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LETTER TO THE EDITOR

Synchronous adenocarcinoma of the lung and neuroendocrine carcinoma of the ileum

Daniel Reim · Gregor Weirich · Bruno Neu · Monther Bajbouj · Björn L. D. M. Brücher

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We report here on a very rare coincidence of synchronous neuroendocrine carcinoma in the ileum and adenocarcinoma in the lung, which was not found in the setting of multiple endocrine neoplasia. To our knowledge, no previous cases have been reported in which an adenocarcinoma in the lung occurred synchronously with a neuroendocrine carcinoma in the ileum. We present the findings along with a critical discussion of the case and the literature.

A 54-year-old man was admitted to the hospital due to lower gastrointestinal bleeding, with a drop in haemoglobin below 7 mg/dl. His medical history did not include any previously known diseases, and he had no tumour-related symptoms such as weight loss, night sweats, or any endocrine-related symptoms such as watery diarrhoea, flushing or episodes of tachyarrhythmia. Esophagogastroduodenoscopy (EGD) and ileocolonoscopy (including 30 cm of the ileum) did not reveal any pathological findings. Computed tomography (CT) of the chest revealed a 15-mm pulmonary nodule in the right upper lobe. Abdominal CT and scintigraphic bone scans did not show any pathological findings. Capsule endoscopy revealed an ulcerative tumorous lesion in the mid-third of the ileum, which was strongly suspected of causing the bleeding. The 5-HIAA level in 24-h urine samples was not elevated. Postoperative indium-111 octreotide SPECT did not reveal any lesions suspicious for distant metastasis. The patient then underwent surgery of the lung due to the suspected lung cancer and laparotomy due to the suspected small-bowel tumour.

Lung surgery included a lobectomy of the right upper lung and a radical lymphadenectomy. Histopathology revealed a solid, partly papillary, adenocarcinoma of the lung, 1.2 cm in size, poorly differentiated, focally positive on periodic acid–Schiff (PAS) staining and had a typical trefoil factor family-1 (TTF-1) immunoreactivity and no reactivity to neuroendocrine proteins (chromogranin A, synaptophysin, neuron-specific enolase). Local lymph nodes were free of metastases. The International Union Against Cancer (UICC) tumour staging was pT1, pN0 (0/20), cM0.

The median laparotomy was performed 10 days later. Intraoperatively, the small ileal tumour could be identified 35 cm orally from Bauhin's valve. Intraoperative endoscopy of the small intestine revealed no other pathological findings over a length of 150 cm oral from this small lesion. No palpable mesenteric lymph nodes or other pathological findings were identified. Segmentectomy of the ileum was carried out. Histopathological examination of the surgical specimen identified the known 0.9-cm lesion, and close examination of the

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D. Reim (✉)
Department of Surgery, Cancer Center,
Technical University of Munich,
Ismaninger Strasse 22,
81675 Munich, Germany
e-mail: reim@chir.med.tu-muenchen.de

G. Weirich
Department of Pathology, Cancer Center,
Technical University of Munich,
Munich, Germany

B. Neu · M. Bajbouj
Department of Internal Medicine II, Cancer Center,
Technical University of Munich,
Munich, Germany

B. L. D. M. Brücher
Department of Surgery & Comprehensive Cancer Center,
University of Tuebingen,
Tübingen, Germany

entire specimen detected another two nodules (0.1 and 0.3 cm in size). All of the tumours showed a nested and tubular architecture, typical of enterochromaffin cell carcinoids of the distal ileum. The largest tumour showed invasion of the lamina muscularis propria. Immunohistochemistry demonstrated reactivity with antibodies directed against cytokeratins, chromogranin A, serotonin, synaptophysin and neuron-specific enolase. Pancreatic polypeptide, gastrin and substance P were negative. In accordance with the UICC guidelines, these multiple highly differentiated neuroendocrine tumours were not staged, and a diagnosis of multiple locally aggressive carcinoids of the distal ileum was made. The tumour resection was complete (R0), and the tumor was classified as a highly differentiated pT2 neuroendocrine carcinoma.

Small-bowel cancers are very rare tumour entities, representing only 1% of all gastro-intestinal (GI) malignancies. These tumours occur mainly in the sixth and seventh decades of life but may develop at any age. Due to their location, small-bowel malignancies are diagnosed late, when they obstruct the gastrointestinal passage. This patient presented to the emergency room with haemodynamic instability, which is a rare symptom in small-bowel tumours, as ulceration of the lesions is uncommon. The reported frequency of gastrointestinal haemorrhage varies from 5 to 23%. The patient did not report any symptoms of ileus such as dyspepsia, nausea, vomiting, abdominal pain, or reduced bowel movement. The procedure of choice for locating the source of obscure haemorrhage is endoscopy of the upper GI tract and colonoscopy for the lower GI tract, as these are the main locations in which ulcerations are found. Small-bowel ulcerations usually have a diameter of 0.5–1.0 cm and are difficult to detect. CT and magnetic resonance imaging are not able to detect these lesions with certainty, with reports describing a diagnostic yield of only 21%. Other detection methods are angiography, push endoscopy, enteroclysis and red blood cell scintigraphy, but none of these procedures has proved fully effective. Indium-111 octreotide scans may be helpful in detecting the tumour by providing indirect evidence of a small-bowel carcinoid. The diagnostic tool of choice appears to be video capsule endoscopy, which provides direct visual proof of an ulcerative lesion and allows estimation of its size and location in the small bowel. The procedure with the highest sensitivity and specificity for detecting small-bowel lesions reported is intraoperative endoscopy during explorative laparotomy.

Metastatic nodules from small-bowel carcinomas may histopathologically resemble primary carcinomas in distant organs, but the pathologist confirmed that the pulmonary lesion thus had no resemblance to a possible adenocarcinoma in the small bowel. According to some reports, primary cancers of the lung are capable of metastasizing into the small bowel. In this case, however, histopathological analysis of the small-bowel lesion showed no similarity to the initially diagnosed adenocarcinoma of the lung, which proved existence of two different synchronously developed cancers.

There are very few reports in the literature reporting simultaneous primary lung and small-bowel cancers, although the incidence of independent secondary malignancies can be as high as 50%. Small-bowel carcinoids are reported to correlate with second primary malignancies in 30–50% of cases, followed by appendix and colorectal neuroendocrine malignancies. These figures mostly refer to the incidence of metachronous secondary cancers. Tichansky reported that synchronously occurring malignancies (diagnosed within a time range of 6 months before or after the diagnosis of a colorectal neuroendocrine cancer) appear in nongastrointestinal regions with a frequency of only 30%—implying that 70% of synchronously developing tumours were found within the gastrointestinal tract. In contrast to this, metachronous malignancies were found in 22% of cases within a period of 20 years after carcinoid disease. Approximately 82% of the metachronous malignancies were found in sites outside the gastrointestinal tract; 9.4% of the patients described in the study had a synchronous pulmonary cancer. The overall risk of developing a synchronous lesion was 8%. A possible explanation for the increased risk of developing a second malignancy might be a genetic predisposition for cancer.

In patients known to have neuroendocrine tumours, the possibility of multiple endocrine neoplasia always has to be considered. In the present case, indium-111 octreotide SPECT was used to examine the patient for lesions in the pancreas, thyroid, and other distant organs. There was no evidence of any further lesions. Elevated calcium levels suggesting hyperparathyroidism were not detected. The precise pathogenesis of secondary cancers associated with neuroendocrine carcinoma is still unclear. There have been reports showing that secretory peptides such as gastrin and cholecystokinin are able to influence tissue growth in colorectal and gastric cancers. It has been shown that cholecystokinin receptors and gastrin receptors are also expressed in pulmonary, ovarian, thyroid, and brain tumours. Neurotensin is thought to have proliferative effects in lung cancers. In addition, neuroendocrine tumours are able to produce peptides that are known to play an important role in carcinogenesis. Growth factors such as platelet-derived growth factor, epidermal growth factor, transforming growth factor, insulin-like growth factor and fibroblast growth factor have been found in gastrointestinal carcinoids. Another group implicated a high level of COX 1 and 2 expression in small-bowel tumour cells as a pathogenetic factor. Deactivation of certain tumour-suppressor genes by hypermethylation has also been demonstrated as one step in carcinogenesis.

The mean survival period for patients with small-bowel cancers has been reported to be 31.8 months in a series published by our own group. The presence of metastasis at

the time of diagnosis is a relevant prognostic factor for survival (68.4% with M0 versus 28.6% with M1). R0 resection is another prognostic factor for survival. There have been no reports so far describing the prognosis in patients with synchronous secondary malignancies, and it is therefore intended that follow-up for the patient in this case will focus on the malignancy that has the poorer prognosis, which is the small-bowel cancer. Unfortunately, there are no clear guidelines for appropriate follow-up. In analogy with colorectal cancers, a 3-month interval appears to be justified, as well as regular octreotide scintigraphy.

In conclusion, small-bowel malignancies are rarely related to second primary malignancies such as lung cancers. Conventional diagnostic procedures are often not sensitive enough to detect malignant tumours in the small bowel. Video capsule endoscopy may be the diagnostic tool of choice, particularly when colonoscopy and EGD do not identify a source of obscure gastrointestinal haemorrhage. Histopathological confirmation of lesions is necessary. Resection is the treatment of choice both in early-stage small-bowel cancer and in early-stage non-small-cell lung cancer.