ORIGINAL ARTICLE

AG-2021-173
doi.org/10.1590/S0004-2803.202200001-20

Small bowel is largely affected in Behçet's disease: a long-term follow-up of gastrointestinal symptoms

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Received: 25 August 2021
Accepted: 7 October 2021

ABSTRACT – Background – Behçet's disease is a rare immune-mediated disorder that can affect the gastrointestinal tract. The prevalence and extension of small bowel involvement is largely unknown. **Objective** – The aim of this study was to describe the small bowel lesions diagnosed by double-balloon enteroscopy (DBE) and to verify if these findings were associated to the presence of gastrointestinal symptoms and disease activity after long-term follow-up. **Methods** – This study included 19 Behçet's disease patients who underwent DBE. After a mean follow-up of 15 years the endoscopic findings were associated to the presence of gastrointestinal symptoms, disease activity and current therapy through collection of electronic medical records. **Results** – A total of 63.2% patients were female and the mean age was 37 years at the time of DBE. Mean disease duration at baseline was 24 years. 11 patients had no gastrointestinal symptoms and eight patients presented either abdominal pain, gastrointestinal bleeding or diarrhea. The average procedure time was 1 hour and 30 minutes and the ileum was achieved in all patients but one. Small bowel ulcers were diagnosed in 78.9%, with 63.1% of jejunal involvement. Two patients presented only small bowel edema and two were normal by DBE. Eight patients had concomitant gastric ulcers. Gastrointestinal symptoms prior to DBE were present in 36.8% of the patients and, after follow-up, all of them persisted with some of the symptoms. Bleeding was reported by three patients at baseline and persisted in only one patient. The frequency of treatment with steroids and immunomodulators was 31.6% and 57.9% at baseline, respectively, and 21% in both at the end of the follow-up. No patient was treated with biologics at the time of the DBE procedure and the current rate of biologic use is 21%. **Conclusion** – Small bowel involvement in Behçet's disease was frequently demonstrated by DBE even in asymptomatic patients. Understanding clinical evolution of the disease over the years and the impact of such diagnosis still represents a challenge, possibly with the need for novel treatment.

Keywords – Behçet's disease; double-balloon enteroscopy; ulcers; small intestine; long-term.

INTRODUCTION

Behçet's disease (BD) was first described by Hulusi Behçet in 1937, and represents a rare chronic immune-mediated disorder usually manifested by oral and genital ulcers and uveitis[1]. It is characterized by relapses and clinical remissions cycles which can lead to life-threatening depending on the involved complications[2].

The International Group for the Study of Behçet's Disease (ISGBD) defined a criteria for BD diagnosis, with 85% sensitivity and 96% specificity. ISGBD criteria requires recurrent oral ulcer with at least three episodes in 12 months, associated with two of the following findings: genital ulcer, eye lesions, skin lesions and positive pathergy test, which is characterized by the development of a wheal or pustule at the needle prick site within 48 hours[3].

BD is mainly diagnosed between the third and fourth decade of life[4,5] and it has been reported worldwide, although some cases cluster along the old "Silk Road", which extends from East Asia to the Mediterranean basin[6].The estimated prevalence of BD on the "Silk Road" is 14 cases per 100,000 inhabitants[7]. One of the highest incidence has been reported in Anatolia, Turkey, estimated at 420 cases per 100,000 inhabitants[8]. Japan also has a different rate than Western countries, 15 cases per 100,000 inhabitants. On the other hand, it was observed in countries such as United Kingdom, USA, Germany and Portugal with incidence rates of 0.6, 0.12, 4.16 and 2.4 cases per 100,000 inhabitants, respectively[9-11]. Although controversial, some studies have shown that men and women are equally affected[9], with arthritis occurring more frequently in the female population[12].There is an association between the major histocompatibility complex HLA–B51 allele and BD, which is present in 67.3% of cases[13,14] but the association with environmental factors has also been described[15].

The frequency of gastrointestinal tract (GIT) involvement among patients with BD varies from 2.8% to 58% in different cohorts[16]. Peker et al. highlighted three reasons why the BD diagnosis of GIT lesions is a challenge: first, it is a rare disease; second, mild symptoms may be overlooked; and lastly, the absence of symptoms despite of the presence of GIT lesions[17]. Moreover, other diseases, like Crohn's disease, have similar BD symptoms making differential

Declared conflict of interest of all authors: Queiroz NSF: Consulting fees from Janssen, Takeda and Abbvie. Sobrado Junior CW: Consulting fees from Janssen, Takeda and Abbvie. Facanali CBG, Facanali Junior MR, Ribeiro Junior U, Safatle-Ribeiro AV: they have no conflict of interest.
Disclosure of funding: no funding received.
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diagnosis difficult[18]. Thus, in patients presenting GIT symptoms, abdominal imaging is required, such as barium study x-ray[19], computed tomography[20], and magnetic resonance enterography[17].

Zou et al., who performed upper and lower gastrointestinal endoscopies on 168 Chinese patients, showed that 35.1% of them presented GIT lesions, including some asymptomatic patients[21]. Few studies have evaluated the small bowel in patients with BD by video capsule endoscopy[22-24], however there is a paucity of studies with balloon-assisted enteroscopy, either double balloon enteroscopy (DBE) or single-balloon enteroscopy, which has already been described as a safe, and effective method for this kind of assessment[25].

Given that GIT manifestations of BD are associated with significant morbidity and mortality, the appropriate staging of small bowel involvement is of ultimate importance for the proper management of the disease. Thus, the aim of this study was to describe the GIT small bowel lesions diagnosed by DBE and to verify if these findings were associated to the presence of GIT symptoms and disease activity after 15 years of follow-up.

METHODS

This is a single-center prospective analysis of a retrospectively collected database cohort. (FIGURE 1).

Nineteen patients, aged over 18 years, with an established diagnosis of BD, according to the International Study Group for Behçet's disease criteria[26], underwent DBE between 2005 and 2006 for small bowel assessment. Medical evaluation, including anamnesis and physical exam regarding the presence of abdominal pain, diarrhea and gastrointestinal bleeding was assessed within a 30-day period previously to the performance of DBE. All DBE procedures were performed by a single experienced endoscopist. BD patients were treated according to the outpatient clinic protocol.

Between January and June 2020 these patients were re-evaluated for the presence of abdominal pain, diarrhea and gastrointestinal bleeding. All patients were followed by a single physician in the outpatient clinic.

Ethical approval was obtained from institutional and national Ethics Committee, registered under CAAE 35869520.9.0000.0068.

RESULTS

DBE was performed in 19 patients with an established diagnosis of BD, under deep sedation without complications. Twelve (63.2%) patients were female, and the mean age was 37 years (34 to 80 years-old) at the time of DBE. Mean disease duration at baseline was 24 years (18–40).

Eleven patients had no GIT symptoms, and eight patients presented either abdominal pain, gastrointestinal bleeding or diarrhea.

The average procedure time was 1 hour and 30 minutes (ranging of 1 to 3 hours), and the ileum was achieved in all patients but one. Small bowel ulcers were diagnosed in 78.9% (15/19), with 63.1% of jejunal involvement (12/19). Two patients presented only small bowel edema and two were normal by DBE (FIGURE 2 and FIGURE 3). Eight patients had concomitant gastric ulcers.

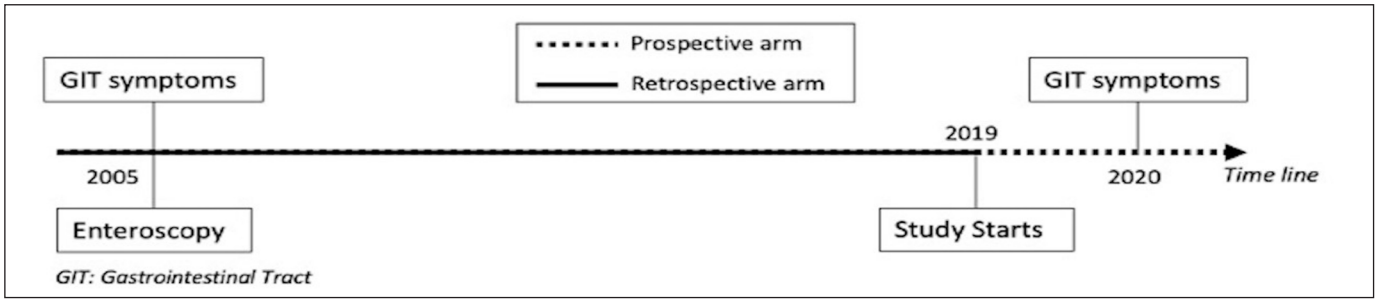

FIGURE 1. Algorithm of the Study Design.

Case	Gender	Current Age (years)	Current Disease Durantion (years)	Enteroscopy Gain	Enteroscopy Findings	Distribution Pattern
1	F	37	25	Medium Ileum	Ileal ulcers < 5 mm	Multiple
2	F	41	18	Medium Ileum	Duodenal and Jejunal ulcers < 5 mm	Multiple
3	F	54	20	Proximal Ileum	Duodenal and Jejunal ulcers < 5 mm	Multiple
4	F	45	25	Proximal Ileum	Jejunal Edema and Lymphangiectasis	Multiple
5	F	48	18	Proximal Ileum	Normal	–
6	M	58	22	Proximal Ileum	Gastric and Jejunal ulcers < 5 mm	Multiple
7	M	59	34	Proximal Ileum	Duodenal and jejunal ulcers < 5mm	Multiple
8	M	51	20	Proximal Ileum	Ileal Edema	–
9	F	56	30	Proximal Ileum	Duodenal, Jejunal and Ileal ulcers < 5 mm	Multiple
10	M	44	20	Proximal Ileum	Gastric, duodenal and jejunum ulcers >5, < 10 mm	Multiple
11	F	80	40	Medium Ileum	Gastric and Jejunal ulcers < 5 mm	Multiple
12	M	58	19	Proximal Ileum	Gastric and Jejunal ulcers < 5 mm	Multiple
13	F	62	19	Terminal Ileum	Gastric ulcers < 5 mm	Multiple
14	M	43	27	Proximal Ileum	Duodenal and Jejunal Ulcers < 5 mm	Multiple
15	F	41	18	Medium Ileum	Gastric and Duodenal ulcers < 5 mm	Multiple
16	F	58	29	Proximal Jejunum	Jejunal ulcers > 5, <10 mm	Multiple
17	F	75	19	Terminal Ileum	Gastric, Duodenal, Jejunal and Ileal ulcers < 5 mm	Multiple
18	M	51	21	Distal Ileum	Ileal ulcers < 5 mm	Mulitple
19	F	34	29	Proximal Ileum	Gastric, Duodenal and Jejunal ulcers < 5 mm	Mulitple

FIGURE 2. Clinical features of patients with Behçet's Disease and Enteroscopy Findings.

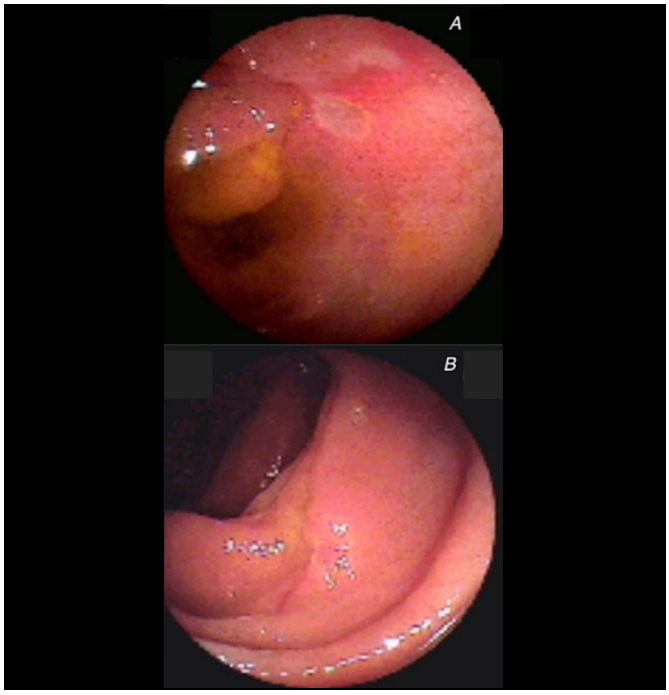

FIGURE 3. A) Case 18: multiple ulcers in distal ileum. **B)** Case 10: Jejunal ulcer.

GIT symptoms prior to DBE were present in 36.8% of the patients and, after follow-up, all of them persisted with some of the symptoms (FIGURE 4). Bleeding was reported by 3/19 patients at baseline and persisted in only one patient.

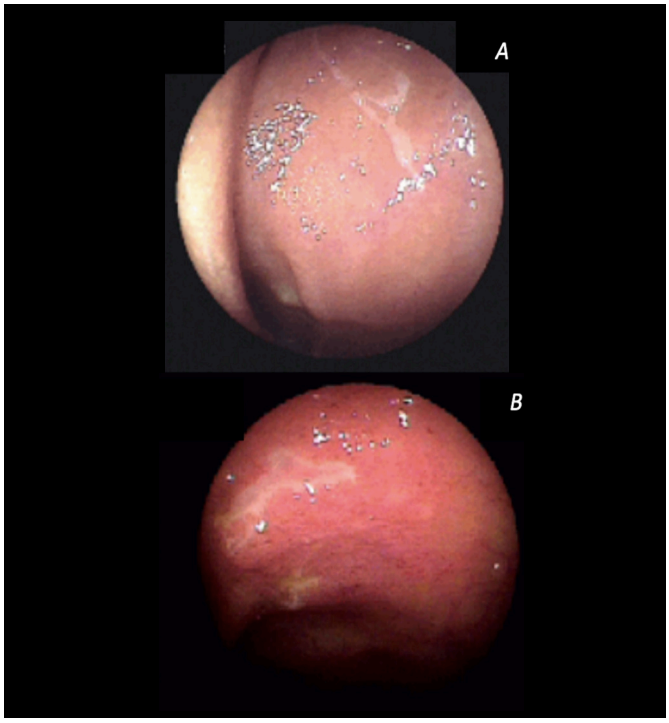

FIGURE 4. A) Case 19: Superficial ulcer covered by fibrin in the duodenum. **B)** Case 17: Presence of ulcers covered by fibrin in the ileum.

Treatment at baseline and at the end of follow-up is described in FIGURE 5. The frequency of treatment with steroids and immunomodulators was 31.6% and 57.9% at baseline, respectively, and 21% in both at the end of the follow-up. There was no patient using immunobiologicals at the time of the DBE procedure, and currently, about 21% of them are using them.

	Gastrointestinal symptons in 2005-06			Gastrointestinal symptons in 2020		
Case	Abdominal Pain	Diarrhea	Gastrointestinal Bleeding	Abdominal Pain	Diarrhea	Gastrointestinal Bleeding
1	–	–	–	–	–	–
2	–	–	–	–	–	–
3	+	+	+	+	–	–
4	+	+	+	+	–	–
5	–	–	–	–	–	–
6	–	–	–	–	–	–
7	+	–	–	+	–	–
8	–	–	–	–	–	–
9	–	–	–	–	–	–
10	–	–	–	–	–	–
11	+	–	–	+	+	–
12	–	–	–	–	–	–
13	–	–	–	–	–	–
14	–	–	–	–	–	–
15	+	–	–	+	–	–
16	+	–	–	+	–	–
17	–	–	–	–	–	–
18	–	–	+	–	–	+
19	–	–	–	–	–	–

FIGURE 5. Previous and Current Gastrointestinal Symptoms of patients with Behçet's Disease.

At the time of DBE, all patients were taking some medication (FIGURE 6). Eleven patients were using immunosuppressants, being one on immunosuppressive monotherapy and nine on immunosuppressants associated with prednisone and colchicine. There were also three patients using colchicine associated with thalidomide. Over the 15-years follow-up, six patients have used at least one immunobiological.

DISCUSSION

Small bowel ulcers were frequently diagnosed by DBE in BD patients, even in those asymptomatic from the gastrointestinal point of view. However, the impact of this finding still represents a challenge on the long-term clinical progression of the disease.

Small bowel endoscopy have been useful in detecting and staging lesions involving the GIT in BD. DBE allows the assessment of the entire small intestine[27], with direct visualization of the lesion, tissue biopsies and, possible, treatment[25,28,29]. Nowadays, small intestine assessment through DBE has been rarely performed in BD patients, since video capsule endoscopy represents a less invasive procedure, despite of not allowing biopsies.

In the present study, DBE demonstrated that the jejunum was the most affected region, although the duodenum and the ileum could also present some ulcers[30]. Accordingly, a Brazilian study using capsule endoscopy, demonstrated that the jejunum was affected in 80%, presenting erosions and ulcers[24].

Of all asymptomatic patients (12/19) at the time of DBE, 52.6% of them presented lesions in the small intestine. This rate is considerable higher than the reported frequencies ranging from 3% to 25%[2,31-33] from studies that evaluated only lower and upper GIT, reinforcing the importance of total small bowel evaluation. Ileocecal region was previously described as the most commonly affected region[16].

Case	Treatment at DBE period	Current Treatment	Surgical History
1	colchicine and azathioprine	colchicine	No
2	azathioprine, chloroquine, colchicine and prednisone	gabapentin, colchicine and amitriptyline	No
3	colchicine, fluoxetine and methotrexate	azathioprine, chloroquine, amitriptyline, cyclobenzaprine, fluoxetine and prednisone	No
4	prednisone and sulfasalazine	certolizumab 200mg every 15 days, methotrexate, prednisone, gabapentin and amitrptyline	No
5	cyclosporine, colchicine and sulfasalazine	infliximab every 10 weeks	No
6	cyclosporine and prednisone	colchicine	No
7	colchicine, indomethacin, methotrexate, prednisone and benzathine penicillin monthly	methotrexate	No
8	colchicine	without medication	No
9	colchicine and thalidomide	without medication	Cholecystectomy
10	chlorambucil, thalidomide, colchicine, chloroquine and benzathine penicillin monthly	infliximab every 10 weeks	No
11	raloxifene	without medication	Cholecystectomy
12	colchicine, prednisone, amitriptyline and thalidomide	colchicine	No
13	amitriptyline, azathioprine, chloroquine, colchicine and pentoxifylline	amitriptyline and colchicine	No
14	cyclosporine, prednisone and colchicine	colchicine	No
15	colchicine and amitriptyline	without medication	No
16	methotrexate, fluoxetine, chloroquine and pentoxifylline	amitriptyline, gabapentin and colchicine	Cholecystectomy
17	azathioprine	methotrexate, prednisone and secukimumab	No
18	cyclosporine, pentoxifylline and colchicine	without medication	No
19	colchicine	prednisone and colchicine	Appendectomy

FIGURE 6. Previous and Current treatment of patients with Behçet's Disease.

Stomach is usually lesser affected in BD. However, one study of Twain, including 28 patients, demonstrated a prevalence of 43% of gastric involvement, besides isolated duodenal ulcers or both[34]. Higher rates of minor gastric ulcers were also observed during anterograde DBE in the present study, and the majority had concomitant small bowel segment involved.

The most prevalent described GIT manifestations associated with BD are abdominal pain, diarrhea and bleeding[35], mostly being mild symptoms[36]. After long-term follow-up and clinical management, only one patient persisted with bleeding. It is important to mention that the presence of small bowel ulcers or erosions might cause occult bleeding leading to anemia in these patient population.

Although BD may progress with severe GIT complications, such as fistulas or perforations[37], no major complication was detected in this cohort followed over a 15-year period.

The treatment for GIT manifestations in BD is not standardized, with different classes of medications being used for each symptom presented, and it is also based on severity and complications[38]. Even though the majority of patients included in this analysis were asymptomatic, it was observed a high proportion of small bowel lesions. Such endoscopic findings might be relevant, since small intestine lesions may contribute to a worse prognosis over the years, increasing the morbidity and mortality[16]. However, whether the proactive management of small bowel lesions in asymptomatic patients aiming changing in disease course is unknown. Noteworthy, for other immune-mediated diseases affecting GIT, such as Crohn's disease, early intervention and disease monitoring is associated with better long-term outcomes[39]. In this study, it was not possible to evaluate disease progression, as patients were not reassessed by DBE, but it is important to highlight that and the proportion of patients presenting GIT symptoms remained stable over time.

The most widely used medications, such as five aminosalicylic acid, corticosteroids and immunomodulators[40], anti-tumor necrosis factors, including infliximab and adalimumab, have recently been included in the arsenal of new treatments of different manifestations of BD, including GIT, with good efficacy and safety[38,41]. This temporal trend was clearly demonstrated in this cohort with a marked increase in the use of biological therapy over time. Other promising immunobiologicals, such as anti-interleukin 1, 6, 17 and 12/23 need further studies to demonstrate their effectiveness in treating GIT symptoms of BD[42].

This study showed that there are patients who presented GIT symptoms and patients that do not presented GIT symptoms, as recently suggested by some authors, concerning different inflammatory pathways for distinct BD phenotypes[43,44]. This fact corroborates the complexity of the disease and the difficulty of its treatment and management.

The study has some limitations, including the small sample size and the fact that data was obtained from one single institution. However, the strong points are the long-term follow-up of a rare disease and the evaluations carried out by a single professional.

CONCLUSION

The early diagnosis of small bowel lesions in BD patients, even in asymptomatic patients, might have an impact on therapeutic management.

Thus far, there is no curative treatment to BD. Understanding clinical evolution of the disease over the years and the impact of such diagnosis, still represents a challenge, possibly with the need for novel treatment.

New studies with long-term endoscopic follow-up will be able to determine whether the disease progresses or not endoscopically.

Authors' contribution

Facanali CBG: substantial contributions to the conception, acquisition, interpretation of data work. Facanali Junior MR: formal analysis of data for the work. Ribeiro Junior U: drafting the work and revising it critically for important intellectual content. Queiroz NSF: drafting the work and revising it critically for important intellectual content. Carlos Sobrado Junior CW: final editing/end reviewing. Safatle-Ribeiro AV: project administration, supervision, enteroscopy examination. Final approval of the version to be published. Guarantor of the article.

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Facanali CBG, Facanali Junior MR, Ribeiro Junior U, Queiroz NSF, Sobrado Junior CW, Safatle-Ribeiro AV. O intestino delgado é amplamente afetado na doença de Behçet: um acompanhamento de longo prazo dos sintomas gastrointestinais. Arq Gastroenterol. 2022;59(1):117-22.

RESUMO – **Contexto** – A doença de Behçet é uma doença imunomediada rara que pode afetar o trato gastrointestinal. A prevalência e extensão do envolvimento do intestino delgado é desconhecida. **Objetivo** – O objetivo deste estudo foi descrever as lesões do intestino delgado diagnosticadas por enteroscopia de duplo balão (EDB) e verificar se esses achados estavam associados à presença de sintomas gastrointestinais e atividade da doença após seguimento de longo prazo. **Métodos** – Este estudo incluiu 19 pacientes com doença de Behçet que foram submetidos a EDB. Após seguimento médio de 15 anos, os achados endoscópicos foram associados à presença de sintomas gastrointestinais, atividade da doença e terapia atual por meio de coleta de prontuário eletrônico. **Resultados –** Um total de 63,2% dos pacientes eram do sexo feminino e a média de idade era de 37 anos no momento da EDB. A duração média da doença no início do estudo foi de 24 anos. 11 pacientes não apresentaram sintomas gastrointestinais e oito pacientes apresentaram dor abdominal, sangramento gastrointestinal ou diarréia. O tempo médio do procedimento foi de 1 hora e 30 minutos e o íleo foi atingido em todos os pacientes, exceto em um. Úlceras de intestino delgado foram diagnosticadas em 78,9%, sendo 63,1% de acometimento jejunal. Dois pacientes apresentaram apenas edema de intestino delgado e dois apresentaram EDB normais. Oito pacientes tinham úlceras gástricas concomitantes. Sintomas gastrointestinais prévios à EDB estavam presentes em 36,8% dos pacientes e, após o seguimento, todos persistiram com alguns dos sintomas. Sangramento foi relatado por três pacientes no início do estudo e persistiu em apenas um paciente. A frequência de tratamento com esteroides e imunomoduladores foi de 31,6% e 57,9% no início do estudo, respectivamente, e 21% em ambos ao final do seguimento. Nenhum paciente foi tratado com biológicos no momento da EDB e a taxa atual de uso de biológicos é de 21%. **Conclusão** – O envolvimento do intestino delgado na doença de Behçet foi frequentemente demonstrado por EDB mesmo em pacientes assintomáticos. Compreender a evolução clínica da doença ao longo dos anos e o impacto de tal diagnóstico ainda representa um desafio, possivelmente com a necessidade de novos tratamentos.

Palavras-chave – Doença de Behçet; enteroscopia com duplo balão; úlceras; intestino delgado; longo prazo.

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