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CASE REPORT

TTF-1 positive small cell cancers: Don't think they're always primary pulmonary!

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Abstract

Thyroid transcription factor 1 (TTF-1) plays a key role in morphogenesis of the lungs and is expressed in up to 90% of pulmonary small cell carcinomas. This explains why this marker is frequently used in the search for the primary origin of metastatic endocrine tumours. Here we report on a TTF-1 expressing mixed endocrine-exocrine carcinoma of the common bile duct in a patient with pulmonary nodules that did not appear to be neoplastic. TTF-1 positivity in pulmonary and extrapulmonary neuroendocrine tumours is reviewed, and we conclude that TTF-1 expression in neuroendocrine tumours of the small-cell type are not uncommon at extrapulmonary locations. Therefore, immunohistochemistry for TTF-1 in such tumours should be interpreted with caution.

Key words: Thyroid transcription factor 1; Small cell carcinoma; Mixed endocrine-exocrine tumour; Common bile duct; Immunohistochemistry

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INTRODUCTION

Thyroid transcription factor 1 (TTF-1) is a homeodomain-containing nuclear transcription factor which belongs to the Nkx2 gene family; it is expressed in the forebrain, thyroid and lung. TTF-1 plays a key role in morphogenesis of the lungs[1] and is expressed in up to 90% of pulmonary small cell carcinoma[2]. This explains why this marker is frequently used to search for the primary origin of metastatic neuroendocrine tumours.

In this article we report the case of a TTF-1 positive mixed endocrine-exocrine tumour of the common bile duct.

CASE REPORT

A 74-year-old woman was admitted to the Erasme Uni-

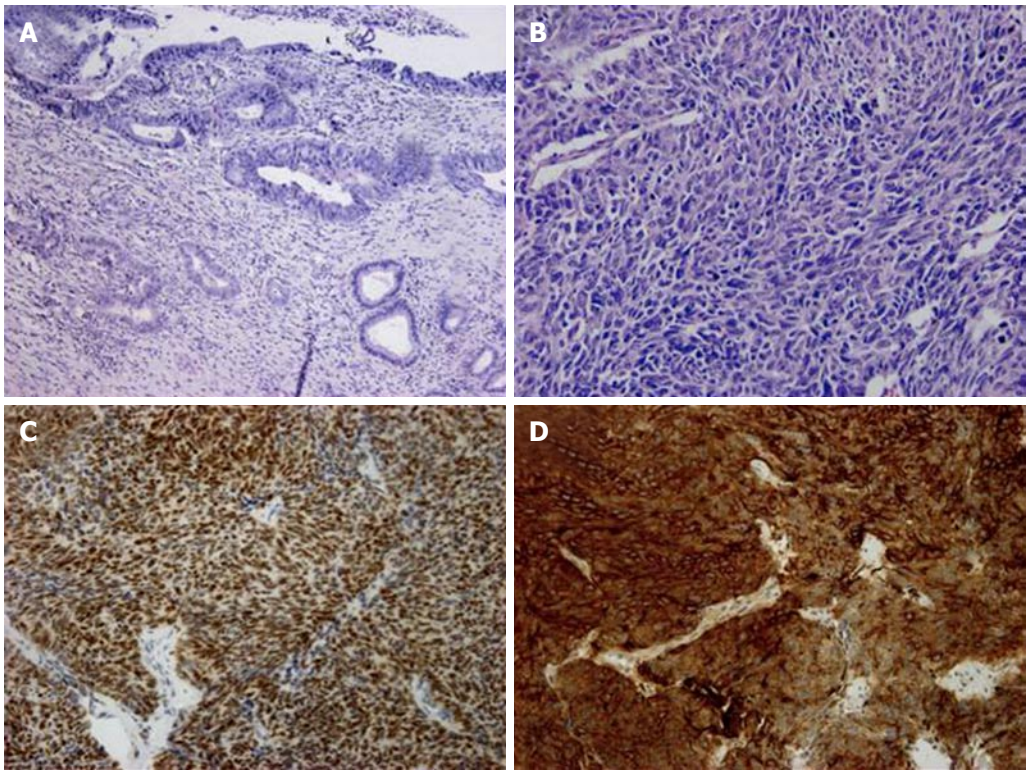

Figure 1 Histological images of the patient. A: Invasive neoplastic glands adjacent to dysplastic epithelium of the common bile duct (haematoxylin-eosin, 100 ×); B: Small cell cancer component (haematoxylin-eosin, 200 ×); C: TTF-1 immunostaining of the small cell cancer component (200 ×); D: CD56 immunostaining of the small cell cancer component (200 ×).

versity Hospital because of jaundice, anorexia and a 3-mo history of weight loss (10 kg). In her medical history, we noted hypertension, hysterectomy, ovariectomy and resection of a melanoma of the right forearm. There was no tobacco or alcohol use. Laboratory data showed a cholestatic jaundice with a bilirubin level of 5 mg/dL and an alkaline phosphatase level twice the normal value. The tumour markers carcino-embryonic antigen and CA19.9 were negative. Abdominal magnetic resonance imaging displayed a mass, approximately 2 cm diameter, in front of the pancreatic head with dilation of the main pancreatic duct and of the common bile duct. At endoscopic cholangiopancreatography, a tumoural lesion of the papilla and a distal stenosis of the common bile duct were seen with an upstream dilation. Biopsy of the papilla and brush cytology of the stenosis were inconclusive. In the search for metastases, a chest tomography was performed and two pulmonary nodules were observed, in the right upper and the right lower lobe, respectively. The lower one was hypermetabolic at positron emission tomography-computed tomography (CT). Bronchoscopy excluded any endobronchial lesion; bronchoalveolar fluid lavage, CT-guided fine needle aspiration (FNA) and transbronchial biopsy revealed many macrophages but no neoplastic cells.

Given the absence of histopathologically confirmed metastases, a Whipple resection was performed. Gross examination didn't reveal any obvious mass; we observed a macrocalcification, and pancreatic tissue surrounding this calcification was indurated. The fresh tissue was formalin-fixed, routinely processed and stained with haematoxylin-eosin.

Histologically, the indurated lesion presented two patterns. First, we observed a glandular tumoural pattern arising from the epithelium of the common bile duct which presented high grade dysplasia with nuclear stratification and irregular and hyperchromatic nuclei (Figure 1A). This adenocarcinoma component had invaded the duodenal wall. Another part of the tumour showed an endocrine pattern with neoplastic cells arranged in solid nests and displaying little cytoplasm, irregular nuclei and inconspicuous nucleoli (Figure 1B). This part of the tumour was positive for TTF-1 (Dako, 1:2000) and CD56 (Klinipath, 1:1000) immunohistochemistry (Figure 1C and D). Mitotic figures were frequent and perineural invasion was present. One metastatic lymph node was found in the peripancreatic fat.

Two months after the duodenopancreatectomy, an octreoscan showed multiple hepatic metastases; there was no recruitment of the pulmonary nodules.

DISCUSSION

Mixed endocrine-exocrine carcinoma (MEEC) is uncommon in the extrahepatic bile duct, representing less than 0.4% of tumours at this location[3]. MEEC is defined as a malignant tumour containing at least 30% of each component; the natural history of MEEC with a small cell cancer component follows the disease progression of this latter[4].

Table 1 Thyroid transcription factor 1 expression in pulmonary and extrapulmonary endocrine tumours

Authors	Carcinoid[1]		SCC	
	P	EP	P	EP
Folpe *et al*[2]	27/60 (45)	ND	20/21 (95)	ND
Agoff *et al*[7]	ND	0/49 (0)	ND	7/16 (44)
Cai *et al*[8]	11/16 (69)	1/58 (2)	ND	ND
Du *et al*[9]	15/53 (23)	0/28 (0)	ND	ND
Kaufmann *et al*[10]	6/12 (50)	1/20 (5)	30/37 (81)	12/15 (80)
Lin *et al*[11]	13/30 (43)	0/95 (0)	27/30 (90)	ND
Oliveira *et al*[12]	19/20 (95)	0/39 (0)	ND	ND
Saqi *et al*[13]	8/15 (53)	0/63 (0)	ND	ND
Srivastava *et al*[14]	7/20 (35)	0/103 (0)	ND	ND
Cheuk *et al*[15]	ND	ND	43/52 (82.7)	21/50 (42)
Jones *et al*[16]	ND	ND	ND	17/44 (39)
Li *et al*[17]	ND	ND	ND	9/42 (21)
Lu *et al*[18]	ND	ND	ND	9/15 (60)
McCluggage *et al*[19]	ND	ND	ND	11/13 (84)
Yun *et al*[20]	ND	ND	ND	15/21 (71)
Ordonez *et al*[21]	ND	ND	27/28 (96)	4/54 (7)
Total	106/226 (46)	2/455 (< 1)	147/168 (87.5)	105/270 (39)

[1]Typical and atypical carcinoids are regrouped in this category. SCC: Small cell cancer; P: Pulmonary; EP: Extrapulmonary; ND: Not done.

Two histologic subtypes of small cell cancer of the common bile duct exist: a "composite type" which is frequently retrieved in the gallbladder and consists of small cell cancer and adenocarcinoma (as in this case), and a "pure type" which consists only of small cell cancer[5].

Metastatic disease of the pancreas accounts for less than 2% of all pancreatic malignancies[6]. In this case, given the presence of a hypermetabolic pulmonary nodule, a pancreatic metastatic involvement had to be excluded. It could be argued that the positive TTF-1 in our case points to a primary pulmonary origin; the octreoscan was, however, negative in the pulmonary nodules and strongly positive in the hepatic metastases. Moreover, bronchoalveolar fluid lavage, CT-guided FNA and transbronchial biopsy did not reveal any neoplastic cells. Therefore, and because of the dysplastic lesions observed in the common bile duct adjacent to the invasive tumour, we believe that our case is a primary tumour of the common bile duct.

Table 1 summarizes TTF-1 expression in neuroendocrine tumours from pulmonary and extrapulmonary origin[2,7-21]. TTF-1 might be helpful in differentiating pulmonary carcinoid tumours from extrapulmonary carcinoids. Agoff *et al*[7], Cai *et al*[8], Du *et al*[9], Lin *et al*[11], Oliveira *et al*[12], Saqi *et al*[13] and Srivastava *et al*[14] could not demonstrate TTF-1 expression in extrapulmonary carcinoid tumours while TTF-1 expression varied from 23% to 95% in pulmonary carcinoids[7-14]. Two primary gastric carcinoid tumours were TTF-1 positive, one in the series of Kaufmann *et al*[10] and one in the series of Cai *et al*[8].

With regard to high-grade endocrine tumours (small cell cancers), the situation is, however, quite different. Agoff *et al*[7], Cheuk *et al*[15], Jones *et al*[16], Kaufmann *et al*[10], Li *et al*[17], Lu *et al*[18], McCluggage *et al*[19] and Yun *et al*[20] showed TTF-1 expression in 44%, 42%, 39%, 80%, 21%, 60%, 84% and 71% of extrapulmonary small cell cancers, respectively[7,10,15-20]. In the series of Ordonez *et al*[21], only 7% of extrapulmonary small cell cancers expressed TTF-1. The hypothesis that small cell cancer originates from totipotent stem cells differentiating into various cell types (e.g. TTF-1 positive stem cells for pulmonary small cell cancer)[22] could explain why TTF-1 expression is retrieved in some foregut small cell cancers. However, this hypothesis cannot explain TTF-1 expression in non-foregut endocrine tumours.

In conclusion, we report a MEEC with TTF-1 expressing small cell cancer component of the common bile duct. A literature review indicates that TTF-1 is helpful in discriminating pulmonary from extrapulmonary carcinoid tumors. In searching for the primary origin of high-grade endocrine tumours (small cell cancers), TTF-1 should, however, not be used.

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