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EDITORIAL

Crohn's disease with gastroduodenal involvement: Diagnostic approach

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Abstract

Crohn's disease (CD) is a chronic idiopathic inflammatory disease of gastrointestinal tract characterized by segmental and transmural involvement of gastrointestinal tract. Ileocolonic and colonic/anorectal is a most common and account for 40% of cases and involvement of small intestine is about 30%. Isolated involvement of stomach is an extremely unusual presentation of the disease accounting for less than 0.07% of all gastrointestinal CD. To date there are only a few documented case reports of adults with isolated gastric CD and no reports in the pediatric population. The diagnosis is difficult to establish in such cases with atypical presentation. In the absence of any other source of disease and in the presence of nonspecific upper gastrointestinal endoscopy and histological findings, serological testing can play a vital role in the diagnosis of atypical CD. Recent studies have suggested that perinuclear anti-neutrophil cytoplasmic antibody and anti-Saccharomycescervisia antibody may be used as additional diagnostic tools. The effectiveness of infliximab in isolated gastric CD is limited to only a few case reports of adult patients and the long-term outcome is unknown.

Key words: Gastrointestinal tract; Crohn's disease; Isolated gastric involvement; Perinuclear anti-neutrophil cytoplasmic antibody; Anti-Saccharomycescervisia antibody

Core tip: The stomach is rarely the sole or predominant site of Crohn's disease (CD) accounting for less than 0.07% of all gastrointestinal CD. Serological testing and meticulous histopathological examination by excluding other causes of granulomatous gastritis can play a vital role to arrive at the correct diagnosis.

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INTRODUCTION

Crohn's disease (CD) can affect any region from mouth to the anus. Isolated Gastroduodenal involvement is an extremely unusual event. The CD is diagnosed usually on the basis of clinical, laboratory, upper gastrointestinal (GI) scopy and histopathology. The anti-Saccharomycescervisia antibody (ASCA) is relatively good specific marker with minimal sensitivity. However, it is difficult to diagnose it in patients with isolated involvement of stomach and duodenum. In such circumstances other granulomatous conditions must be excluded with careful evaluation of the patient to hit the accurate pathological cause[1,2].

The famous criteria to diagnose this rare condition are: (1) evidence of noncaseating granulomas on histopathology; and (2) confirmation of changes of Crohn's disease on endoscopy or radiography[3-10].

EPIDEMIOLOGY

Incidence

It occurs in 0.5% to 4% patients of CD[3-6]. Isolated stomach and duodenum involvement accounts for less than 0.07% of all cases of CD[1].

Pattern of involvement

Most patients show involvement of terminal ileum and distal segment of large intestine[4,5,7]. Contiguous involvement of stomach and duodenal involvement is most common (60%)[6,10-12].

PATHOPHYSIOLOGY

For pathogenesis of isolated gastric CD multiple hypothesis were postulated: (1) the hygiene hypothesis relatively less trained and weak immunological system leading to ineffective immune response to newer antigens; (2) the environmental factors *i.e.*, geography, smoking, drugs, diet are also main contributing factors[13,14]; (3) immune mechanism - It is being postulated that the immune reactivity in this disease is due to "loss of immune tolerance" to self antigens of intestinal flora, resulting into an inappropriate granulomatous immune response of Chron's disease[15,16]; and (4) role of chemical mediators - interferon-γ, interleukin (IL)-12, IL-18 and increased expression of T-bet[17-19]. T-cells are not undergoing apoptosis[20-25].

CLINICAL PRESENTATIONS

Age

The disease mainly seen in the age group 30-40 years[6].

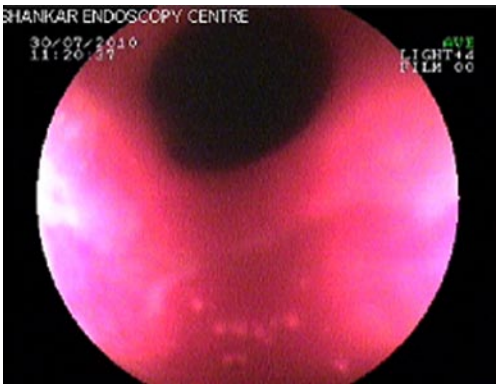

Figure 1 Endoscopic findings include patchy erythematic, gastric outlet narrowing.

Sex predilection

Male to female ratio is 1.2:1[6,12].

Symptoms and signs

Majority of the patients are usually symptomless[9]. Most of the patients are presenting with pain in epigastric region, relieved by antacids and food intake[4,9,11]. In cases with stricture formation persistent pain, nausea and vomiting are common[4]. Many times,it may simulates acid peptic disease clinically[4]. Acute blood loss may rarely occur[4,9,11,26,27].

Uncommon presentations

Uncommon presentations of CD may manifest as a single symptom or sign, such as impairment of linear growth, delayed puberty, perianal disease, mouth ulcers, clubbing, chronic iron deficiency anemia or extra-intestinal manifestations preceding the gastrointestinal symptoms, mainly arthritis or arthralgia and rarely osteoporosis[2]. In such cases, the diagnosis is challenging and can remain elusive for some time.

DIAGNOSTIC EVALUATION

Radiological signs

Aphthous ulcer is the early feature on radiography[28]. The characteristic features are presence of nodularity in the mucosa giving classic appearance of "cobblestone"[4]. Radiography examination using double-contrast medium is useful in cases with stenoses or strictures which are mainly seen in advanced disease[6,12,27,29,30]. A barium enema should be done in suspected cases of gastro colic fistula[4].

Endoscopy

Endoscopy with biopsy is an effective diagnostic modality[6,9,27,30]. Endoscopic findings include patchy erythema, gastric outlet narrowing (Figure 1) mucosa is friable, thickening of mucosa and ulcerations linear as well as aphthous[4,7,9,12]. The ulcers of CD are typically linear or serpiginous in contrast to the peptic

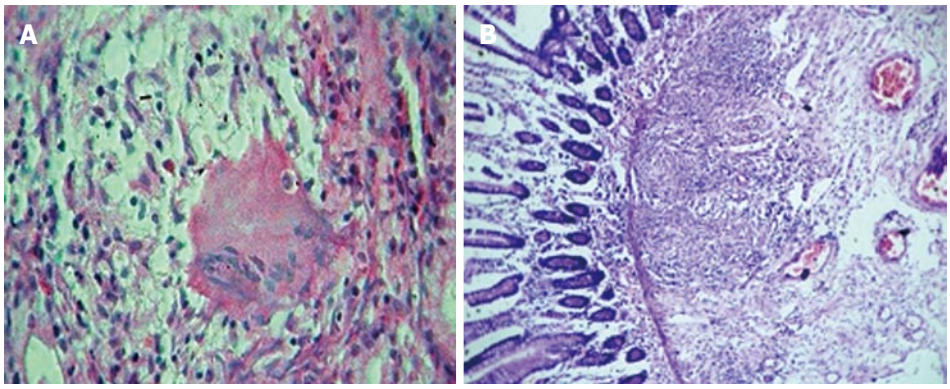

Figure 2 Biopsy showing non-caseating granulomas and oedema in the submucosa (HE × 10). A: Non-caseating granulomas; B: Oedema alongwith granulation tissue.

ulcers[27]. In cases with diffuse stomach involvement a linitis plastica appearance,is seen[31,32]. Sophisticated endoscopic features such as, bamboo-joint-like appearance and notched sign can be seen[33].

Biopsy findings

The biopsy findings are often nonspecific. Exclusion of other causes of granulomatous lesions is important. Granulomas without caseation are noted in 5% to 83% of cases (Figure 2)[9,12]. The differential diagnosis of granulomatous gastritis are *H. pylori* infection, gastric sarcoidosis, tuberculosis, syphilis, *etc*[7,9,32]. So presence of granuloma is not a definitive criterion to arrive at the diagnosis. *H. pylori* negative chronic gastritis is common feature.

Additional histological features are mucosal edema, crypt abscesses, lymphoid aggregates and fibrosis[32-34].

Serological markers

Currently, it has been stated that perinuclear anti-neutrophil cytoplasmic antibody (pANCA) and ASCA can be used as supportive diagnostic tools. Indeed, ASCA is detected in 55%-60% of children and adults with CD and only 5%-10% of controls with other gastrointestinal disorders. This finding pANCA highlights the relatively good specificity but poor sensitivity of ASCA as a marker for CD. pANCA on the other hand is more specific to ulcerative colitis.

Genetic studies

In addition, some *NOD2/ CARD15* gene polymorphisms were found to be associated with CD with gastroduodenal involvement. It is possible that these genes might also help to support the diagnosis in the atypical presentation of CD in the future[2].

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes corrosive gastritis due to ingestion of lye, gastric scirrhous carcinoma, Ménétrier's disease. Pseudolymphoma, amyloidosis can also mimic CD[29]. Although Ménétrier's disease can involve the entire stomach and produce ulcérations, it does not cause transmural disease[29]. Malignant and infiltrative processes are to be ruled out by the histological findings.

TREATMENT

Medical treatment

Proton pump inhibitors in combination with steroids are the first line of treatment in active CD. Some of the studies proved steroid-induced remission in active disease[10,11,35-39]. But, 6-Mercaptopurine and azathioprine are proved to be helpful to maintain steroid induced remission.

Balloon dialation

Strictures are treated successfully with balloon dilation[4,5,40-43].

Surgical intervention

Some of the patients requires surgical intervention, where patients are not responding to medical treatment[44]. Other situations are massive and persistent upper gastrointestinal hemorrhage, gastric outlet obstruction, and fistula or abscess formation[4,5,7,10,12,45]. The important indication is duodenal obstruction[6]. The surgical modalities of treatment include bypass surgery with gastrojejunostomy[6,7,9]. Gastrojejunostomy with highly selective vagotomy is an ideal line of management[44]. Delayed gastric emptying is a postoperative complication seen in 24% of cases, but this may be seen in stricturoplasty also[6,46,47]. Additional post operative complications are anastomotic leak, enterocutaneous fistula, intraabdominal abscess, and stomal ulceration[48].

CONCLUSION

To conclude, CD with isolated gastric involvement is an extremely unusual event in clinical practice. Endoscopic biopsy along with battery of laboratory tests is an effective tool to hit the correct diagnosis by exclusion of

various causes of granulomatous gastritis. This prevents untoward mortality and/morbidity related to disease and treatment.

REFERENCES

1 **Ingle SB**, Pujari GP, Patle YG, Nagoba BS. An unusual case of Crohn's disease with isolated gastric involvement. *J Crohns Colitis* 2011; **5**: 69-70 [PMID: 21272809 DOI: 10.1016/j.crohns.2010.10.001]

2 **Ingle SB**, Hinge CR, Dakhure S, Bhosale SS. Isolated gastric Crohn's disease. *World J Clin Cases* 2013; **1**: 71-73 [PMID: 24303469 DOI: 10.12998/wjcc.v1.i2.71]

3 **Isaacs KL**. Upper gastrointestinal tract endoscopy in inflammatory bowel disease. *Gastrointest Endosc Clin N Am* 2002; **12**: 451-462, vii [PMID: 12486938 DOI: 10.1016/S1052-5157(02)00006-5]

4 **Burakoff R**. Gastroduodenal Crohn's disease. In: Bayless TM, Hanauer SB, editors. Advanced therapy of inflammatory bowel disease. Hamilton, Ontario: BC Decker, 2001: 421-423

5 **Banerjee S**, Peppercorn MA. Inflammatory bowel disease. Medical therapy of specific clinical presentations. *Gastroenterol Clin North Am* 2002; **31**: 185-202, x [PMID: 12122731 DOI: 10.1016/S0889-8553(01)00012-7]

6 **Reynolds HL**, Stellato TA. Crohn's disease of the foregut. *Surg Clin North Am* 2001; **81**: 117-135, viii [PMID: 11218159 DOI: 10.1016/S0039-6109(05)70276-0]

7 **van Hogezand RA**, Witte AM, Veenendaal RA, Wagtmans MJ, Lamers CB. Proximal Crohn's disease: review of the clinicopathologic features and therapy. *Inflamm Bowel Dis* 2001; **7**: 328-337 [PMID: 11720325 DOI: 10.1097/00054725-200111000-00010]

8 **Sands BE**. Crohn's disease. In: Feldman M, Friedman LS, Sleisenger MH, editors. Sleisenger and Fordtran's gastrointestinal and liver disease, 7th ed. Philadelphia: Saunders, 2002: 2005-2038

9 **Loftus EV**. Upper gastrointestinal tract Crohn's disease. *Clin Perspect Gastroenterol* 2002; **5**: 188-191

10 **Nugent FW**, Richmond M, Park SK. Crohn's disease of the duodenum. *Gut* 1977; **18**: 115-120 [PMID: 856671 DOI: 10.1136/gut.18.2.115]

11 **Nugent FW**, Roy MA. Duodenal Crohn's disease: an analysis of 89 cases. *Am J Gastroenterol* 1989; **84**: 249-254 [PMID: 2919581]

12 **Wagtmans MJ**, Verspaget HW, Lamers CB, van Hogezand RA. Clinical aspects of Crohn's disease of the upper gastrointestinal tract: a comparison with distal Crohn's disease. *Am J Gastroenterol* 1997; **92**: 1467-1471 [PMID: 9317064]

13 **Bach JF**. The effect of infections on susceptibility to autoimmune and allergic diseases. *N Engl J Med* 2002; **347**: 911-920 [PMID: 12239261 DOI: 10.1056/NEJMra020100]

14 **Danese S**, Sans M, Fiocchi C. Inflammatory bowel disease: the role of environmental factors. *Autoimmun Rev* 2004; **3**: 394-400 [PMID: 15288007 DOI: 10.1016/j.autrev.2004.03.002]

15 **Lodes MJ**, Cong Y, Elson CO, Mohamath R, Landers CJ, Targan SR, Fort M, Hershberg RM. Bacterial flagellin is a dominant antigen in Crohn disease. *J Clin Invest* 2004; **113**: 1296-1306 [PMID: 15124021 DOI: 10.1172/JCI200420295]

16 **Targan SR**, Landers CJ, Yang H, Lodes MJ, Cong Y, Papadakis KA, Vasiliauskas E, Elson CO, Hershberg RM. Antibodies to CBir1 flagellin define a unique response that is associated independently with complicated Crohn's disease. *Gastroenterology* 2005; **128**: 2020-2028 [PMID: 15940634 DOI: 10.1053/j.gastro.2005.03.046]

17 **Neurath MF**, Weigmann B, Finotto S, Glickman J, Nieuwenhuis E, Iijima H, Mizoguchi A, Mizoguchi E, Mudter J, Galle PR, Bhan A, Autschbach F, Sullivan BM, Szabo SJ, Glimcher LH, Blumberg RS. The transcription factor T-bet regulates mucosal T cell activation in experimental colitis and Crohn's disease. *J Exp Med* 2002; **195**: 1129-1143 [PMID: 11994418 DOI: 10.1084/jem.20011956]

18 **Monteleone G**, Biancone L, Marasco R, Morrone G, Marasco O, Luzza F, Pallone F. Interleukin 12 is expressed and actively released by Crohn's disease intestinal lamina propria mononuclear cells. *Gastroenterology* 1997; **112**: 1169-1178 [PMID: 9098000 DOI: 10.1016/S0016-5085(97)70128-8]

19 **Pizarro TT**, Michie MH, Bentz M, Woraratanadharm J, Smith MF, Foley E, Moskaluk CA, Bickston SJ, Cominelli F. IL-18, a novel immunoregulatory cytokine, is up-regulated in Crohn's disease: expression and localization in intestinal mucosal cells. *J Immunol* 1999; **162**: 6829-6835 [PMID: 10352304]

20 **Ina K**, Itoh J, Fukushima K, Kusugami K, Yamaguchi T, Kyokane K, Imada A, Binion DG, Musso A, West GA, Dobrea GM, McCormick TS, Lapetina EG, Levine AD, Ottaway CA, Fiocchi C. Resistance of Crohn's disease T cells to multiple apoptotic signals is associated with a Bcl-2/Bax mucosal imbalance. *J Immunol* 1999; **163**: 1081-1090 [PMID: 10395708]

21 **Sturm A**, Leite AZ, Danese S, Krivacic KA, West GA, Mohr S, Jacobberger JW, Fiocchi C. Divergent cell cycle kinetics underlie the distinct functional capacity of mucosal T cells in Crohn's disease and ulcerative colitis. *Gut* 2004; **53**: 1624-1631 [PMID: 15479683 DOI: 10.1136/gut.2003.033613]

22 **Sakaguchi S**. Naturally arising Foxp3-expressing CD25+CD4+ regulatory T cells in immunological tolerance to self and non-self. *Nat Immunol* 2005; **6**: 345-352 [PMID: 15785760 DOI: 10.1038/ni1178]

23 **Maul J**, Loddenkemper C, Mundt P, Berg E, Giese T, Stallmach A, Zeitz M, Duchmann R. Peripheral and intestinal regulatory CD4+ CD25(high) T cells in inflammatory bowel disease. *Gastroenterology* 2005; **128**: 1868-1878 [PMID: 15940622 DOI: 10.1053/j.gastro.2005.03.043]

24 **Hart AL**, Al-Hassi HO, Rigby RJ, Bell SJ, Emmanuel AV, Knight SC, Kamm MA, Stagg AJ. Characteristics of intestinal dendritic cells in inflammatory bowel diseases. *Gastroenterology* 2005; **129**: 50-65 [PMID: 16012934 DOI: 10.1053/j.gastro.2005.05.013]

25 **Wehkamp J**, Harder J, Weichenthal M, Schwab M, Schäffeler E, Schlee M, Herrlinger KR, Stallmach A, Noack F, Fritz P, Schröder JM, Bevins CL, Fellermann K, Stange EF. NOD2 (CARD15) mutations in Crohn's disease are associated with diminished mucosal alpha-defensin expression. *Gut* 2004; **53**: 1658-1664 [PMID: 15479689 DOI: 10.1136/gut.2003.032805]

26 **Rogler G**. Update in inflammatory bowel disease pathogenesis. *Curr Opin Gastroenterol* 2004; **20**: 311-317 [PMID: 15703658 DOI: 10.1097/00001574-200407000-00003]

27 **Rutgeerts P**, Onette E, Vantrappen G, Geboes K, Broeckaert L, Talloen L. Crohn's disease of the stomach and duodenum: A clinical study with emphasis on the value of endoscopy and endoscopic biopsies. *Endoscopy* 1980; **12**: 288-294 [PMID: 7428736 DOI: 10.1055/s-2007-1021762]

28 **Levine MS**. Crohn's disease of the upper gastrointestinal tract. *Radiol Clin North Am* 1987; **25**: 79-91 [PMID: 3823395]

29 **Cary ER**, Tremaine WJ, Banks PM, Nagorney DM. Isolated Crohn's disease of the stomach. *Mayo Clin Proc* 1989; **64**: 776-779 [PMID: 2770360 DOI: 10.1016/S0025-6196(12)61750-9]

30 **Danzi JT**, Farmer RG, Sullivan BH, Rankin GB. Endoscopic features of gastroduodenal Crohn's disease. *Gastroenterology* 1976; **70**: 9-13 [PMID: 1245289]

31 **Alcántara M**, Rodriguez R, Potenciano JL, Carrobles JL, Muñoz C, Gomez R. Endoscopic and bioptic findings in the upper gastrointestinal tract in patients with Crohn's disease. *Endoscopy* 1993; **25**: 282-286 [PMID: 8330547 DOI: 10.1055/s-2007-1010315]

32 **Fenoglio-Preiser CM**, Noffsinger AE, Stemmermann GN, Lantz PE, Listrom MB, Rilke FO. The non neoplastic stomach. In: Gastrointestinal Pathology. 2nd ed. Philadelphia: Lippincott-Raven, 1999: 153-236

33 **Hashiguchi K**, Takeshima F, Akazawa Y, Matsushima K, Minami H, Yamaguchi N, Shiozawa K, Ohnita K, Ichikawa T, Isomoto H, Nakao K. Bamboo joint-like appearance of the stomach: a stable endoscopic landmark for Crohn's disease regardless of anti-tumor necrosis factor alpha treatment. *Med Sci Monit* 2014; **20**: 1918-1924 [PMID: 25308423 DOI: 10.12659/MSM.891060]

34 **Halme L**, Kärkkäinen P, Rautelin H, Kosunen TU, Sipponen P. High frequency of helicobacter negative gastritis in patients with Crohn's disease. *Gut* 1996; **38**: 379-383 [PMID: 8675090 DOI:

10.1136/gut.38.3.379]
35 **Oberhuber G**, Püspök A, Oesterreicher C, Novacek G, Zauner C, Burghuber M, Vogelsang H, Pötzi R, Stolte M, Wrba F. Focally enhanced gastritis: a frequent type of gastritis in patients with Crohn's disease. *Gastroenterology* 1997; **112**: 698-706 [PMID: 9041230 DOI: 10.1053/gast.1997.v112.pm9041230]
36 **Parente F**, Cucino C, Bollani S, Imbesi V, Maconi G, Bonetto S, Vago L, Bianchi Porro G. Focal gastric inflammatory infiltrates in inflammatory bowel diseases: prevalence, immunohistochemical characteristics, and diagnostic role. *Am J Gastroenterol* 2000; **95**: 705-711 [PMID: 10710061 DOI: 10.1111/j.1572-0241.2000.01851.x]
37 **Miehsler W**, Püspök A, Oberhuber T, Vogelsang H. Impact of different therapeutic regimens on the outcome of patients with Crohn's disease of the upper gastrointestinal tract. *Inflamm Bowel Dis* 2001; **7**: 99-105 [PMID: 11383598 DOI: 10.1097/00054725-200105000-00004]
38 **Valori RM**, Cockel R. Omeprazole for duodenal ulceration in Crohn's disease. *BMJ* 1990; **300**: 438-439 [PMID: 2107896 DOI: 10.1136/bmj.300.6722.438]
39 **Griffiths AM**, Alemayehu E, Sherman P. Clinical features of gastroduodenal Crohn's disease in adolescents. *J Pediatr Gastroenterol Nutr* 1989; **8**: 166-171 [PMID: 2709248 DOI: 10.1097/00005176-198902000-00008]
40 **Korelitz BI**, Adler DJ, Mendelsohn RA, Sacknoff AL. Long-term experience with 6-mercaptopurine in the treatment of Crohn's disease. *Am J Gastroenterol* 1993; **88**: 1198-1205 [PMID: 8338087]
41 **Matsui T**, Hatakeyama S, Ikeda K, Yao T, Takenaka K, Sakurai T. Long-term outcome of endoscopic balloon dilation in obstructive gastroduodenal Crohn's disease. *Endoscopy* 1997; **29**: 640-645 [PMID: 9360875 DOI: 10.1055/s-2007-1004271]
42 **Dancygier H**, Frick B. Crohn's disease of the upper gastrointestinal tract. *Endoscopy* 1992; **24**: 555-558 [PMID: 1396364 DOI: 10.1055/s-2007-1010544]
43 **Murthy UK**. Repeated hydrostatic balloon dilation in obstructive gastroduodenal Crohn's disease. *Gastrointest Endosc* 1991; **37**: 484-485 [PMID: 1916177 DOI: 10.1016/S0016-5107(91)70789-X]
44 **Marcello PW**, Schoetz DJ. Gastroduodenal Crohn's disease: surgical management. In: Bayless TM, Hanauer SB, editors. Advanced therapy of inflammatory bowel disease. Hamilton, Ontario: BC Decker, 2001: 461-463
45 **Murray JJ**, Schoetz DJ, Nugent FW, Coller JA, Veidenheimer MC. Surgical management of Crohn's disease involving the duodenum. *Am J Surg* 1984; **147**: 58-65 [PMID: 6691553 DOI: 10.1016/0002-9610(84)90035-7]
46 **Worsey MJ**, Hull T, Ryland L, Fazio V. Strictureplasty is an effective option in the operative management of duodenal Crohn's disease. *Dis Colon Rectum* 1999; **42**: 596-600 [PMID: 10344680 DOI: 10.1007/BF02234132]
47 **Yamamoto T**, Bain IM, Connolly AB, Allan RN, Keighley MR. Outcome of strictureplasty for duodenal Crohn's disease. *Br J Surg* 1999; **86**: 259-262 [PMID: 10100799 DOI: 10.1046/j.1365-2168.1999.01022.x]
48 **Yamamoto T**, Allan RN, Keighley MR. An audit of gastroduodenal Crohn disease: clinicopathologic features and management. *Scand J Gastroenterol* 1999; **34**: 1019-1024 [PMID: 10563673 DOI: 10.1080/003655299750025138]

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