Title page

a) Title:

Long-term survival in patient with node-positive adult-onset Xp11.2 translocation renal cell carcinoma

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d) Running head:

An adult case of Xp11.2 translocation RCC

e) Key words:

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f) Conflict of interest: None

Abstract

Adult-onset Xp11.2 translocation renal cell carcinoma is a rare malignancy that has an aggressive clinical course and poor prognosis. The reasons for this include the fact that most patients have an advanced clinical stage at diagnosis and also that there is a lack of effective systemic therapy. We herein present the case of a 32-year-old woman suffering from node-positive Xp11.2 translocation renal cell carcinoma, who has undergone radical nephrectomy with an extensive retroperitoneal lymph node dissection, followed by two times of surgical resection for recurrent nodal disease. The patient has experienced no recurrent disease 4.5 years after the last operation and remains free of disease. Surgical approach to recurrent disease, if the recurrent site can be judged to be limited, might be one of feasible treatment options in patients with Xp11.2 translocation renal cell carcinoma.

Introduction

Renal cell carcinoma (RCC) associated with Xp11.2 translocation/TFE3 (transcription factor E3) gene fusion has been recently identified [1, 2]. We report herein an adult case of node-positive RCC associated with Xp11.2 translocation/TFE3 gene fusion who achieved long-term survival by radical nephrectomy with an extensive retroperitoneal lymph node dissection, followed by two times of surgical resection for recurrent nodal disease.

Case Report

In April 2003, a 32-year-old woman was referred to our department with right-sided abdominal pain and fever. Computed tomography (CT) scan revealed a 9-cm mass in the right kidney and multiple enlarged lymph nodes in the retroperitoneal lesion. The patient had no relevant past history or family history. Laboratory tests at admission showed mild anemia and increased CRP (6.9 mg/dL). Bone scintigram and brain CT scan revealed no distant metastasis. The patient underwent right radical nephrectomy combined with retroperitoneal lymph node dissection. Tumor cells with papillary and alveolar architecture were identified in the resected kidney, and were also found in 10 of the 19 dissected lymph nodes. The pathological diagnosis of this tumor at that time was “unclassified tumor” resembling collecting duct carcinoma. The patient received adjuvant chemotherapy with the combination of methotrexate, epirubicin, and cisplatin, which has been frequently administered against urothelial cancer in Japan [3]. However, enlargement of para-aortic lymph nodes outside the dissected area was detected at 5 months after the first operation, and the patient received paclitaxel-based chemotherapy. Since reduction in the size of these metastases was not achieved, the patient underwent dissection of the enlarged lymph nodes in December 2003. Pathological examination showed the same histology as when the tumor was removed at the first operation. Metastasis to the right iliac

bone was found at 13 months after the first operation, and radiotherapy at a dose of 65 Gy/26 f was performed. In December 2005, abdominal CT scan revealed enlarged lymph nodes outside the area dissected at the first and second lymphadenectomies (Fig. 1A); 18FDG-positron emission tomography (PET) showed uptake by the enlarged nodes (Fig. 1B). The patient underwent a third lymphadenectomy.

Given the clinical characteristics of the present case, the possibility of RCC associated with Xp11.2 translocations/*TFE3* gene was considered and extensive pathological examination was undertaken in both primary tumors and specimens obtained from lymph node metastases. The primary kidney tumor obtained at first operation consisted of cells with clear cytoplasm and partially eosinophilic cells with a micropapillary growth pattern lacking fibrovascular cores (Fig. 2A). Nuclei of many tumor cells were moderate-intensity (2+) TFE3. In the immunohistochemical study for TFE3 protein, we confirmed an evident positive reaction for this protein by using alveolar soft part sarcoma as a positive control and typical clear cell carcinoma as a negative control. Additionally, neoplastic cells were diffusely positive for cytokeratin 19, P504S, and CD10. The tumor cells, however, were negative for cytokeratin 7, keratin 903, UEA-1, and TFEB. In the lymph nodes resected at first, secondary, and third operations, the tumor had nested in papillary architecture and was composed of clear cells with voluminous cytoplasm (Fig. 2B). Psammoma body formation was noted in the stroma (Fig. 2C). Nuclei of almost all tumor cells from lymph node metastases showed a diffuse and strongly positive reaction (2+~3+) for TFE3 protein (Fig. 2D), but not for TFEB. Additionally, melanosome (HMB45) was positive for eosinophilic tumor cells with a nested formation microscopically resembling alveolar soft part sarcoma (ASPS). On the basis of these morphologic and immunohistochemical findings, these tumors were finally diagnosed as RCC associated with Xp11.2 translocations / *TFE3* gene fusion (probably *ASPL-TFE3* RCC).

The patient has experienced no recurrent disease including lymph node metastasis and osseous metastasis 4.5 years after the third operation and remains free of disease to date.

Discussion

Xp11.2 translocation RCC was recognized in the 2004 World Health Organization (WHO) classification of RCC for the first time [1]. Recently, several different Xp11.2 translation RCCs have been identified and they result in gene fusion between the TFE3 gene located on chromosome Xp11.2 and several partners: the ASPL gene at chromosome 17q25, the PRCC gene at 1q21, the PSF gene at 1p34, the NonO gene at Xq12, and the CLTC gene at 17q23 [2]. Of these, *ASPL-TFE3* gene fusion and *PRCC-TFE3* gene fusion are reported to be common in Xp11.2 translocation RCC [4]. Although there are some characteristic morphological features in Xp11.2 translocation RCCs, it is very difficult to distinguish between these tumors and conventional clear cell RCCs by simple Hematoxylin-eosin staining. To differentiate Xp11.2 translocation RCC from other RCCs, immunohistochemical studies of antibody against the C-terminal of TFE3 protein are generally employed. Argani et al. reported that nuclear immunoreactivity for TFE3 protein was a highly sensitive and specific assay for Xp11.2 translocation RCC or alveolar soft part sarcoma (ASPS) [5]. Although normal tissues and other malignancies were reported to have no detectable level of TFE3 protein by immunohistochemistry [5], native TFE3 protein is known to be expressed ubiquitously. Accordingly, an evident positive reaction for TFE3 protein at an intensity level above 2+ and widespread distribution should be confirmed by immunohistochemical staining of ASPS as a positive control for TFE3 protein [6].

Xp11.2 translocation RCC is reported to frequently occur in children and accounts for 26-41% of pediatric renal carcinomas [4]. On the other hand, its incidence is very low in adults, and Komai et al. reported that Xp11 translocation RCC was found in only 7 out of 443 adult RCC patients [7]. Although Xp11.2 translocation RCC has a relatively good prognosis in pediatric cases, adult-onset Xp11.2 translocation RCC is reported to have a poor prognosis [2,7,8]. The reasons for this include the fact that most patients have an advanced clinical stage at diagnosis

and also that there is a lack of effective systemic therapy. Both chemotherapy and immunotherapy have no effect on metastatic lesions [2,7,9]. Recently, Malouf et al. reported that partial response was observed in 3 of 11 patients (27%) who received sunitinib and the median progression-free survival in these patients was 8.2 months [9]. They concluded that targeted therapy, especially sunitinib treatment, could achieve objective response and prolonged progression-free survival in patients with Xp11.2 translocation RCC. Choueiri et al. also reported similar results [10]. Further clinical study should be required to make clear the clinical effectiveness of systemic therapy with targeted agents in these patients.

There is also a possibility that adequate surgical resection can improve the prognosis. In patients with Xp11.2 translocation RCC, the significance of lymph node dissection is reported to be greater than that for conventional RCC [4,7]. The present case underwent extensive dissection of potentially metastatic lymph nodes at the first operation, and found metastases in 10 of the 19 dissected lymph nodes. However, the lymph nodes on the left side of the aorta and those under the aortic bifurcation were not dissected at the first operation, so metastasis was later found at these sites. Since chemotherapies were not effective and molecular targeted agents were not available at that time, we performed surgical resection of relapsed lymph node metastases. Before undergoing the third operation, we performed 18FDG-PET scanning in addition to CT scan in order to assess the viability of the lymph node metastases and to detect the presence of occult metastasis elsewhere. The 18FDG-PET scanning revealed significant uptake only in nodal metastatic site and the result was also confirmed pathologically. Since the present patient remains free of disease 4.5 years after third operation, surgical approach to recurrent disease, if the recurrent site can be judged to be limited, might be one of feasible treatment options in these patients.

References

1. Argani P, Ladanyi M: Renal carcinoma associated with Xp11.2 translocation/TFE3 gene fusion. In: Eble JN, Sauter G, Epstein JI et al. (eds). *Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs*. IARC Press. Lyon, France, 2004; 37-38
2. Argani P, Olgac S, Tickoo SK, Goldfischer M, Moch H, Chan DY, Eble JN, Bonsib SM, Jimeno M, Lioreta J, Billis A, Hicks J, Demarzo AM, Reuter VE, Ladanyi M: Xp11 translocation renal cell carcinoma in adults: expanded clinical, pathologic, and genetic spectrum. Am J Surg Pathol. 2007;31:1149-1160.
3. Kuroda M, Kotake T, Akaza H, Hinotsu S, Kakizoe T: Efficacy of dose-intensified MEC (methotrexate, epirubicin and cisplatin) chemotherapy for advanced urothelial carcinoma: a prospective randomized trial comparing MEC and M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin). Japanese Urothelial Cancer Research Group. Jpn J Clin Oncol. 1998;28:497-501.
4. Geller JI, Argani P, Adeniran A, Hampton E, De Marzo A, Hicks J, Collins MH: Translocation renal cell carcinoma: lack of negative impact due to lymph node spread. Cancer 2008;112:1607-1616.
5. Argani P, Lal P, Hutchinson B, Lui MY, Reuter VE, Ladanyi M: Aberrant nuclear immunoreactivity for TFE3 in neoplasms with TFE3 gene fusions: a sensitive and specific immunohistochemical assay. Am J Surg Pathol. 2003;27:750-761.
6. Yamaguchi T, Kuroda N, Imamura Y, Hes O, Kawada T, Nakayama K: Imprint cytologic features in renal cell carcinoma associated with Xp11.2 translocation/TFE3 gene fusion in an adult: a case report. Acta Cytol. 2009;53:693-697.
7. Komai Y, Fujiwara M, Fujii Y, Mukai H, Yonese J, Kawakami S, Yamamoto S, Migita T, Ishikawa Y, Kurata M, Nakamura T, Fukui I: Adult Xp11 translocation renal cell carcinoma

diagnosed by cytogenetics and immunohistochemistry. Clin Cancer Res. 2009;15:1170-1176

8. Franzini A, Picozzi SC, Politi PL, Barana L, Bianchi F, Alfano G, Gatti G, Fanciullacci F, Gariboldi M, Strada M, Leone BE: A case of renal cancer with TFE3 gene fusion in an elderly man. Clinical, radiological and surgical findings. Urol Int. 2007;78:179-181.
9. Malouf GG, Camparo P, Oudard S, Schleiermacher G, Theodore C, Rustine A, Dutcher J, Billemont B, Rixe O, Bompas E, Guillot A, Boccon-Gibod L, Couturier J, Molinie V, Escudier B: Targeted agents in metastatic Xp11 translocation/TFE3 gene fusion renal cell carcinoma (RCC): a report from the Juvenile RCC network. Ann Oncol 2010; 21(9): 1834-1838.
10. Choueiri TK, Lim ZD, Hirsch MS, Tamboli P, Jonasch E, McDermott DF, Cin PD, Com P, Vaishampayan U, Heng DY, Tannir NM: Vascular endothelial growth factor-targeted therapy for the treatment of adult metastatic Xp11.2 translocation renal cell carcinoma. Cancer DOI: 10.1002/cncr.25512

Figure legends

Figure 1:
A, Abdominal CT scan revealed enlarged lymph node in the area of the aortic bifurcation (arrow).
B, 18FDG-PET scanning showed significant uptake in this lesion (arrow).

Figure 2:
A, The primary kidney tumor consists of eosinophilic cells with a micropapillary growth pattern lacking fibrovascular cores.
B, Metastatic tumor to lymph node is composed of clear cells with voluminous cytoplasm (arrow).
C, Psammoma bodies are seen in the lymph node metastasis (arrow).
D, TFE3 immunohistochemical study of tumor cells in lymph node metastasis shows nuclear labeling for TFE3 protein.

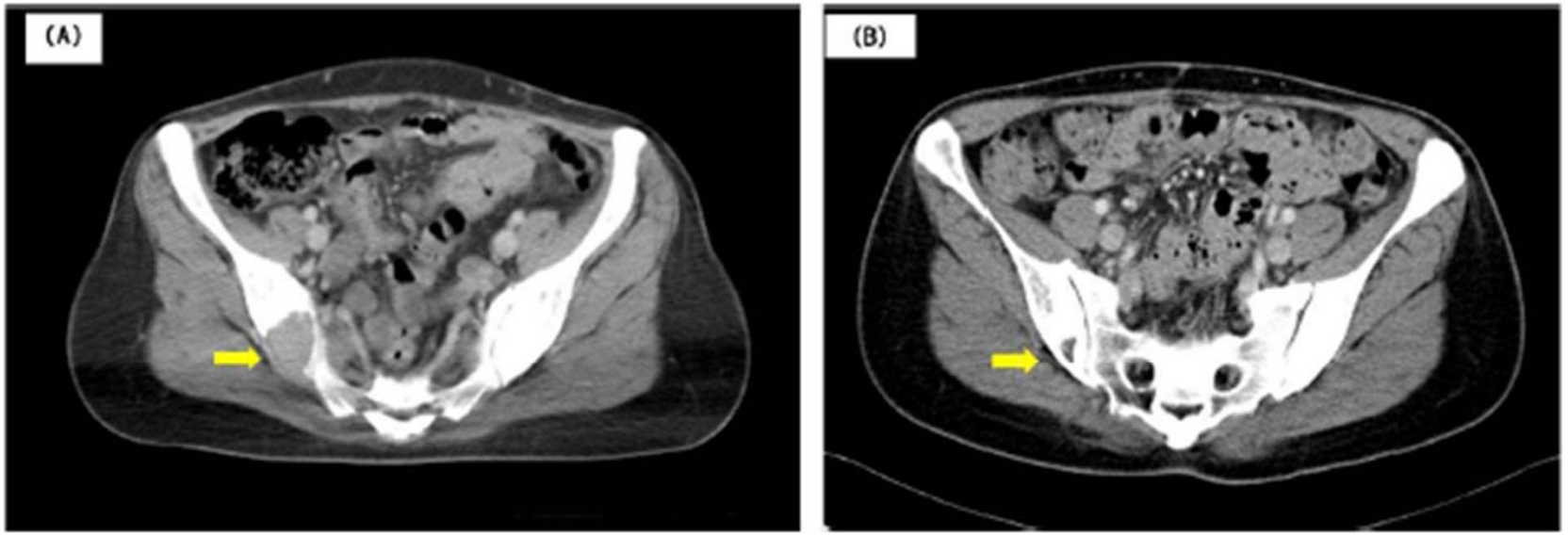
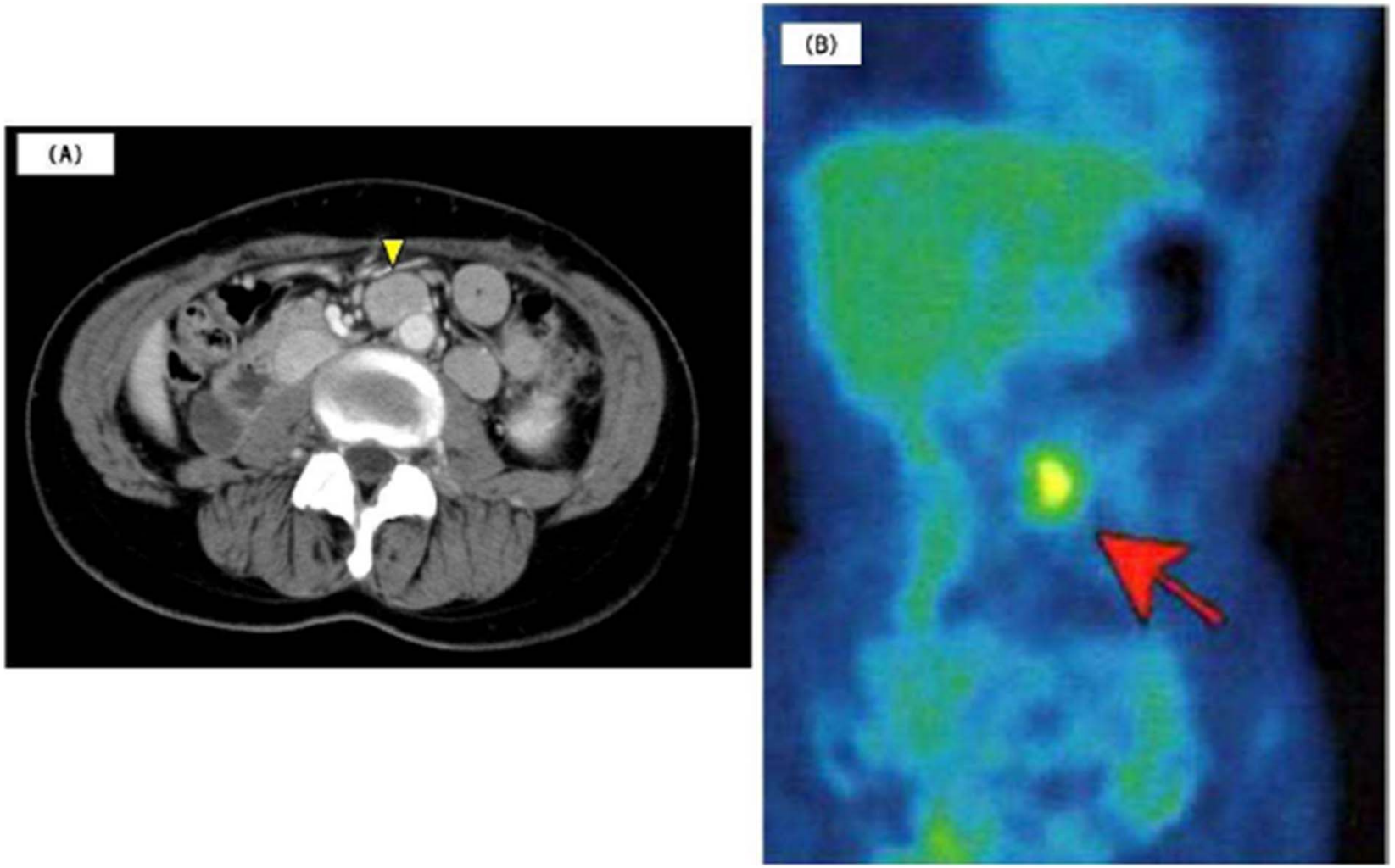


Figure 1:
A, Pelvic CT scan showed osteolytic lesion in the right iliac bone at 13 months after the first operation.
B. Complete remission was obtained with radiotherapy at a dose of 65 Gy/26 f for this lesion.



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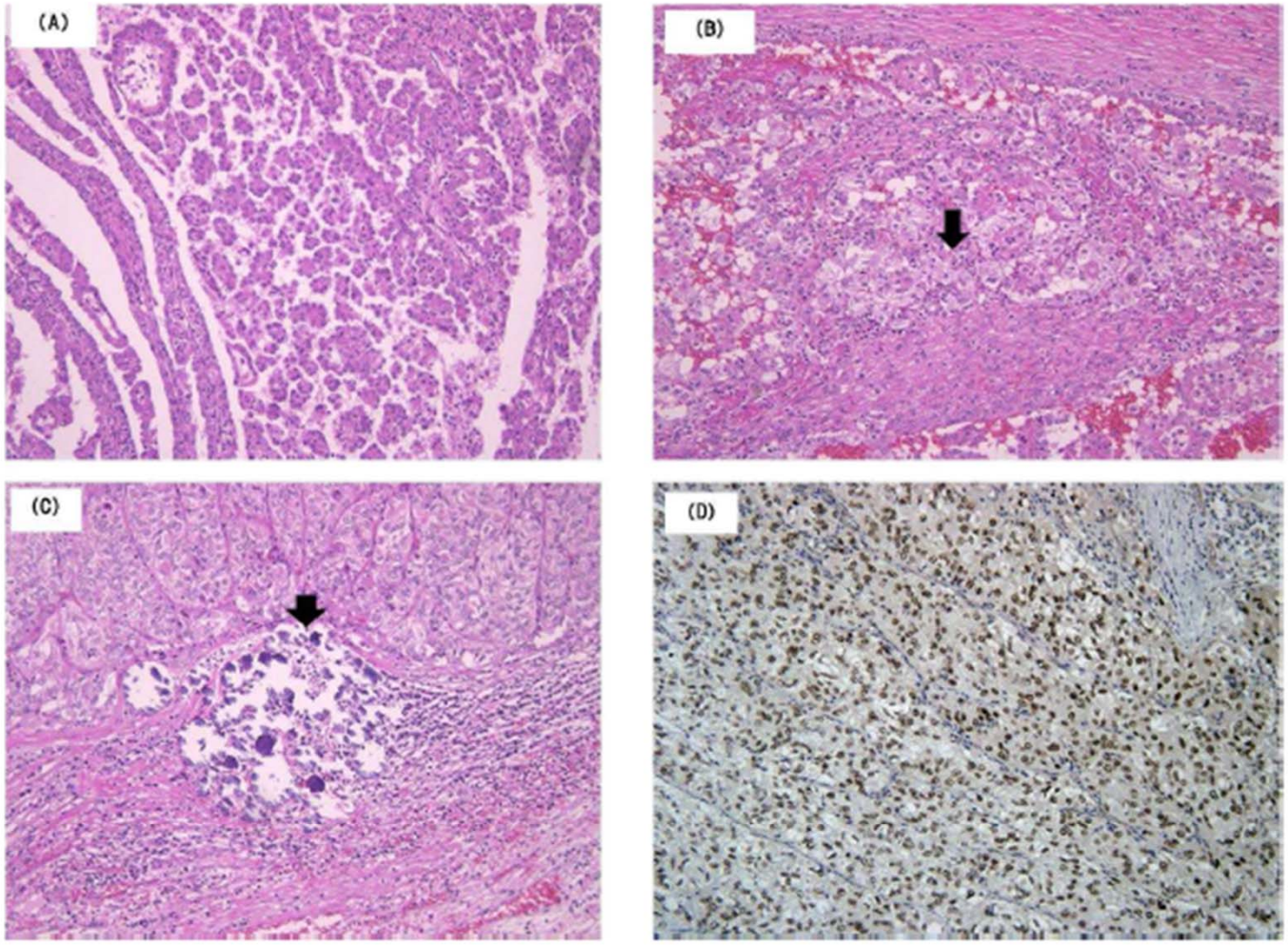

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