CASE REPORT

Helicobacter pylori-negative Russell body gastritis: does the diagnosis call for screening for plasmacytic malignancies, especially multiple myeloma?

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SUMMARY

Russell body gastritis (RBG) is a rare entity with unestablished pathophysiology, endoscopic findings, clinical manifestations and treatments. Literature is scarce on this clinical entity with unclear clinical significance. Of 18 cases reported, 12 tested (+) for *Helicobacter pylori* and improved with treatment, but it remains unclear whether this link is coincidental or bears some clinical significance. We describe a case of elderly woman who had a follow-up oesophagogastroduodenoscopy for chronic peptic ulcers, and biopsy showed positive immunohistochemical stains for κ and λ , indicating a polytypic population of plasma cells. Immunostaining for *H pylori* was negative. Biopsies were also (–) for gastric carcinoma, lymphoma and plasmacytoma. Considering her RBG-suggestive histology and her symptoms of bone pains and anaemia, multiple myeloma screening was considered clinically relevant. The purpose of this review was to educate clinicians and gastroenterologists about this unique entity and explore its association with multiple myeloma or other plasmacytic malignancies.

BACKGROUND

Russell bodies (RBs) are eosinophilic, large, homogeneous immunoglobulin-containing inclusions usually found in a plasma cell undergoing excessive synthesis of immunoglobulin (chronic inflammation) and is characteristic of the distended endoplasmic reticulum resulting from secretion disturbance.¹ Russell body gastritis (RBG) is a rare entity which was first described and named by Tazawa and Tsutsumi² in 1998. Histologically, it shows RB-containing plasma cells called *Mott Cells* with polyclonal proliferation (positive for κ and λ chains). It is important to exclude conditions such as signet cell cancer, mucosa-associated lymphoid tissue lymphoma (MALToma), malignant lymphoma and monoclonal gammopathy of undetermined significance (MGUS), to avoid a confusion.³ However, the polyclonal nature of RBG helps differentiate it from plasma cells tumours (plasmacytoma) which have monoclonal proliferation.⁴ Although the link of RBG with *Helicobacter pylori* has been postulated, the clinical importance and its relationship to these malignancies are yet unclear. The purpose of this review was to educate clinicians and gastroenterologists about this unique entity and explore its association with multiple myeloma or other plasmacytic malignancies.

CASE PRESENTATION

A 76-year-old White woman with a medical history of hypothyroidism, hypertension, inflammatory bowel disease and arthritis was referred for follow-up of chronic peptic ulcers diagnosed around ~4 years ago when she presented to an outside hospital with upper gastrointestinal bleed, diagnosed to have antral ulcer on esophagogastroduodenoscopy (EGD), and was started on proton pump inhibitor (PPI) therapy. She denied repeat bleeding but a follow-up EGD performed a few months later showed persistence of ulcers. The last EGD from the outside hospital performed in June 2012 showed small antral ulcers, biopsy negative for malignancy or *H pylori*, and at that point these ulcers were labelled refractory and she was advised antrectomy. During our interview, she denied bleeding in stools, melena, epigastric pain, weight loss, nausea, vomiting or non-steroidal anti-inflammatory drug (NSAID) use. Her haemoglobin level was 8.5 g/dL and gastrin level was 245 pg/mL, but the rest of the laboratory tests was unremarkable. EGD showed normal oesophagus and gastro-oesophageal junction, with no antral ulcers, but a few small polyps in the fundus were seen on retroflexion, along with areas of cobblestoned, whitish, raised and irregular mucosa (figure 1A). The fundic biopsies showed oxyntic mucosa with chronic, inactive gastritis; and (–) immunostaining for *H pylori* (figure 1B). In situ hybridisation (ISH) stained (+) for κ and λ , indicating a polytypic population of plasma cells (figure 1C,D). On detailed history-taking and physical examination, she reported having bone pains and chronic anaemia. Due to the presence of plasma cells, reported coexistence of MGUS in two cases and the patient's symptoms, it was decided to obtain oncology consultation to exclude plasmacytic malignancies.

OUTCOME AND FOLLOW-UP

The patient underwent evaluation and was found to have multiple myeloma.

DISCUSSION

Russell (1890) found examples in a large number of malignant growths of human origin as a feature of small round-cell infiltration at the margin.⁵ Russell concluded that these bodies were an essential component of the neoplastic process, unrelated to degeneration or inflammation of tissue secondary to such neoplastic change.⁵ RBs represent a general response of the cell to the accumulation of

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Figure 1 (A) Endoscopic image of the fundus of the stomach showing whitish elevated lesions which were biopsied; (B) biopsy (H&E stain) at high power showing plasma cell infiltrate; immunohistochemical staining positive for (C) κ and (D) λ .

abundant, non-degradable proteins that fail to exit from the endoplasmic reticulum.⁵

Tazawa and Tsutsumi,² in 1998, hypothesised the relation of RBG with *H pylori* causing inflammatory changes leading to RB formation in gastric mucosa. They showed improvement in inflammatory changes and RB with *H pylori*. Since then it has been postulated that chronic antigenic stimulation caused by *H pylori* infection can result in plasma-cell hyperactivation and consequently hyperproduction of immunoglobulins with numerous RB formation.⁶ Table 1 reviews the available literature on this topic and summarises the findings of all reported cases of RBG. Twelve of 18 cases were found to be *H pylori* (+), and 11/12 of those cases improved with *H pylori* treatment, which were confirmed with subsequent EGD/biopsies. It strongly suggests that *H pylori* (+) cases of RBG should be aggressively treated for *H pylori* and subsequently followed endoscopically. The 6/18 cases which were *H pylori* (–) have been an interesting mix: two patients were HIV positive, one with candida oesophagitis and one with MGUS, but any significant association is yet to be established.

Previous case reports suggest that RBG should be differentiated from neoplastic diseases such as signet ring cell carcinoma, malignant lymphoma, MALToma, plasmacytoma, multiple myeloma and MGUS.^{3 7 8} It can also present with chronic inflammatory and immunological disorders such as Hashimoto's thyroiditis, rheumatoid arthritis and ulcerative colitis.^{9 10} The first clue to differentiate may be immunohistochemistry, which excludes monoclonal origin of plasma cells present in most plasma cell malignancies (figure 1C,D). Presence of polyclonal pattern of plasma cells, absence of nuclear atypia and mitosis and negative staining for cytokeratins are factors which favour diagnosis of RBG, while excluding malignancies. However, the clinical significance of *H pylori* negative RBG is yet unclear, and

reported coexistence with MGUS and other malignancies may make a case for further investigation in these patients to exclude plasmacytic malignancies.

In summary, we report a case of extremely rare entity *H pylori* (–) RBG with polyclonal differentiation (ISH positive for κ and λ chains), and present the literature review on it. Furthermore, it is a common knowledge that multiple myeloma may have RBs of monoclonal nature in bone marrow and other organs, hence we postulate that in a patient like ours with RBG (although with polyclonal differentiation), multiple myeloma should be excluded especially if the patient is symptomatic.

Learning points

- ▶ Russell body gastritis presents as polyclonal plasma cells staining (+) for κ and λ chains.
- ▶ Carefully evaluate for Russell body gastritis and exclude potential conditions with similar oesophagogastroduodenoscopy findings of histologically identical gastric carcinoma (signet ring cell), malignant lymphoma, mucosa-associated lymphoid tissue and plasmacytoma.
- ▶ All patients should be tested for *Helicobacter pylori*, considering likely association with *H pylori* and case reports showing improvement with *H pylori* treatment.
- ▶ *H pylori* might have an association with multiple myeloma as in our case report. It needs further research on a larger sample size.
- ▶ Proton pump inhibitor therapy and endoscopic surveillance are considered for management of disease.

Table 1 Review of available literature of Russell body gastritis, including endoscopy and histological findings

First author (year)	Sex/age	Symptoms	Endoscopic findings	Location	Biopsy findings	HP	DAEHP	Others
Tazawa (1998) ²	M/53	Epigastralgia	Multiple ulcer scars with redness and swelling	Antrum	'Histiocytoid cells'—plasma cells with polyclonal pattern Russell bodies. First named it as Russell body gastritis	+	+	Alcoholic liver injury
Erbersdobler (2004) ¹¹	F/80	Epigastric pain and nausea	3 cm, irregular mucosal swelling	Fundus	Confirmed candida and showed plasma cells with Russell bodies with polyclonal pattern	—		Candida oesophagitis. Ethanol and analgesic misuse
Ensari (2005) ¹²	M/70	Dyspepsia and nausea for months	Flattened gastric folds and oedema pangastritis	Body and antrum	Moderate gastritis with Russell body with polyclonal nature	+		
Drut (2006) ¹³	M/34	Epigastric pain, acute diarrhoea, blood-stained stools	2 cm, raise with central rounded macule (1 cm)	Body	Moderate-to-severe gastritis with Russell body with polyclonal distribution	—		HIV (+), IVDA, chronic alcoholic
Wolkersdörfer (2006) ¹⁴	M/54	Chronic dyspeptic symptoms.	Mild erythema, oedema and small erosions	Antrum	Mild chronic and inactive gastritis with mild foveolar hyperplasia in the antrum, Russell bodies with polyclonal proliferation	+	—	MGUS, MM excluded
Paik (2006) ⁶	F/47	Mild epigastralgia	Focal erythematous swelling	Antrum	Spherical eosinophilic globules—Russell body	+	+	
Paik (2006) ⁶	F/53	Epigastric bloating, hunger-pain for months	Geographical yellowish nodular raised, clear margin	Body	Spherical eosinophilic globules—Russell body	+	+	
Pizzolitto (2007) ¹⁵	F/60	Epigastric pain	Minute-raised granular	Antrum	Moderate-to-severe gastritis with Russell body	+	+	
Licci (2009) ¹⁶	M/59	Recurrent epigastric pain	Mild hyperaemia in only antral region	Antrum	Moderate glandular atrophy with polyclonal Russell bodies	+	+	HIV (+)
Habib (2010) ¹⁷	M/75	Non-compliant with reflux medications, intermittent coffee-ground emesis	Oesophagitis and nodular chronic active gastritis	Antrum	Regenerative changes and a dense chronic inflammatory infiltrate composed of numerous Russell body with polyclonal distribution	—		History of alcohol use, renal failure, dyslipidaemia, and prior rhabdomyolysis
Del Gobbo (2011) ⁹	F/78	Epigastric pain	Hyperaemic gastric mucosa	Antrum and GE junction	Moderate chronic gastritis in the antral region gastro-oesophageal junction mucosa showed Russell body	—		Treated only PPI
Wolf (2011) ¹⁸	M/67	Asymptomatic	Locally advanced exophytic tumour within the antrum mucosa		Diffuse gastric cancer composed of classical signet ring cells. Presence of Russell bodies with polyclonal proliferation	+		Ex-intravenous drug user, hepatitis C +, insulin-dependent DM
Coyne (2012) ¹⁹	M/49	Nausea, epigastric pain, weight loss	Severe, raised, erosive gastritis and oedematous, duodenitis with erythema		Russell body gastritis	—		
Karabagli (2012) ²⁰	M/60	Dyspepsia	Erythema in gastric body, large, irregular, fungating, ulcerated, nearly circumferential mass at incisura angularis of the stomach	Body	Mononuclear cellular infiltration with dysplastic changes and Russell body	+	+	
Bhalla (2012) ⁷	M/82	Dyspepsia, loose stools, loss of appetite and weight	Gastritis		Russell bodies present	—		HIV +
Miura (2012) ⁸	F/63	Chest and back pain	Elevated lesion in the antrum mucosa	Antrum	Monoclonal proliferation plasma cells containing Russell bodies. Excluding B-cell lymphoma and plasmacytoma difficult. Molecular analyses of IgH gene showed gene rearrangement was negative. Thus dx as Russell body gastritis	+	+	
Yoon (2012) ²¹	M/57	Intermittent non-severe epigastric soreness, mostly preprandial, which subsided postprandially	Multiple polypoid lesions, 0.5–1 cm in diameter, on lower body of stomach and antrum, and a relatively distinct slightly raised white flat nodular lesion, 2 cm in diameter, on mid-body posterior	Body	Abundant plasma cell with Russell body immunohistochemical staining was positive on kappa and lambda light chains suggesting polyclonal nature	+	+	Past h/o gastric/colon polyps, atrophic gastritis. FH of colon ca and HCC
Yoon (2012) ²¹	M/43	None	A whitish oval shaped flat lesion, 2 cm in diameter, lesion had nodular appearance, with slight depression in the centre	Posterior wall of antrum	Abundant plasma cell with Russell body; immunohistochemical staining were positive for κ and λ light chains	+	+	
This study	F/76	None	Multiple small polyps in the fundus were seen on retroflexion, along with cobblestoned erythematous and irregular mucosa	Fundus	Oxyntic mucosa with chronic, inactive gastritis; immunostaining for <i>H. pylori</i> was negative, ISH stained (+) for κ and λ indicating a polytypic population of plasma cells	—		Bone pains and anaemia. Found to have multiple myeloma on f/u. Will follow-up with results

HP, *Helicobacter pylori*; DAEHP, disappear after eradication of *H. pylori*; F, female; ISH, in situ hybridisation; M, male; MGUS, monoclonal gammopathy of undetermined significance; PPI, proton pump inhibitor.

Competing interests None.

Patient consent Obtained.

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