Case Report

Intraductal papillary neoplasm of the bile duct, gastric type, arising in the intrapancreatic common bile duct could progress to colloid carcinoma: report of a case

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Abstract: Intraductal papillary neoplasm of the bile duct (IPNB) exists in a pathway of multistep-carcinogenesis toward cholangiocarcinoma. Four subtypes are observed in IPNB, pancreatobiliary type, intestinal type, gastric type, and oncocytic type, similarly to the corresponding disease in the pancreas, intraductal papillary mucinous neoplasm (IPMN). IPNB can present with or without macroscopically visible mucin secretion. IPNB usually progresses to tubular adenocarcinoma. However, there are a limited number of well-described cases of gastric-type IPNB progressing not to tubular adenocarcinoma but to colloid carcinoma. Herein, we present a case of an 82-year-old female patient with gastric-type IPNB in the intrapancreatic common bile duct without macroscopically visible mucin secretion, which progressed to colloid carcinoma. As IPNB, especially without visible mucin secretion, is considered to be a heterogeneous group of diseases, such an unexpected association could occur.

Keywords: Intraductal papillary neoplasm of the bile duct, intraductal papillary mucinous neoplasm, gastric type, colloid carcinoma

Introduction

Intraductal papillary neoplasm of the bile duct (IPNB) has been designated as a papillary growth of neoplastic epithelium with a fibrovascular core [1]. It exists in a pathway of multi-step-carcinogenesis toward cholangiocarcinoma [2]. IPNB shares clinicopathological features with pancreatic intraductal papillary mucinous neoplasm (IPMN). Four subtypes of IPMN, pancreatobiliary type, intestinal type, gastric type, and oncocytic type, are also observed in IPNB in that order of frequency [1], and the intestinal type tends to be associated with colloid carcinoma in cases of an invasive component [3]. Colloid carcinoma developing in IPNB usually presents with macronodular growth in contrast to the periductal infiltrative growth of tubular adenocarcinoma [2].

IPNB includes tumors without macroscopically visible mucin secretion. IPNB with visible mucin secretion exhibits striking similarities to IPMN. On the other hand, IPNB without visible mucin secretion harbors heterogeneous lesions: many of them more or less resembling usual cholangiocarcinomas and others more similar to IPMN [4].

Herein, we present a case of an 82-year-old female patient with IPNB without visible mucin secretion, which developed in the intrapancreatic common bile duct. It was classified as gastric-type IPMN and showed invasion as a form of colloid carcinoma. Gastric-type IPNB containing an invasive component of colloid carcinoma is rare, and the number of well-described cases is limited [5].

Clinical findings

An 82-year-old female patient presented to our hospital with a complaint of jaundice, itching, and brown urine lasting for the past two weeks. Physical examination revealed systemic jaundice of the skin and bulbar conjunctiva. No remarkable findings were noted on abdominal physical examination. Liver function tests
showed the following elevated values: total bilirubin 10.1 mg/dL, direct bilirubin 7.9 mg/dL, aspartate transaminase 122 IU/L, alanine transaminase 153 IU/L, alkaline phosphatase 1280 IU/L, and gamma-glutamyl transpeptidase 699 IU/L. The CA19-9 level was elevated to 390 U/mL (normal range: 0-37 U/mL). Abdominal contrast-enhanced computed tomography (CT) revealed a tumor in the intrapancreatic common bile duct, measuring 20 × 18 mm (Figure 1A). The peripheral portion of the tumor was predominantly enhanced on the arterial phase compared with the plain CT image (B, C). The peripheral portion of the tumor (arrow) was predominantly contrast-enhanced on the arterial phase (C) compared with the plain computed tomography image (B). (D) The tumor (arrow) showed low-signal intensity on a T1-weighted image. (E) The tumor (arrow) showed high-signal intensity on a T2-weighted image.

Figure 1. Computed tomography (A-C) and magnetic resonance imaging (D, E) findings. (A) The tumor (arrow) was located in the intrapancreatic common bile duct, measuring 20 × 18 mm. (B, C) The peripheral portion of the tumor (arrow) was predominantly contrast-enhanced on the arterial phase (C) compared with the plain computed tomography image (B). (D) The tumor (arrow) showed low-signal intensity on a T1-weighted image. (E) The tumor (arrow) showed high-signal intensity on a T2-weighted image.

Pathological findings

The surgically resected specimen revealed a tumor, measuring 22 × 20 × 18 mm, in the intrapancreatic common bile duct (Figure 2A).
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On the cut surface, it showed a mucinous appearance and it infiltrated into the wall of the bile duct with pushing borders (Figure 2B).

Histopathologically, the tumor was composed of intraductal and invasive components. The intraductal component showed papillary growth with fibrovascular cores; the invasive component revealed abundant extracellular mucin (Figure 3A). The invasive component and the intraductal component showed gradual transition with an intervening area of mucin-hypersecreting dilated glands (Figure 3B). The intraductal component consisted of tumor cells containing abundant mucin in the cytoplasm and mildly enlarged nuclei with indistinct nucleoli (Figure 3C). The invasive component was composed of tumor cells present in the periphery of the mucinous lake or floating in the mucinous lake; their nuclei were moderately enlarged with prominent nucleoli (Figure 3D).

The antibodies used and the results of immunohistochemistry (IHC) are shown in Table 1. Tumor cells were entirely positive for CK7 (Figure 4A), and only the invasive component was weakly positive for CK20 (Figure 4B). All tumor cells were negative for CDX2 (Figure 4C). MUC1 immunostaining was observed in the secreted mucin but not in tumor cells (Figure 4D). MUC2 immunostaining was present only focally in the intraductal component and diffusely in the invasive component (Figure 4E). MUC5AC displayed patchy positivity in the intraductal component and diffuse positivity in the invasive component (Figure 4F). Almost all the tumor cells were positive for MUC6 (Figure 4G). The Ki-67 labeling index was 4.6% in the intraductal component and 32% in the invasive component, based on counting 1000 cells (Figure 4H). Diffuse nuclear accumulation of p53 was observed in both components (Figure 4I).

The diagnosis of gastric-type IPNB (mucin-containing MUC6+ cells) associated with colloid carcinoma (abundant extracellular mucin with weakly CK20+ and MUC2+ tumor cells) was rendered.

A mutational analysis of KRAS codon 12 and 13 was performed. It did not reveal any mutation in these codons.

Discussion

IPNB accounts for 7% to 38% of all bile duct carcinomas [6-8]. It can develop at the biliary confluence (59%), in the distal common bile duct (31%), or within the liver (10%). As for invasion (seen in 74% of cases), IPNB in the distal bile duct (93%) shows the highest frequency,
followed by IPNB in the hilus (65%); IPNB within the liver shows the lowest frequency (25%) [8].

Regarding the histopathological subtypes of the invasive component, Rocha et al. reported that 27 of 29 (93%) IPNB analyzed displayed tubular carcinoma; the other two cases were colloid carcinoma and minimally invasive carcinoma with mucinous features [8]. The survival of patients is related to the histopathological subtype of the invasive component: those with mucinous carcinoma have a better prognosis than those with tubular adenocarcinoma [8]. The survival of patients with IPNB has been shown to be better than that of patients with conventional cholangiocarcinoma [6, 9, 10]. As mucinous carcinoma was identified in the invasive component in our case, the prognosis of the patient is expected to be relatively better.
In terms of IHC, CK20 is expressed in more than half of IPNBs; the intestinal type is associated with CK20 expression, whereas the gastric type does not usually show CK20 expression [3]. The MUC expression patterns are correlated with the histopathological subtypes of IPNB [1, 3]. MUC1 expression is occasionally seen in the pancreaticobiliary type. MUC2 expression is observed in approximately half of IPNB cases; its expression is more often seen in the intestinal type than in the pancreaticobiliary, gastric, and oncocytic types. MUC5AC can be expressed in any of the four types, without being specific to any one type. MUC6 expression is observed in the gastric type and oncocytic type. In our case, MUC6 expression but no CK20 expression in the intraductal component was consistent with gastric-type IPNB, since it did not show oncocytic morphology.

IPNB includes tumors without macroscopically visible mucin secretion. Ohtsuka et al. reported that IPNB without macroscopically visible mucin secretion exhibits p53 positivity in half of the cases, while IPNB with visible mucin secretion does not show p53 positivity [4]. This finding is also true in our case, in which visible mucin secretion was not apparent and diffuse nuclear accumulation of p53 was observed. With regard to carcinogenesis, IPNB and biliary intraepithelial neoplasia (BilIN) have been proposed as 2 precursor lesions of invasive cholangiocarcinoma [2]. IPNB and BilIN are supposed to be analogous to IPMN and pancreatic intraepithelial neoplasia (PanIN), respectively.

Nuclear p53 accumulation is reported to be more frequently observed in PanIN-3, which includes carcinoma in situ, than in carcinoma in situ arising in IPMN [11, 12]. Since IPNB with visible mucin secretion is less invasive than IPNB without visible secretion and shows p53 negativity on IHC, it is similar to IPMN, suggesting that IPNB with visible mucin secretion may follow a similar carcinogenic pathway to that of IPMN and that it would be the prototype of the IPNB carcinogenic pathway [4]. On the other hand, IPNB without visible mucin secretion is more invasive than IPNB with visible mucin secretion and has some propensity toward nuclear accumulation of p53 on IHC, which is more similar to PanIN than to IPMN. These findings indicate that some IPNBs without visible mucin secretion might originate via a similar pathway from BilIN to conventional cholangiocarcinoma [4]. However, in our case, the invasive component was colloid carcinoma with a MUC1+/MUC2+ expression pattern. Colloid carcinoma arising from IPNB generally exhibits a MUC1+/MUC2+ expression pattern [2]. These facts suggest that the tumor in our case developed through an IPNB carcinogenic pathway, since invasive carcinoma arising from BilIN consists of tubular adenocarcinoma showing a MUC1+/MUC2+ expression pattern [2].

The genetic background of IPNB is not similar to that of IPMN [13]. GNAS codon 201 mutation, which is found in two thirds of IPMNs and is a more common mutation than KRAS [14, 15], is a less common mutation than KRAS in IPNB [16]. In addition, KRAS mutation, which was not detected in our case, is also less common in IPNB than in IPMN [13]. The pathogenesis of IPNB might be distinct from that of IPMN in spite of the morphological similarities. Large

**Table 1. Antibodies used in the present study**

<table>
<thead>
<tr>
<th>Antibody to</th>
<th>Clone</th>
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<th>Pretreatment</th>
<th>Source</th>
<th>Immunohistochemical results</th>
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<td>Novocastra</td>
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HIER: heat-induced epitope retrieval; Dako: Dako, Glostrup, Denmark; Novocastra: Novocastra Laboratories, Newcastle upon Tyne, UK.
Figure 4. Immunohistochemical findings. A. Almost all the tumor cells were positive for CK7 (× 100). B. Only the invasive component was weakly positive for CK20 (× 100). C. All tumor cells were negative for CDX2 (× 100). D. MUC1 immunostaining was observed in secreted mucin but not in tumor cells (× 100). E. MUC2 immunostaining was observed only focally in the intraductal component and diffusely in the invasive component (× 100). F. Patchy MUC5AC positivity was observed in the intraductal component and diffuse MUC5AC positivity was noted in the invasive component (× 100). G. Almost all the tumor cells were positive for MUC6 (× 100). H. The Ki-67 labeling index was 4.6% in the intraductal component and 32% in the invasive component (× 100). I. Diffuse nuclear accumulation of p53 was observed in both components (× 100).
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and comprehensive sequencing studies are needed to clarify the genetic background of IPNB.

In conclusion, we report a rare case of gastric-type IPNB progressing to colloid carcinoma. As IPNB, especially IPNB without macroscopically visible mucin secretion, seems to be more diverse than IPMN, such an unexpected association would be more likely to occur in cases of IPNB than in cases of IPMN.

Disclosure of conflict of interest

None.

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References


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