CASE REPORTS

Healing of protein losing hypertrophic gastropathy by eradication of *Helicobacter pylori* – Is *Helicobacter pylori* a pathogenic factor in Ménétrier's disease?

E Bayerdörffer, M M Ritter, R Hatz, W Brooks, G Ruckdeschel, M Stolte

Abstract

Hypertrophic gastropathy – that is, Ménétrier's disease – was found, in a retrospective analysis, to be associated with *Helicobacter pylori* in more than 90% of patients. It is proposed that hypertrophic gastropathy represents a special form of *H pylori* gastritis in these patients. A case is described of a 28 year old woman with Ménétrier's disease associated with proved protein loss from the stomach. Treatment with cimetidine for more than three years had little benefit when colonisation by *H pylori* was detected. Density of *H pylori* colonisation and activity of gastritis, which was also present in the first biopsy specimens taken five years ago, were more pronounced in the body than in the antrum, which is in agreement with the characteristics of *H pylori* gastritis found in other cases with Ménétrier's disease. A 14 day antibacterial treatment course with 750 mg amoxicillin three times a day combined with 40 mg omeprazole three times a day was started in April 1991. This resulted in eradication of *H pylori* and the return to normal of giant folds and the mucosal histology. Serum protein concentrations returned to normal within six weeks and remained normal at two endoscopies during a two year follow up. This case report suggests that a subgroup of the patients with Ménétrier's disease may be healed by the eradication of *H pylori*.

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Medical Department II
E Bayerdörffer
M M Ritter

Department of Surgery
R Hatz

Department of Surgical
Research
W Brooks

and Department of
Microbiology, Klinikum
Großhadern, University
of Munich, Germany
G Ruckdeschel

Department of
Pathology, Klinikum
Bayreuth, Germany
M Stolte

Correspondence to:
Dr E Bayerdörffer, Medical
Department II, Klinikum
Großhadern, University of
Munich, Marchioninstr 15,
W-8000 München 70,
Germany.

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for this organism.³ This prompted us to test this hypothesis by eradicating the organism.

Case report

In February 1986 a 23 year old woman was admitted to hospital for investigation of hypoproteinaemia, which had been detected three years ago. She had noticed morning oedema of the eyelids and ankles, and a previous evaluation in another hospital had showed hypoproteinaemia with 46 g/l, but she was discharged without a conclusive diagnosis. Morning oedema persisted, and she denied having abdominal discomfort, nausea, vomiting, diarrhoea, weight loss or melaena. There was no history of taking any drugs apart from a combination of levothyroxine (100 µg daily) and triiodothyronine (10 µg) for goiter. On physical examination her weight of 59 kg was within normal limits for height of 1.65 m.

All laboratory investigations were within normal limits, except total protein, which was reduced to 39 g/l. Serum protein electrophoresis showed a global reduction of albumin with 26 g/l, α₂ globulin 3.4 g/l, β globulin 4.5 g/l, and γ globulin 3.3 g/l, and IgG and IgA immunoglobulins were also reduced at 2.40 g/l and 0.5 g/l, respectively (normal range >8.0 and >0.9 g/l, respectively). Protein concentration in a specimen of 24 hour urine was mildly increased at 480 mg.

After ⁵¹Cr-labelled albumin was given intravenously, 13.4% of the radioactivity was recovered in the stool over a four day period (normal range <1%), and another test showed 15.2% of the activity to be present in morning aspirates of gastric juice on the three successive days (normal range <1%). Basal acid output was 2.1 H⁺ mmol/h with a peak acid output of 22.7 mmol/h after stimulation with pentagastrin. Gastrin serum concentration was normal (45 ng/l, normal <180 ng/l).

Examination of the stools failed to show the presence of pathogenic bacteria, and was repeatedly negative for occult blood. Colonoscopy, including the terminal ileum, and a radiological double contrast examination of the jejunum and ileum were unremarkable. Jejunal biopsy specimens did not show any periodic acid Schiff positive macrophages and disaccharidases activity was normal.

Hypertrophic gastropathy (Ménétrier's disease) is described as a condition of unknown origin, which is characterised by endoscopy by tortuous enlarged gastric folds predominantly localised at the greater curvature or within the entire body region of the stomach. Histologically, it is characterised by considerable elongation and tortuosity of the pits, and cystic dilatations of the body mucosa. The inflammatory cell content is increased, especially in the pit region.¹

Protein loss from the stomach is found in more than three quarters of patients, and oedema may be the first clinical sign. Other clinical features are non-specific.^{1,2}

A recent retrospective investigation of 138 patients with hypertrophic gastropathy showed a high percentage of associated *Helicobacter pylori* gastritis, suggesting a possible pathogenic role

Time course of laboratory findings before and after eradication of *H pylori*. Every turn of the continuous curves represents a laboratory examination. The dotted line represents the lower limit of the normal.

A gastroscopy done in April 1986 showed enlarged gastric folds of the body mucosa. Biopsy specimens taken from the antrum and body for histological examination showed moderate unspecific gastritis and considerable foveolar hyperplasia only in the body. On this basis the diagnosis of Ménétrier's disease was established.

Treatment with cimetidine 1 g/day was started, which resulted in an increase in serum protein concentrations to the lower limits of normal for albumin and γ globulins for a period of two months (Figure). In August 1987 the patient became pregnant and cimetidine treatment was stopped. During pregnancy she suffered a further drop in serum protein concentrations, with the lowest total serum protein of 35 g/l and a serum albumin of 25 g/l measured at the time of birth. The clinical course was at its worst during pregnancy with continuous oedema. At term, she gave birth to a healthy girl with normal protein electrophoresis.

Cimetidine was again given after delivery, and again led to a short term increase in serum protein concentrations (Figure). Cimetidine was continued until April 1991, with little success (Figure).

When it came to our notice that *H pylori* gastritis was being discussed as a possible cause of Ménétrier's disease,^{4,6} two biopsy specimens were cultured for *H pylori*. Four biopsy speci-

mens were taken for histological tests and for the detection of *H pylori* colonisation in the antrum and corpus. Because the patient was *H pylori* positive, treatment with cimetidine was stopped and a combined treatment with 750 mg amoxicillin three times a day and 40 mg omeprazole three times a day was begun in April 1991, which were both limited to 14 days. Eradication of *H pylori* was shown by a further gastroscopy four weeks after antibacterial treatment, and another gastroscopy after one year (Table). Furthermore, at the control gastroscopy four weeks after treatment giant folds in the gastric body had returned to normal. Finally, serum protein concentrations increased and reached normal values six weeks after treatment had stopped and have remained normal for 20 months at the time of writing (Figure).

Methods

ENDOSCOPY AND BIOPSY

At each endoscopic examination two antral biopsy specimens were taken for *H pylori* culture and six additional specimens, three from the antrum and three from the body, for histological examination. A total of six specimens, including some from the body of the stomach, achieves 98% reliability for detection of *H pylori* gastritis and for confirming eradication of *H pylori*.⁷ At each endoscopic examination serum samples were taken and frozen at -25°C for later measurement of *H pylori* antibodies and gastrin concentrations.

MICROBIOLOGY

Two biopsy specimens were retained for microbiological investigation and were transported in Port-A-Cul medium (Becton & Dickinson, Heidelberg, Germany) at room temperature within four hours to the Department of Microbiology. These specimens were processed immediately upon arrival and streaked on sheep blood agar (blood agar base 2, Oxoid) with Skirrow supplement and non-selective media for aerobic and anaerobic bacteria. Plates were incubated for five to seven days at 37°C in an atmosphere produced by the commercial gas generating kit Anaerocult C (Merck, Darmstadt, Germany). *H pylori* was identified by colony morphology and biochemical tests for urease, catalase, and oxidase activity.

HISTOLOGY

Four biopsy specimens taken from the antrum and body^{7,8} were first placed in neutral buffered formalin, and were then stained with haematoxylin and eosin to grade gastritis, and with Warthin-Starry stain to grade mucosal colonisation by *H pylori*, as described elsewhere.⁸ Briefly, the gradings for the grade of gastritis were; no lymphocytes and plasma cells=0, single lymphocytes=1, few lymphocytes=2, moderate lymphocytes=3, dense lymphocytes=4, and for the grade of *H pylori* (HP) colonisation were; no HP=0, focal HP=1, few HP=2, moderate HP=3, and dense HP=4, and for grade of activity

Grade of *H pylori* colonisation, grade and activity of gastritis in antrum and body, *H pylori*-IgG antibodies, and serum gastrin before and after antibacterial treatment in a patient with Ménétrier's disease

Parameter	Examination	Before treatment	Four weeks after treatment	12 Months after treatment
Grade of HP colonisation, antrum		+++	-	-
Grade of HP colonisation, body		++++	-	-
Grade of gastritis, antrum		++++	+++	++
Grade of gastritis, body		++++	++	+++
Grade of activity, antrum		+++	-	-
Grade of activity, body		++++	-	-
HP-IgG antibody titre		1:7000	1:1500	1:800**
Serum gastrin		44 pg/ml	60 pg/ml	20 pg/ml

Grade of *H pylori* colonisation, and grade and activity of gastritis were +++++=severe, +++=moderate, ++=low, +=minimal - as reported in reference 8. *Grade ++ (=low, or 2) is equivalent to 'low grade' in the Sydney system.²² HP-IgG antibodies are presented in titres with 1:800 (**) as cut off point for uninfected persons.

they were; no neutrophil granulocytes=0, single neutrophils=1, few neutrophils=2, moderate neutrophils=3, dense neutrophils=4.

TREATMENT

The patient was treated with 40 mg omeprazole three times daily combined with 750 mg amoxicillin three times daily (Amoxypen tablets, Grünenthal, Stolberg, Germany), both limited to 14 days. Endoscopic examinations were performed four weeks after treatment had finished to check for eradication,⁹ and again after one year.

IMMUNOLOGICAL CHARACTERISATION

The proliferative response of peripheral blood lymphocytes was investigated in this patient before and after *H pylori* eradication. The peripheral blood mononuclear cell fraction (PBMC) was obtained from heparinised blood samples by centrifugation over a Ficoll hypaque gradient. The proliferative response of these cells was determined by measuring DNA synthesis by ³H-thymidine incorporation after a four day culture period. The supernatant of a whole cell sonicate of the heat inactivated *H pylori* strain NCTC 11637 outer membrane proteins was used as a bacterial antigen preparation being added to the cultures at a concentration of 5 µg/ml. Concanavalin A and phytohaemagglutinin were used as control stimulants.

H PYLORI SERUM ANTIBODIES

H pylori specific antibodies in the patient's serum were measured by a standardised enzyme linked immunosorbent assay (ELISA) developed in our laboratory. This assay used an acid-glycin extract prepared from the *H pylori* strain NCTC 11637. Serum samples were tested up to a serial dilution of 1:6400. *H pylori* negative patient serum was used as a negative control. Specifically bound anti-*H pylori*-IgG antibodies were detected using peroxidase conjugated Fab₂ fragments of rabbit antihuman IgG (γ chain specific) (Dakopats, Glostrup, Denmark). Absorbance was measured at 492 nm on an automated ELISA reader after adding a solution of o-phenylenediamine. Serum samples showing an absorbance of three times the background (titre more than 1:800) were considered as antibody positive.

SERUM GASTRIN

This was determined using a standard gastrin radioimmunoassay (Becton & Dickinson, Orangeburg, USA).

Results

Initial treatment with cimetidine 800 mg daily resulted in an increase in total serum protein, for only several weeks which, however, did not reach the lower normal range (Figure). The effect of cimetidine on the immunoglobulin concentration was similar, which remained low during the entire initial treatment period (Figure).

In 1900, at the annual endoscopic examination, we detected *H pylori* colonisation in the antrum and body; the Table shows the gastritis classification. Retrospective evaluation of the histological specimens from earlier examinations, including those which had been the basis of the diagnosis of Ménétrier's disease, also showed *H pylori* colonisation in our patient.

At this time we used a *H pylori* eradicating regimen, a combination of high dose omeprazole and amoxicillin,⁸ for the first time. This new treatment regimen proved successful in our patient, as was shown when eradication of *H pylori* was checked four weeks after the treatment finished.

The first sign of clinical improvement was an increase in the serum concentration of total protein and albumin, which was accompanied by an increase in serum immunoglobulins (Figure).

H pylori was eradicated, which prevailed for at least one year. This was accompanied by a concomitant decrease in the activity and grade of gastritis (Table).

There was a considerable decline of the *H pylori*-IgG antibodies. Serum gastrin concentrations were within the normal range but declined after eradication treatment (Table). The immunological investigation showed no proliferative response of PBMC to *H pylori* antigens in this patient before and after treatment.

Discussion

Protein losing hypertrophic gastropathy is considered to be a life threatening disease, which may lead to death in some cases either as a direct result of hypoproteinaemia^{1,2} or as a result of the development of subsequent cancer triggered by chronic hypoglobulinaemia or development of atrophic gastritis.¹⁰ This report shows that, at least in some of the patients, the disease may be healed by eradication of *H pylori*.

Recently, a study investigating 138 patients with hypertrophic gastropathy showed that this condition is associated with *H pylori* in about 90% of patients.³ It is proposed that hypertrophic gastropathy represents a special form of *H pylori* gastritis in these patients.

In this patient with protein losing hypertrophic gastropathy we identified a more pronounced *H pylori* colonisation in the body, and a higher activity of gastritis in the body than in the antrum, which is in agreement with the characteristics of *H pylori* gastritis found in most of the 138 patients in the study of Stolte *et al.*³

We report a patient whose protein losing hypertrophic gastropathy was cured by eradication of *H pylori*. A similar course of this disease has been described in preliminary reports of Salmeron *et al*, Herz *et al*, and our group.^{5,11,12} Based on these findings we suggest that *H pylori* is a pathogenic factor in at least a subgroup of patients with hypertrophic gastropathy. A pathogenic role for *H pylori* in our patient is further suggested by the time relation between treatment and improvement of clinical symptoms. The return to normal of the serum protein concentration occurred during the period of

antibiotic treatment for the first time since the diagnosis six years before.

The detection of *H pylori* in the original biopsy specimens of our patient dating back to 1985 proves that the organism was not acquired later in the disease, and thus may be a causative factor in the development of hypertrophic gastropathy in our patient.

Treatment of hypertrophic gastropathy has been tried with atropine, hexamethonium, tranexamic acid, prednisolone,¹² and most promisingly with H₂ receptor antagonists, such as cimetidine. Partial regression of endoscopic and clinical findings has been reported under prolonged treatment with cimetidine, but spontaneous regression has also been seen.¹³⁻¹⁵ As a possible mechanism of cimetidine treatment, tightening of the paracellular junctions has been suggested.¹⁶ The treatment regimen used in our patient consisting of 40 mg omeprazole three times a day in combination with amoxicillin 750 mg three times a day given for 14 days to eradicate *H pylori* has so far not been reported. This regimen represents an improved modification of a previous regimen with 40 mg omeprazole twice daily in combination with 1000 mg amoxicillin twice daily for 10 days.⁹ We report a quick and complete return to normal of abnormal endoscopic, histological, and laboratory changes, which had persisted for one year. Maintenance treatment has not been required and so this can be judged as healing of the disease.

The natural history of Ménétrier's disease resembles that of *H pylori* gastritis in many ways. Krag *et al*¹⁷ suggested the existence of several variations of the disease, especially a hypersecretory hyperchlorhydric version, and another form with hypochlorhydria, protein loss, and hypoproteinaemia, and various combinations. These apparently different forms have also been described by other authors.¹⁵ From our point of view they merely resemble different developmental stages of *H pylori* gastritis.³ The natural history of hypertrophic gastropathy often results in a spontaneous regression of the hypertrophic folds, with coincident development of atrophic gastritis in the body,¹⁵ which may be also the end point of progressive *H pylori* gastritis, which occurs in a number of patients.^{2,15} Also consistent with the natural history of *H pylori* gastritis is that the development of atrophy refrains from the body mucosa, which happens in most patients with *H pylori* gastritis. This condition may result in ongoing protein loss leading to subsequent death because of associated complications.

The immunological characterisation of the patient's peripheral response towards *H pylori* antigens was similar to other *H pylori* infected patients without Ménétrier's disease, which is in accordance with data from other investigators.^{18,19}

A further complication of protein losing hypertrophic gastropathy is hypogammaglobulinaemia, which increases the risk of fatal infections and the risk of subsequent cancer. Previous studies have found a high correlation between hypertrophic gastropathy and gastric cancer.^{2,20} Based on our recent knowledge of *H pylori* we would prefer to attribute this pos-

sibly increased frequency of subsequent cancer to its association with chronic *H pylori* gastritis.²¹ Furthermore it is proposed that hypogammaglobulinaemia is possibly a risk factor for an increased frequency of cancer.¹⁰

The data presented suggest that *H pylori* gastritis is a pathogenic factor in at least a subgroup of patients with hypertrophic gastropathy. Treatment should therefore be considered using a regimen that eradicates *H pylori*. Furthermore, such treatment could help in the differential diagnosis of other diseases associated with hypertrophic gastric folds, such as diffuse gastric carcinoma or lymphoma.

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