesions consisting of islet cells including adenomas and

hyperplastic cells, we considered that the patient may have MEN1 gene mutatuion. Genetic analysis using a blood specimen showed a mutation in exon 9 of MEN1 gene (1460+1 del14insCT). This mutation was previously reported in Japanese patients with MEN1, and is probably responsible for this disease (10).

Treatment of PETs in patients with MEN1 gene mutation has been to recommend surgery for patients with functional tumors or tumors that are large enough to be demonstrable by radiographic tests. The indications and optimal timing for surgery are still not clear and must be modified for patients based on age, health status, and clinical symptoms. Prophylactic total pancreatectomy for clinically insignificant tumors cannot be advocated (7. 9). In addition, some patients with MEN1 and PETs who had a second operation for recurrence and metastasis of PETs achieved long-term survival (9). In the present case, a surgical approach to recurrent tumor and metastatic lesions of the liver was also beneficial to survival. To date, the patient has not chemotherapy after the second operation. Careful follow-up may be the prudent approach for detecting new metastatic lesions.

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Figure legends

Figure 1

Computed tomography showed two enhanced lesions at the head of the pancreas (Arrows show each lesion).

Figure 2

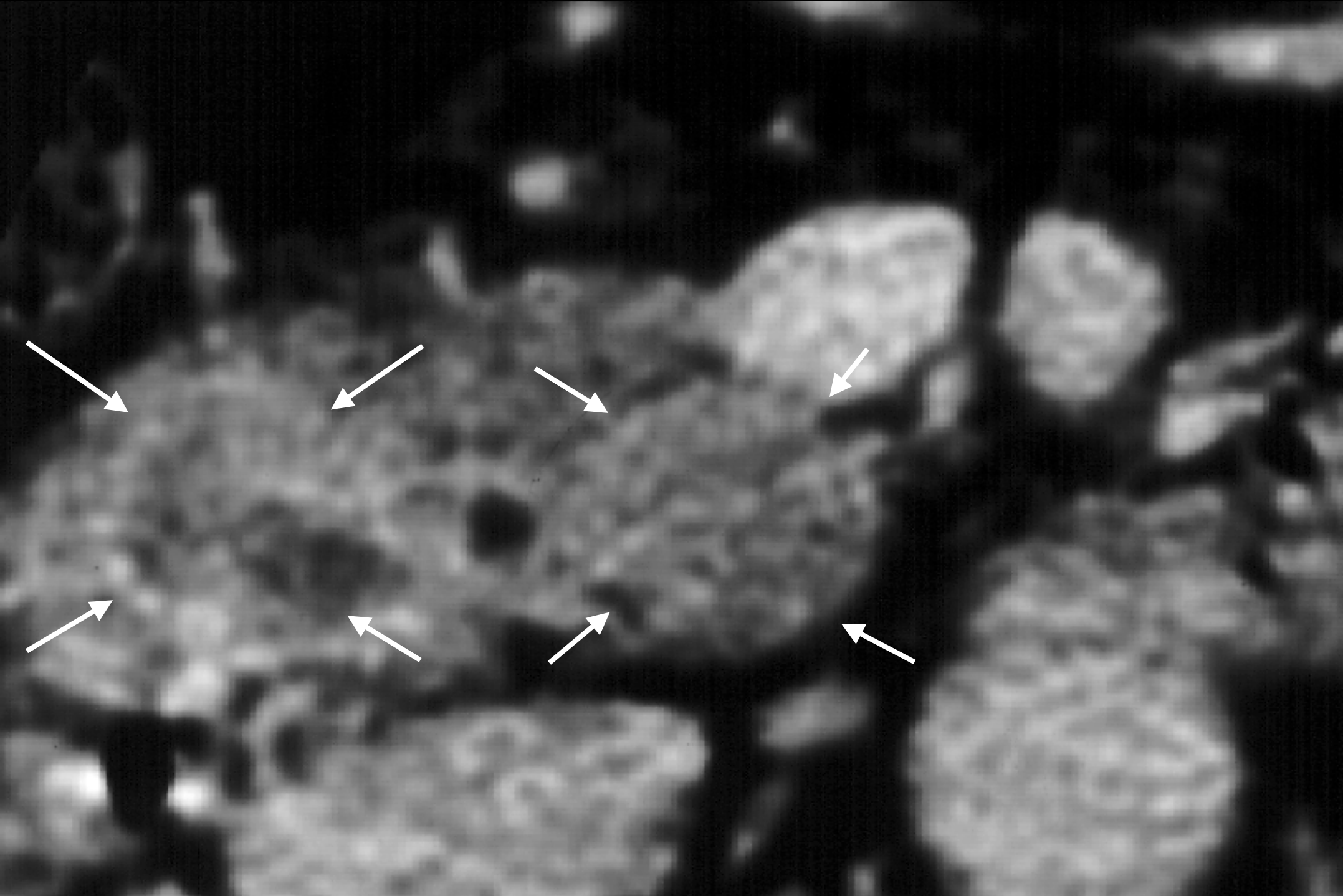
Macroscopic findings showed two separate lesions in the head of the pancreas (**a**) (Arrow shows each lesion.). Pathological findings showed neoplastic cells **(b,** hematoxylin and eosin staining, X 100) that were stained for pancreatic polypeptide by the immunoperoxidase technique (**c**, X 80).

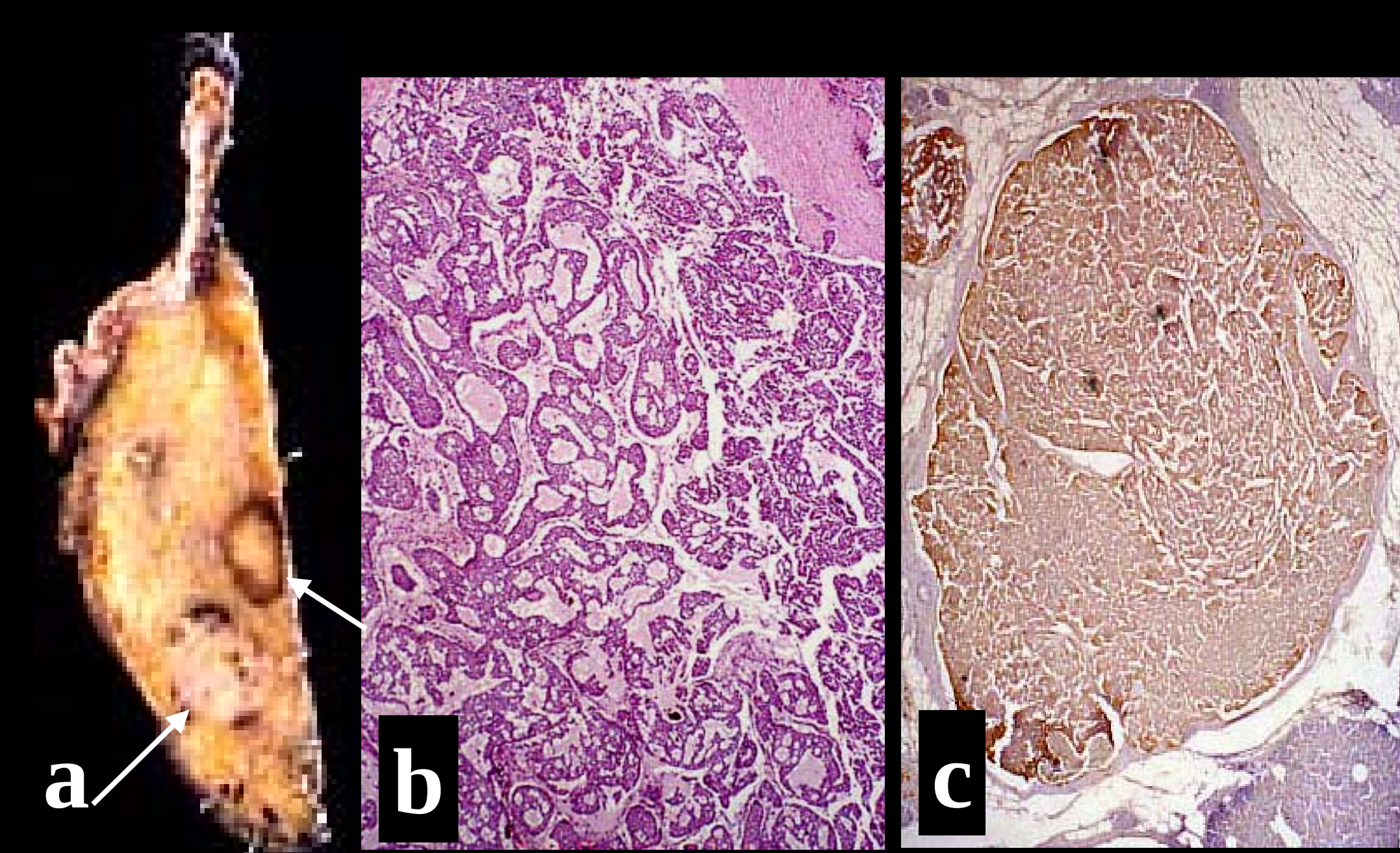
Figure 3

Computed tomography showed enhanced lesions in the body (**a**) and tail (**b**) of the pancreas, and segment 3 and segment 8 of the liver (**c**). (Arrow shows the position of the lesion.)

Figure 4

Pathological findings showed two neoplastic lesions in the tail of the pancreas (**a,** hematoxylin and eosin staining, X 100) and a few mitoses per high-power field (**b**, X 200). These cells were immunohistochemically pancreatic polypeptide-positive (**c,** X 80) and some were stained for insulin (**d**, X 100).

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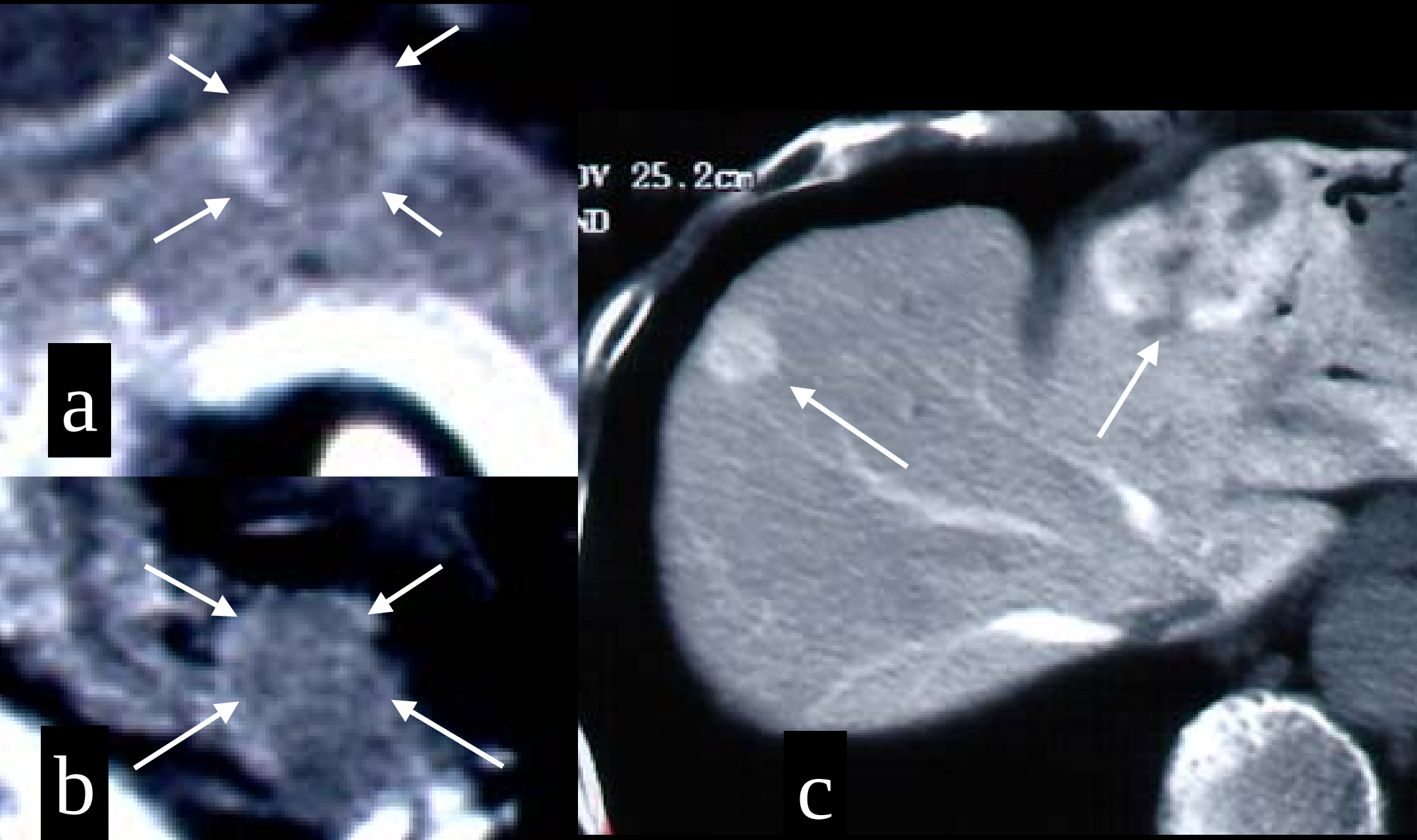
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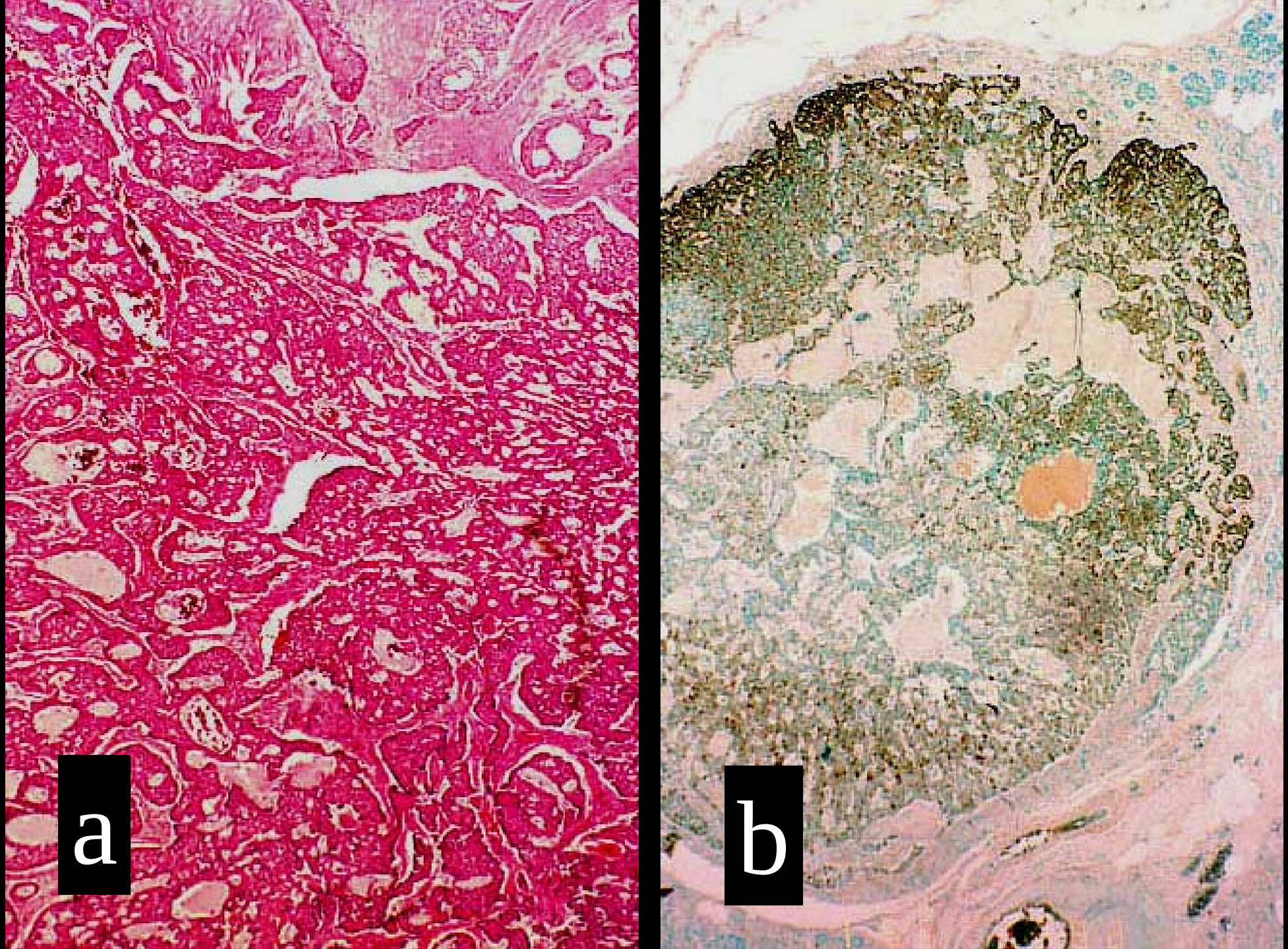
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