How to recognise a Behçet's ulcer from other types of oral ulceration? Defining Behçet's ulceration by an International Delphi Consultation

A. Poveda-Gallego[1,2,3], I. Chapple[2,3,4], M. Iacucci[5], J. Hamburger[2], P.I. Murray[1,6], S. Rauz[1,6], G.R. Wallace[1] and the Behçet's Disease Expert Panel

[1]Institute of Inflammation and Ageing, College of Medical and Dental Sciences, University of Birmingham; [2]School of Dentistry, Institute of Medical and Dental Sciences, College of Medical and Dental Sciences, University of Birmingham; [3]Birmingham Dental Hospital, Birmingham Community Health Foundation Trust, Birmingham; [4]Birmingham's NIHR BRC in Inflammation Research, University of Birmingham; [5]Institute of Immunology and Immunotherapy, College of Medical and Dental Sciences, University of Birmingham; [6]Birmingham and Midland Eye Centre, Sandwell and West Birmingham NHS Trust, Birmingham, UK.

Abstract

Objective

To define the clinical characteristics of oral ulceration (OU) in Behçet's disease (BD), to allow differentiation from other causes of OU, including aphthous ulcers, by an International Delphi consultation. To develop a clinical guideline on how to recognise BD ulcers.

Methods

Round 1. 40 clinical images of OU in BD, recurrent aphthous stomatitis (RAS), inflammatory bowel disease (IBD) and mucous membrane pemphigoid (MMP) were shown. Participants answered, independently, which images would be consistent with a BD ulcer.

Round 2. The results from marking independently were shown. The panel remarked the questions through iteration process. The images not agreed to be a possible BD ulcer were discarded.

Round 3. 10 clinical descriptors that may define BD ulcers were suggested. Participants ranked the level of importance for each descriptor on each image presented.

Round 4. Participants re-ranked their level of agreement for each descriptor through iteration process. Whether the clinical pictures would be different from RAS was also explored. A final agreement was reached.

Results

This study has shown clear differentiation between BD, IBD and MMP ulcers when defining them by phenotype through clinical images only. On the other hand, no differentiation between RAS and BD ulcers was found. The most important clinical descriptors that define BD ulcers have been agreed.

Conclusion

New clinical guidance for Health Care Professionals (HCP) on how to recognise a BD ulcer has been proposed. This should elucidate an earlier diagnosis, quicker access to treatment and control of the disease enhancing patient's quality of life.

Key words

Behçet's disease, delphi, aphtous, oral ulceration, guidelines

Ana Poveda-Gallego, BDS, MSc
Iain Chapple, BDS, PhD
Marietta Iacucci, MD, PhD
John Hamburger, BDS, MSc
Philip I. Murray, MD, PhD
Saaeha Rauz, MD, PhD
Graham R. Wallace, BSc, PhD

Please address corrrespondence to:
Ana Poveda-Gallego
Institute of Inflammation and Ageing,
College of Medical and Dental Sciences,
University of Birmingham,
Edgbaston,
B15 2TT Birmingham, UK.
E-mail: p.g.ana@bham.ac.uk

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International expert panel:
Prof G. Hatemi, Prof D. Bang,
Prof C. Chams-Davatchi, Prof Y. Yazici,
Prof R. Kucukoglu, Prof G. Mumcu,
Prof J. Nowatzky, Dr D. Saadoun,
Dr B. Bodaghi, Dr A. Richards,
Dr B. Rajlawat, Dr J.G. Ovalles Bonilla

Oral medicine expert panel:
Dr J. Higham, Dr R. Ariyaratnam

Independent observer:
Dr R. Albuquerque

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Introduction

Behçet's disease (BD), first described in 1937 by the Turkish dermatologist Hulusi Behçet, is an autoinflammatory disease characterised by oral and genital aphthous ulceration, complicated by multisystem involvement that includes eye, skin, joint and central nervous system (CNS) lesions. Its aetiology remains unknown, but there is an important genetic basis to BD, with HLA-B*51 being the strongest associated allele in all studies (1-4).

BD tends to present in the third decade of life and has a similar predilection for both sexes. Even though the disease is reported worldwide, BD has a higher prevalence in the old "Silk Route" populations, varying from 80-370 per100000 in Turkey, in contrast to 0.1–7.5 per 100,000 in Europe and the USA (3). In 2017, the prevalence in the UK was 14.61 (95% CI 13.35–15.88) per 100 000 population, this is in contrast with previous studies that suggested a lower incidence of 6.4 per 100,000 (5, 6).

As there are no specific pathognomonic laboratory tests, BD diagnosis is reached on clinical criteria (7). Oral ulceration (OU) is frequently the first symptom patients will develop and is one of the disease's hallmarks for its diagnosis (8). This is reflected on the importance the International Study Group Criteria (ISG) 1990 gives to OU, as patients must have experienced at least 3 episodes of recurrent oral ulceration (minor, major, or herpetiform aphthous type-ulceration) over a 12-month period (9). In the revised International Criteria for Behçet's disease (10), OU scores 2 points in a numerical scoring process with a score >4 points needed to establish diagnosis.

OU is defined as a total breach of the oral epithelium, leaving the connective tissue exposed to the oral cavity (11-13). Causes are multiple and may present in a variety of forms. It ranges from simple trauma (14), drug- induced or infective aetiologies such as herpes simplex, coxsackie (15), or syphilis (16), to most serious connotations such as HIV (17, 18) or an underlying malignant process (19, 20). OU can also be a significant manifestation of several systemic diseases (21), including inflammatory bowel disease (IBD) (22, 23) dermatological diseases such as lichen planus (24), mucous membrane pemphigoid (MMP) (25, 26) or as part of autoinflammatory syndromes (27) amongst others. Hence recognition of each possible aetiology and its clinical appearance is important and not exempt from diagnostic challenges.

As OU is a key feature in BD patients, to provide an early and appropriate referral it is pivotal that Health Care Professionals (HCP) can (a) recognise OU, (b) differentiate types of OU, and (c) recognise which type of OU would be consistent with a possible diagnosis of BD: in the clinical scenario where the OU is consistent with a possible BD diagnosis, the HCP should then question the patient about extraoral sites of ulceration to further investigate whether they may fulfil the diagnostic criteria for BD.

BD patients that suffer with OU will typically present with aphthous type ulcers, also described as recurrent aphthous stomatitis (RAS)-type. RAS can be divided into minor, major and herpetiform, all three clinical forms have a very distinctive clinical phenotype described elsewhere (28, 29).

The possibility of BD ulcers having distinctive clinical characteristics which may be different from RAS has previously been suggested in clinical settings and amongst BD specialists with limited results (30, 31).

We have used the Delphi process (32, 35) to explore the hypothesis that there is a specific clinical phenotype of OU in BD patients that may differ from other clinical forms, including RAS, IBD and MMP with the aim to define such clinical characteristics. By doing so, we hope to provide clearer guidance to HCP on when to consider BD, raising awareness of the disease.

Methods

Our research took place in accordance with the University of Birmingham, UK Ethics with reference number ERN_18-0524. Jisc online survey tool® with the University of Birmingham approval was used to create the questionnaires for the Delphi rounds (36).

UK oral medicine panel

Prior the start of the study, an oral medicine expert panel (including APG) from two UK Oral Medicine units (Birmingham and Manchester) was formed to select the clinical pictures for Round 1. The panel validated the questions and questionnaires developed for the study: 4 rounds were planned (Supplementary Fig. S1). Statistical analysis and the parameters for dropping items were agreed.

International expert panel

To form the expert panel, 2 parameters were used: the individual's expertise in diagnosing BD and their geographical location: 18 international BD experts were identified by the authors: Delphi Study Information Sheet, invitation letter and consent form were sent via email to all potential participants (Suppl. Fig. S2).

Clinical images

A total of 80 intraoral images from the Oral Medicine Database at Birmingham Dental Hospital Birmingham Community Healthcare (BCHC) NHS Trust with the following diagnosis (20 BD, 20 RAS, 20 MMP and 20 IBD) were initially selected by the author.

The images had been taken by the Clinical Illustration department team for standardisation of quality. All the patients had consented to level A-Consent for publication granted.

The Oral Medicine panel later agreed (80%) on 40 OU images: 10 BD, 10 RAS, 10 MMP and 10 IBD. This was based on (a) the OU being highly representative for each disease in their expert views, and (b) the quality of the photographs.

The questionnaire was consequently created by the author (APG) via Jisc online survey tool ® service with the approval of the University of Birmingham for its use (36). In this way, the quality of the images remained throughout the process and the results were anonymised.

To randomise the order of each clinical picture in the questionnaire, Random Integer Set Generator® programme was used, thus minimising the risk of selection bias (37).

Rounds

- *Round 1:* 40 clinical images of OU as part of BD, RAS, IBD and MMP were included. The international experts were asked which clinical pictures were, to their views, consistent with a BD ulcer.
- *Round 2:* Participants agreed on which clinical images would be consistent with a BD ulcer after iteration process. The rest were discarded.
- *Round 3:* 10 clinical descriptors that may support a diagnosis of BD ulcer were suggested. Participants ranked their levels of agreement as well as level of importance for each descriptor on each image presented.
- *Round 4:* Participants re-ranked their agreement with a chance to change their score following disclosure of the results obtained in Round 3. Whether the clinical images would be different from a possible simple RAS diagnosis was also explored. A final agreement was reached.

Detailed information on the questionnaire and each round is found in Supplementary Fig. S3. Clinical images shown by disease group and question number can be found in Supplementary Fig. S4.

Analysis

Each statement was analysed quantitatively by the percentage of agreement ratings, importance rankings and the number of comments made for each statement, and qualitatively using thematic analysis. Criteria for dropping items between rounds was stated prior the start of the rounds, from round 1 to 2, the results which had a yes answer and a minimum of 70% agreement would be selected. In round 3 and 4, quantitative analysis was carried out measuring the percentage of agreement, importance ranking and the number of comments.

Evolution of consensus was shown by increase in agreement percentages, convergence of range with standard deviation of importance ratings and decrease in comments made. Sensitivity, Specificity, Positive and Negative Predictive Values were calculated (Suppl. Fig. S5).

As part of quality validation process, this study followed the proposed quality criteria by Diamond *et al*. (2014) (33) with a 4 score: the number of rounds was stated prior the start of the study in the Delphi Study Information Sheet for the participants to see. The oral medicine panel experts validated the clinical pictures chosen by the author for Round 1 as well as the clinical parameters to be used in Round 2 by consensus method prior the start of the rounds. The authors had a reproducible criterion for selection of participants as the expert panel invitation was targeted to BD experts around the globe, considering the different specialties involved in BD patient's care, and not only focusing on oral medicine experts to avoid further subspecialist bias. Finally, levels of agreement and criteria for dropping items from one round to the other were stated in each round.

Results

From 18 experts contacted, there was a 73% response rate, with 12 experts agreeing to participate in the study. 7 countries were involved: Turkey with 3 members, France, United States and United Kingdom with 2 members each, and finally Iran, and Spain with 1 respectively. The panel was comprised of Rheumatologists (4), Ophthalmologists (1), Dermatologists (3), Oral Medicine (3) and Internal medicine (1) specialists.

Round 1 and 2: Independent marking and iteration process (remarking)

Participants were asked which clinical images would support the diagnosis of a BD ulcer: when analysing the results per disease group, 14 images had a 100% agreement (2 possibly being BD ulcers, 12 not), 3 images had 90% agreement of not being BD ulcers and 9 reached 80% agreement (8 being BD ulcers, 1 not) (Table Ia).

When the results were shown to participants, a higher agreement was reached: 20 images reached 100% agreement (4 being a BD ulcer, 16 not being a BD ulcer), 6 images reached 90% agreement (5 being a BD ulcer, 1 not). 80% agreement was reached in 4 images (3 being BD ulcers, 1 not) (Table Ib).

Table Ic shows the results of participant's overall agreement for each question (marked independently and then showing the results of other participants) paired with each disease (BD, RAS, MMP and IBD) Experts reached a clear consensus on differentiating IBD and MMP ulcers as not consistent with a possible diagnosis of BD in comparison with RAS ulcers with participants' accuracy average of 0.74 (Suppl. Fig. S5).

Sensitivity, Specificity, Positive and Negative Predictive Values were refined in each question and per participant from when marking independently to showing the results as part of the iteration process. Number of comments did also decrease, and levels of agreement increased (Suppl. Fig. S5).

Round 3

Prior to the start of this round, the Oral Medicine independent expert panel met a second time to discuss/agree on the clinical parameters that would be necessary to define a BD ulcer. After a literature search done by the author (APG); nouns and adjectives that would describe BD and RAS- type ulcers were sought. The initial clinical parameters were shown to the group, who ranked individually as well as collectively whether the parameters would or would not help to define/ describe a BD ulcer as per their clinical expertise. An independent observer also ranked the clinical parameters. Consequently, 10/15 parameters as shown in the methods were finally used in both Rounds 3 and 4 (Suppl. Fig. S6).

In Round 3 each clinical picture that reached over 50% agreement in Round 2 with a yes answer (supporting a possible BD diagnosis) was presented to the panel alongside the 10 clinical parameters. The levels of agreement were shown. Experts could choose as many parameters as they wished to support their decision. 17/40 clinical pictures were consequently used. From the 17 pictures, 9 were consistent with a clinical diagnosis of BD ulcers and 8 simple RAS, reflecting how the experts were able to correctly select the pictures that represented aphthous ulcers in relationship to simple RAS and RAS-BD by clinical phenotype only and discard the other causes of OU presented including IBD and MMP as discussed in Rounds 1 and 2.

When what clinical parameters to define a BD ulcer were important overall on each image selected was asked, margin scored the highest (84%), followed by shape (77%), colour (71%), base of ulcer (67%), depth (62%) and location (55%). Size (43%), surrounding tissues (31%), number (25%) and aggravating factors (10%) were consistently not as important for all the participants in this round, which was marked independently. (Fig. 1) Free text for comments was also collected (Suppl. Fig. S5).

Table I.

Round 1: Marking independently.
Analysing per disease group

%	BD (y)	RAS(y)	IBD(n)	MMP(n)
100	1	1	5	7
90	0	0	3	0
80	3	5	0	1
70	3	2	2	0
60	1	1	0	2
50	2	0	0	0
40	0	0	0	0
30	1	1	0	0

Round 2: Iteration (Showing the results).
Analysing per disease group

%	BD (y)	RAS(y)	IBD(n)	MMP(n)
100	1	3	7	9
90	4	1	1	0
80	2	1	1	0
70	1	0	1	1
60	1	2	0	0
50	0	1	0	0
40	1	0	0	0
30	0	1	0	0
10	0	1	0	0

Comparing both rounds per question and disease group.

BD ulcers Question	Round 1	Round 2	MMP ulcers: Question	Round 1	Round 2
1	50%	45%	8	80%	100%
2	80%	91%	13	100%	100%
3	80%	82%	14	60%	100%
10	70%	91%	18	100%	100%
15	50%	64%	21	100%	100%
25	60%	82%	24	100%	100%
29	100%	100%	26	100%	100%
31	70%	73%	27	100%	100%
35	70%	91%	37	60%	73%
39	80%	82%	40	100%	100%
RAS ulcers: Question	**Round 1**	**Round 2**	**IBD ulcers: Question**	**Round 1**	**Round 2**
6	80%	100%	4	90%	100%
11	80%	100%	5	90%	91%
16	10%	9%	7	100%	100%
17	60%	55%	9	70%	73%
19	80%	82%	12	90%	100%
20	70%	91%	23	100%	100%
22	20%	36%	28	100%	100%
33	70%	63%	30	70%	82%
34	80%	64%	32	100%	100%
36	80%	100%	38	100%	100%

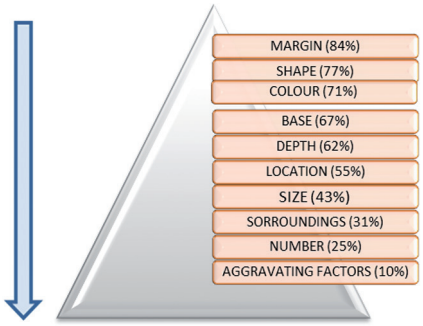

Fig. 1.

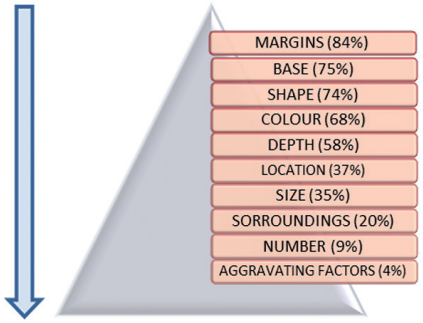

Fig. 2.

Round 4

Firstly, panel experts were asked to re-rank clinical parameters and its level of importance when determining a BD ulcer, this time with Round 2 results shown. After iteration process, margin continued to be the most important clinical parameter when defining a BD ulcer amongst the experts (84%). This was followed by base (75%), shape (74%) colour (68%) and depth (58%). Location (37%), size (35%), surroundings (20%), number (9%) and aggravating factors (4%) were consistently not as important for the participants in this round (Fig. 2).

Secondly, the experts responded to the following two questions: (1) Do you agree with the previous results shown? (2) Would you consider this image to be different from the diagnosis of RAS? For question 1, 13 out of the 17 questions the participants reached 90–100% agreement. In 2/17 of questions the participants reached 70% agreement, two questions (Q.14 30%, Q.15 44.4%) reached below 50% agreement (Suppl. Fig. S7a).

For the second question, all the images scored at least 50% agreement consistent with a No answer, with 14/17 receiving a consensus <60%. This shows that the images presented, though agreed to be consistent with the possible diagnosis of a BD ulcer, could not be distinguished from RAS (Suppl. Fig. S7b).

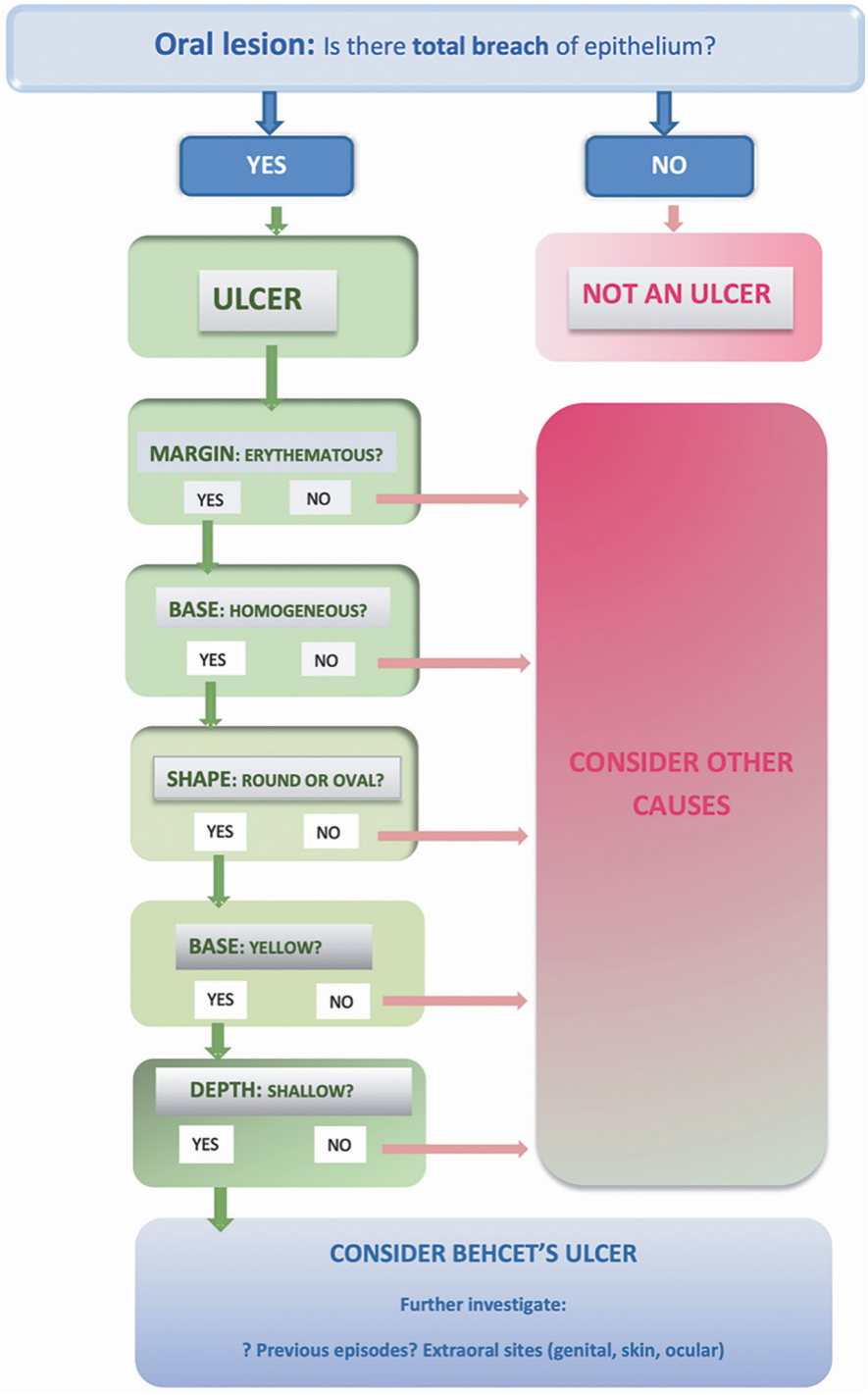

Fig. 3.

Discussion

Oral ulceration (OU), particularly RAS-type of ulceration, is present in most BD sufferers with some authors suggesting frequency from 97% to 100% (38).

A service evaluation carried out at the Behçet's National Centre of Excellence in Birmingham City Hospital (UK) has shown that not all the referrers can identify OU nor RAS-type OU. There has also been discussion amongst BD experts that BD ulcers may differ from RAS-type and that there may be some

clinical characteristics specific to the disease.

To date, there is limited evidence in the literature that would support this, with some studies pointing an increase of major RAS in BD cases and others the herpetiform type (39). This is in contrast with other observations which postulate that minor aphthae-like lesions are the most common clinical variant seen, whereas major and herpetiform are rare (40-42). Another study indicates that major RAS is common in patients with BD, and is associated with a more severe, repeated, and prolonged oral disease. Nevertheless, the presence of major RAS in BD does not predict a more severe systemic illness (43, 44). Site may also play a role, with the soft palate and oropharynx considered as the most common location for BD ulcers (45).

As the Delphi method has already been used in many medical specialties and is a robust method to reach agreement, we decided to use this type of study using a BD experts' international panel. We aimed to reach consensus as whether 1- experts could distinguish BD ulcers from other causes of oral ulceration including not only RAS but other autoimmune and autoinflammatory diseases such as MMP and IBD 2- what clinical parameters would support their decision. A third aim was to use the clinical parameters agreed to then inform further clinical guidance for non-BD experts.

To prove differentiation amongst other causes of OU 3 other cohorts were used. They all have different aetiologies but certain clinical features in common: recurrent oral ulceration and similar extraoral site involvement (with exception of RAS) making, once more, the diagnosis challenging. Interestingly, in the first-round participants were able to identify all the 10 IBD OU pictures shown in the questionnaire as not BD, strongly suggesting specific characteristics in IBD oral manifestations which will aid diagnosis and differentiation amongst this cohort of patients that can be difficult, as previous described elsewhere (14, 46-48).

All the MMP-OU cases were discarded with 9 of the pictures reaching 100% agreement and 1 reaching 73% agreement (*Q.37*) showing a clear consensus and in accordance with MMP-OU, being a blistering condition, not typically presenting as aphthous ulcers and acting as the negative control group (49, 50).

However, the results clearly reflect the challenges to differentiate RAS vs BD ulcers in a panel of BD experts, which was then further explored in Rounds 3 and 4.

When ranking the results in round 3 margin was the most important clinical parameter when defining a BD ulcer amongst the experts. This was followed by shape, colour, base, depth, location as shown in Figure 1.

In Round 4, the results of each image with the ranked agreement in order of importance was shown to participants, who were asked to remark on the results and choose at least 5 clinical parameters that would support their decision. Margin continued to be the most important clinical parameter, followed by base, shape, colour and depth respectively (Fig. 2).

This translates into an erythematous margin, a yellow, shallow, homogeneous base and round shape being the most important descriptors to define a BD ulcer and were the clinical criteria used by the authors to develop the clinical guidelines for non-BD experts.

In summary, our proposed clinical guidelines suggest that HCPs should recognise OU as a total breach of the epithelium, leaving connective tissue exposed, and suspect a BD ulcer if the margins are erythematous, the base homogenous *versus* non-homogeneous, the shape round/oval *versus* others, the base yellow *versus* red, and the depth shallow *versus* deep, and consider other aetiologies if this is not the case, as presented in Figure 3.

The final and key question for this study was to consider whether the clinical images shown would defer from a RAS diagnosis. 76% of overall agreement was that it was not possible to differentiate between RAS and BD ulcers by clinical images only, showing no difference between the two possible diagnoses. Consequently, the authors suggest that, when following the clinical guideline flowchart, HCPs should also consider RAS, and only suggest BD if further sites as per the BD criteria are involved, to avoid over-diagnosis of the disease and incorrect referral. There may be some limitations to this part of the study: the number of images selected on the last 2 rounds may be not enough to show sufficient differentiation, and further studies with higher power may be needed.

The study showed a clear differentiation between IBD, MMP and BD ulcers and no differentiation between BD and RAS when showing clinical images only. It has aimed to define the most important descriptors in a BD ulcer, which have now helped to develop further clinical guidance to non-BD experts (Fig. 3).

Conclusion

This International Delphi study showed clear differentiation between BD, IBD and MMP but much less clarity comparing RAS and BD ulcers. The most important clinical parameters to define a BD ulcer have been agreed and have fed into further clinical guidelines for non-BD experts in hope that an early and correct clinical diagnosis can be suspected and reached. A new clinical guidance has now been proposed and presented.

This is the first time an attempt to define the specific clinical characteristics in oral BD through Delphi consultation has been conducted. Even though we have shown no limited differentiation from RAS-type ulcers, this international collaboration aims to increase awareness of BD as a possible differential diagnosis among other causes of oral ulceration within non-oral medicine and non-BD experts. The new clinical guidance proposed will aid and prompt non-BD experts to consider BD as a possible diagnosis reducing numerous specialist appointments, earlier diagnosis of the disease, quicker access to treatment and consequently higher quality of life for this cohort of patients.

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