in modulating folliculogenesis.[10] In this case we were unable to determine whether the renin secreting cells were tumour cells or perivascular ovarian stromal cells. A similar problem has been encountered in renin secreting renal cell carcinoma; the evidence has been reviewed.[11] The ovary secretes prorenin into the blood, and ovarian tumours may also secrete prorenin and active renin and cause hypertension. Tumours secreting active renin cause severe hypertension and hypokalaemia. Our patient had only mild hypertension and normal blood potassium levels. Hence it is probable that the mild rise in blood pressure was caused by the raised haematocrit rather than secretion of active renin by the tumour. We did not find evidence of renin synthesis in two other cases of sex-cord stromal tumours (unpublished observations). Plasma prorenin concentration is a good tumour marker for Wilms's tumour and other renin secreting tumours, but its role in other neoplasms is not clear. The investigation of biologically inactive prorenin as a tumour marker in ovarian tumours may prove rewarding.

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Sequential malt lymphomas of the stomach, small intestine, and gall bladder

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Abstract

Low grade lymphomas of mucosa associated lymphoid tissue (MALT) are indolent neoplasms that, although tending to remain localised for many years, may spread to other mucosal sites. A 53 year old woman treated by total gastrectomy for low grade MALT lymphoma of the stomach developed a recurrence in the small bowel 18 years later, and a further recurrence involving the gall bladder after three years in complete clinical remission after chemotherapy. In situ hybridisation showed that the small intestine and gall bladder recurrences had the same pattern of light chain restriction. Tumour from all three sites was shown to be derived from a single clone by the demonstration of an identical immunoglobulin heavy chain gene rearrangement by the polymerase chain reaction. The case illustrates the propensity of MALT lymphomas to "home" to mucosal sites and gives an insight into their behaviour over an extended follow up.

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Keywords: MALT lymphoma; extranodal marginal zone lymphoma; stomach; small intestine; gall bladder.

Low grade mucosa associated lymphoid tissue (MALT) lymphomas behave in an indolent fashion, remain localised to the site of origin for many years before dissemination, and respond favourably to local measures. A 10 year survival rate of 75% is quoted for low grade gastric tumours[1] but there is little information on the behaviour of this tumour over a longer period of follow up. Involvement of two mucosal sites either concurrently or sequentially is a well recognised characteristic of these tumours. Examples include simultaneous involvement of the small bowel and stomach, bilateral presentation of salivary gland tumours, and recurrence of MALT lymphoma of the thyroid in the duodenum after three years.[2–4] Involvement of the gall bladder by MALT lymphoma is rare, there being only two previously reported cases to our knowledge in the literature.[5 6] We report a case of recurrent MALT lymphoma of the stomach involving multiple mucosal sites, including the gall bladder, over 21 years.

Case report

A 53 year old woman presented in 1973 with anorexia and vomiting. At gastroscopy, the mucosa was atrophic and showed multiple areas of haemorrhage. A histamine test meal revealed complete achlorhydria. At laparotomy

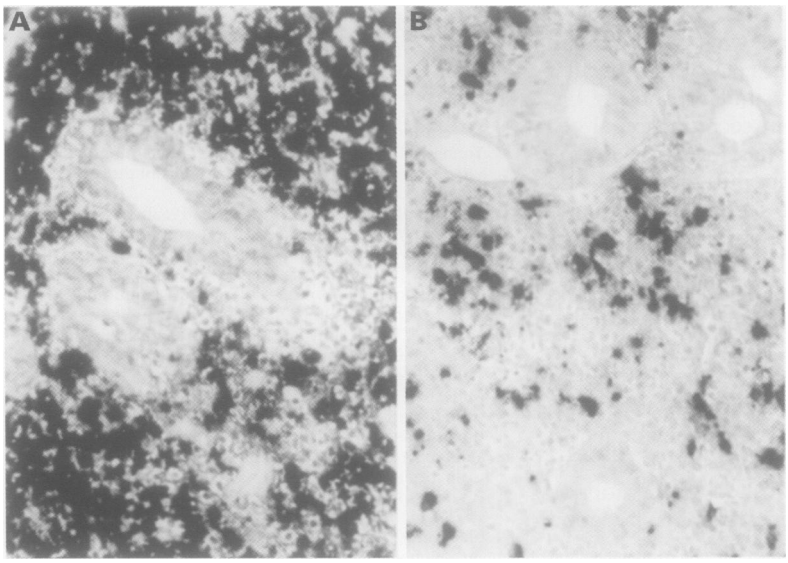

Figure 1 In situ hybridisation of the jejunal biopsy for (A) κ light chain and (B) λ light chain.

a frozen section was reported as lymphosarcoma and total gastrectomy was performed with anastomosis of the jejunum to the oesophagus and enteroanastomosis between the afferent and efferent loops of the small bowel. The patient made a full recovery and remained in good health for 18 years.

In 1991 she presented with symptoms of malabsorption including a low serum albumin of 20 g/dl, low zinc, magnesium, and calcium. A barium follow through was suggestive of diffuse lymphomatous involvement of the jejunum and proximal ileum, which was confirmed by endoscopic biopsy. Complete resolution of clinical symptoms followed a low grade chemotherapy regimen. Three years later she presented with nausea and vomiting. She was slightly jaundiced and an abdominal ultrasound showed an enlarged gall bladder containing multiple gall stones. Cholecystectomy was performed and four gall stones were extracted from the common bile duct. During the procedure a few enlarged lymph nodes were observed in the porta hepatis. The spleen was normal. Histological examination revealed low grade MALT lymphoma involving the gall bladder and local lymph nodes. She was treated with a low grade chemotherapy regimen and was disease free 36 months later when last reviewed.

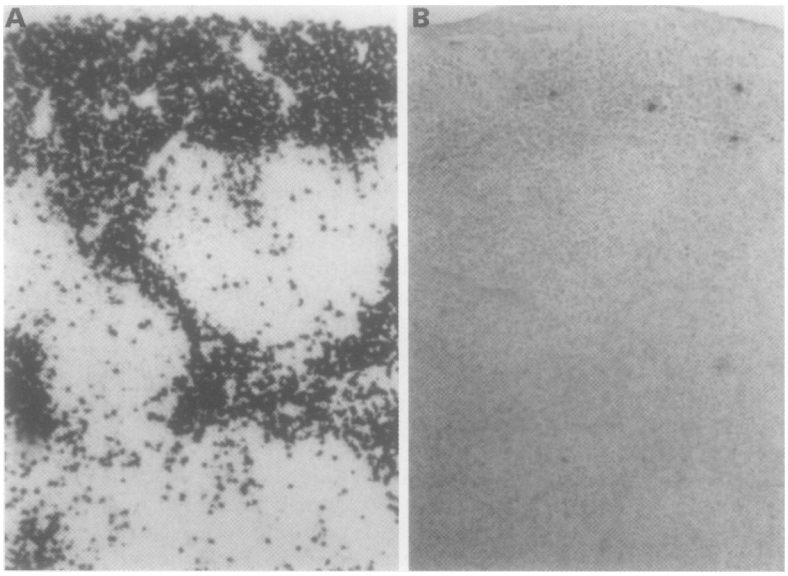

Figure 2 In situ hybridisation of the gall bladder for (A) κ light chain and (B) λ light chain.

Materials and methods

Sections (4 μm) stained with haematoxylin and eosin from all three specimens were retrieved from the archives of the Victoria Infirmary, Glasgow, and reviewed. In situ hybridisation (ISH) for light chain mRNA was performed using the method described by Hell *et al* with slight modification.[7 8] The probes used were double digoxigenin labelled oligodeoxynucleotide probes (R&D systems, Abingdon, Oxfordshire, UK) to κ and λ chain mRNA. Detection was achieved using an alkaline phosphatase labelled antidigoxigenin antibody (Boehringer Mannheim, Lewes, East Sussex, UK) with NBT/BCIP (Sigma, Poole, Dorset, UK) as substrate. The slides were counterstained with haematoxylin and mounted using Faramount (Dako, High Wycombe, Bucks, UK).

For the polymerase chain reaction (PCR) a 10 μm section was cut from each specimen and placed in separate tubes. After dewaxing, the sections were digested overnight at 37°C with proteinase K (Sigma) at 500 μg/ml. The proteinase K was inactivated at 95°C for 10 minutes and 5 μl from each sample was used in the PCR. The PCR was a semi-nested procedure using Fr3 and LJH primers in the first round, and Fr3 and VLJH primers in the second. The products were analysed on a 10% polyacrylamide gel that was poststained with ethidium bromide and viewed under ultraviolet light.

PATHOLOGICAL FINDINGS

The initial gastrectomy specimen was described as being diffusely thickened with a macroscopic appearance suggestive of linitis plastica. The mucosa was roughened and irregular. Histological review revealed the typical features of a low grade B cell lymphoma of MALT type. There was pronounced mucosal atrophy associated with diffuse lymphocytic infiltration of the lamina propria and submucosa. There was focal infiltration of the muscularis propria and serosa. The infiltrate consisted mainly of small lymphocytes and centrocyte-like cells surrounding and over running residual reactive follicles. Plasma cell differentiation was noted focally in the superficial aspect of the lamina propria. Lymphoepithelial lesions were not demonstrated in the available blocks. No lymph nodes were available for assessment. There was evidence of lymphomatous involvement of both the duodenal and oesophageal resection margins. Light chain restriction was not convincingly demonstrated by ISH. Examination of the duodenal biopsy revealed broadening of villi, crypt atrophy, a diffuse lymphoplasmacytic infiltrate within the lamina propria, and lymphoepithelial lesions formed by centrocyte-like cells. Kappa light chain restriction was demonstrated by ISH in the tumour cells showing plasmacytic differentiation (fig 1).

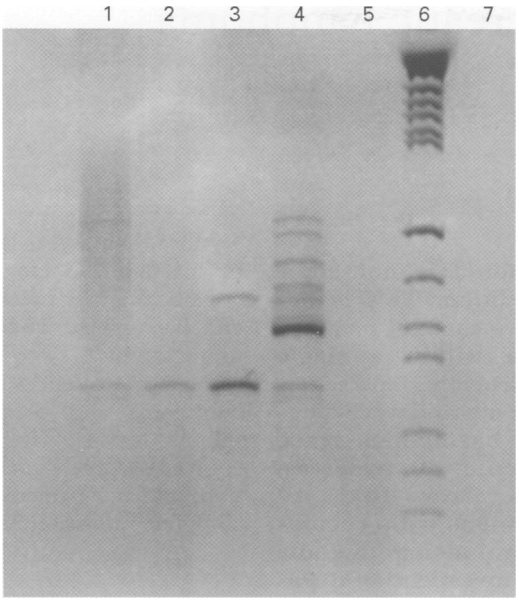

Figure 3 PCR products visualised by ethidium bromide showing an identical immunoglobulin heavy chain gene rearrangement in the three tumours. Lane 1, gall bladder lymphoma; lane 2, duodenal lymphoma; lane 3, gastric lymphoma; lane 4, positive control (known B cell lymphoma); lane 5, negative control; lane 6, DNA molecular weight markers; lane 7, negative control.

On macroscopic examination the gall bladder wall was diffusely thickened and the mucosa displayed a rather polypoid appearance. Histological examination revealed a diffuse lymphomatous infiltrate identical to that seen in the previous duodenal biopsy and gastric resection. The tumour involved the entire thickness of the gall bladder wall and was composed of centrocyte-like cells with extensive plasma cell differentiation. Occasional lymphoepithelial lesions and residual reactive germinal centres were identified. Kappa light chain restriction in the plasma cell component was again demonstrated by ISH (fig 2). The lymph nodes from the porta hepatis showed marginal zone involvement by centrocyte-like cells, typical of spread from an extranodal B cell lymphoma of MALT type. All three tumours displayed an identical immunoglobulin heavy chain gene rearrangement on analysis by PCR (fig 3).

Discussion

We have described a case of low grade MALT lymphoma of the stomach sequentially involving multiple mucosal sites over a period of 21 years. The lymphoma has behaved in a relatively indolent fashion and the patient was in remission at latest follow up. The supposition that the small intestine and the gall bladder tumours were recurrences rather than new primaries is supported by the demonstration of common clonality of the three tumours by PCR. It is noteworthy that the recurrences have continued to display the low grade pattern of the original gastric tumour with no suggestion of transformation to a higher grade over such a long follow up. The pattern of involvement of the small bowel in this case is unusual. The patient presented after 18 years of relative well-being with severe weight loss and clear evidence of severe malabsorption. Barium studies showed diffuse small bowel infiltration and the biopsy confirmed MALT lymphoma. The clinical features described resemble those seen in Mediterranean lymphoma (immunoproliferative small intestinal disease (IPSID)) the most common manifestation of MALT lymphoma in the Middle East but rare in the West.[4] In Europe, small intestinal MALT lymphoma more commonly presents as a localised tumour mass resulting in obstruction. The similarity to IPSID was also apparent on histological examination of the small bowel biopsy where plasma cell differentiation was prominent. Light chain production, as identified in our case, however, is rare in IPSID. The malabsorption responded dramatically to chemotherapy.

Involvement of the gall bladder by low grade MALT lymphoma is rare, there being only two previously described cases.[5 6] As in the other published cases, our patient presented with a typical history of cholelithiasis and the diagnosis of lymphoma only became obvious on histological examination. The reason for recurrence in this case may have been as a direct consequence of incomplete resection at initial gastrectomy, albeit after an interval of 18 years. Disease free resection margins however may be no guarantee of future protection from local relapse as recurrences have been described in patients thought to have had an initial curative resection.[9] This phenomenon is thought to be due to the presence of multiple microscopic foci of tumour within the gastric mucosa distant from the main tumour mass.[10] Moreover, plasma cells derived from a small intestinal MALT lymphoma have been detected in the apparently normal gastric mucosa of the same patient, indicating the ability of this tumour to colonise distant mucosal sites.[2]

This case illustrates many of the properties of low grade MALT lymphoma. The tumour was slow growing, produced a variety of clinical problems, and demonstrated a propensity for spread to other mucosal sites rather than for systemic dissemination. The late recurrence after an 18 year interval has implications for the definition of cure especially in younger patients.

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