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SHORT REVIEW

Extranodal marginal zone (MALT) lymphoma in common variable immunodeficiency

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ABSTRACT

We describe two patients with common variable immunodeficiency (CVID) who developed extranodal marginal zone lymphoma (formerly described as mucosa-associated lymphoid tissue lymphoma or MALT lymphoma). One patient, with documented pernicious anaemia and chronic atrophic gastritis with metaplasia, developed a *Helicobacter pylori*-positive extranodal marginal zone lymphoma in the stomach. Three triple regimens of antibiotics were necessary to eliminate the *H. pylori*, after which the lymphoma completely regressed. Patient B had an *H. pylori*-negative extranodal marginal zone lymphoma of the parotid gland, which remarkably regressed after treatment with clarithromycin.

Reviewing the literature, we found eight cases of extranodal marginal zone lymphoma complicating CVID, but probably many more cases labelled as non-Hodgkin's lymphoma are hidden in the literature.

Until more data are available on the predictive value of noninvasive screening for pathology of the stomach, we recommend endoscopy to assess the gastric status in CVID patients in order to detect these malignancies at an early stage.

Elimination of *H. pylori* infection is the treatment of choice in *Helicobacter*-positive extranodal marginal zone lymphoma. The possibility of elimination failure, most probably due to frequent and prolonged exposure to antibiotics in this patient group, should be taken into account. Treatment with antibiotics in *Helicobacter*-negative extranodal marginal zone lymphoma must be considered.

KEYWORDS

Common variable immunodeficiency, extranodal marginal zone, *Helicobacter pylori*, hypogammaglobulinaemia, lymphoma, MALT

INTRODUCTION

In 1983, Isaacson and Wright introduced the term mucosa-associated lymphoid tissue (MALT) lymphoma to characterise a primary low-grade B-cell lymphoma originating in the gut-associated lymphoid tissue.[1] Nowadays, the nomenclature has been changed to extranodal marginal zone lymphoma, representing extranodal low-grade B-cell lymphoma with a similar histology, also occurring in the salivary glands and lungs.

The normal gastric mucosa contains no organised lymphoid tissue. Bacterial colonisation of the gastric mucosa leads to lymphoid infiltration, which becomes the basis for the evolution to extranodal marginal zone lymphomas. There are several strands of evidence for a causal relationship between *Helicobacter pylori* and extranodal marginal zone lymphoma. First of all, *H. pylori* infection is present in more than 90% of the patients with this lymphoma.[2-4] Immunological studies show *in-vitro* and *in-vivo* evidence for a causal relationship between *H. pylori* and extranodal marginal zone lymphoma.[5,6] Perhaps most importantly, several studies prove that elimination of *H. pylori* leads to regression of this type of lymphoma in approximately three quarters of the cases.[7-12] Other micro-organisms, such as *Chlamydia psittaci*, *Borrelia burgdorferi* and *Campylobacter jejuni*, have been incriminated to play a causal role.[13-16]

Hypogammaglobulinaemia is a primary immunodeficiency disorder. The two main types are X-linked hypogammaglobulinaemia (XLA) and common variable immunodeficiency (CVID). These diseases do not only predispose to infection but also bear increased risk of cancer. In XLA, there is an increased risk for colorectal cancer,[17] whereas patients with CVID have an almost 50-fold increased risk for gastric cancer and a 30-fold increased risk for lymphoma.[18] The risk for lymphoma in CVID is estimated to lie between 1.4 and 7%.[19-21]

In this paper, we present two CVID patients who incipiently developed extranodal marginal zone lymphoma, underlining the need for awareness of this complication in such patients. We also give a brief review of the cases of extranodal marginal zone lymphoma in CVID described in the literature.

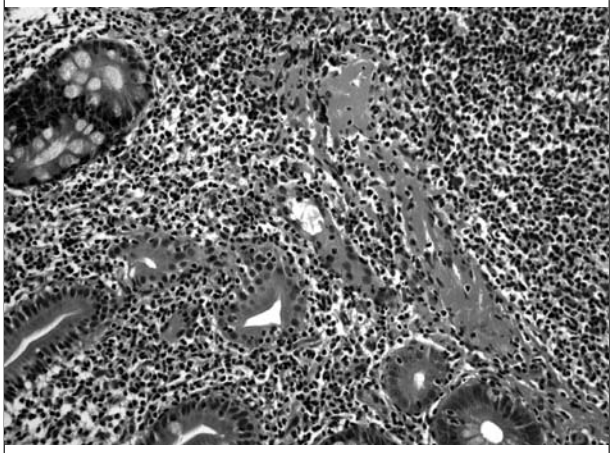
CASE REPORTS AND METHODS

Patient A, a male born in 1937, had suffered from recurrent infections of the (upper) respiratory tract, ear, nose, throat region and gastrointestinal tract since early childhood. In 1965, at the age of 28, the diagnosis of CVID was made. This was a reason to start prophylactic antibiotics. In 1985, pernicious anaemia was diagnosed and vitamin B12 substitution was started. In 1991, the patient was first seen in our hospital and since then has been treated with intravenous immunglobulins. In spite of this treatment, recurrent infections of the respiratory tract necessitated antibiotic prophylaxis.

In 1991, gastroscopy yielded chronic atrophic gastritis with a severe intestinal metaplasia of the fundus. Serum gastrin was 250 ng/l (normal range 10 to 70 ng/l). The severe metaplasia was the reason for regular endoscopies, which always showed the same picture. In October 1999, *H. pylori* infection was diagnosed. The patient received a ten-day course of amoxicillin 500 mg three times a day, metronidazole 500 mg three times a day and omeprazole 40 mg once a day. In February 2000 a control gastroscopy was performed. Histology and culture of the biopsies still showed *H. pylori*, which appeared to be resistant to metronidazole and tetracycline and susceptible to amoxicillin and clarithromycin *in vitro*. Treatment was installed with clarithromycin 500 mg twice daily, amoxicillin 500 mg four times a day and ranitidine bismuth citrate 400 mg twice daily. The next endoscopy in August 2000 revealed normal mucosa without evidence of *H. pylori* infection in the biopsies. One year later, active *H. pylori*-associated gastritis with a extranodal marginal zone lymphoma was found localised in the corpus (*figure 1*). No translocation t(11;18) was found with the fluorescence *in situ* hybridisation (FISH) and reverse transcription polymerase chain reaction (tr-PCR) methods. After two weeks of treatment consisting of high-dose amoxicillin (4 g/day), clarithromycin (1.5 g/day) and pantoprazole, *H. pylori* was no longer detectable by histology and C^{14}-urea breath test. Control endoscopy with extensive biopsies in February 2002 did not reveal any signs of extranodal marginal zone lymphoma, neither did any of the six-monthly follow-up endoscopies since then.

Patient B, a male born in 1967, presented in 2001 with a short period of fever and splenomegaly after a tropical journey. A specific tropical disease could not be diagnosed. However, a history of the recent development of frequent upper respiratory tract infections and occasional abdominal pain with diarrhoea directed us to the diagnosis of CVID. Treatment with intravenous immunoglobulins was started in 2001. During the regimen of monthly supplementation, infections remained a problem and immunoglobulins had to be increased by dose and administered every three weeks. In 2004 the patient complained of jaw pains and loss of weight. Physical examination revealed a periauricular tumour. A biopsy showed a low-grade extranodal marginal zone lymphoma from the salivary gland. Positron emission tomography (PET) showed only elevated activity at the cervical site. Gastroscopy with multiple biopsies showed a normal gastric mucosa. There was no evidence for *H. pylori* infection in the biopsies, by culture, PCR and C^{14}-urea breath test. No translocation t(11;18) was found either. Because of the absence of *H. pylori* infection, several other micro-organisms such as cytomegalovirus, Epstein Barr virus, hepatitis B and C virus, human herpes virus 6, *Bartonella henselae, Mycoplasma* and *Chlamydia* species were excluded by PCR in the tissue of the lymphoma. In addition, 16S RNA in the tissue was negative. The patient was treated with high-dose clarithromycin for six weeks. After this treatment the tumour vanished clinically as well as on positron emission tomography.

Figure 1. *Gastric biopsy from the pyloric region with dense, monomorphous small lymphocytic infiltrate and a lymphoepithelial lesion*



Immunohistochemistry showed CD20 positivity, confirming that this represents extranodal marginal zone lymphoma.

REVIEW OF THE LITERATURE

To review the literature on CVID and extranodal marginal zone lymphoma, we performed a PubMed search in English using the following terms: CVID, agammaglobulin(a)emia, hypogammaglobulin(a)emia, lymphoma, extranodal

marginal zone lymphoma, MALT, cancer, neoplasia, and *Helicobacter pylori*.

This search yielded eight cases of extranodal marginal zone lymphoma in CVID, most of which were published quite recently. The pertinent data from these cases are presented in *table 1*. In 2001, Reichenberger *et al*. published a case report of a CVID patient with a pulmonary MALT lymphoma.[23] In 2002, Cunningham-Rundles *et al*. published a cohort study of 248 CVID patients. In a period of 25 years, 22 cases of B-cell lymphoma were found, five of which were classified as MALT lymphomas. Three of these were pulmonary lymphomas, and two where localised in the salivary glands. There are no data of the *H. pylori* status in these patients.[22] Tcheureckdjian *et al*. recently published two CVID patients with nonparotid cranial MALT lymphomas (*table 1*).[24]

DISCUSSION

In this paper, two patients with CVID and extranodal marginal zone (MALT) lymphoma are described. In both patients the diagnosis was not suspected clinically. In one patient the lymphoma was associated with *H. pylori* infection, and both responded to antimicrobial therapy.

Although malignant lymphoma as a complication of CVID is well established,[11-28] there is a limited number of published reports on extranodal marginal zone lymphoma in CVID, and these are recent. Most probably, quite a number of cases of extranodal marginal zone lymphoma are hidden in the older literature on lymphoma and CVID.

In our own series of 49 patients with hypogammaglobulinaemia, published in 2002, patient A was the only case of extranodal marginal zone lymphoma; one other case of non-Hodgkin's B cell lymphoma was encountered in that series.[29]

As described, antibiotics cause regression of *H. pylori*-positive extranodal marginal zone lymphoma and are therefore the treatment of first choice. It turned out to be difficult to eliminate the *H. pylori* in patient A; multiple courses were needed. Why was it so hard to treat the infection? A possible explanation could be the exposure to multiple antibiotics, and subsequent resistance in our patient. The *H. pylori* isolate of patient A was found to be resistant to tetracycline and metronidazole *in vitro*. *H. pylori* resistance to metronidazole is well known; in developing countries resistance is up to almost 100%, whereas in developed countries resistance ranges from 10 to 50%. Detecting resistance to metronidazole predicts the success of treatment. For instance, treatment of a metronidazole-resistant *H. pylori* infection with a triple regimen consisting of metronidazole, clarithromycin and a proton pump inhibitor meets with a success rate of 73% against 97% for a susceptible strain.[30] Finding macrolide resistance (which was not the case here) is a much stronger predictor for treatment failure. *H. pylori* resistance for amoxicillin is rare.[30,31]

Another factor explaining the failure to eradicate *H. pylori* in our patient may be that there is impaired host response against *H. pylori* in CVID. In that respect, Borody *et al*. have attributed treatment failure to low concentrations of interleukin 4 in whole blood.[32,33] We have no information on the interleukin-4 concentration in our patients.

Table 1. *Published cases of extranodal marginal zone lymphoma in common variable immunodeficiency patients*

Case	Ref.	Sex	Localisation	*H. pylori*	Treatment	Result
1	21	F	Parotid	Unknown	1. Radiation and excision 2. Excision, CHOP, rituximab	Recurrence after initial therapy
2	21	F	Lung	Unknown	None	Clinically well
3	21	F	Parotid	Unknown	1. Excision 2. Excision and radiation	Recurrence after initial therapy
4	21	M	Lung	Unknown	1. CVP and rituximab 2. CHOP	Recurrence after initial therapy
5	21	F	Lung	Unknown	Rituximab, CHOP	No recurrence
6	22	F	Lung	Bacterial infection excluded, *H. pylori* not especially mentioned	1. Chlorambucil and prednisone 2. Chlorambucil	Primary partial remission but recurrence
7	23	F	Cranial	Unknown	Dexamethasone, doxorubicin, cyclophosphamide and vinblastine	Complete remission
8	23	F	Cranial	Unknown	Rituximab	Complete remission

CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CVP = cyclophosphamide, vincristine, prednisone; rituximab = monoclonal antiCD20.

The difficulty to treat *H. pylori* in this patient is reminiscent of the failing treatment of *Campylobacter jejuni* infections in hypogammaglobulinaemic patients, in whom a bactericidal effect of serum is lacking due to the deficiency of IgM.[34] We have found defective bactericidal activity of serum of this patient against *H. pylori* (Desar, manuscript in preparation), but it is currently unclear to what extent this contributed to the difficulty of treatment.

In patient B, *H. pylori* infection could not be demonstrated. It is intriguing that the tumour nevertheless responded to antibiotic treatment. The hypothesis was that in this patient, who had been treated regularly with β-lactam antibiotics such as amoxicillin-clavulanic acid, *Chlamydia* might have been the cause of continuous stimulation of (the lymphatic tissue surrounding) the parotid gland. Lymphoma associated with *C. psittaci* has been reported especially in the ocular region. DNA of *Chlamydia* has been detected in 80% of tumour biopsies and in 50% of peripheral blood mononuclear cells (PBMCs) of these patients.[13] Even regression has been shown with treatment with doxycyclin.[14] Since the tumour has not relapsed so far, it is most likely that this is due to a direct antimicrobial effect of the macrolide. The alternative, an immunomodulatory effect, would probably have led to a more transient success.[35] As described, a variety of microbial agents have been incriminated as potential causes of extranodal marginal zone lymphoma. In our patient, we did not find evidence for other pathogens, especially macrolide-susceptible ones. Further studies on the effect of antibiotic therapy in the treatment of *H. pylori*-negative extranodal marginal zone lymphoma are needed. In the individual patient, one may consider trying antibiotic treatment before embarking on treatment with anti-B-cell monoclonal antibodies, radiotherapy or cancer chemotherapy, as has been done in the literature (*table 1*).

In conclusion, extranodal marginal zone lymphomas are an important complication of CVID. They can arise insidiously. Based on the current knowledge of CVID and the lack of data on the predictive value of noninvasive screening for pathology of the stomach, we believe it is good clinical practice to screen for antrum gastritis, neoplasia (carcinoma as well as extranodal marginal zone lymphoma) and *H. pylori* infection by endoscopy. As mentioned, the risk of gastric carcinoma and extranodal marginal zone lymphoma is high in CVID patients, conform the risk of other tumours in which screening is well accepted.[18-29,36] Symptoms present late in an advanced stage of disease with serious clinical consequences. After an initial evaluation, a follow-up regimen could be scheduled depending on the findings. In case of serious dysplasia, we recommend endoscopic screening on a regular basis at six-monthly intervals; patients with mild dysplasia should be screened each year. If the initial screening shows no dysplasia, screening can be done every three to five years. A cost-benefit analysis of such policy cannot be given at this point in time, but the patient group is limited.

With respect to the noninvasive tests, the value of the urease breath test needs further evaluation in these patients. Because of the failure to mount an antibody response, *H. pylori* serology is not useful. When *H. pylori* is detected in a patient with CVID, it is probably wise to start specific antimicrobial treatment, but eradication may fail. Furthermore, the findings of *Chlamydia* DNA in lymphoma tissue and PBMCs in patients with extranodal marginal zone lymphoma of the ocular adnexa warrant systematic research on other micro-organisms with help of DNA techniques and subsequently considering of antibiotic treatment.

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