Synchronous adenocarcinoma and low grade B-cell lymphoma of mucosa associated lymphoid tissue (MALT) of the stomach

A.C. WOTHERSPOON & P.G. ISAACSON
Department of Histopathology, University College London Medical School, London, UK

Date of submission 8 February 1995
Accepted for publication 17 June 1995

WOTHERSPOON A.C. & ISAACSON P.G.
(1995) Histopathology 27, 325-331

Synchronous adenocarcinoma and low grade B-cell lymphoma of mucosa associated lymphoid tissue (MALT) of the stomach

We describe nine cases of gastric adenocarcinoma (six intestinal and three diffuse type) occurring in the stomach synchronously with primary low grade B-cell lymphoma of mucosa associated lymphoid tissue. In four cases the two neoplasms were admixed to form collision tumours. Where collision was present between lymphoma and adenocarcinoma of intestinal type no lymphoepithelial lesions were seen involving neoplastic glands. Helicobacter pylori-like organisms were seen in seven cases (78%) which is consistent with an aetiological role for this organism in both tumours in the stomach.

Keywords: stomach, mucosa associated lymphoid tissue (MALT), adenocarcinoma, Helicobacter pylori

Introduction

Ninety-five percent of primary gastric tumours are of epithelial origin and the majority of the remainder are lymphomas. Although the finding of multiple gastric carcinomas is no longer considered uncommon, the development of synchronous gastric adenocarcinoma and primary gastric lymphoma, while well documented in a number of individual case reports, is relatively rare. We report nine cases of gastric low grade B cell lymphoma of mucosa associated lymphoid tissue (MALT) with co-existing gastric adenocarcinoma.

Materials and methods

Cases of combined primary gastric lymphoma and gastric carcinoma were retrieved from the surgical and referral files of the Department of Histopathology, University College London Medical School. The histological features were reviewed in routine haematoxylin and eosin stained sections. Carcinomas were classified as intestinal or diffuse using the criteria of Lauren. Where sufficient paraffin-embedded material was available, immunohistochemical staining was performed with antibodies to CD20, CD3, cytokeratin (CAM5.2) and the immunoglobulin kappa and lambda light chains using the avidin/biotin complex and the indirect immunoperoxidase technique.

Results

Nine cases of combined gastric primary lymphoma and carcinoma were identified. All cases had been referred to one of us (PGI) either for assessment of the lymphoid infiltrate (six cases) or for interest. Available clinical details, macroscopic appearances and pathology are summarised in Table 1. In six cases only adenocarcinoma had been diagnosed on biopsy material and in two cases a pre-operative diagnosis of lymphoma was made. In one case biopsies had shown both carcinoma and lymphoma.

In each case the lymphoma showed characteristic features of low grade B-cell MALT lymphoma with a diffuse infiltrate of centrocyte-like (CCL) cells which in some areas, were seen surrounding reactive germinal centres. Invasion and destruction of normal epithelium to form lymphoepithelial lesions was seen in all cases. In five cases material was available for immunohistochemical staining (cases 1, 3, 4, 6 and 8). In these cases
Table 1. Summary of clinical, macroscopic and morphological features.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/sex</th>
<th>Biopsy diagnosis</th>
<th>Macroscopic</th>
<th>Carcinoma type</th>
<th>Carcinoma penetration</th>
<th>Lymphoma type</th>
<th>Lymphoma penetration</th>
<th>Relationship ML/Ca</th>
<th>H. pylori status</th>
<th>Lymph node status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55/F</td>
<td>Lymphoma</td>
<td>Nodular and thickened mucosa throughout the stomach flattened smooth mucosa in antrum</td>
<td>Diffuse</td>
<td>Serosa</td>
<td>LG B-cell lymphoma of MALT</td>
<td>Submucosa</td>
<td>Collision</td>
<td>Positive</td>
<td>Metastatic carcinoma</td>
</tr>
<tr>
<td>2</td>
<td>55/F</td>
<td>Carcinoma</td>
<td>Hypertrophic giant plicae and an ulcerated polypoid lesion 4 cm in diameter on posterior wall</td>
<td>Intestinal</td>
<td>Submucosa</td>
<td>L + HG B-cell lymphoma of MALT</td>
<td>Serosa</td>
<td>Collision</td>
<td>Positive</td>
<td>Metastatic carcinoma</td>
</tr>
<tr>
<td>3</td>
<td>UK/M</td>
<td>Lymphoma and carcinoma</td>
<td>NA</td>
<td>Intestinal</td>
<td>Serosa</td>
<td>LG B-cell lymphoma of MALT</td>
<td>Serosa</td>
<td>Collision</td>
<td>Not seen</td>
<td>NA</td>
</tr>
<tr>
<td>4</td>
<td>60/F</td>
<td>Carcinoma</td>
<td>Infiltrating ulcerated tumour 6 cm in maximum diameter</td>
<td>Intestinal</td>
<td>Serosa and omentum</td>
<td>LG B-cell lymphoma of MALT</td>
<td>Submucosa</td>
<td>Separate</td>
<td>Positive</td>
<td>Metastatic carcinoma</td>
</tr>
<tr>
<td>5</td>
<td>34/F</td>
<td>Carcinoma</td>
<td>2 cm diameter area of mucosal thickening along the lesser curve</td>
<td>Diffuse</td>
<td>Serosa</td>
<td>LG B-cell lymphoma MALT</td>
<td>Serosa</td>
<td>Separate</td>
<td>Positive</td>
<td>Reactive</td>
</tr>
<tr>
<td>6</td>
<td>67/F</td>
<td>Carcinoma</td>
<td>Pyloritic depressed area with atrophic antral mucosa and small erosions</td>
<td>Intestinal</td>
<td>Mucosa</td>
<td>LG B-cell lymphoma MALT</td>
<td>Submucosa</td>
<td>Separate</td>
<td>Positive</td>
<td>NA</td>
</tr>
<tr>
<td>7</td>
<td>55/F</td>
<td>Carcinoma</td>
<td>NA</td>
<td>Intestinal</td>
<td>Submucosa</td>
<td>LG B-cell lymphoma of MALT</td>
<td>Mucosa</td>
<td>Separate</td>
<td>Positive</td>
<td>NA</td>
</tr>
<tr>
<td>8</td>
<td>55/F</td>
<td>Lymphoma</td>
<td>Atrophy of antral mucosa</td>
<td>Diffuse</td>
<td>Submucosa</td>
<td>LG B-cell lymphoma of MALT</td>
<td>Serosa</td>
<td>Separate</td>
<td>Not seen</td>
<td>Reactive</td>
</tr>
<tr>
<td>9</td>
<td>69/F</td>
<td>Carcinoma</td>
<td>NA</td>
<td>Intestinal</td>
<td>Serosa</td>
<td>LG B-cell lymphoma of MALT</td>
<td>Submucosa</td>
<td>Collision</td>
<td>Positive</td>
<td>Metastatic carcinoma and lymphoma</td>
</tr>
</tbody>
</table>

ML, malignant lymphoma; Ca, carcinoma; UK, unknown; LG, low grade; L & HG, low grade with focal high grade transformation; NA, data not available.
the infiltrating CCL cells were CD20 positive and immunoglobulin light chain restriction was demonstrated in four of five cases. In the remaining case immunoglobulin staining was unsatisfactory due to poor fixation. Anti-cytokeratin stains highlighted the lymphoepithelial lesions and a reactive CD3 positive T-cell infiltrate was seen. In case 2 an additional small area of high grade transformation was apparent which was intimately associated with the infiltrating carcinoma.

In six cases the adenocarcinoma was of intestinal type and in three of these cases the lymphoma and carcinoma merged to form a collision tumour. In these cases the CCL cells did not form lymphoepithelial lesions with the neoplastic glands. In the remaining three cases the carcinoma was of the diffuse type. In two of these cases the tumours were separate but, in one case, individual adenocarcinoma cells could be identified surrounded by neoplastic CCL cells. In the collision tumour composed of diffuse-type adenocarcinoma the intermingling malignant epithelial cells were difficult to identify using conventional H & E stained sections. These cells were highlighted by immunostaining with anti-cytokeratin antibodies (Figure 1).

*Helicobacter pylori*-like organisms were identified in seven of nine cases. In one case (case 3) very little normal gastric mucosa was present for study and in the other case no evidence of the organism could be seen on any of five sections of mucosa examined.

**Discussion**

Adenocarcinoma is the commonest tumour arising in the stomach, accounting for approximately 95% of gastric neoplasms. The majority of the remainder are lymphomas, while mesenchymal tumours are rare. The association of adenocarcinoma with primary gastric lymphoma was first reported in 1931 by Schuback et al. Since then there have been 15 further cases in the western literature and 25 cases in the Japanese literature. The majority of these exist as single case reports with the largest western study comprising two cases. The cases from the English-language literature which are described in more detail are summarized in Table 2. The majority of carcinomas in these reports were of intestinal type. The type of lymphoma associated with the carcinoma varies, reflecting the previous controversy in lymphoma classification and the difficulty in the classification of extra-nodal lymphoma. In only one report was the lymphoma classified as MALT-type. There is an additional single case report of the coexistence of gastric adenocarcinoma and 'pseudolymphoma'. As it is now accepted that the majority of lesions previously diagnosed as pseudolymphoma are actually low grade B-cell lymphomas of MALT type, it is probable that this represents a further case of combined gastric lymphoma-carcinoma.

The development of adenocarcinoma following resection for pre-existing benign gastric pathology is well recognized and theories for their pathogenesis have been formulated. This so-called stump carcinoma usually develops within a few centimetres of the anastomosis site, a mean of 20 years following partial gastrectomy. Following gastrectomy, atrophic and chronic gastritis, inflammatory and adenomatous polyps, intestinal metaplasia and cystic glandular dilatation are all seen in the gastric stump. Both reflux and increased N-nitroso compounds, as a result of achlorhydria and bacterial overgrowth, have been implicated in the development of stump carcinomas. Adenocarcinoma following resection for lymphoma is also well recognized. In addition to factors resulting from surgery, radiotherapy and chemotherapy may play a role in the development of these tumours. In all our cases the carcinoma and lymphoma appeared simultaneously, and, therefore, these factors cannot explain the pathogenesis of the two tumours.

Infection of the stomach by the gram negative spiral bacteria *H. pylori* has been implicated both in the development of gastric adenocarcinoma and gastric lymphoma of MALT type. Various histological and serological studies have shown an association between *H. pylori* infection and intestinal type gastric adenocarcinoma in 19% to 94% and in diffuse type in 32% to 100% of cases. The exact role of *H. pylori* infection in gastric carcinogenesis remains uncertain but either the direct production of cytokines, proteolytic enzymes and ammonia or the secretion of free radicals, toxins and growth factors by the induced inflammatory response might modulate the growth and function of epithelial cells leading to atrophy, intestinal metaplasia and, eventually, carcinoma. The role of *H. pylori* in gastric lymphomagenesis is better defined. The normal gastric mucosa is devoid of organized lymphoid tissue, which is specifically acquired in response to infection by *H. pylori*. *H. pylori* has been shown to be strongly associated with the development of gastric lymphoma of MALT type, being found in excess of 90% of cases. In vitro studies have shown that the neoplastic cells of low grade gastric MALT lymphomas proliferate specifically in response to *H. pylori* antigens in a T cell dependent fashion. Eradication of the organism in patients with gastric MALT lymphoma diagnosed by endoscopic biopsy has led to the regression of the tumour. It is therefore...
likely that *H. pylori* plays an important role in the development of both the lymphoma and carcinoma in these cases and provides a unifying theory for their pathogenesis.

The nature of the lymphoepithelial lesion, characteristic of MALT lymphomas at all sites, remains enigmatic. This distinctive invasion of the overlying epithelium was first recognized in 1979 in cases of immunoproliferative small intestinal disease (IPSID) and was subsequently found to be characteristic of MALT lymphomas in the stomach and at other sites. Native MALT of the Peyer's patch and
### Table 2. Summary of feature of synchronous gastric adenocarcinoma and lymphoma reported in the English-language literature

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age/Sex</th>
<th>Pre-operative BX diagnosis</th>
<th>Carcinoma type</th>
<th>Carcinoma penetration</th>
<th>Carcinoma LN status</th>
<th>Lymphoma type</th>
<th>Lymphoma penetration</th>
<th>Lymphoma LN status</th>
<th>Relationship lymphoma/carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabinovitch et al.</td>
<td>64/M</td>
<td>ND</td>
<td>Intestinal adenoca</td>
<td>Mucosa</td>
<td>NR</td>
<td>Lymphosarcoma</td>
<td>Serosa</td>
<td>NR</td>
<td>Separate</td>
</tr>
<tr>
<td>Jernstrom et al.</td>
<td>72/F</td>
<td>ND</td>
<td>Well diff adenoca</td>
<td>Serosa</td>
<td>Positive</td>
<td>Lymphocytic lymphosarcoma</td>
<td>Serosa</td>
<td>Positive</td>
<td>Intimate</td>
</tr>
<tr>
<td>Manier et al.</td>
<td>65/M</td>
<td>ND</td>
<td>Poorly diff adenoca</td>
<td>Superficial</td>
<td>Negative</td>
<td>Histiocytic</td>
<td>Serosa</td>
<td>Positive</td>
<td>Contiguous, not intermingling</td>
</tr>
<tr>
<td></td>
<td>72/M</td>
<td>ND</td>
<td>Poorly diff adenoca</td>
<td>NR</td>
<td>Positive</td>
<td>Histiocytic</td>
<td>NR</td>
<td>Positive</td>
<td>Collision, not intermingling</td>
</tr>
<tr>
<td>Kane et al.</td>
<td>74/M</td>
<td>Adenoca and lymphoma</td>
<td>Poorly diff adenoca</td>
<td>Mucosa</td>
<td>Negative</td>
<td>Lymphocytic</td>
<td>Submucosa</td>
<td>Positive</td>
<td>Separate</td>
</tr>
<tr>
<td>Planker et al.</td>
<td>65/M</td>
<td>Adenoca</td>
<td>Mod diff intestinal</td>
<td>Mucosa</td>
<td>Negative</td>
<td>Immunocytoma</td>
<td>Musc prop</td>
<td>Positive</td>
<td>Collision</td>
</tr>
<tr>
<td>Czernek et al.</td>
<td>74/M</td>
<td>Adenoca</td>
<td>Well diff adenoca</td>
<td>Mucosa</td>
<td>Negative</td>
<td>ML mixed type</td>
<td>Serosa</td>
<td>Negative</td>
<td>Separate</td>
</tr>
<tr>
<td>Kasahara et al.</td>
<td>77/F</td>
<td>Adenoca</td>
<td>Well diff adenoca</td>
<td>Musc muc</td>
<td>Negative</td>
<td>B-cell ML small cleaved</td>
<td>Serosa</td>
<td>Negative</td>
<td>Contiguous, not intermingling</td>
</tr>
<tr>
<td>Noda et al.</td>
<td>61/M</td>
<td>Adenoca and lymphoma</td>
<td>Well diff tubular x2</td>
<td>Submucosa</td>
<td>Negative</td>
<td>Diffuse large cell</td>
<td>Serosa</td>
<td>Negative</td>
<td>Intermingling</td>
</tr>
<tr>
<td>Akosa et al.</td>
<td>79/M</td>
<td>Adenoca and lymphoma</td>
<td>Mod diff adenoca</td>
<td>NR</td>
<td>NR</td>
<td>LG lymphoma MALT type</td>
<td>NR</td>
<td>NR</td>
<td>Separate</td>
</tr>
</tbody>
</table>

Bx, biopsy; LN, lymph node; ND, not done; NR, not recorded; Adenoca, adenocarcinoma. Well diff, well differentiated; Mod diff, moderately differentiated; poorly diff, poorly differentiated; musc prop, muscularis propria; Musc muc, muscularis mucosa; ML, malignant lymphoma
acquired reactive MALT show infiltration of the overlying epithelium by lymphocytes, and it is thought that the lymphoepithelial lesion is the neoplastic equivalent of this lymphocyte-epithelial cell interaction. In MALT lymphoma there is infiltration of CCL cells between glandular epithelial cells with an intimate relationship between the membranes of each cell resulting in marked ultrastructural changes in the epithelial cell. Although the stimulus for the formation of lymphoepithelial lesions remains unknown, this suggests that there may be a membrane bound signal. In cases where gastric MALT lymphoma and carcinoma are in intimate contact no lesions are seen. We have also observed that such lesions are not formed with metaplastic or dysplastic glands (data not shown) suggesting that, although MALT lymphomas of the intestine will form lymphoepithelial lesions with native epithelium, the stimulus for this is lost on metaplastic, dysplastic and neoplastic epithelial cells.

This report highlights the need for histopathologists to be aware of the possibility of synchronous adenocarcinoma and lymphoma in the stomach. This is particularly important in cases of diffuse-type carcinoma when the appearance of large atypical (epithelial) cells within the infiltrate of CCL cells may be dismissed as being the scattered transformed cells which characteristically form part of the infiltrate in low grade MALT lymphoma. On the other hand, it must be remembered that obliteration of normal glands by infiltrating CCL cells may result in scattered isolated benign epithelial cells which should not be interpreted as being cells from an infiltrative diffuse-type adenocarcinoma. In only one of nine cases in this series was the coexistence of lymphoma and carcinoma apparent in the pre-operative biopsies. In the majority of cases the biopsy diagnosis of carcinoma led to definitive surgical resection of the tumour. In the cases where biopsies showed only low grade MALT lymphoma initial treatment with anti- H. pylori therapy, while possibly causing remission of the lymphoma, would be inappropriate management of carcinoma. It is, therefore, advisable that patients with MALT lymphoma undergo careful endoscopic assessment with the performance of numerous biopsies from normal and from any suspicious areas before embarking on anti- H. pylori therapy for lymphoma.

Acknowledgements

We would like to thank Professors Martinelli and Bearzi and Drs Doglioni, Shrimanker, Clarke, Vella and Bontempi for submitting cases for review.

References

Gastric carcinomas and MALT lymphoma

36. Wyatt JI, Rathbone BJ. Immune response of the gastric mucosa to Campylobacter pylori. Scand. J. Gastroenterol. 1988; 23(suppl. 142); 44–49.
学霸图书馆
www.xuebalib.com

本文献由“学霸图书馆-文献云下载”收集自网络，仅供学习交流使用。

学霸图书馆（www.xuebalib.com）是一个“整合众多图书馆数据库资源，提供一站式文献检索和下载服务”的24小时在线不限IP图书馆。
图书馆致力于便利、促进学习与科研，提供最强文献下载服务。

图书馆导航：
图书馆首页 文献云下载 图书馆入口 外文数据库大全 疑难文献辅助工具