CASE REPORT

Regression of gastric T cell lymphoma with eradication of *Helicobacter pylori*

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Abstract

***Helicobacter pylori* is thought to be important in the pathogenesis of chronic active gastritis, peptic ulceration, gastric adenocarcinoma, and gastric B cell lymphoma of mucosa associated lymphoid tissue. The mechanism of evolution from chronic gastritis to monoclonal B cell proliferation is not known but is thought to be dependent on antigen specific T cells to *H pylori* and its products. Here, we report a case of gastric T cell lymphoma associated with chronic *H pylori* gastritis which regressed with eradication of the organism. This is the first report of a gastric T cell lymphoma regressing with *H pylori* eradication, and suggests a causal link between primary gastric T cell lymphoma and this organism.**

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Keywords: *Helicobacter pylori*; T cell lymphoma

Helicobacter pylori is known to have an important role in the pathogenesis of chronic active gastritis, peptic ulceration,^{1,2} gastric adenocarcinoma,³ and gastric B cell lymphoma of mucosa associated lymphoid tissue (MALT).^{4,5} MALT does not occur naturally in the gastric mucosa but lymphoid follicles accumulate at this site in response to *H pylori* infection and B cells infiltrate gastric epithelium to form lymphoepithelium, constituting MALT. The mechanism of evolution from chronic gastritis to monoclonal B cell proliferation is not yet known but is thought to be dependent on antigen specific T cells to *H pylori* and its products.^{6,7} The presence of *H pylori* in nearly all cases of low grade MALT lymphoma and regression of tumour with eradication of the organism^{4,8} strongly support a causal link between the two. MALT lymphoma is an uncommon tumour with an indolent natural history and prolonged confinement to the site of origin. It is classically described as a B cell malignant neoplasm morphologically characterised by centrocyte-like cell proliferation.⁹ Here, we report a case of gastric T cell lymphoma associated with chronic *H pylori* gastritis which regressed with eradication of the organism. To our knowledge, resolution of T

cell lymphoma with eradication of *H pylori* has never been reported.

Case report

A 24 year old man presented for investigation of chronic abdominal pain, dyspepsia, and weight loss. There was a past history of situs inversus, infective endocarditis, and appendectomy for a gangrenous appendix. The patient had suffered dyspeptic symptoms and lower abdominal pain intermittently for many years. He had no symptoms referable to the nasosinuses. Clinical examination revealed no lymphadenopathy or skin changes. He had a normal upper gastrointestinal endoscopy at age 14 years. He was a non-smoker, did not drink alcohol regularly, and took no regular medications. There was a family history of colon cancer.

At this presentation he described worsening of abdominal symptoms associated with considerable weight loss. He underwent upper gastrointestinal endoscopy, colonoscopy, and small bowel series. The upper gastrointestinal endoscopy revealed two small chronic gastric ulcers which were biopsied, as was the gastric antral mucosa and duodenum. Colonoscopy and small bowel series were normal.

Microscopy of the gastric biopsies showed active chronic gastritis with a small number of *H pylori* and occasional small intramucosal lymphoid aggregates but no lymphoid follicles (fig 1). *H pylori* were demonstrated using the Warthin Starry stain (fig 2). In addition, in several biopsies there was a diffuse infiltrate of small to intermediate lymphoid cells with rounded or indented small nuclei and a moderate amount of cytoplasm containing small red granules (fig 4). This infiltrate replaced glands, and occasional lymphoepithelial lesions were also present (fig 3). No angiocentricity was noted. Duodenal biopsies showed mild non-specific changes.

Immunohistochemistry showed that the atypical lymphoid cells were T cells (CD3 positive; CD79a and CD20 negative) (fig 5). They also expressed natural killer (NK) antigen (CD56 positive), and a small proportion of cells were CD8 positive (fig 6).

Abbreviations used in this paper: MALT, mucosa associated lymphoid tissue; PCR, polymerase chain reaction; TCR, T cell receptor; NK, natural killer.

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Figure 1 Gastric biopsy showing dense lymphoid infiltrate replacing glands. Note the benign lymphocytic aggregate towards the left of the photomicrograph (haematoxylin and eosin, $\times 100$).

Figure 4 Gastric biopsy showing prominent red granules in the cytoplasm of lymphoid cells and a lymphoepithelial lesion of natural killer-like T cell lymphoma (haematoxylin and eosin, $\times 1000$ oil).

Figure 2 Plentiful *Helicobacter pylori* in gastric pit confirmed on Warthin Starry stain ($\times 400$).

Figure 5 Gastric biopsy of natural killer-like T cell lymphoma showing positivity in epsilon CD3 immunohistochemical stain (epsilon CD3, $\times 200$).

Figure 3 Gastric biopsy showing dense lymphoid infiltrate, with replacement and destruction of glandular architecture (haematoxylin and eosin, $\times 400$ oil).

Figure 6 Gastric biopsy of natural killer-like T cell lymphoma showing positivity in CD56 immunohistochemical stain (CD56, $\times 600$).

Genotyping of *H. pylori* was not performed. DNA was extracted from a 10 μ m section of paraffin embedded tissue and polymerase chain reaction (PCR) showed monoclonality for the T cell β receptor (TCR β) chain confirming a T cell lymphoma.¹⁰ McCarthy *et al* have reported the primers and conditions for amplification of the TCR β chain.¹¹ A discrete amplicon of ~60 bp was demonstrated in reactions containing primers D₁/J₂ while no product was detected in the D₂/J₂ and V/J₂ reaction. PCR reactions designed to detect immunoglobulin gene arrangement and bcl-2 translocation were also negative. PCR and immunohistochemistry findings were therefore consistent with a diagnosis of a gastric NK-like T cell lymphoproliferative disorder.

The patient was treated with quadruple therapy for eradication of *H. pylori* (bismuth, ranitidine, amoxicillin, and metronidazole). Further investigations to stage his lymphoma and exclude the presence of coeliac disease or

inflammatory bowel disease as a precursor were performed. Serum electrophoretogram, gallium scan, bone marrow aspirate and trephine, and computed tomography scans of the thorax, abdomen, and pelvis were normal apart from the known situs inversus. He was HIV antibody negative.

A repeat upper gastrointestinal endoscopy was performed at two, three, and 12 months post *H. pylori* eradication therapy and multiple mapping biopsies were taken at each occasion. There was no evidence of lymphoma present at these examinations and *H. pylori* was absent. The small bowel biopsies were also normal. The patient has remained clinically well two years after diagnosis.

Discussion

Primary gastrointestinal T cell lymphoma is a rare condition.¹² T cell lymphoma of the intestine is a well recognised complication of coeliac

disease and other malabsorptive conditions¹³ and is thought to be related to chronic antigenic stimulation. These T cell lymphomas are aggressive, and most patients die of their disease within two years of diagnosis.

Primary gastric T cell lymphoma is also rare. Nakamura *et al* in a large study of 237 cases of gastric lymphoma found that, of 15 (6%) patients with T cell lymphoma, 73% (11/15) had coexisting *H pylori* infection.¹² Shimada-Hiratsuka *et al* reported five T cell lymphomas showing NK markers (CD16 and CD56) and variable TCR gene rearrangements, while two HLTV-1 positive lymphomas were NK negative.¹⁴ The morphology showed mildly enlarged atypical lymphoid cells with convoluted nuclei in four cases and "immunoblastic" features in one case. Lymphoid follicles were present in four cases, as were occasional lymphoepithelial lesions. These lymphomas were in gastrectomy specimens and there is no reference to a gastric T cell lymphoma response to *H pylori* eradication.

CD56 positive lymphomas are a heterogeneous category usually presenting extranodally with an aggressive course, and in REAL classification fall under the "angiocentric lymphoma" category, although better named NK/T cell lymphoma.¹⁵ Specific T cell lymphoma types, mainly peripheral T cell lymphomas, can rarely show CD56 positivity together with CD3/Leu4 expression and TCR gene rearrangements, and are called NK-like T cell lymphomas.¹⁵ Our case probably falls within this grouping.

Extranodal T cell lymphomas typically show a range of cell types making morphological categorisation difficult but a homogeneous population of atypical lymphoid cells with lymphoepithelial lesions and architectural effacement of glands are useful histological features suggesting a gastric lymphoma. The presence of cytoplasmic granules in our case suggests a cytotoxic lymphocytic proliferation (NK or T cell).¹⁵ Immunophenotyping on paraffin embedded tissue showed a T cell population (CD3 epsilon positive, possibly CD8 positive) with NK features (CD56 positive), and TCR gene monoclonality confirmed the diagnosis of an NK-like T cell lymphoma.

As mentioned above, *H pylori* produces monoclonal B cell proliferation presumed to be via stimulation of antigen specific T cells. There may be a similar proliferative response by cytotoxic T cells to *H pylori* or these stimulated helper T cells. In *H pylori* gastritis there is a predominantly TH1-type response.⁷ Activated TH1-type inducer cells provide T cell help for generation of cytotoxic T cells, and monoclonal expansion of these cells may lead to formation of a T cell lymphoma.

This is the first report of a gastric T cell lymphoma regressing with *H pylori* eradication, and suggests a causal link between primary gastric T cell lymphoma and this organism.

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