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Capsule Endoscopy in the Management of Refractory Coeliac Disease

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ABSTRACT

Background & Aims: There is no literature on the role of repeat small bowel capsule endoscopy (SBCE) in patients with refractory coeliac disease (RCD) following treatment with steroids +/- immunosuppressants.
Methods: The findings on SBCEs from a group of patients with histologically proven RCD (n=23) were compared to the findings from patients with uncomplicated coeliac disease (n=48). All patients had concurrent duodenal histology and serology taken at the time of SBCE.
Results: Patients with RCD had a greater extent of mucosal involvement on SBCE than patients with uncomplicated CD (42.4±34.1% vs 9.7±21.7%, p=0.0001). Following treatment with steroids and / or immunosuppressants, patients with RCD had an improvement in the extent of affected small bowel mucosa (42.4±34.1% vs 26.4±28.9% p=0.012). There was no statistical difference in histology and serology taken at the time of the first and second SBCE in patients with RCD.
Conclusions: Our study suggests that SBCE is valuable in documenting the extent of mucosal involvement in patients with RCD. This is the first study that delineates the value of a second look SBCE to assess improvement in the extent of disease in the small bowel following treatment.

Key words: coeliac disease – refractory coeliac disease – small bowel capsule endoscopy – immunosuppressants – steroids.

Abbreviations: CD: coeliac disease; GFD: gluten free diet; EATL: enteropathy associated T cell lymphoma; RCD: refractory coeliac disease; SM: small bowel; SBCE: small bowel capsule endoscopy.

INTRODUCTION

Coeliac disease (CD) has a prevalence of about 1% in the general population [1, 2]. About 0.31 to 10% of patients with CD go on to develop refractory coeliac disease (RCD) [3-7]. Such a varied prevalence of RCD reflects the difficulties encountered when diagnosing RCD on histology [7]. Persistent symptoms, absence of gluten ingestion for at least 6 to 12 months and persistence of histological changes on duodenal biopsies define RCD [8]. The absence of (Type I) or presence (Type II) of abnormal intraepithelial lymphocytes on duodenal histology can distinguish between the 2 subtypes of RCD [9]. PCR gene amplification on cells can differentiate between polyclonal (Type I) T cell receptors and monoclonal T cell receptors (Type II) [10, 11].

Refractory coeliac disease type I has the same histological appearance as uncomplicated CD with normal surface CD3 and CD8 expression and intracellular CD3 in intraepithelial lymphocytes that is similar in patients with a persistent ingestion of gluten [7]. It is therefore crucial to rule out gluten contamination when RCD is suspected as otherwise an inappropriate diagnosis of RCD I is made. Histological diagnosis of RCD II is also not full proof. An anomalous population of lymphocytes and a monoclonal T-cell receptor arrangement can also be found in the initial stages of CD diagnosis and in CD patients with persistent exposure to gluten [7, 12, 13]. Immunostaining can lead to a very inaccurate estimation of CD3+, CD8- cells [7]. It also does not distinguish between surface and intracellular CD3 [14]. Fresh biopsies are needed for flow cytometry, which can also be affected by variable cell yields and the lack of localization of the cells isolated [15].

Repeat duodenal histology is currently recommended following 3 months of treatment in RCD I. If response to treatment is observed, duodenal biopsies are repeated annually with quantification of aberrant intraepithelial lymphocytes. Repeat histology is also recommended in RCD II following initial treatment with steroids [16].

Despite duodenal histology currently being the gold standard for diagnosing RCD, the previously mentioned factors and the non-uniform pattern of CD in the small bowel (SB) [17] necessitate additional modalities for a confirmative diagnosis of RCD and for monitoring of its progression.

Endoscopic evaluation of the SB by small bowel capsule endoscopy (SBCE) is currently recommended whenever RCD is diagnosed [18]. This is to ensure no complications related to RCD have developed. These commonly occur in the distal SB and include enteropathy associated T cell lymphoma (EATL), B cell lymphoma, adenocarcinoma and ulcerative jejunoilieitis [19].

In addition to being a useful modality in diagnosing complications, SBCE has the potential to provide information on the extent of disease [19]. Although there has been some interest in SBCE providing information on the extent of diseased mucosa in the SB, this has only been assessed in patients with uncomplicated CD [20, 21]. No studies have looked at the extent of mucosal involvement at diagnosis of RCD and on second look SBCE to assess improvement in the extent of affected mucosa following treatment.

The aim of this study was to assess whether SBCE can provide additional information on RCD at the time of diagnosis apart from ruling out complications. We also assessed the role of a follow up SBCE after treatment with steroids +/- immunosuppressants.

METHODS

Study design and patients

Data on 23 patients with histologically confirmed RCD was prospectively compared to data from 48 patients with uncomplicated CD with persistent symptoms requiring SBCE, in whom RCD had been excluded histologically. The study was carried out over a 2-year period at Sheffield Teaching Hospitals, the national centre for the investigation and management of CD in the United Kingdom. They all underwent a gastroduodenoscopy with duodenal biopsies and a SBCE within 3 months of obtaining duodenal biopsies.

Duodenal histology

Details of histology that was obtained at the time of SBCE were collected. This was classified according to the modified Marsh Classification [22]. At least two samples from the duodenal bulb and four samples from the second part of the duodenum were taken during gastroduodenoscopy. The most severe histological grade for duodenal histology was considered as the overall histological grade for each patient. Initial reporting of duodenal histology was undertaken by one of three gastrointestinal histopathologists. All cases were then reviewed by a single gastrointestinal histopathologist with expertise in CD. Immunohistochemistry was performed on all samples for T-helper and T cytotoxic suppressor cells. Whenever a null clone was identified, T-cell receptor gene re-arrangement studies were carried out to exclude the presence of lymphoma.

Small bowel capsule endoscopy

Patients were asked to drink 2 litres of Klean-Prep® prior to undergoing SBCE. All patients underwent SBCE using the Pillcam SB3 (Medtronic, Minneapolis, USA) [23]. Details on gastric and SB passage time, extent of abnormal SB and macroscopic features of CD on SBCE were carefully examined. Macroscopic features of CD included villous atrophy, nodularity and mosaic pattern of mucosa, fissuring, scalloping of folds and ulcers (Figs. 1, 2, 3). The SBCEs were read by two expert reviewers (more than 300 SBCEs per year) blinded to both indications for SBCE and to results of duodenal histology. In the case of a disagreement about findings, a third expert reviewer was involved in the adjudication process.

Statistical analysis

Statistical analysis was carried out using SPSS version 23 (IBM Corp. Released 2015. IBM SPSS Statistics for Mac, Version 23.0. Armonk, NY: IBM Corp.). Descriptive data was

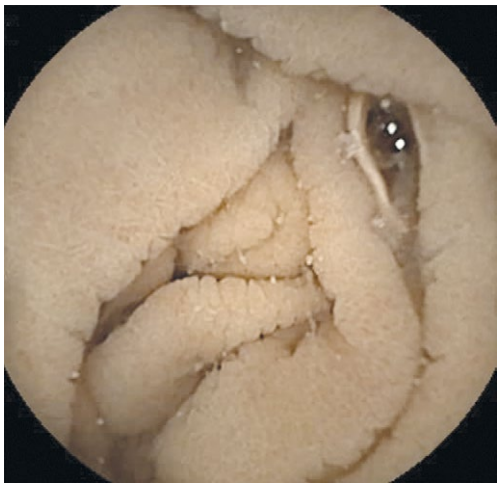

Fig. 1. Scalloping of mucosa in a patient with uncomplicated coeliac disease.

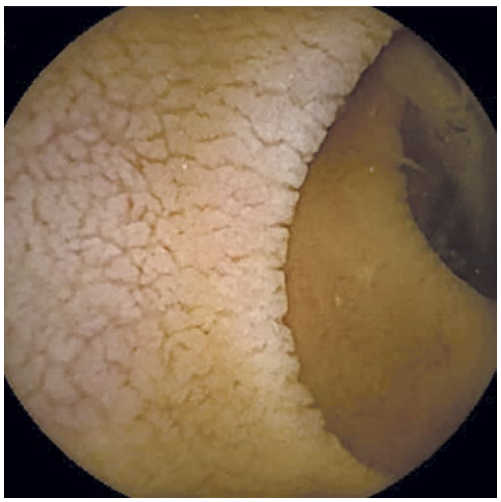

Fig. 2. Fissuring and scalloping of mucosa in a patient with type I refractory coeliac disease.

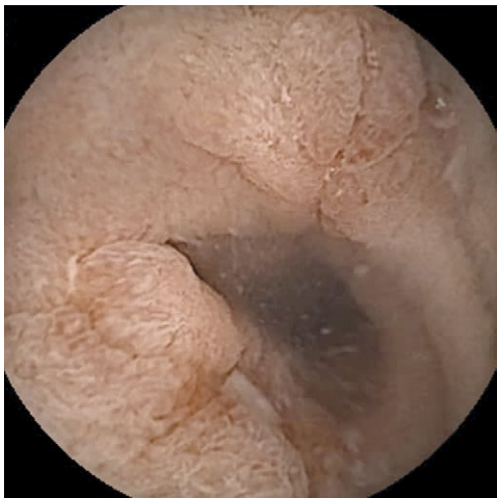

Fig. 3. Mucosal ulceration in a patient with refractory coeliac disease type II.

measured in the form of frequencies and percentages in the case of categorical variables and using mean and standard deviations if variables were continuous. Non-parametric statistical tests were used in view of the small cohort of patients in this study. The Fisher's Exact Test was used to compare categorical variables. The Mann-Whitney U test compared independent, continuous variables such as, for example, extent of disease on SBCE in both groups of patients. The Wilcoxon Signed Ranks Test was used to assess the statistical difference between 2 related variables; for example, the extent of disease on the first and second SBCE in patients with RCD. Results were considered to be statistically significant if the p value was less than 0.05.

Ethical considerations

The study was approved by the local research and development department of Sheffield Teaching Hospital NHS Foundation Trust under the registration number STH19998.

RESULTS

A total of 71 patients (51 females; 71.8%) with CD were included in this study. Refractory coeliac disease was present in 23 patients (32.4%) and uncomplicated CD was present in 48 patients (67.6%). The mean age of patients at the first SBCE was 52.5 (SD±15.5) years and the mean duration of disease before undergoing the first SBCE was 84 (SD±105.4) months. There was no statistical difference in the mean age at first SCBE (p=0.176), duration of disease (p=0.395) and gender (0.171) between the two groups.

Comparison of patients with refractory CD and uncomplicated CD

Patients with RCD had a more severe Marsh classification of disease on duodenal histology than patients with uncomplicated CD at the time of the first SBCE (p=0.034) (Table I).

There was no statistical significant difference in the positivity of endomysial antibody (EMA) (p=0.345), levels of anti-tissue transglutaminase antibody (anti-TTG) (p=0.691), anti-gliadin antibody IgG (p=0.801) and anti-gliadin antibody IgA (p=0.798) between patients with uncomplicated CD and RCD.

Table I. Marsh classification of histology in both groups of patients;

Marsh classification	CD [n, (%])	RCD [n, (%)]
0	6 (13.0%)	1 (4.3%)
1	8 (17.4%)	0
2	5 (10.9%)	0
3a	8 (17.4%)	4 (17.4%)
3b	10 (21.7%)	8 (34.8%)
3c	9 (19.6%)	10 (43.5%)

CD: coeliac disease; RCD: refractory coeliac disease

Patients with RCD (n=9; 39.1%) were more likely to have involvement beyond the proximal SB than patients with uncomplicated CD (n=4; 8.3%) (p=0.003). The length of abnormal mucosa and the percentage of abnormal SB mucosa were significantly longer in patients with RCD than in patients with uncomplicated CD (p=0.0001). Patients with RCD had significantly more scalloping (p=0.001), villous atrophy (p=0.017) and ulcers (p=0.004) in the SB than patients with uncomplicated CD (Table II). On applying the Bonferroni correction, the length of abnormal mucosa (p=0.001), the percentage of abnormal SB mucosa (p=0.001), the presence of scalloping (0.01) and ulcers (p=0.04) in the SB retained statistical significance.

Patients with refractory coeliac disease

Most patients with RCD (16, 69.6%) had type I disease. Patients had the following symptoms at the time of the first SBCE: diarrhea 9 (39.1%), fatigue 4 (17.4%), bloating 3 (13.0%), abdominal pain 3 (13.0%), weight loss 4 (17.4%), night sweats 1, (4.35%). None of the patients had other associated autoimmune conditions.

Patients received the following treatment between SBCEs: 6 patients (26.1%) received immunosuppressants (azathioprine, mycophenolate, 6-mercaptopurine), 10 patients (43.5%) were given budesonide or prednisolone, 5 patients (21.7%) received a combination of both immunosuppressants and steroids and 2 failed immunosuppressant therapy and were treated with interleukin 15 monoclonal antibody in addition to steroids. A SBCE was repeated after a mean of 17.0 months (SD±12.1) (Table III).

Eighteen patients continued with their medication as their second SBCE showed improvement in the extent of disease in the small bowel. Three patients with RCD I who had more extensive disease on the second SBCE were on budesonide at the time and had azathioprine added to their regime. Another two patients with RCD I with more extensive disease on the second SBCE who were on azathioprine, had budesonide added. Another patient with RCD II had a course of Cladribine following his failure to respond to mycophenolate.

There was no statistically significant difference in the positivity of endomysial antibody (EMA) (p=0.298), levels of anti-TTG (p=0.328) and anti-gliadin antibody IgG (p=0.345) between the first and second SBCE in patients with RCD.

Table II. Differences on capsule endoscopy in both groups

	Refractory coeliac disease (RCD) / uncomplicated coeliac disease (CD)	Mean	Std. Deviation	p value
Gastric passage time (minutes)	CD	27.1	26.4	0.606
	RCD	41.8	51.1	
Small bowel passage time (minutes)	CD	287.8	147.6	0.471
	RCD	296.5	102.1	
Time mucosa abnormal (minutes)	CD	30.5	72.1	0.0001
	RCD	137.0	121.5	
% abnormal mucosa	CD	9.7	21.7	0.0001
	RCD	42.4	34.1	
Villous atrophy	CD	8 (16.7%)		0.017
	RCD	10 (45.5%)		
Scalloping	CD	14 (29.2%)		0.001
	RCD	16 (72.7%)		
Mosaic pattern	CD	14 (29.2%)		0.287
	RCD	10 (43.5%)		
Ulcers	CD	1 (2.1%)		0.004
	RCD	6 (26.1%)		
Fissuring	CD	10 (20.8%)		0.389
	RCD	7 (30.4%)		
Nodularity	CD	1 (2.1%)		0.403
	RCD	1 (7.1%)		

CD: coeliac disease; RCD: refractory coeliac disease

Anti-gliadin IgA improved at the time of repeat SBCE (5.86 vs 3.87 U/ml) (p=0.003).

There was no statistical difference in histology taken at the time of the first and second SBCE in patients with RCD (p=0.136). However, there was an improvement in the length of abnormal SB mucosa (p=0.015) and the percentage of affected SB mucosa (p=0.012) when SBCE was repeated following treatment (Table IV). A smaller number of patients had diffuse disease on repeat SBCE. There was a significant reduction in the number of patients with ulcers in the small bowel (Table V). All patients had ulcers in the proximal small bowel except for one patient who had distal small bowel ulcers.

Although the number of patients with RCD II was small, patients with RCD type II had a greater extent of SB mucosal involvement than those with RCD type I on both the first (76.7% ±21.2 vs 31.0% ±29.2, p=0.005) and repeat SBCE (54.7% ±21.9 vs 15.7%±23.8, p=0.001).

DISCUSSION

This is the first study that assesses the role of a second look SBCE in patients with RCD. We found that the percentage of mucosa affected on repeating a SBCE in patients with RCD decreased from 42.4% to 26.4%.

The definition of RCD includes symptoms of malabsorption, persistent histological changes of villous atrophy and a thorough history confirming that a patient is following a strict gluten free diet (GFD) [8, 24, 25]. Otherwise histological changes can be attributed to persistent gluten exposure [26]. Even though serology is largely negative in patients with RCD, positive serology has been reported in between 13% and 49% of these patients [27, 28]. Our study has shown no difference in serological markers between patients with RCD and those with CD and no difference on repeating serological markers in patients with RCD. A diagnosis of RCD should be independent of serological antibody levels as current literature suggests that there is a low sensitivity for coeliac serology in detecting persistent villous atrophy in patients with CD [29].

Distinguishing patients with RCD from those with uncomplicated CD is pertinent due to the risk of transformation from RCD I to II and the high mortality associated with RCD due to complications that can develop such as adenocarcinoma, EATL, B cell lymphoma and jejunoileitis [30-34]. Type I RCD has a good prognosis with a 5 year survival of 96% [35]. Five year survival in patients with type II RCD can vary between 53 to 58% but can be as low as 8% if EATL develops. Survival after 5 years from diagnosis is usually better (90 – 96%) in patients with RCD I [36, 37]. Although a histological diagnosis is so far considered the gold standard for diagnosing RCD, the existence of some pitfalls in achieving a histological diagnosis of RCD means that this cannot be completely relied upon. This study provides an additional role for SBCE that can support a histological diagnosis of RCD by demonstrating more extensive SB disease in those with RCD.

Two studies exist on the use of SBCE to follow up patients with CD managed with a GFD. Murray et al. [20] demonstrated improvement in the extent of intestinal involvement 6 months after GFD in 79% of patients. Lidums et al. [21] demonstrated

Table III. Characteristics of patients with refractory coeliac disease

Patient	Gender	Age at first SBCE	Marsh duodenal histology at first SBCE	Marsh duodenal histology at second SBCE	% extent small bowel mucosa on first SBCE	% extent small bowel mucosa on second SBCE	Treatment
1	male	55	3b	3c	49.8%	69.4%	mycophenolate
2	male	68	3c	1	15.6%	18.1%	budesonide
3	female	46	3c	3a	0.5%	5.9%	azathioprine
4	female	54	3b	3a	15.7%	15.7%	budesonide
5	male	67	3c	3b	74.8%	97.8%	budesonide
6	male	67	3c	3c	27.6%	34.2%	azathioprine
7	male	28	3c	3b	19.2%	4.4%	azathioprine
8	male	41	3c	3b	51.3%	21.6%	prednisolone
9	female	71	3a	0	100.0%	4.3%	prednisolone
10	female	51	3b	3b	3.4%	3.2%	budesonide, azathioprine
11	female	53	3c	3a	20.6%	15.2%	budesonide, mycophenolate
12	female	68	3b	3c	80.3%	29.7%	budesonide
13	female	51	3b	3a	77.9%	37.1%	azathioprine
14	female	74	3c	3a	98.2%	65.4%	budesonide
15	male	65	3c	3c	100.0%	85.5%	budesonide
16	female	69	3a	0	28.3%	15.8%	prednisolone, azathioprine
17	female	55	3a	3b	18.3%	0.0%	6-mercaptopurine, budesonide
18	female	56	3c	3b	22.6%	0.0%	budesonide
19	female	71	3b	3a	66.5%	11.0%	budesonide
20	female	25	0	0	0.0%	0.0%	6-mercaptopurine
21	male	49	3b	3a	54.1%	41.6%	budesonide, interleukin 15 monoclonal antibody
22	male	62	3b	3b	incomplete	incomplete	budesonide, interleukin 15 monoclonal antibody
23	female	38	3a	3b	8.0%	4.4%	budesonide, azathioprine

SBCE: small bowel capsule endoscopy

an improvement in villous atrophy macroscopically in 12 adult patients with CD on repeat SBCE after 12 months of GFD. However, there was persistent villous abnormality on duodenal histology in 42% of patients [21]. In this study, we focused on a special group of patients with RCD that required additional treatment to GFD. To date there is no study on the role of a second SBCE in the follow up of patients with RCD receiving steroids and / or immunosuppressants.

Management with a combination of steroids and / or immunosuppressants or ciclosporin is recommended when RCD I is diagnosed [38-42]. Type II RCD is treated more aggressively with Cladribine or stem cell transplantation in

Table IV. Comparison of features on first and repeat SCBE in patients with refractory coeliac disease

	Mean	Std. Deviation	p value
1st SCBE: Gastric passage time (minutes)	43.6	51.7	0.601
2nd SCBE: Gastric passage time (minutes)	31.1	28.1	
1st SCBE: Small bowel passage time (minutes)	296.5	102.1	0.765
2nd SCBE: Small bowel passage time (minutes)	307.5	144.5	
1st SCBE: Time mucosa abnormal (minutes)	137.0	121.5	0.015
2nd SCBE: Time mucosa abnormal capsule (minutes)	73.6	88.6	
1st SCBE: % abnormal mucosa	42.4%	34.1%	0.012
2nd SCBE: % abnormal mucosa	26.4%	28.9%	

SBCE: small bowel capsule endoscopy

Table V. Features of coeliac disease in patients with RCD on the first and second SBCE.

	Features of CD on first SBCE	Features of CD on second SBCE	Significance (p value)
Region (proximal / proximal & mid / distal / diffuse)	12 (52.2) / 4 (17.4) / 1 (4.3)/ 4 (17.4)	12 (52.2) / 6 (26.1) / 0 / 2 (8.6)	0.0001
Villous atrophy	10 (43.4)	7 (30.4)	0.659
Scalloping	16 (69.6)	15 (65.2)	0.280
Fissuring	7 (30.7)	11 (47.8)	0.500
Mosaic pattern	10 (43.5)	15 (65.2)	0.074
Nodularity	1 (4.3)	1(4.3)	0.846
Ulcers	6 (26.1)	1 (4.3)	0.009

CD: coeliac disease; RCD: refractory coeliac disease SBCE: small bowel capsule endoscopy

view of the potential complications that can arise [43-45] Other treatment such as Interleukin 15 monoclonal antibody have been trialed in patients with RCD II [46]. Refractory coeliac disease also responds less well to immunosuppressants and steroids [47]. The risk of EATL can be potentially enhanced when Azathioprine is administered to patients with RCD II [16]. In a more recent study by Murray et al. [48], patients with RCD I and II responded clinically and histologically to open capsule budesonide.

By using SBCE, we have successfully managed to show an improvement in the extent of mucosal involvement following initiation of immunosuppressants +/- steroids. Coeliac disease most commonly affects the proximal SB and the length of SB affected beyond the duodenum varies. Repeating duodenal histology following several months of treatment with immunosuppressants and/or steroids might not be representative of disease improvement or stability as this is only representative of the disease in the duodenum. In fact, histological improvement following treatment with steroids and/or immunosuppressants in patients with RCD has not always been demonstrated. In a study by Brar et al. [49], clinical improvement but not histological improvement of disease was demonstrated following treatment. Histological improvement in RCD patients following treatment was also absent in our study. Patients with an improvement in disease extent but the same histological grade on duodenal biopsies can be classified as partial or slow responders to treatment. It might only be a matter of time before disease grade in the duodenum improves further. Patients with the same extent of disease on the second SBCE need to be targeted more aggressively with the addition of steroids or immunosuppressants or a complete change in treatment. Also, a diagnosis of RCD II in these patients needs to be excluded by, for example, deep enteroscopy for histology.

Repeating a SBCE within 12 to 18 months is prudent to allow enough time for small bowel mucosal healing and rule out further complications. Although assessment with a repeat SBCE should be carried out in conjunction with symptoms, caution should be applied as symptoms solely cannot be relied upon. Most studies reporting on the correlation between symptomatology and extent of disease on SBCE in patients with CD have shown a poor relationship [21, 50-52]. Relying on symptoms alone to assess response to steroids +/- immunosuppressants therefore, can be misleading.

In our study, more patients with RCD had type I disease similar to two other studies from the US [27] and Germany [37]. However, other studies have reported a higher frequency of RCD II than RCD I [28, 36]. Distinction between RCD I and II can be made histologically by analyzing the population of intraepithelial lymphocytes and by recognizing differences in CD3 and CD8 patterns [53]. Although the distinction on SBCE between RCD I and II has to be interpreted with caution due to the small number of patients especially in the RCD II group, mucosal changes can be more extensive in RCD II than RCD I. Limited literature also exists on this aspect [54].

One limitation of this study is the small cohort of patients with RCD studied. This prevented us from making certain sub-group analysis on different treatments given in patients with RCD. However, RCD is an uncommon disorder with very limited literature in relation to SBCE. Other studies on RCD have also included a small number of patients despite some having a multicentre design and spanning a number of years [46, 55]. A longer follow up period is also required to assess the true significance of the reduction of mucosal abnormality seen on SBCE in RCD and the longer-term prognosis.

CONCLUSIONS

We have demonstrated that the extent of disease on SBCE in patients with RCD can be greater than in patients with uncomplicated CD. This can be used as further evidence of RCD in patients where a diagnosis of RCD is still uncertain. In addition, SBCE can detect an improvement in the length of macroscopic disease following treatment and hence, serves as a useful adjunct in the follow up of patients with RCD. This is the first study to report that a second look SBCE can play a key role in the follow up of patients with RCD receiving immunosuppressant and steroid therapy.

Conflicts of interest: None to declare.

Authors' contributions: R.S. and D.S.S. planned the manuscript and were involved in editing and revisions of the article. S.C.Z. was responsible for data collection, statistical analysis of results, writing, editing and submitting the manuscript. S. S. C. was involved in revisions and editing of the manuscript.

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