CASE REPORT

Disease recurrence following cetuximab completion and declining a gastrectomy: what next to manage Ménétrières disease?

Mitesh Patel,¹ Marcus Mottershead²

¹Birmingham Heartlands Hospital, Birmingham, West Midlands, UK
²Department of Gastroenterology, Birmingham Heartlands Hospital, Birmingham, UK

Correspondence to

Dr Mitesh Patel,
 mpatel59@doctors.org.uk

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SUMMARY

Ménétrières disease is a rare mucosal hyperproliferative disorder of the stomach, however, the evidence for long-term care remains limited, especially if a gastrectomy is declined. We present a case of 25-year-old Caucasian woman with a history of end-stage renal failure (ESRF) who experienced worsening symptoms of abdominal pain, haematemesis and abdominal swelling, with her serum albumin dropping to 20 g/L and haemoglobin to 4.9 g/dL. Endoscopy showed markedly hyperplastic gastric folds consistent with Ménétrières disease, confirmed histologically by gland dilation and gastric pit expansion. Intravenous cetuximab was prescribed for 12 months, with clinical, biochemical and endoscopic improvement. However, 5 weeks post cetuximab completion, there was relapse to 50% gastric coverage with Ménétrières. A discussion around gastrectomy was rejected by the patient. This is the first report of relapsing Ménétrières disease in a female patient with ESRF; we suggest that long-term cetuximab should be considered if a gastrectomy is declined.

BACKGROUND

This is the first case report to describe a young woman with end-stage renal failure (ESRF) on haemodialysis, diagnosed with Ménétrières disease and successfully managed with intravenous injections of the epidermal growth factor receptor (EGFR) antagonist cetuximab. Both symptom and disease remission occurred throughout treatment. However, following completion of 12 months of cetuximab, endoscopic evidence of recurrence was apparent within 5 weeks, with a gastrectomy being declined because of the associated reduction in quality of life.

CASE PRESENTATION

A 23-year-old Caucasian woman presented with a 2-week history of generalised abdominal pain, haematemesis and abdominal swelling. Initially, she experienced vomiting of fresh red matter and later noted multiple small clots in it; she describing her pain as sharp and constant. She had a history of ESRF secondary to glomerulonephritis and requiring haemodialysis, previous thrombosis of the right jugular, subclavian and cephalic veins, and persistent anaemia. No family history of gastrointestinal disease was present and the patient had an 8 pack-year smoking history and no alcohol intake. Examination was unremarkable, however, biochemically she had a haemoglobin (Hb) of 6.2 g/dL. Over

the next 16 months, the patient experienced recurrent dark black coloured stools, vomiting, haematemesis and abdominal pain with the lowest drop in Hb to 4.9 g/dL, requiring 24 units of packed red blood cells (PRBC), despite receiving monthly intravenous iron injections for chronic anaemia. Her serum albumin also dropped to 20 g/L and she became increasingly lethargic and dyspnoeic over shorter distances.

INVESTIGATIONS

Initial endoscopy 1 week following admission showed prominent gastric body folds but no inflammation or ulceration in the upper gastrointestinal tract. Abdominal imaging revealed significantly distended and thickened gastric rugae. A repeat endoscopy 11 months after presentation showed markedly hypertrophied gastric folds with polypoid features, appearances consistent with Ménétrières disease (figure 1A). Histology confirmed the diagnosis, demonstrating specialised gastric mucosa measuring 2 mm on average with prominent expansion of the gastric pits and a corkscrew appearance (figure 2). Cystic dilation of glands in the basal portion of the mucosa was observed with mild inflammation and some smooth muscle tracts in the lamina propria. Staining was negative for *Helicobacter pylori* and Cytomegalovirus (CMV). Four months after initiating cetuximab, less extensive disease was noted on endoscopy. At 6 months, an endoscopy showed that the entire fundus and greater curvature now had normal mucosa with the lesser curvature the only site of hypertrophied folds, representing 25% of the total gastric area compared with 90% pre cetuximab (figure 1B). Unfortunately, an endoscopy 5 weeks post cetuximab completion revealed more extensive disease covering 50% of the total area (figure 1C).

DIFFERENTIAL DIAGNOSIS

Ménétrières disease embodies key clinical, biochemical and histological features, characteristically affecting males aged 30–50. On presentation, vomiting, abdominal pain and peripheral oedema are the most common symptoms.¹ Biochemically, high gastrin and low serum albumin are found, however, a definitive diagnosis requires a full thickness gastric biopsy, predominantly showing giant rugal folds proximally in the body and fundus of the stomach alongside a high gastric pH.² Histology demonstrates dilated gastric glands and foveolar hyperplasia with absent inflammatory or dysplastic cells.

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Figure 1 Endoscopy showing Ménétriers disease with (A) hypertrophied gastric folds with polypoid features in the upper and lower stomach, (B) remission of Ménétriers disease with the lesser curvature the only site of hypertrophied folds, and (C) relapse of Ménétriers disease 5 weeks after cetuximab completion.

The symptoms experienced by the patient can be linked with numerous gastrointestinal pathologies. However, the giant gastric folds on endoscopy can also simulate several pathologies. Zollinger-Ellison syndrome is a hyperplastic gastropathy, resulting from gastrin release secondary to a gastrinoma, with 90% leading to peptic ulcer disease, commonly observed in the superior segment of the duodenum.³ A diagnosis requires the presence of fasting hypergastrinaemia, gastric acid hypersecretion and high secretin release on stimulation. Additional differentiating findings on endoscopy are strictures in the pylorus or oesophagus.⁴

Acute and chronic gastritis can both cause giant rugal folds with profuse parietal cells histologically. One study showed that chronic active gastritis was the cause in 81% of cases, with a coexisting *H. pylori* infection resulting in 92% of cases.⁵ The theory in *H. pylori* infection is that overexpression of glucagon-like peptide (GLP-2) results in giant folds, resolving with eradication of the infection.⁶

An important differential diagnosis to rule out is gastric cancer, most commonly presenting with weight loss and persistent abdominal pain. Examination findings can indicate chronic disease with a possible abdominal mass palpable. Endoscopy

Figure 2 Histological examination of this full thickness gastric body biopsy showing prominent expansion of the gastric pits, which have a corkscrew appearance in places. There is also cystic dilation of glands in the basal portion of the mucosa.

may demonstrate thick rugal folds, or gastric ulcers experienced by 25% of patients.⁷

TREATMENT

Following a diagnosis of Ménétriers disease, cetuximab treatment was started. Intravenous cetuximab injections were administered every 3 weeks over a 12-month period following an induction phase of weekly injections. A loading dose of 400 mg/m² was prescribed for 1 week, then 250 mg/m² for 2 weeks before administering three weekly injections thereafter. 20 mg omeprazole once daily was prescribed throughout cetuximab treatment and was increased to a dose of 40 mg following completion of cetuximab, as the patient developed dyspepsia.

OUTCOME AND FOLLOW-UP

Symptomatically, the patient improved rapidly, with an increased appetite, a reduced frequency of haematemesis and diminishing abdominal pain within the first month of cetuximab treatment. She remained well throughout the treatment, requiring only 2 units of PRBC, although she did experience folliculitis as a side effect of cetuximab, mainly facial in nature.

After 3 months of initiating cetuximab, less extensive disease was noted on endoscopy, with 50% of the total gastric area hypertrophied compared with 90% pre cetuximab. At 6 months, the entire fundus and greater curvature now had normal mucosa with the lesser curvature the only site of hypertrophied folds, representing 25% involvement of the total gastric area.

However, on endoscopy 5 weeks after completion of the cetuximab regime, the Ménétriers appeared more extensive again and the patient was experiencing dyspepsia, being managed with omeprazole. Also, with a subsequent drop in Hb to 6.6 g/dL, she required 6 units of PRBC within the first 3 months post cetuximab completion. As the patient is currently on the kidney transplant list and feels that this is the main

priority, she is not consenting to a gastrectomy, which would impact on her quality of life, especially if she undergoes a kidney transplant again in the future. An application has been accepted for further cetuximab funding for the patient.

DISCUSSION

Ménétriers disease is a rare mucosal hyperproliferative disorder of the body and fundus of the stomach. The aetiology remains unclear, although an infective CMV source is often found in children.⁸ At the cellular level, EGFR in foveolar mucus cells are overstimulated by its ligand transdermal growth factor alpha,⁹ causing excess mucus secretion and nutrient malabsorption. Coffey and coauthors carried out a trial involving seven patients managed with cetuximab injections weekly for 1 month and continued treatment for up to 40 months. Four patients showed remission histologically with an enhanced quality of life observed in all patients. However, four patients required a gastrectomy for a long time.¹⁰

Cetuximab has been recommended as first-line for the management of Ménétriers disease with gastrectomy suggested for non-responders. Alternative hypotheses for the pathogenesis of Ménétriers disease include histamine receptor overstimulation, with famotidine being reported to treat Ménétriers in the duodenum following 3 months of treatment,¹¹ while cimetidine prevents protein leakage.¹² Octreotide controls EGFR signalling and case reports have suggested that monthly subcutaneous octreotide can improve symptoms and endoscopic findings.¹³ Other medical therapies reported to have treated Ménétriers include steroids and antibiotics,¹⁴ although they have not been used in clinical studies.

Historically, in the event of failed medical therapy or severe symptoms, a gastrectomy would be performed. Despite Ménétriers disease principally affecting the body and fundus of the stomach, a total gastrectomy is favoured over a partial gastrectomy because of an enhanced quality of life.¹⁵ In addition, a link between Ménétriers disease and gastric cancer has been found, increasing the likelihood by 15%.¹⁵ This risk is reduced by a gastrectomy; however, if it is not carried out, long-term endoscopic investigations are advised every 1–2 years to identify a malignancy.

Following completion of cetuximab, endoscopic evidence of Ménétriers relapse can occur with the patient remaining asymptomatic. This is significant because of the associated higher incidence of gastric cancer in Ménétriers disease. Therefore, it is important to endoscopically monitor disease in asymptomatic patients.

No management guidelines are currently available in the UK if patients do not consent to a gastrectomy following cetuximab completion. Owing to the limited literature available, in these cases we suggest that an application for lifelong treatment of cetuximab be requested, with the hope of long-term disease control and remission.

Patient's perspective

The patient is, at present, on the kidney transplant list and feels that this is the main priority in her life, as she currently attends haemodialysis sessions three times a week. As her quality of life will be affected by a gastrectomy, she does not at this time want surgical management of her Ménétriers disease while a chance of undergoing a kidney transplant in the future remains. She is, however, keen to remain on cetuximab injections to reduce the likelihood of symptom relapse, which frightened her because of the acute onset and impact on her activities of daily living.

Learning points

- ▶ Ménétriers disease is a rare gastric pathology and haematemesis can be part of the initial presentation of the disease.
- ▶ Intravenous cetuximab injections can cause remission of Ménétriers disease. However, if the disease relapses following completion of cetuximab and a gastrectomy is not possible, lifelong cetuximab therapy may be initiated.
- ▶ Endoscopic evidence of relapse of Ménétriers disease may occur without clinical symptoms being present. This is important because of the reported higher incidence of gastric cancer.

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Competing interests None.

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REFERENCES

- 1 Rich A, Toro TZ, Tanksley J, *et al.* Distinguishing Ménétrier's disease from its mimics. *Gut* 2010;59:1617–24.
- 2 Menetrier P. Des polyadenomes gastriques et de leur rapports avec le cancer l'estomac. *Arch Physiol Norm Pathol* 1888;1:32–55, 236–65.
- 3 Meko JB, Norton JA. Management of patients with Zollinger-Ellison syndrome. *Annu Rev Med* 1995;46:395–411.
- 4 Anderson DK. Current diagnosis and management of Zollinger Ellison syndrome. *Ann Surg* 1989;210:685–703.
- 5 Tran T, Hung P, Laucirica R, *et al.* The clinical significance of thickened gastric folds found on upper gastrointestinal series. *J Clin Gastroenterol* 2002;35:138–43.
- 6 Watanabe K, Beinborn M, Nagamatsu S, *et al.* Ménétrier's disease in a patient with *Helicobacter pylori* infection is linked to elevated glucagon-like peptide-2 activity. *Scand J Gastroenterol* 2005;40:477–81.
- 7 Wanebo HJ, Kennedy BJ, Chmiel J, *et al.* Cancer of the stomach. A patient care study by the American College of Surgeons. *Ann Surg* 1993;218:583–92.
- 8 Occena RO, Taylor SF, Robinson CC, *et al.* Association of cytomegalovirus with Ménétrier's disease in childhood: report of two new cases with a review of literature. *J Pediatr Gastroenterol Nutr* 1993;17:217–24.
- 9 Toubia N, Schubert ML. Menetrier's disease. *Curr Treat Options Gastroenterol* 2008;11:103–8.
- 10 Fiske WH, Tanksley J, Nam KT, *et al.* Efficacy of cetuximab in the treatment of Menetrier's disease. *Sci Transl Med* 2009;1:8ra18.
- 11 Wu CS, Lin CJ, Chen TC, *et al.* Ménétrier's disease: a new variant with duodenal involvement. *Am J Gastroenterol* 1997;92:1041–3.
- 12 Gadour MO, Salman AH, El Samman el Tel W, *et al.* Menetrier's disease: an excellent response to octreotide. A case report from the middle east. *Trop Gastroenterol* 2005;26:129–31.
- 13 Raderer M, Oberhuber G, Tempel E, *et al.* Successful symptomatic management of a patient with Menetrier's disease with long-term antibiotic treatment. *Digestion* 1999;60:358–62.
- 14 Sanchez C, Brody F, Pucci E, *et al.* Laparoscopic total gastrectomy for Menetrier's disease. *J Laparoendosc Adv Surg Tech A* 2007;17:32–5.
- 15 Chusid EL, Hirsch RL, Colcher H, *et al.* Spectrum of hypertrophic gastropathy; giant rugal folds, polyposis and carcinoma of the stomach—case report and review of the literature. *Arch Intern Med* 1964;114:621.

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