CASE REPORT

Metachronous biliary carcinoma with intraductal pancreatic adenocarcinoma 13 years after curative resection of hilar bile duct cancer

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SUMMARY

We report a case of a 68-year-old woman with metachronous bile duct cancer and a pancreatic adenocarcinoma. She had undergone extended left hepatic lobectomy for hilar bile duct carcinoma. However, when she was admitted to our hospital 13 years later for an annual follow-up, abdominal CT revealed a mass in the dilated remnant of her lower bile duct. This was diagnosed as a second primary tumour, a pancreaticoduodenectomy was performed and 15 months after the second operation, she remains recurrence-free. Nineteen cases of patients with metachronous bile duct carcinomas were identified in the literature and have been reviewed.

BACKGROUND

Synchronous multiple cancers of the bile duct are occasionally observed. However, metachronous multiple bile duct carcinomas are uncommon due to the rarity of cholangiocarcinoma and its poor prognosis. Only 19 cases of metachronous bile duct carcinoma (MBDC) have been documented in the literature.

Although several risk factors, such as pancreatocobiliary maljunction and primary sclerosing cholangitis, are associated with cholangiocarcinoma,¹ few reports have explored the relationship between these risk factors and MBDC.² Consequently, little is known about the pathway to invasive malignancy in these patients. We present the case of a 68-year-old woman with MBDC and pancreatic adenocarcinoma and refer to 19 cases of MBDC.

CASE PRESENTATION

A 68-year-old woman was followed up without evidence of recurrence for 13 years after an extended left hepatic lobectomy, bile duct excision and Roux-en-Y hepaticojejunostomy for hilar bile duct carcinoma in situ in 1998. Histological examination at that time revealed a well-differentiated adenocarcinoma with widespread mucosal dysplasia. The depth of the tumour was limited to the mucosal layer, and no lymph node metastasis was observed (pTisN0M0, according to the UICC TMN Classification of Malignant Tumours, seventh edition). The resection margins of the tumour were negative.

However, in 2011, abdominal CT during an annual follow-up revealed a low-density area measuring 1.2 cm×0.8 cm in the dilated remnant of the lower bile duct (figure 1). The patient was an occasional drinker, non-smoker and homemaker and

Figure 1 Dynamic abdominal CT during venous phase of coronal image revealed a mass measuring 1.2 cm×0.8 cm in the dilated remnant of her lower bile duct (arrow).

she did not report any other history of previous hilar bile duct carcinoma and there were no clinical symptoms.

INVESTIGATIONS

An endoscopic retrograde cholangiopancreatography (ERCP) after reconstruction of bile duct is often difficult. However, we were able to undertake ERCP using a side-viewing endoscope, preceded by confirmation of access to the ampulla of Vater via the roux-en Y loop using a conventional forward-viewing endoscope.

ERCP (figure 2A) and MR cholangiopancreatogram (figure 2B) revealed a defect consistent with a tumour and a dilated lower bile duct. There was no evidence of an abnormal junction of the pancreatocobiliary ductal system, for example, a long common channel or a complicated connection.

Cytology of the bile revealed atypical cells, suggesting the possibility of a malignant tumour. Laboratory investigations demonstrated increased levels of serum pancreatic amylase of 116 IU/L (<52 IU/L). However, other investigations were within the normal range, including serum carcinoembryonic antigen and carbohydrate antigen 19-9 (CA19-9).

TREATMENT

The diagnostic findings were highly suggestive of a further invasive malignancy and a pancreaticoduodenectomy was performed. The total operative time was 435 min with an estimated blood loss of 230 mL.

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Figure 2 An endoscopic retrograde cholangiopancreatography (A) and MR cholangiopancreatogram (B) revealed a tumour defect and dilated lower bile duct (arrow). Main pancreatic duct is normal (arrow head).

OUTCOME AND FOLLOW-UP

The surgical specimen revealed a papillary adenocarcinoma with subserosal invasion but without nodal involvement (pT1N0M0; figures 3 and 4A,B). An incidental in situ pancreatic adenocarcinoma was also identified during histological examination of the pancreatic duct (pTisN0M0; figure 4C). The resection margins were negative and the patient remains disease-free at 15 months after the second operation.

DISCUSSION

To differentiate multiple primary malignant tumours from recurrence of the original tumour, three criteria have been proposed. First, each tumour must demonstrate definite indications of

Figure 3 (A) Gross specimen of the pancreaticoduodenectomy. (B) Papillary tumour in the lower bile duct.

malignancy, second, each tumour must be distinct and third, the possibility that one tumour is a metastasis of another must be excluded.³

In this case, the tumours can be considered to be metachronous multiple primary lesions as the histopathological subtypes of the tumours were different (tubular adenocarcinoma and papillary adenocarcinoma); the two tumours were spatially separated with uninvolved surgical margins and the main body of the second tumour was distantly separated from the bile duct stump of the first operation; finally, the second bile duct carcinoma was detected 13 years after the first curative operation making it extremely unlikely that the second tumour was a metastasis or remnant tumour arising from the initial malignancy.

Little is known about the aetiology of MBDC and the current literature describes only 19 patients.^{2 4-13} Pancreaticobiliary maljunction is generally accepted as a risk factor for bile duct carcinoma. It has been defined as a union of the pancreatic and biliary ducts that is located outside of the duodenal wall and surrounded by the sphincter of Oddi. Pancreatic juice flows back into the bile duct continuously which results in metaplastic epithelial changes in the bile duct.¹⁴ However, only two cases

Figure 4 (A) Histological section of the bile duct reveals papillary adenocarcinoma. (B) The adenocarcinoma invaded subserosal layer in the bile duct (arrow). (C) Epithelium in the main pancreatic duct reveals adenocarcinoma in situ.

have suggested a relationship between MBDC and pancreaticobiliary maljunction.²

More recently, it has been recognised that a dysfunction in the sphincter of Oddi can cause pancreaticobiliary reflux in patients with normal pancreaticobiliary junction, and the pathophysiology of carcinogenesis observed in patients with pancreaticobiliary maljunction is similar in patients with pancreaticobiliary reflux and a normal pancreaticobiliary junction.¹⁵

In this case, the residual lower bile duct was dilated and it is possible that the dilation arose because of reflux of pancreatic juice into the bile duct. However, this hypothesis could not be verified as the pancreatic enzyme levels in fluid from the remaining dilated bile duct were not measured. It is suggested that patients with MBDC have a genetic predisposition to carcinogenesis and KRAS and p53 mutations have frequently been implicated as genetic risk factors for bile duct carcinomas. We hypothesised that certain genetic mutations played a role in the carcinogenesis of MBDC in our case. We performed immunohistochemical staining for p53 protein overexpression and KRAS mutation analysis of the hilar bile duct cancer and the non-cancerous epithelia of the initial surgical specimens and of the lower bile duct cancer of the second surgical specimens. However, we observed neither p53 protein overexpression nor KRAS mutation in these specimens.

Although the precise mechanism of carcinogenesis has not yet been clarified in patients with MBDC, patients who have experienced carcinoma in the bile duct have a long-term risk of carcinogenesis, even after undergoing curative surgical treatment.

There have been only a small number of case reports describing the prognosis of MBDC and these advocate repeated

curative resection as the optimal treatment to achieve long-term survival. Although repeated resection for MBDC is often difficult and causes frequent complications, long-term follow-up of patients with bile duct tumours is still advised as early detection of secondary cancer will permit further curative surgical treatment and promote long-term survival.

Contributors HM was operator of the patient and wrote the paper. TF supervised the care of the patient and AT approved the final manuscript.

Competing interests None.

Patient consent Obtained.

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Learning points

- The pathophysiology of metachronous bile duct carcinoma (MBDC) has not been well documented, and this case highlights the need for further studies exploring the mechanisms of carcinogenesis in these patients.
- Patients who have undergone curative surgical treatment for cholangiocarcinoma require careful long-term follow-up to identify recurrence and detect metachronous tumours.
- Although repeated resection for MBDC is difficult in many cases, repeated curative resection is the optimal treatment to achieve the long-term survival.

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