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SHORT REPORTS

Gastric MALT lymphoma with t(14;18)(q32;q21) involving *IGH* and *BCL2* genes that responded to *Helicobacter pylori* eradication

Four recurrent chromosomal translocations are recognised in mucosa-associated lymphoid tissue (MALT) lymphomas: t(11;18)/*API2-MALT1*, t(1;14)/*IGH-BCL10*, t(14;18)/*IGH-MALT1* and t(3;14)/*IGH-FOXP1*. In contrast, t(14;18)/*IGH-BCL2*, the genetic hallmark of follicular lymphoma, has been observed in only rare cases of MALT lymphoma. Oesophagogastroduodenoscopy revealed an ulcer in erythematous granular mucosa at the gastric corpus in a 55-year-old man. A diagnosis of MALT lymphoma was made on the basis of typical histological and immunohistochemical features of biopsy specimens: a diffuse infiltrate of centrocyte-like cells surrounding reactive lymphoid follicles and forming lymphoepithelial lesions, and a CD20+, IgD−, CD5−, CD10−, Bcl6−, cyclinD1− immunophenotype. Four months after the successful eradication of *Helicobacter pylori*, there was endoscopic regression with probable minimal residual disease detected by biopsy, but histological relapse was recognised 12 months after eradication. Interphase fluorescence *in situ* hybridisation revealed t(14;18)/*IGH-BCL2*, but not the translocations typically seen in MALT lymphoma. This is the first report of a gastric MALT lymphoma with t(14;18)/*IGH-BCL2* that responded to *H pylori* eradication.

Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) is genetically characterised by the recurrent translocations t(11;18)(q21;q21)/*API2-MALT1*, t(1;14)(p22;q32)/*BCL10-IGH*, t(14;18)(q32;q21)/*IGH-MALT1* and t(3;14)(p14;q32)/*FOXP1-IGH*.[1 2] Recent evidence suggests that at least some of these translocations may be associated with distinct clinicopathological features.[1 3] The t(14;18)(q32;q21)/*IGH-BCL2* is found in the majority of follicular lymphomas and some diffuse large B-cell lymphomas.[4] However, MALT lymphomas carrying this translocation are extremely rare and their clinical features are virtually unknown.

Case report

A 55-year-old asymptomatic man underwent oesophagogastroduodenoscopy (OGD) as screening for gastric carcinoma. OGD revealed an open ulcer with surrounding granular erythematous mucosa in the upper corpus (fig 1A). Histological examination of biopsy specimens taken adjacent to the ulcer margin and from nearby erythematous spots showed a diffuse infiltrate of centrocyte-like and small lymphocyte-like cells surrounding reactive lymphoid follicles in a marginal zone distribution, forming prominent lymphoepithelial lesions (fig 2A). Monocytoid differentiation and plasmacytoid cells with Dutcher bodies were also observed. Immunohistochemistry showed the neoplastic cells to express CD20, CD79a and Bcl2, but not CD3, CD5, CD10, CD43, Bcl6, cyclinD1 or IgD (fig 2A). On the basis of these findings, a diagnosis of MALT lymphoma was made.

Staging investigations including endosonography,[5] CT of the chest and abdomen, colonoscopy, small bowel follow-through, peripheral blood and bone marrow examination, and ^{18}F-fluorodeoxyglucose positron emission tomography showed Lugano stage 1 disease.[6] *H pylori* was detected by the rapid urease test, histology and serology, and was eradicated with rabeprazole 40 mg/day plus amoxicillin 2000 mg/day for 2 weeks. Successful eradication of *H pylori* was confirmed by [^{13}C]urea breath test 2 months after treatment. Serological investigation for hepatitis C virus (HCV) infection was negative.

Follow-up OGD 4 months after eradication showed disappearance of the initial lesion with small residual scars (fig 1B). Several biopsy specimens obtained from the scars and the surrounding mucosa displayed mildly oedematous lamina propria with scattered plasma cells and eosinophils, but no evidence of lymphoma. However, one specimen, taken from an erythematous spot, contained aggregates of small lymphoid cells (fig 2B), consistent with histologically defined probable minimal residual disease (pMRD).[7] Further OGD and biopsy at 7 months also showed endoscopic regression with pMRD. However, histological relapse, defined as a definite lymphomatous infiltrate, was recognised at 12 months, despite the absence of endoscopically evident lymphoma. At this time, [^{13}C]urea breath test, rapid urease test and histology all remained negative for *H pylori*. Follow-up investigations at 15, 18, 21 and 24 months showed only atrophic changes endoscopically, although focal histological evidence of lymphoma was seen on several of the biopsy specimens taken. The patient is currently under careful observation without any additional treatment.

Molecular genetic findings

The presence of MALT lymphoma-associated chromosome translocations was assessed by interphase fluorescence *in situ* hybridisation (FISH) on formalin-fixed, paraffin-embedded tissues.[2] FISH probes were obtained from Vysis/Abbott, Maidenhead UK, except for the *FOXP1* and *BCL10* break-apart probes (kindly provided by Dr A Banham, Oxford, and Professor R Siebert, Kiel, respectively). FISH on pretreatment specimens showed a split signal with *IGH* and *BCL2* break-apart probes but not with *MALT1*, *BCL10*, *BCL6*, *CCND1* or *FOXP1* probes. FISH using a dual-colour dual-fusion translocation probe showed co-localisation of *IGH* and *BCL2* signals (fig 2C) indicating the presence of t(14;18)/*IGH-BCL2*. t(14;18)/*IGH-BCL2* was also identified in follow-up biopsy specimens, including those showing pMRD. Extra copies were observed by FISH with the *MALT1* break-apart probe and with the centromere-specific probe for chromosome 18, but not with *BCL2* or *IGH* probes. These findings suggest the presence of partial trisomy 18.

Discussion

Although the case reported in this study is positive for t(14;18)/*IGH-BCL2*, the diagnosis of MALT lymphoma is beyond doubt. This is supported by the characteristic histological and immunohistochemical findings: centrocyte-like cells surrounding reactive lymphoid follicles, prominent lymphoepithelial lesions, and the CD20+, CD5−, CD10−, Bcl6−, IgD− and

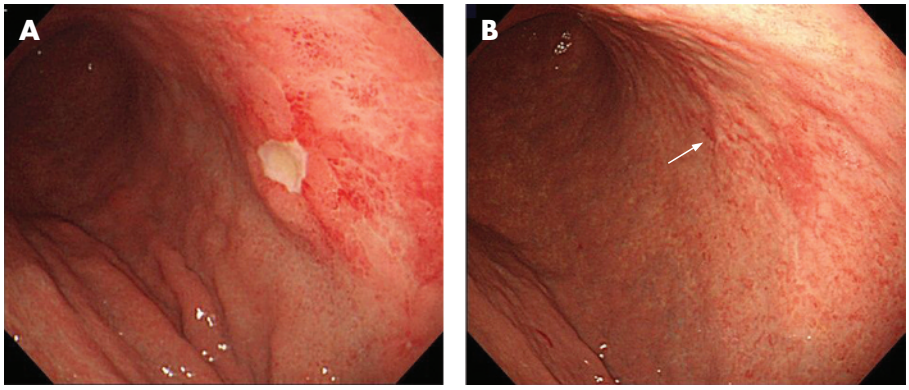

Figure 1 (A) Pretreatment oesophagogastroduodenoscopy (OGD) revealed a superficial lesion comprising an open ulcer, multiple scars and erythematous granular mucosa on the posterior wall of the upper corpus. (B) Follow-up OGD 4 months after *Helicobacter pylori* eradication showed regression of the initial lesion with multiple scars and mildly erythematous mucosa. The arrow indicates a healed scar from the ulcer in (A). Informed consent was obtained for publication of this figure.

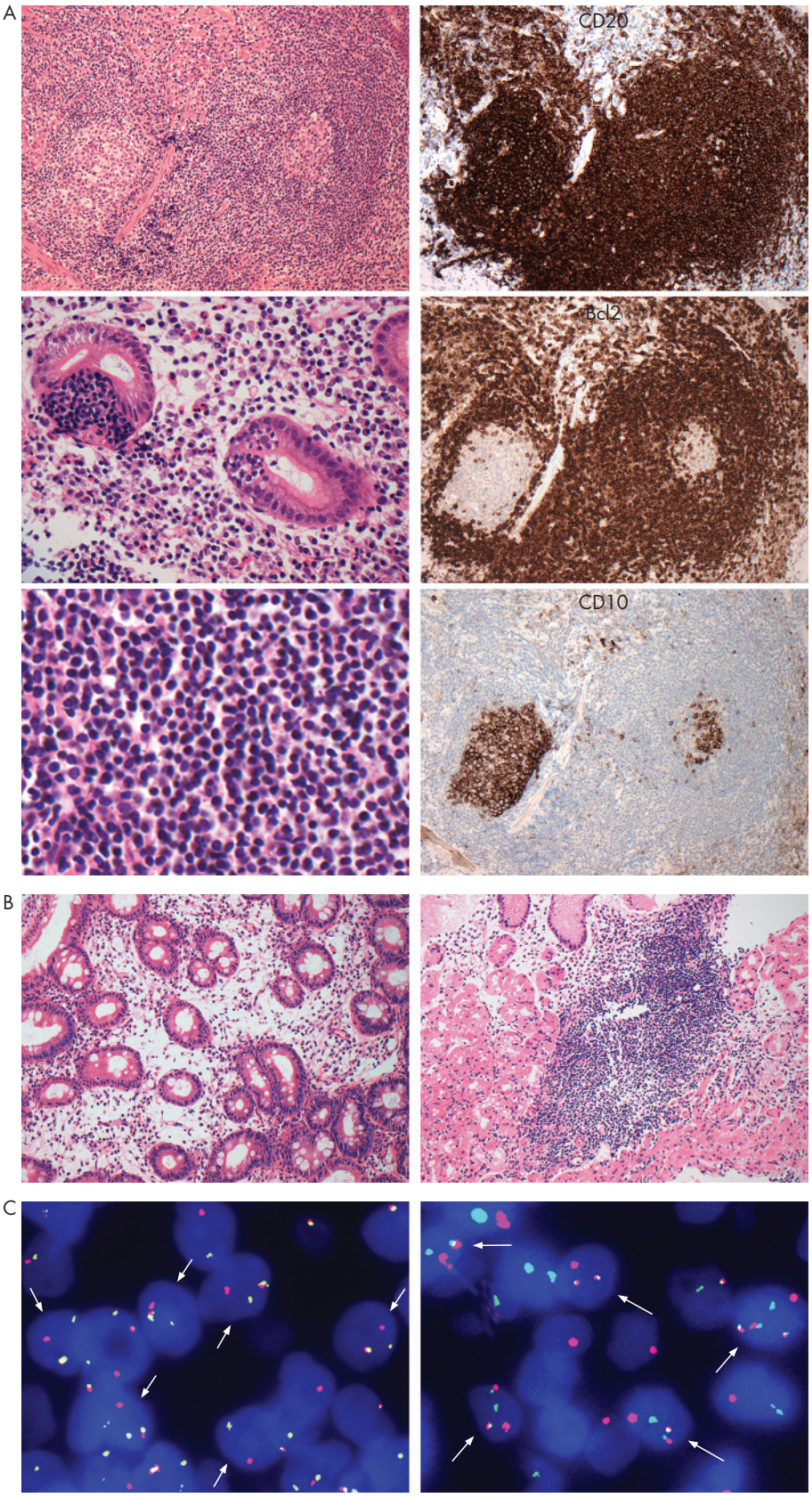

Figure 2 (A) Histological and immunohistochemical features of pretreatment biopsy specimens taken from the erythematous mucosa adjacent to the ulcer. A diffuse infiltrate of CD20+, CD10− centrocyte-like and small lymphocyte-like cells surrounding reactive Bcl2− lymphoid follicles and forming typical lymphoepithelial lesions can be seen. (B) Histological pictures of follow-up biopsy specimens 4 months after *Helicobacter pylori* eradication. A specimen obtained from the healed ulcer (fig 1B, arrow) shows mildly oedematous lamina propria with fibroblasts and scattered plasma cells and eosinophils, without evidence of lymphoma (left). However, another specimen taken from an erythematous spot displays aggregates of small lymphoid cells among fundic glands, consistent with probable minimal residual disease (right). (C) Interphase fluorescence *in situ* hybridisation (FISH) with *BCL2* dual-colour break-apart probe reveals splitting of the green and red signals (left, arrows). FISH with *IGH/BCL2* dual-colour, dual-fusion translocation probe shows co-localisation of the red and green signals (right, arrows), indicating t(14;18)/*IGH-BCL2*. Informed consent was obtained for publication of this figure.

cyclinD1− immunophenotype. Follicular lymphoma occasionally develops in the stomach, and may mimic MALT lymphoma by showing parafollicular marginal zone differentiation and lymphoepithelial lesions.[8] However, the neoplastic cells in the present case did not express the germinal centre B-cell markers CD10 or Bcl6, and the follicles present in the specimens showed reactive morphological features and were Bcl2−.

t(14;18)/*IGH-BCL2* is observed not only in follicular lymphoma, but also in about 20% of diffuse large B-cell lymphomas, occasionally in chronic lymphocytic leukaemia, and rarely in other lymphomas.[4 9] This translocation has been identified in a few cases of MALT lymphoma, most notably in the salivary gland or stomach of patients with chronic HCV infection.[10 11] Our patient was HCV negative, but had gastric colonisation by *H pylori*. Although *H pylori* eradication is now the first choice treatment for gastric MALT lymphoma,[1 5] the translocation status of MALT lymphomas can influence their responsiveness to *H pylori* eradication. Most cases with a t(11;18)/*API2-MALT1* fail to respond to such treatment.[12] The responsiveness to eradication therapy of patients carrying t(1;14)/*IGH-BCL10*, t(14;18)/*IGH-MALT1* or t(3;14)/*IGH-FOXP1* is less well established. In the present case with t(14;18)/*IGH-BCL2*, *H pylori* eradication resulted in endoscopic regression with pMRD. Such pMRD is often observed in gastric MALT lymphomas after *H pylori* eradication.[13 14] Although the long-term clinical significance of pMRD remains to be elucidated, a watch-and-wait strategy is considered appropriate for such patients, including the present case.[13 14]

The mechanisms by which t(14;18)/*IGH-BCL2* might promote and/or sustain a MALT lymphoma have not been established. Aiello *et al*[10] reported a case of salivary gland MALT lymphoma in a patient with Sjögren syndrome, who developed a clonally related follicular lymphoma 2 years later. t(14;18)/*IGH-BCL2* was detected in both the MALT and follicular lymphomas. The authors suggested that the follicular lymphoma might have resulted from colonisation of pre-existing reactive follicles by t(14;18)/*IGH-BCL2*-positive MALT lymphoma cells and subsequent interactions between the translocation and the germinal centre microenvironment. This hypothesis is in keeping with growing evidence that the characteristics of lymphoma cells may be influenced by the microenvironment in which they are set. In the present case, chronic *H pylori* infection may have provided conditions favouring the development and maintenance of MALT lymphoma. Within the germinal centre, forced overexpression of the anti-apoptotic protein Bcl2 by t(14;18)/*IGH-BCL2* is thought to promote survival and expansion of the neoplastic clone.[4] However, the role of the t(14;18)/*IGH-BCL2* in MALT lymphoma is less clear as both normal marginal zone B cells and the majority of MALT lymphomas express Bcl2 in the absence of the translocation. Nevertheless, like other lymphoma-associated translocations, t(14;18)/*IGH-BCL2* alone is probably insufficient for lymphoma formation, and, in the present case, over-expression of Bcl2 is likely to cooperate with additional genetic abnormalities to promote the development of MALT lymphoma.

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Informed consent was obtained for publication of the person's details in this report.

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Fatal circumstances of human herpesvirus 6 infection: transcriptosome data analysis suggests caution in implicating HHV-6 in the cause of death

Human herpesvirus 6 (HHV-6), a T-lymphotropic enveloped double stranded DNA virus of the Herpesviridae family, can be divided into two major variants, designated A and B. The B variant is associated with exanthema subitum (roseola infantum, 6th disease), characterised by fever and lymphadenopathy, followed or not by a maculo-papular rash primarily on the neck and trunk. HHV-6, however, is also an important opportunistic agent in patients with impaired immune systems. In recent years, increased antibody titres and positive amplification of the viral genome by PCR have been shown in chronic fatigue syndrome, lymphoproliferative diseases, autoimmune thyroiditis, Sjögren syndrome, rheumatoid arthritis, Crohn's disease, and sarcoidosis.[1] Complications of primary infection in infancy and childhood and simultaneous occurrence of sudden death or short-term mortality include pneumonitis, hepatosplenomegaly, fulminant hepatitis, aseptic meningitis, intussusception, thrombocytopenic purpura, fatal haemophagocytic syndrome, and disseminated infection.[2–4]

However, the aetiological contribution of the virus in fatal cases is still debated and the presence of HHV-6 in a latent status supports the possibility that viral DNA may be amplified in tissue without clinical signs for any of the related diseases. In order to examine the relationship of causality between HHV-6 infection and mortality in infants and children, we investigated HHV-6 infection in four children, who died suddenly or shortly after hospital admission.

Index cases

Case 1 is a female baby (body weight 2580 g, body length 47 cm) born by vaginal delivery following 37 weeks' gestation (Apgar 7/8/9).