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CASE REPORT

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Simultaneous gastric adenocarcinoma and MALT-type lymphoma in *Helicobacter pylori* infection

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Abstract A 79-year-old women with upper abdominal pain, vomiting and weight loss was found at endoscopy to have a large tumour mass in the gastric body. Histology of forceps biopsies revealed an adenocarcinoma of intestinal type. Gastrectomy was performed, but extensive lymph node metastasis precluded a curative surgical approach. Histopathological study of the specimen, however, revealed two distict malignancies, which arose in the setting of *Helicobacter pylori*-associated chronic gastritis with partial mucosal atrophy. One tumour was a gastric carcinoma, while the other was a primary B-cell lymphoma of the stomach (CD20-positive). The lymphoma comprised both a low-grade component (mucosa-associated lymphoid tissue- or MALT-type lymphoma), and a high-grade component (large cell lymphoma with CD30-positive giant cells). Infection with *H. pylori* was confirmed by the serological presence of IgG antibodies to *H. pylori*-antigens, including antibodies against the 128 kDa protein of the cytotoxin-associated gene (*cagA* gene) of *H. pylori*.

Key words Gastric cancer · Gastric mucosa-associated-lymphoid tissue type (MALT) lymphoma · *Helicobacter pylori* · *CagA* gene

Introduction

With the recognition of *Helicobacter pylori* as a new and important pathogenic factor in gastric diseases, new concepts have emerged for the aetiopathogenesis of chronic gastritis, gastroduodenal ulcer disease, and also for gastric malignancies [15]. Meanwhile, both gastric adenocarcinomas and primary gastric lymphomas are considered to be related *H. pylori* infection [6, 21].

For gastric carcinoma, five case-control studies reported a significantly increased cancer prevalence among patients with serological evidence for *H. pylori* infection [13, 17, 32, 34, 54], while two did not [26, 44]. Evidence for a role of *H. pylori* in the development of primary gastric lymphoma is provided by histological studies [12, 51, 59], one case-control study [35], and by experimental studies [16, 19]. However, as only a small percentage of infected persons develop cancer, the precise role of *H. pylori* in gastric carcinogenesis is still unknown.

We report a rare case of simultaneous gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue (MALT)-type lymphoma in a patient with evidence of *H. pylori* infection.

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Case report

Clinical history

A 79-year old white female patient was admitted to hospital for persistent upper abdominal pain, vomiting, and 10 kg weight loss within 2 months. Radiology of the stomach revealed a lesion at the greater curvature (Fig. 1). Serological measurements of carcinoembryonic antigen (patient: 3.5 ng/ml; normal: less than 5 ng/ml) and CA 19–9 (patient: 19 ng/ml; normal: less than 37 ng/ml) were unremarkable.

Gastroscopy revealed a large ulcerated tumour mass in the gastric body. Multiple biopsies were sampled from its centre and margin and on histology most biopsies revealed a tubular adenocarcinoma, consistent with gastric cancer of intestinal type. In addition, some biopsies revealed ulceration and some sheets of large undifferentiated cells. The latter were interpreted as a poorly differentiated part of the adenocarcinoma. At this time, no immunocytochemical studies were performed.

Gastrectomy was performed, including dissection of some regional lymph nodes and of the omentum. However, advanced lymph node metastasis precluded a curative surgical approach. The postoperative course was uneventful.

Pathological findings

In the gastrectomy specimen, two grossly separate lesions were present in the stomach. A first tumour mass, measuring 8×5 cm,

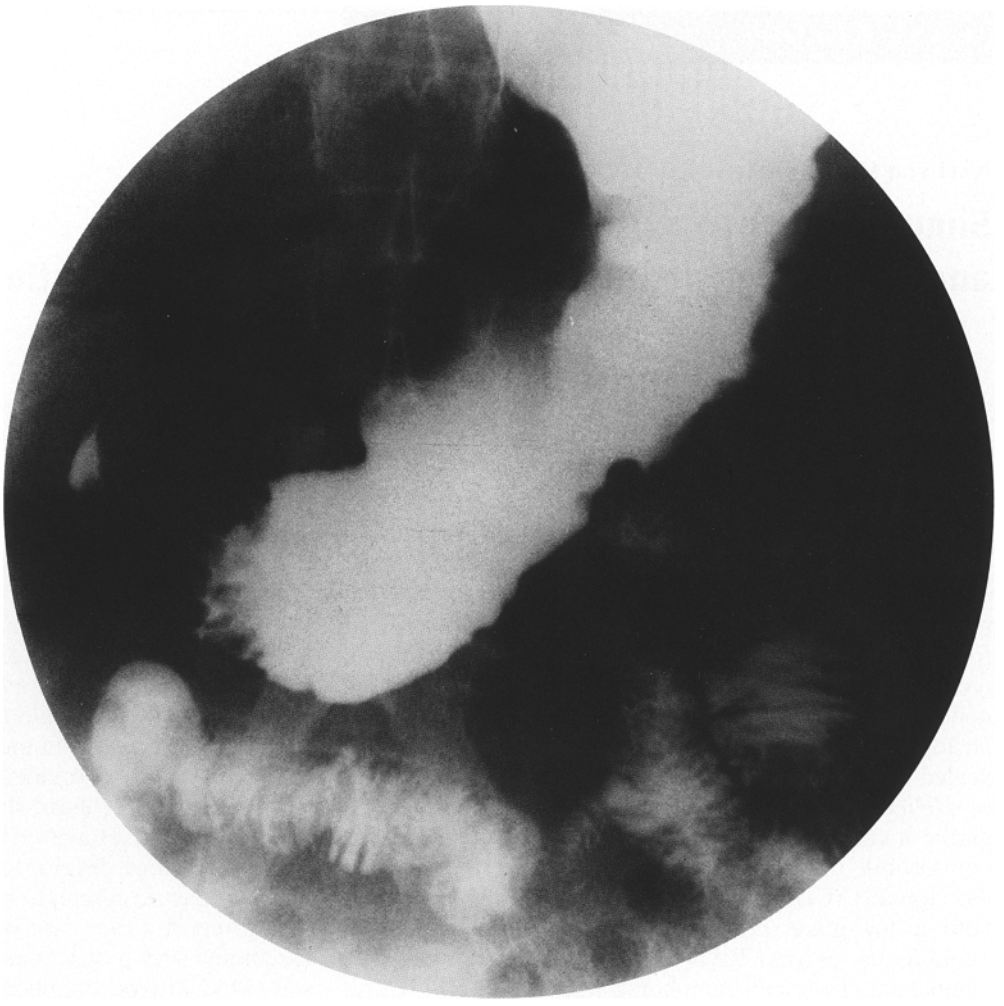

Fig. 1 Radiograph of the stomach, showing a filling defect at the greater curvature

was localized in the body at the greater curvature. At its margin, only the mucosa was thickened, while in its centre (4×3 cm) transmural thickening and deep ulceration were present. Aside, a second 3×1.8 cm elevated plaque-like lesion was situated, which was separated by 2 cm of intervening normal mucosa from the other tumour.

By histology, the smaller lesion consisted of irregular tubular glands formed by atypical epithelial cells with several mitotic figures (Fig. 2), as was seen previously in the majority of endoscopic biopsies. This intestinal-type adenocarcinoma expanded within the mucosa, with focal invasion into the upper half of the submucosa (not shown).

The larger lesion comprised two different but interrelated cell populations. At its margin, small- to medium-sized centrocyte-like cells infiltrated the mucosal lamina propria (Fig. 3a), and also some glands (lympho-epithelial lesions, Fig. 3b). This low-grade MALT-type lymphoma component was limited to the mucosa and upper submucosa. In the ulcerated central part of the lesion, however, large undifferentiated tumour cells, including some bizarre or multinucleated giant cells, were intermingled with the small- to medium-sized lymphoma cells (Fig. 3c). These larger lymphoma cells represented a high-grade lymphoma component. Only the latter infiltrated from the ulcerated mucosa into the perigastric fat tissue.

Immunotyping of paraffin-embedded tissue revealed small and large lymphoma cells to be immunoreactive for the B-cell surface molecule CD20 (Fig. 3d). In addition, some of the large lymphoma cells were positive for CD30 (Fig. 3d, inset). The proliferative activity of lymphoma cells was rather high, as evidenced by up to 80% of cells expressing the nuclear Ki-67 antigen (not shown).

Regional lymph nodes were enlarged, forming masses. Most of nodes were infiltrated by large cell lymphoma metastases, while no metastasis of the adenocarcinoma was found.

Beside these gross lesions, moderate diffuse chronic gastritis was present in the antrum and corpus region, with lymphofollicular hyperplasia, partial glandular atrophy, foveolar hyperplasia, and intestinal metaplasia. *H. pylori*-like organisms were present (not shown).

In summary, a diagnosis of simultaneous gastric adenocarcinoma (pT1b; early gastric cancer, type IIa; intestinal-type cancer) [3], and gastric MALT-type lymphoma, B-cell, high-grade secondary to low-grade, was made (stage EI_2) [43].

Serological studies and findings

A serum sample was obtained at the time of surgery and was investigated by an enzyme-linked immunoassay (PyloriStat, Serva, Heidelberg, Germany) for the presence of antibodies to *H. pylori*. A positive IgG antibody titre confirmed the diagnosis of previous infection with *H. pylori*. For further characterization of the antibodies, the patient's serum (1:100 dilution) was blotted with proteins, separated by sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE), from the supernatant of a known cytotoxin-positive *H. pylori* strain. Antibodies in the patient's serum recognized the 128 kDa protein band of *H. pylori* (Fig. 4).

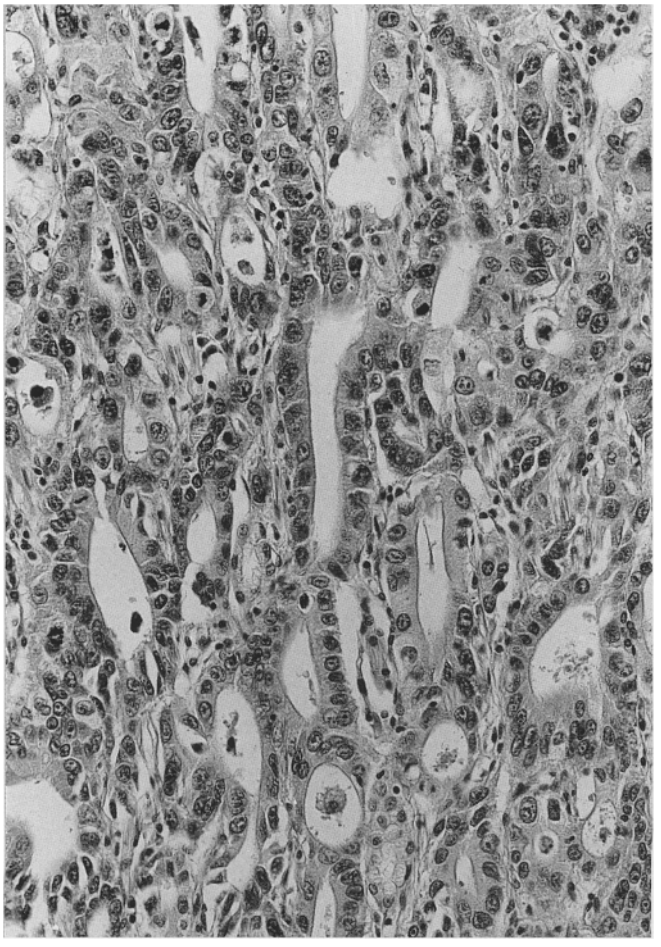

Fig. 2 Gastric intestinal-type adenocarcinoma: irregular tubular glands are formed by atypical epithelial cells with several mitotic figures. H&E, ×435

Discussion

The simultaneous association of gastric carcinoma with gastric lymphoma is a rare event. Our computer-assisted literature search revealed only a total of 15 cases reported in the European and North American literature [1, 2, 11, 22–24, 27, 28, 31, 40–42, 46, 47, 56]. In addition, 35 cases have been reported in the Japanese literature, a region where gastric cancer is more common [24, 25]. In virtually all the cases of simultaneous gastric carcinoma and lymphoma, the diagnosis of two co-existing tumours was not established prior to surgery. In this patient, the endoscopist appeared to be confronted with one lesion, and the histopathologist recognized but misinterpreted differences of histology as tumour heterogeneity. As in this patient, forceps biopsies from gastric CD30 (Ki-1)-positive large cell lymphomas are frequently mistaken for carcinomas when the biopsies are not subjected to further immunohistochemical studies [37].

The extreme rareness of simultaneous primary gastric lymphoma and gastric carcinoma was previously considered to reflect a mere coincidence, rather than a direct relationship [48]. At present, however, carcinoma and lymphoma of the stomach are both considered to be related to *H. pylori* infection [6, 21]. If this latter hypothesis is true, co-existent gastric cancer and lymphoma should be expected to be more frequent, at least at the microscopical level. However, even several larger series of patients undergoing surgery for gastric carcinoma or lymphoma did not note this association [5, 29, 43, 52]. In addition, epidemiological observations indicate that the rate of gastric cancer mortality is decreasing, while deaths from malignant lymphomas, including gastric lymphomas, have risen [30]. These discrepancies may, of course, in part be referred to treatment of first gastric malignancy, which usually comprises partial or total gastrectomy. Thereby, the gastric area at risk for a metachronous second malignancy is clearly reduced. Only 18 cases of gastric stump carcinoma occurring after surgery of gastric lymphoma have been reported so far [48, 62].

Apart from epidemiological evidence, the role of *H. pylori* in gastric carcinogenesis is still unclear. Thus, recent studies focused on differences of pathogenicity among *H. pylori* strains. Besides other criteria the more virulent strains of *H. pylori* are characterized by the presence of a bacterial vacuolating toxin gene (*vacA* gene) expressing a cytotoxic 87 kDa protein [8, 9, 18, 39], and by the presence of a cytotoxin-associated gene (*cagA* gene) encoding for a 128 kDa protein [7, 8, 57]. Antibodies to the *cagA* gene product are significantly more prevalent among patients with duodenal ulcers [7, 8], and gastric cancer [10, 45]. The serological findings in our patient are consistent with the latter observation.

Like gastric carcinoma, the role of *H. pylori* in the pathogenesis of gastric lymphoma is still unclear. Although a *H. pylori*-induced T-cell-mediated stimulation was suggested as a possible mechanism for lymphoproliferation [19], the low prevalence of primary gastric lymphoma, compared with high prevalence of *H. pylori*-associated chronic gastritis, militates for the existence of additional factors [30, 36]. It was hypothesized that the strain of the infecting organism may be a key variable for lymphomagenesis in *H. pylori* infection [21]. Our finding of positive antibodies to the *cagA* gene product in a patient with gastric MALT-type lymphoma suggests that more virulent strains of *H. pylori*, expressing the *cagA* gene, may also be relevant to lymphomagenesis, in addition to carcinogenesis [10, 45].

Besides *H. pylori*, another infective agent, Epstein-Barr virus (EBV), is also assumed to play a possible role in gastric tumorigenesis. EBV-DNA and EBV-encoded small RNA (*EBER-1*) were found in the uncommon gastric lymphoepithelioma-like carcinoma, as well as in some common gastric cancers [14, 49, 50]. Moreover, EBV-DNA and *EBER-1* were also found, albeit rarely, in gastric lymphomas of other than MALT type [33]. In our patient, no such data concerning a possible EBV infection are available.

Most gastric lymphomas develop against a background of an acquired MALT, and many of them recapitulate the structural features of MALT organization, as

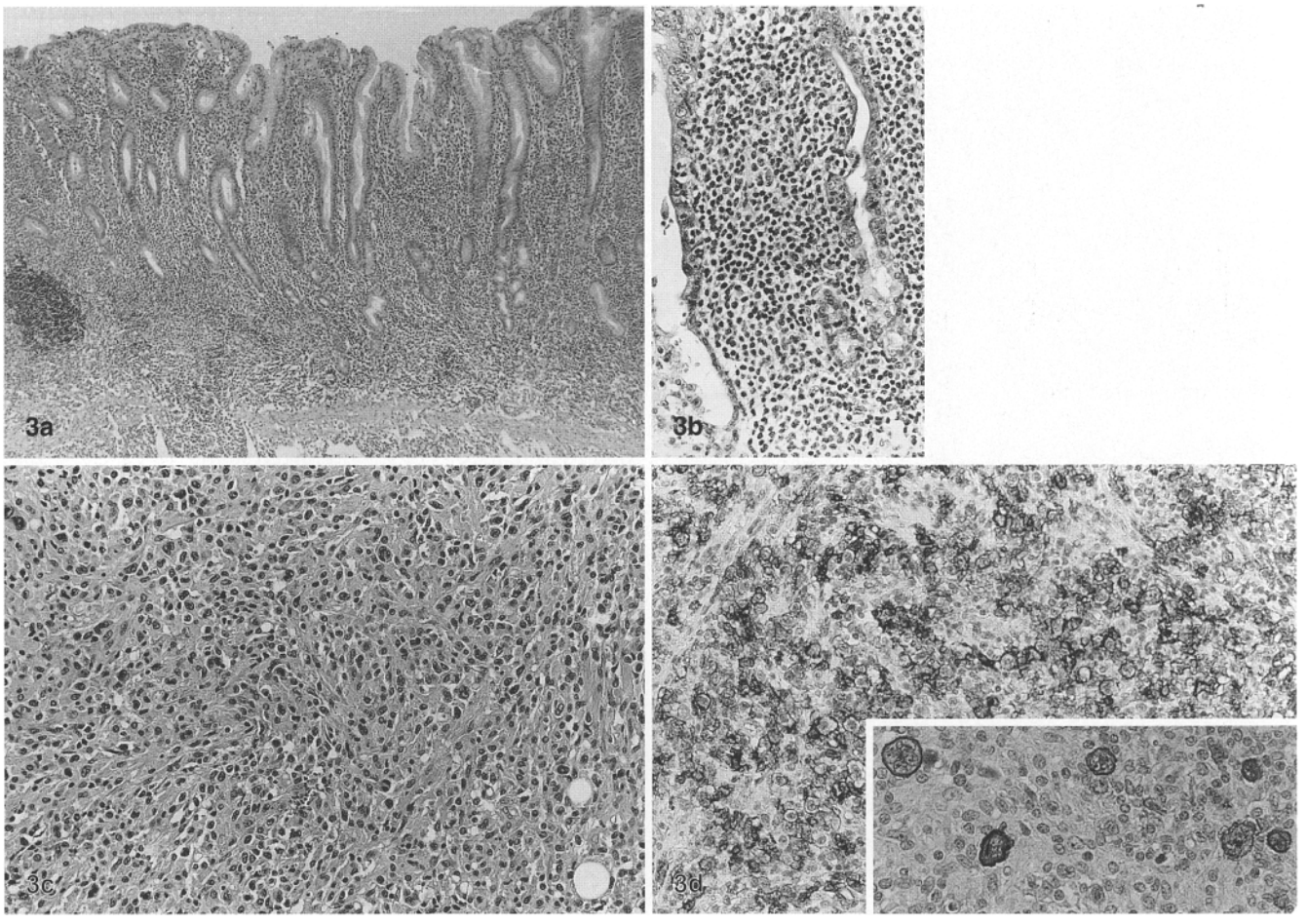

Fig. 3a Gastric MALT-type lymphoma, low-grade component: the mucosa is infiltrated by small- to medium-sized centrocyte-like cells, which separate the gastric glands. On the *left*, the neoplastic lymphoid cells surround a residual non-neoplastic follicle. H&E, ×39. **b** Lymphoma cells infiltrating gastric glands. H&E, ×310. **c** Gastric MALT-type lymphoma, high-grade component: large undifferentiated tumour cells, including some multinucleated giant cells, are intermingled with small lymphoid cells. H&E, ×310. **d** Immunotyping shows small and large lymphoma cells to be positive for the B-cell surface molecule CD20 (×310). In addition, some of the large lymphoma cells are positive for CD30 (*inset*, ×435)

typified in Peyer's patches [20]. Hence, it has been suggested that these tumours be classified as MALT-type lymphomas, in contrast to non-Hodgkin's lymphomas, and Hodgkin's lymphomas [16, 20]. It is not known whether the genesis of low-grade and high-grade gastric MALT-type lymphomas is identical, although there is some evidence that high-grade tumours may arise secondary to low-grade MALT-type lymphomas [4]. Our present case supports the latter hypothesis, as the high-

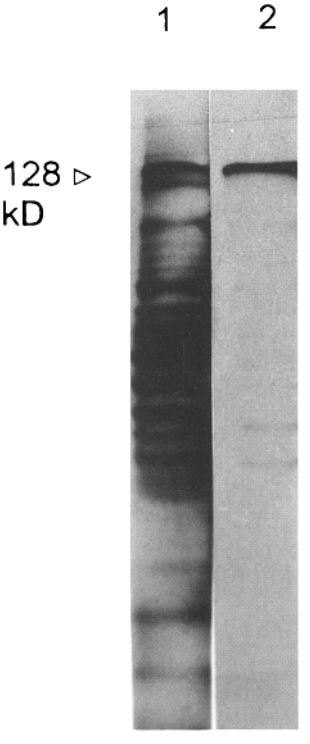

Fig. 4 Patient's serum (*lane 1*) and a positive control (*lane 2*, specific rabbit antiserum), blotted with supernatant from a known cytotoxin-positive *Helicobacter pylori*-strain separated by SDS-PAGE. The bands in *lane 1* represent several proteins which are recognized by the patient serum, including a 128 kDa protein of *H. pylori*, corresponding to the *cagA* gene product (cf. *lane 2*)

grade component centred within a low-grade MALT-type lymphoma.

There are recent reports of the regression of low-grade MALT-type lymphomas at short-term follow-up after medical eradication of *H. pylori* [53, 55, 58, 60, 61]. Hence, antibiotic therapy has been proposed prior to surgery in patients with gastric low-grade MALT-type lymphomas [53, 55, 58, 60, 61]. Virtually all of these cases presented as if they had gastritis at endoscopy, without frank evidence of neoplasia, so the responsive lesions probably represented a very early stage of gastric lymphoma. Antibiotic therapy may fail to cure gastric lymphomas, when there is a bulky tumour with a high-grade component [38], or when gastric lymphoma is associated with carcinoma, as in the patient presented here. Future studies will have to define the precise biological role of *H. pylori* in gastric tumorigenesis, and the role of antibiotic treatment.

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