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BRIEF REPORTS

Histological characteristics of eosinophilic myenteric ganglionitis: an under-recognised cause of chronic intestinal pseudo-obstruction

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Abstract

Eosinophilic myenteric ganglionitis (EMG) is characterised by eosinophilic infiltration of the myenteric plexus. EMG has been rarely reported as a cause of chronic intestinal pseudo-obstruction (CIPO), and its histopathological features are not fully elucidated. We analysed seven patients with CIPO. Three of them were diagnosed with EMG and four patients were categorised as non-EMG. Clinicopathological features were similar in both groups. These features included subtle to mild lymphocytic infiltration at the myenteric ganglia/muscularis propria, loss of myenteric ganglions and interstitial cells of Cajal (ICC), and no significant findings in the mucosa. The exceptions were moderate to severe degree of eosinophilic infiltration at the myenteric ganglia/muscularis propria in EMG. Functional gastrointestinal obstruction may be associated with inflammatory cell infiltration at the myenteric ganglia/muscularis propria, leading to subsequent hypoganglionosis and deficiency of ICC in EMG. Pathologists and clinicians should be aware of this distinction during differential diagnosis of patients with CIPO.

Keywords Eosinophilic myenteric ganglionitis · Chronic intestinal pseudo-obstruction · Auerbach plexus · Myenteric ganglia · Interstitial cells of Cajal · α-Synuclein

Introduction

Chronic intestinal pseudo-obstruction (CIPO) is a rare and intractable disease characterised by impaired gastrointestinal propulsion and symptoms of bowel obstruction in the absence of any lesion occluding the intestinal lumen [1–5]. To date, there is no single diagnostic test or pathognomonic finding for CIPO. Symptoms can be non-specific and CIPO is often mistaken for other diseases, leading to lengthy delays in diagnosis. CIPO is classified as "primary (idiopathic)", "secondary", and familial forms. Based on histopathological examination, primary CIPO can be classified into three major categories of gastrointestinal neuromuscular disorders. Depending on the predominant involvement of enteric neurons, smooth muscles, or interstitial cells of Cajal (ICCs), primary CIPO is classified as a neuropathy, myopathy, or "mesenchymopathy", respectively [3]. Secondary CIPO is due to several diseases such as neurological disorder, psychiatric disorder, endocrinological/metabolic disorder, and paraneoplastic syndrome.

Eosinophilic myenteric ganglionitis (EMG) is an inflammatory neuropathy, which develops mainly in children, characterised by a marked eosinophilic infiltration of the myenteric plexus. Few reports have addressed EMG as a cause of CIPO [6–10], and inflammation within the myenteric ganglia is recognised as a primary cause of functional intestinal obstruction. However, the histopathological features of EMG have not been fully elucidated. Here, we present three adult cases of EMG with CIPO. Furthermore, we evaluated the histopathological characteristics of EMG and non-EMG cases in patients with CIPO.

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Materials and methods

Study population

We screened the archives of the Department of Human Pathology, Juntendo University, School of Medicine, from April 2008 to October 2017 for all adults who underwent colon or rectal resection. The study population consisted of seven patients with CIPO. All patients with CIPO except an EMG patient (case 1) were classified into secondary CIPO because of their comorbidity. All of them underwent sigmoidectomy for sigmoid volvulus. Among them, three were diagnosed with EMG based on criteria for histopathological assessments described below. The other four patients were not diagnosed with EMG and were categorised as non-EMG. To clarify the histopathological findings of EMG and non-EMG cases with CIPO, we selected sigmoid colon surgical specimens from nine patients without CIPO as controls. Patients providing the control samples were pathologically diagnosed with no residual tumour after endoscopic resection for early-stage colonic adenocarcinomas. YA, TH, and YT reviewed the microscopic slides.

Criteria for histopathological assessments

EMG was diagnosed when the number of peri/intraganglional eosinophils per ganglion was more than five, based on the guidelines for histological techniques and reporting on behalf of the Gastro 2009 International Working Group [10, 11]. Eosinophilic and lymphocytic infiltrations were assessed in peri/intraganglion, circular, and longitudinal muscles in dilated and non-dilated (i.e. distal site) portions of the sigmoid colon. Briefly, peri/intraganglional eosinophil or lymphocyte numbers were determined by counting all eosinophils or lymphocytes within a 50-μm radius of the ganglion border [12]. Intramuscular eosinophils and lymphocytes were also counted. Eosinophils and lymphocytes were counted on haematoxylin and eosin- and CD45 (DAKO, Santa Clara, CA, USA)-stained sections, respectively, and at least 10 high-power fields (HPFs) were used. We semi-quantitatively assessed the number of ganglion cells and ICCs using Hu C/D (Thermo Fisher Scientific Inc., Waltham, MA, USA) and CD117 (DAKO) immunohistochemistry. The number of ganglion cells per centimetre of muscularis propria was analysed. ICCs were counted in 10 HPFs of CD117-stained sections. Only the numbers of ICC nuclei were recorded. We further analysed α-synuclein expression in the myenteric plexus using α-synuclein (Santa Cruz Biotechnology, Dallas, TX, USA) immunohistochemistry. This study was reviewed and approved by the Juntendo University School of Medicine Institutional Review Board (#JHS 17-0048).

Results

Clinical findings

Case 1

A 34-year-old woman who suffered severe constipation and twice had an endoscopic reduction for sigmoid volvulus underwent prophylactic sigmoidectomy. She had no other medical history. She had no peripheral blood eosinophilia (312/μl). Serum IgE and autoimmune markers were not investigated. The postoperative specimen showed no ischemic change and mild dilatation of the bowel wall from the rectosigmoid portion to the sigmoid portion. Histopathologically, eosinophilic infiltration was detected in the peri/intraganglion (mean 7, range 5–10/HPF). After the operation, she changed hospitals and ceased attending our hospital.

Case 2

A 61-year-old man with obsessive-compulsive disorder, hypothyroidism, sigmoid volvulus, and a surgical history of hypopharyngeal cancer underwent prophylactic sigmoidectomy. His blood eosinophil counts were normal (82.5/μl). Serum IgE and autoimmune markers were not investigated. The resected specimen showed marked dilatation from the rectosigmoid portion to the sigmoid portion (Fig. 1a). Histopathologically, peri/intraganglion eosinophilic infiltration was detected (mean 12.7, range 8–32/HPF). No recurrence of sigmoid volvulus was observed 2 years after surgery.

Case 3

A 76-year-old man with Parkinson's disease, atrial fibrillation, aortic regurgitation, and sigmoid volvulus presented with vomiting, constipation, and marked abdominal distension. Prior investigation had shown no peripheral blood eosinophilia (70.3/μl), a relatively high total IgE concentration (252 kU/l), and that autoimmune markers (antineutrophil cytoplasmic antibodies, antinuclear antibodies, anti-smooth muscle antibodies) were negative. An emergency surgery was performed. The resected specimen showed marked dilatation from the rectosigmoid portion to the sigmoid portion. Histopathologically, peri/intraganglion eosinophilic infiltration was detected (mean 13.6, range 9–20/HPF). No recurrence of sigmoid volvulus was observed 1 year after surgery.

Histological findings

The summary of clinical and histopathological findings of patients with CIPO is shown in Table 1.

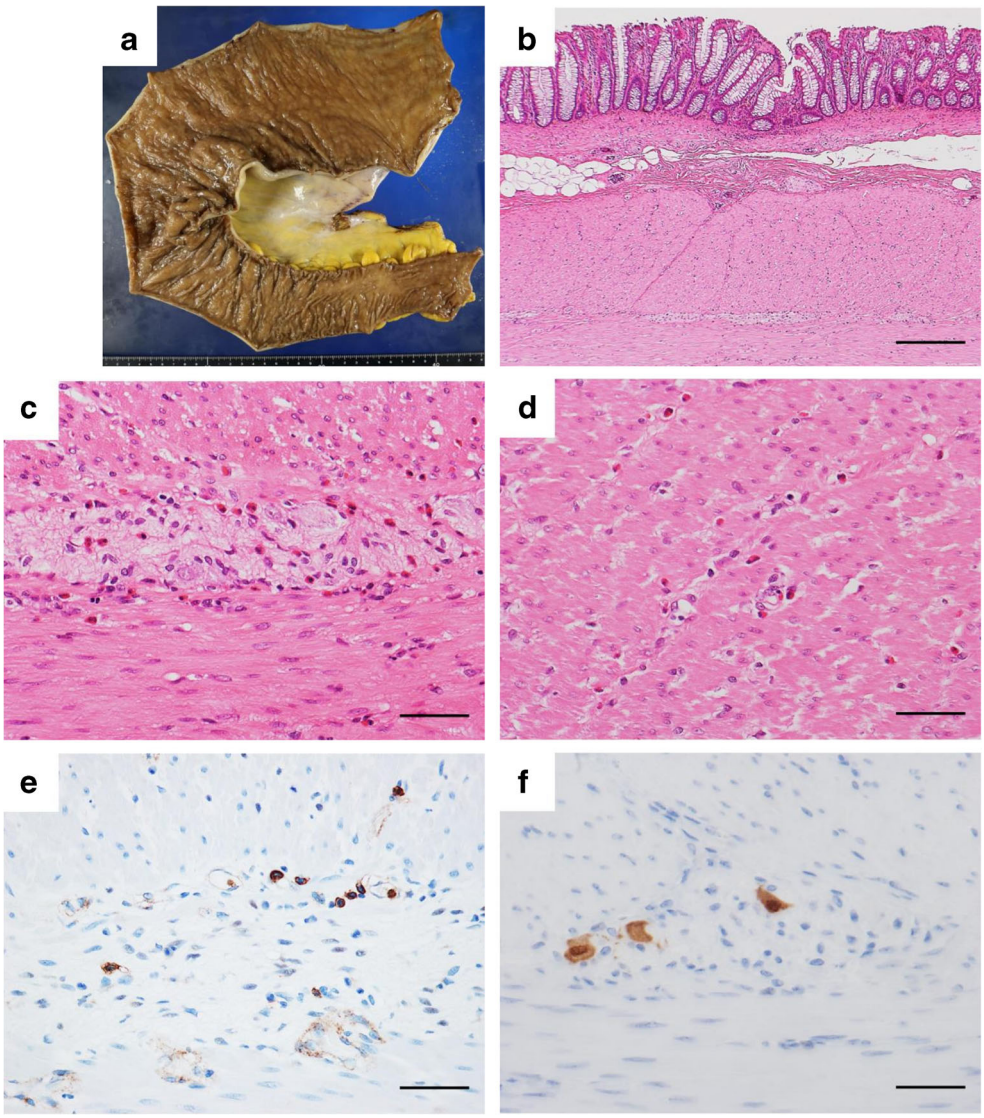

Fig. 1 Histopathological appearance of eosinophilic myenteric ganglionitis. **a** Resected specimen showing marked dilatation from the rectosigmoid portion to the sigmoid portion with thinning of the bowel wall (case 2). **b** No apparent abnormalities identified in the low power view (case 2). **c** Marked eosinophilic infiltration was observed in the myenteric plexus (case 2). **d** Eosinophilic infiltration was observed in the circular muscle (case 2). **e** A CD45-stained section showing mild lymphocytic infiltration in the myenteric plexus (case 3). **f** A Hu C/D-stained section showing decreased numbers of ganglion cells (case 2). Scale bar 50 μm in **c**–**f**, 300 μm in **b**.

Clinical features were similar in patients with CIPO and EMG and those with CIPO in the non-EMG group. No specific mucosal abnormalities were identified and submucosal ganglia were rarely affected (Fig. 1b). Comparison with controls revealed a subtle, mild, and variable degree of peri/intraganglions and muscularis propria eosinophilic and lymphocytic infiltration in both EMG and non-EMG cases (Fig. 1c–e). Additionally, compared with the number of ganglion cells in the control (mean 135.5/cm), ganglion cell numbers were reduced in both EMG and non-EMG cases (Fig. 1f). In EMG cases, peri/intraganglion eosinophilic infiltration was more frequently observed in the dilated portions (mean 11.1/HPF) than in non-dilated portions (mean 0.7/HPF) (Fig. 2). Furthermore, circular and longitudinal muscle eosinophilic infiltration was more frequently observed in dilated portions (mean 7.8/HPF for circular muscle, 1.8/HPF for longitudinal muscle) than in non-dilated portions (mean 0.7/HPF for circular muscle, 0.2/HPF for longitudinal muscle) in EMG cases; however, lymphocytic infiltration did not significantly differ between dilated and non-dilated portions (Fig. 2b). Additionally, the numbers of ganglion cells were also more reduced in the dilated portions (mean 41.8/cm) than in the non-dilated portions (mean 74.2/cm) in EMG cases (Fig. 2c). Finally, the numbers of ICCs were slightly reduced in both EMG (5.6/HPF and 8.2/HPF for dilated and non-dilated portions, respectively) and non-EMG cases (5.5/HPF and 5.6/HPF for dilated and non-dilated portions, respectively) compared with those of the control (9.3/HPF). With respect to α-synuclein expression which is linked genetically and neuropathologically to Parkinson's disease, myenteric plexus showed cytoplasmic staining in all cases examined including control population, EMG, and non-EMG with or without Parkinson's disease. Thus, intracellular aggregates of α-synuclein in myenteric plexus were not observed in patients with Parkinson's disease (Fig. 2).

Table 1 Comparison of clinicopathological findings

	EMG ($n = 3$)		non-EMG ($n = 4$)		Control ($n = 9$)	P value
Clinical findings						
Age	57 (34–76)		65.5 (40–78)		71.4 (64–82)	0.44
Sex (male/female)	2/1		2/2		6/3	1
BMI	20.5 (18.7–22.5)		24.2 (18.5–30.5)		23.4 (19.2–30.8)	0.34
Eosinophil blood count	111.6 (70.3–182.0)		119.5 (37.2–312.0)		128.7 (60.8–291.5)	
Comorbidity						
Parkinson's disease	1		2		0	
Psychiatric disorder	1		1		1	
Endocrinological and metabolic disorders	1		2		3	
Medication						
Psychotropic agent	1		1		1	
Dopaminergic drugs	1		2		0	
Histopathological findings	Dilated site	Non-dilated site	Dilated site	Non-dilated site		
Peri/intraganglional eosinophil (/HPF)	11.1 (7.0–14.5)	0.7 (0–1.45)	1 (0–3.0)	0.2 (0–0.8)	0 (0–0.4)	0.41
Eosinophil in circular muscle (/HPF)	7.8 (2.6–13.2)	0.7 (0–1.6)	0.5 (0–1.8)	0.6 (0–2.4)	0.1 (0–1.0)	0.41
Eosinophil in longitudinal muscle (/HPF)	1.8 (1.0–2.3)	0.2 (0–0.7)	0 (0–0)	0 (0–0)	0 (0–0)	0.41
Peri/intraganglional lymphocyte (/HPF)	4.1 (3.5–5.2)	2.8 (2.0–4.0)	1.6 (0.6–2.6)	2.2 (0.8–3.8)	0.8 (0–2.8)	0.41
Lymphocyte in circular muscle (/HPF)	2.3 (1.2–3.5)	1.7 (0.8–2.8)	1.2 (0.4–1.8)	1.9 (1.2–2.6)	0.8 (0–1.8)	0.41
Lymphocyte in longitudinal muscle (/HPF)	1.5 (0.9–2.1)	1.6 (1.0–2.3)	1.1 (0.8–1.6)	1.8 (0.6–3.0)	0.5 (0–2.0)	0.41
Number of ganglion (/cm)	41.8 (23.7–67.2)	74.2 (61.0–82.9)	46.8 (36.4–58.6)	52.1 (41.0–63.2)	135.5 (63.3–190.0)	0.41
Number of Cajal (/HPF)	5.6 (4–7.7)	8.2 (5.2–10.3)	5.5 (2.8–7.4)	5.6 (5.0–6.0)	9.3 (7.2–11.4)	0.41

Data is described as mean (range)

The clinicopathological findings of the subjects were compared among the three or five groups using the Kruskal-Wallis test and Fisher s exact test

Discussion

Inflammation in neuromuscular tissue can lead to severe intestinal motor impairment such as that observed in some case of CIPO. These cases are termed myenteric ganglionitis because the inflammatory reaction is confined to the myenteric plexus without involvement of the submucosal plexus [13]. Here, we reported three cases in which EMG was associated with CIPO. A common denominator in the three cases was eosinophilic ganglioneuritis along with involvement of circular and longitudinal muscles. Although previous report showed ganglioneuritis in patients with EMG [6–9], these observations suggest that the inflammatory reaction is not confined to the myenteric plexus, and that involvement of muscle layers, particularly that of the circular muscle, is a common pathological manifestation of EMG. Furthermore, loss of myenteric ganglions, observed in the later stage of myenteric ganglionitis [13], was seen in EMG cases. Although congenital aganglionosis/hypoganglionosis of the gastrointestinal tract (i.e. Hirschsprung's disease) has been widely documented in children, little is known about acquired forms of aganglionosis hypoganglionosis of the gastrointestinal tract in adults. Hirschsprung's disease generally shows aganglionosis/hypoganglionosis and ICC deficits in the narrow segment causing obstruction and dilation of the proximal

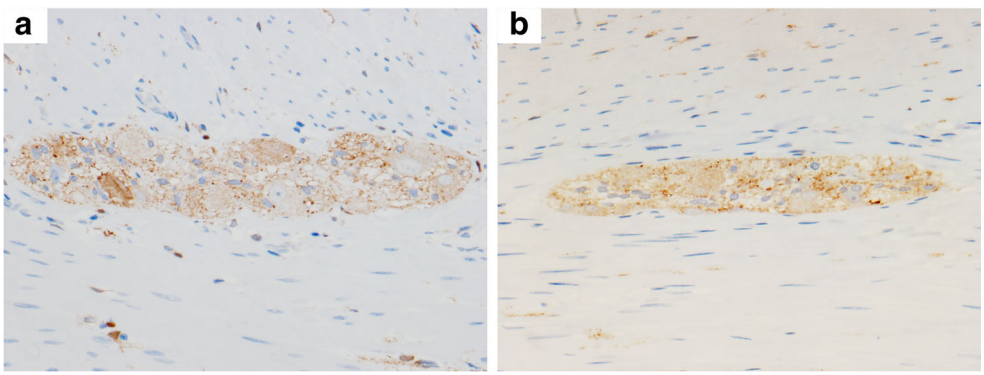

Fig. 2 α-Synuclein expression in the myenteric plexus. Myenteric plexus showed cytoplasmic staining for α-synuclein in a case from EMG (a) and control population (b)

normoganglionic colon [14, 15]. However, our results showed more prominent inflammatory cell infiltrate and decreased number of ganglion cells in the dilated portions in EMG cases. Additionally, we showed loss of intramuscular ICCs accompanied with eosinophilic infiltration in the dilated portions of EMG cases. Furthermore, our immunohistochemical results for α-synuclein showed that expression pattern did not differ in patients with or without Parkinson's disease, suggesting that peripheral α-synuclein aggregates from Parkinson's disease lack pathogenic potential, and neuropathy in myenteric neuron is unlikely to be a causative factor in Parkinson's disease–related gastrointestinal dysmotility [16, 17]. Together, hypoganglionosis in the myenteric plexus and ICC deficits in our patients with EMG may be the consequence of an eosinophilic immune response occurring within the myenteric plexus and adjacent muscular layer, resulting in colonic dilatation and functional intestinal obstruction. However, the triggers that can spur the immune system into action under these conditions remain under investigation. Finally, we cannot exclude the possibility that dilation of the intestines itself could affect the number of ganglion cells and ICCs in EMG cases.

Three of seven patients with CIPO (43%) were diagnosed with EMG, suggesting that EMG may be a leading, yet underrecognised, cause of CIPO with a history of sigmoid volvulus in adults. Our results indicate that samplings from the dilated portions of resected specimens and careful examination are useful for diagnosis. Histologically, important considerations for the differential diagnosis of EMG include eosinophilic gastroenteritis, parasitic infection, collagen vascular diseases, inflammatory bowel disease, and neoplastic diseases, all of which do not commonly cause functional intestinal obstruction. Eosinophilic ganglioneuritis along with involvement of muscle layers and reduction of ganglion cells and ICCs in the dilated portion can be the histopathological clue in EMG cases. Pathologists and clinicians should be aware that EMG is a possible cause of CIPO by considering the clinicopathological features of EMG. Further studies are needed to improve our understanding of EMG.

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Author's contributions Yoichi Akazawa, Takuo Hayashi, and Tsuyoshi Saito conceived and designed the study and wrote, edited, and reviewed the manuscript. Koichiro Niwa and Hirohiko Kamiyama provided and gave patient's clinical information. Noriko Sasahara provided histological and immunohistochemical technical assistance. All authors gave final approval for publication. Takuo Hayashi, Kazuhiro Sakamoto, Akihito Nagahara, and Takashi Yao take full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript.

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Compliance with ethical standards

The information contained in, and preparation of, this manuscript complies with the journal's ethical standards.

Conflict of interest The authors declare that they have no conflict of interest.

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