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ORIGINAL RESEARCH

The Risk of Developing Ocular Involvement Among Behçet's Disease Patients Presenting with Mucocutaneous Involvement at Disease Onset: Data from the International AIDA Network Behçet's Disease Registry

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ABSTRACT

Introduction: Behçet's disease (BD) frequently arises with exclusively mucocutaneous involvement, but some patients will develop major organ involvement, including ocular inflammation. This study aims to assess the patients' demographic and clinical characteristics that may be associated with the development of ocular involvement in patients with BD with exclusively mucocutaneous involvement in the early stages.

Methods: Patients' data were collected in the International AutoInflammatory Disease Alliance (AIDA) Network registry dedicated to BD.

Results: A total of 328 patients with BD were enrolled, 36 (11%) of whom developed ocular involvement over time. The following variables were significantly associated with the development of ocular inflammation at binary logistic regression: positive family history for BD (OR 4.32, 95% CI 1.16–14.72, $p=0.02$), Arab ethnicity (OR 3.6, 95% CI 1.3–9.9, $p=0.01$), presence of major oral aphthous ulceration (OR 3.26, 95% CI 1.18–8.99, $p=0.02$), pseudofolliculitis plus erythema nodosum (OR 4.58, 95% CI 1.33–15.7, $p=0.016$); conversely, white patients/patients of European descent (OR 0.33, 95% CI 0.12–0.91, $p=0.03$) and the presence of a low number (one to two) ulcers at genital aphthous flares (OR 0.002, 95% CI ~0–0.07, $p=0.0006$) were protective against the occurrence of ocular inflammatory manifestations. Genital aphthosis with more than five concurrent ulcers was associated with eye involvement in Arab patients (OR 209.2, 95% CI 5.8–7497, p=0.003).

Conclusions: Major oral aphthosis, genital aphthous attacks with more than five concurrent ulcers, erythema nodosum coexisting with pseudofolliculitis, a positive family history of BD, and Arab ethnicity are associated with a higher risk of ocular involvement when BD arises with the sole mucocutaneous involvement.

Keywords: Uveitis; Retinal vasculitis; International registry; AIDA Network; Rare diseases

INTRODUCTION

Mucocutaneous involvement is the hallmark of Behçet's disease (BD) and often represents the only clinical manifestation for an extended period in these patients. Specifically, mucocutaneous involvement includes the presence of oral aphthosis, which can be classified as minor or major depending on whether they are smaller or larger than 10 mm, genital ulcers, pseudofolliculitis, erythema nodosum, skin ulcers, pyoderma gangrenosum, and rarer skin manifestations [1, 2].

While some patients who initially present with exclusively mucocutaneous involvement will continue to experience only mucocutaneous manifestations, others will develop major organ involvement, including ocular, intestinal, central nervous system, and vascular BD-related affections [3, 4]. Ocular involvement, which is relatively common among patients with BD, can lead to a severe reduction in visual acuity or even complete blindness if not properly diagnosed and treated in a timely manner [5]. Therefore, identifying which patients are more likely to develop ocular involvement over time is of significant practical value and would provide helpful information for stratifying patients who initially present with exclusive mucocutaneous involvement but will later develop ocular inflammation. This study was conducted to assess the demographic and clinical characteristics of BD patients with exclusively mucocutaneous involvement at disease onset that may be associated with the development of ocular involvement in later stages.

METHODS

Patients' data were collected in the International AutoInflammatory Disease Alliance (AIDA) Network registry dedicated to BD [6]. The Ethics Committee of Azienda Ospedaliero-Universitaria Senese, Siena, Italy (Ref. N. 14,951; NCT05200715) approved the study, which was performed according to the Good Clinical

Practice guidelines and the latest Declaration of Helsinki. Written informed consents for involved patients were collected at the time of patient enrollment in the AIDA registry and included permission to use data for research purposes. Clinical data are kept in accordance with the EU General Data Protection Regulations (GDPR), or other counterparts, on the processing of personal data and the protection of privacy (2016/679/EU). All patients included in the study fulfilled the International Study Group (ISG) criteria and/or the International Criteria for Behçet's Disease (ICBD) [7, 8].

This study aims to identify any demographic or clinical patients' features of patients with BD with exclusively mucocutaneous involvement in the early phase of the disease that may represent predictive factors of ocular involvement development in later stages. Therefore, patients presenting exclusively with oral aphthosis, genital aphthosis, and BD-related cutaneous manifestations, in the absence of ocular, intestinal, vascular, or central nervous system involvement for at least 12 months following disease onset, were included in the study. Disease onset was defined as when the patient fulfilled the classification criteria for BD, while ocular involvement was defined as the onset of uveitis, scleritis, or retinal vasculitis. Subsequently, patients who developed ocular involvement were identified and distinguished from those who remained free of ocular manifestations throughout the entire follow-up period. Follow-up was defined as the interval from disease onset (time at fulfillment of classification criteria) to the last available follow-up visit or the date of ocular involvement. Demographic, genetic, and clinical data were retrieved from the AIDA Registry dedicated to BD and subjected to statistical analysis [6].

Oral aphthae were classified as minor (< 10 mm in diameter) or major (> 10 mm), or herpetiform, the latter being characterized by numerous, small, and clustered oral lesions [1]. Patients were also stratified into three groups based on the number of concomitant oral ulcers observed during aphthous attacks: 1–2 ulcers, 3–5 ulcers, and more than five ulcers. A similar stratification was performed according to the number of concomitant genital ulcers during aphthous flares. Cutaneous involvement was evaluated through the presence of pseudofolliculitis, erythema nodosum, and a range of less common skin manifestations, including pyoderma gangrenosum, suppurative panniculitis, cutaneous ulcers, maculopapular eruptions, bullous erythema, hidradenitis suppurativa, urticarial lesions, erythema induratum, and erythema multiforme, which were collectively termed as "other skin manifestations".

The various mucocutaneous manifestations and their combinations (when identified in at least ten patients) were analyzed to assess their potential association with the development of ocular involvement over the course of the disease. Specifically, a binary multiple logistic regression model was employed, in which each patient feature was individually tested as an independent variable, while the presence or absence of ocular involvement over time served as the dependent variable. The total duration of follow-up (in years) was included as an adjustment covariate in all logistic regression models to account for differences in observation time across patients. Similarly, all logistic regression models were adjusted for the use of conventional disease-modifying anti-rheumatic drugs and the use of tumor necrosis factor inhibitors, as these treatments might influence the clinical expression of BD and, consequently, the likelihood of developing ocular involvement. Binary multiple logistic regressions were implemented using a mixed-effects model with both random intercepts and random slopes for ethnicity. This modelling approach allowed for the estimation of (i) the baseline variability in ocular involvement risk attributable to ethnicity, also expressed as the intraclass correlation coefficient (ICC%) in percentage; (ii) the extent to which the effect of each independent variable on ocular involvement varied across ethnic groups; and (iii) the residual variance unexplained by the fixed and random effects.

Based on the estimated beta coefficients, the predicted probability of developing ocular involvement was calculated for each variable significantly associated with the outcome. To this end, the formula $\exp(\beta_0+\beta_1) / [1+\exp(\beta_0+\beta_1)]$ was applied. This probability was further stratified according to the two most represented ethnic groups in the cohort—Arab and white

Table 1 Demographic and clinical features of patients enrolled

Patients' features	Description
Sex (F/M)	182/146
Ethnicity#	
White patients/patients of European descent, *n* (%)	209 (63.7)
Arab, *n* (%)	60 (18.3)
Turkish origin, *n* (%)	43 (13.1)
Hispanic, *n* (%)	6 (1.8)
Other ethnicities, *n* (%)	7 (2.1)
Age at disease onset, years (mean ± SD)	29.1 ± 14.7
Age at disease diagnosis, years (mean ± SD)	34.8 ± 13.9
HLA-B51 positivity, *n* (%)*	156 (47.6)
Positive family history, *n* (%)	35 (10.7)
Pregnancy during the disease, *n* (% on females)	22 (12.1)
Type of ocular involvement over time	
Age at the onset of ocular involvement, years (mean ± SD)	35.8 ± 13.6
Monolateral/bilateral	18/18
Uveitis, *n* (%)	30 (9.1)
Retinal vasculitis, *n* (%)	6 (1.8)
Ocular inflammation by ethnicity	
White patients/patients of European descent, *n* (% within group)	22 (10.5)
Arab, *n* (% within group)	11 (18.3)
Turkish origin, *n* (% within group)	2 (4.7)
Hispanic, *n* (% within group)	0 (0)
Other ethnicities, *n* (% within group)	1 (14.3)

CNS central nervous system, *F* females, *HLA* human leukocyte antigen, *M* males, *n* number, *SD* standard deviation

#not provided in three cases; *in 60 cases HLA-B evaluation not performed

patients/ patients of European descent—as well as individuals of Turkish origin. Actually, given the epidemiologic relevance of Behçet's disease in Turkey, the Turkish group was evaluated separately. The probability was calculated by incorporating the random effects terms (μ_0 and μ_1) into the formula: $\exp(\beta_0+\mu_0+\beta_1+\mu_1) / [1+\exp(\beta_0+\mu_0+\beta_1+\mu_1)]$. The coefficients β_0, β_1 and the random effects μ_0, μ_1 were derived from binary multiple logistic regression models fitted using a mixed-effects framework.

Binary multiple logistic regression analysis was supplemented by the calculation of odds ratios (ORs), obtained by exponentiating the beta coefficients associated with each independent variable of interest, along with their 95% confidence intervals (95% CI) and corresponding *p* values.

Table 2 Associations between the specific patients 'features and the development of ocular involvement among patients presenting with exclusively mucocutaneous involvement at the start of Behçet's disease

Patients' features	Odds ratio (95% CI)	*p* value
Sex (male)	1.15 (0.42–3.07)	0.77
Sex (female)	0.87 (0.32–2.36)	0.77
Age at disease onset, years	0.99 (0.95–1.02)	0.65
Early onset (< 16 years)	1.69 (0.49–5.18)	0.37
HLA-B51 (no- > yes)*	0.99 (0.28–3.53)	0.99
Positive family history for BD (no- > yes)	4.32 (1.16–14.72)	0.02
Pregnancy history after disease onset (no- > yes)#	0.52 (0.02–3.69)	0.57
BMI	1.04 (0.93–1.15)	0.43
Smoking status	1.37 (0.40–4.05)	0.58
Presence of comorbidities (no- > yes)	1.99 (0.69–5.64)	0.19
Rheumatologic comorbidities (no- > yes)	2.09 (0.10–14.83)	0.52
Endocrinologic comorbidities (no- > yes)	0.83 (0.04–5.15)	0.86
Arterial hypertension (no- > yes)	1.46 (0.30–5.36)	0.6
Pneumological comorbidities (no- > yes)	1.23 (0.06–7.71)	0.85
Neurological comorbidities (no- > yes)	2.92 (0.35–15.90)	0.24
Malignant oncological comorbidities (no- > yes)	5.62 (0.26–46.04)	0.14
Ethnic groups##		
Arab (no- > yes)	3.6 (1.3–9.9)	0.01
White patients/patients of European descent (no- > yes)	0.33 (0.12–0.91)	0.03
Turkish origin (no- > yes)	0.56 (0.07–4.75)	0.61
Arab vs white patients/patients of European descent	3.76 (1.31–10.81)	0.01
Arab vs. Turkish	4.03 (0.45–36.1)	0.21
Oral aphthous features		
Concurrent oral ulcers (1–2 lesions)§	0.6 (0.17–2.1)	0.42
Concurrent oral ulcers (3–5)§	1.7 (0.56–5.2)	0.35
Concurrent oral ulcers (> 5)§	0.85 (0.21–3.5)	0.83
Concurrent oral ulcers (3–5 vs. 1–2 lesions)	1.72 (0.48–7.18)	0.42
Concurrent oral ulcers (3–5 vs. 1–2 lesions)	1.04 (0.17–5.61)	0.95
Minor oral aphthous ulcerations (< 10 mm) (no- > yes)	1.07 (0.40–2.80)	0.88
Major oral aphthous ulcerations (> 10 mm) (no- > yes)	3.26 (1.18–8.99)	0.02
Oral herpetiform ulcerations (no- > yes)	0.83 (0.03–7.74)	0.88

Table 2 continued

Patients' features	Odds ratio (95% CI)	*p* value
Genital aphthous features		
Genital aphthosis (no- > yes)	0.6 (0.22–1.62)	0.3
Concurrent genital ulcers (1–2 lesions)[§§]	0.002 (6.8×10^{-5}-0.07)	0.0006
Concurrent genital ulcers (3–5 lesions vs. 1–2 lesions)[§§]	13.35 (0.84–213)	0.07
Concurrent genital ulcers (> 5 lesions vs. 1–2 lesions)[§§]	209.2 (5.8–7497)	0.003
Skin involvement (no- > yes)	1.00 (0.37–2.89)	0.99
Pseudofolliculitis (no- > yes)	1.29 (0.49–3.38)	0.59
Erythema nodosum (no- > yes)	2.05 (0.69–5.83)	0.17
Other skin manifestations (no- > yes)	1.98 (0.36–8.36)	0.38

The odds ratio, 95% confidence intervals (95% CI), and *p* values were derived from a multiple logistic regression model, with the development of ocular manifestations as the dependent variable and patient characteristics as independent variables, adjusted for disease duration and treatments performed. *BMI* body mass index, *HLA* human leukocyte antigen

*Information not provided in 60 (18.3%) cases; #Performed on the subgroup of female patients; ##Considered the ethnic groups with at least 6 included patients; § information provided in 222 (68%) cases; §§ information provided in 152 out of 220 cases with genital ulcers

Descriptive statistical analysis was also performed, including calculating the mean, median, standard deviation, interquartile range, frequency counts, and corresponding percentages. Differences in non-normally distributed continuous variables were assessed using the Mann–Whitney *U* test, while differences in categorical variables were evaluated using the chi-squared test. The significance level was set at 95% (*p* value < 0.05), with *p* values being two-tailed. Statistical analysis was conducted using RStudio software, version 4.3.0.

RESULTS

A total of 328 patients with Behçet's disease (BD) and exclusively mucocutaneous involvement at the disease onset were enrolled; of these, 36 (11%) patients developed ocular involvement over time, as better defined in Table 1. The median follow-up duration was 9.65 (IQR 11.0; range 0.08–64.7) years among patients without ocular involvement and 12.2 (IQR 8.25; range 1.42–24.2) years among patients developing ocular inflammation ($p = 0.26$). Notably, 63.9% of the episodes of ocular involvement occurred within 5 years from the onset of the disease, while 36.1% developed it later ($p = 0.01$). Table 2 provides the data from the binary logistic regression associating the development of ocular involvement with demographic and clinical characteristics of patients with BD. In particular, having a positive family history for BD (OR 4.32, 95% CI 1.16–14.72, $p = 0.02$), belonging to Arab ethnicity (OR 3.6, 95% CI 1.3–9.9, $p = 0.01$), and showing major oral aphthosis (OR 3.26, 95% CI 1.18–8.99, $p = 0.02$) was associated to the development of ocular inflammation over time. Conversely, white patients/ patients of European descent (OR 0.33, 95% CI 0.12–0.91, $p = 0.03$) were protected against the development of ocular inflammation.

By including a random intercept and a random slope for the variables significantly associated with the onset of ocular involvement, we obtained the baseline variance related to the ethnic groups in the onset of ocular involvement, as well as the variance in the effect of each specific variable on the onset of ocular involvement

Table 3 Associations between different combinations of mucocutaneous involvement observed at the start of the disease and the development of ocular inflammation developed over time

Combinations of mucocutaneous affections	Odds ratio (95% CI)	*p* value
Minor oral aphthosis + genital aphthosis	0.96 (0.35–1.6),	0.93
Minor oral aphthosis + pseudofolliculitis	1.54 (0.5–4.7),	0.45
Minor oral aphthosis + erythema nodosum	2.96 (0.82–10.4),	0.1
Minor oral aphthosis + infrequent skin manifestations	0.89 (0.09–8.9),	0.92
Major oral aphthosis + genital aphthosis	4.4 (1.36–14.2),	0.01
Major oral aphthosis + pseudofolliculitis	2.27 (0.64–8.04),	0.2
Major oral aphthosis + erythema nodosum	1.4 (0.27–7.42),	0.69
Genital aphthosis + pseudofolliculitis	0.84 (0.3–2.4),	0.75
Genital aphthosis + erythema nodosum	2.44 (0.76–7.8),	0.13
Genital aphthosis + infrequent skin manifestations	1.08 (0.2–5.8),	0.92
Pseudofolliculitis + erythema nodosum	4.58 (1.33–15.7),	0.016
Pseudofolliculitis + infrequent skin manifestations	3.57 (0.58–22.1),	0.17
Minor oral aphthosis + genital aphthosis + pseudofolliculitis	1.12 (0.29–4.28),	0.86
Minor oral aphthosis + genital aphthosis + erythema nodosum	2.51 (0.6–10.3),	0.2
Major oral aphthosis + genital aphthosis + pseudofolliculitis	3.3 (0.78–14.2),	0.1
Genital aphthosis + pseudofolliculitis + erythema nodosum	4.4 (1.17–16.55),	0.03
Minor oral aphthosis + genital aphthosis + pseudofolliculitis + erythema nodosum	3.6 (0.6–20.2),	0.15

The odds ratio, the corresponding 95% confidence interval (95% CI) and the *p* value were obtained through the binary logistic regression with ocular involvement being the dependent variable and the combinations of mucocutaneous involvement representing the independent variable. All regressions were adjusted for the duration of the total follow-up and the use of conventional or anti-tumor necrosis factor disease modifying anti-rheumatic drugs. Logistic regressions were conducted only when the combination of mucocutaneous affections involved at least ten patients at baseline

across different ethnicities. These data are provided in Supplementary Table 1.

Table 3 provides information on the associations between ocular development over time and the different combinations of ocular involvement observed at the onset of BD, while Table 4 provides the expected probabilities of developing ocular involvement if the patient is affected by the demographic or clinical manifestations that, according to the binary logistic regression analysis, were significantly associated with the development of ocular inflammation over time. More specifically, showing major oral aphthosis plus genital aphthosis (OR 4.4, 95% CI 1.36–14.2, $p=0.01$), pseudofolliculitis plus erythema nodosum (OR 4.58, 95% CI 1.33–15.7, $p=0.016$), and genital aphthosis plus pseudofolliculitis plus erythema nodosum (OR 4.4, 95% CI 1.17–16.55, $p=0.03$) was associated to the development of ocular inflammation over time.

DISCUSSION

Ocular involvement is a common and clinically challenging BD complication, affecting 60–80% of patients and potentially leading to vision loss

Table 4 Probability of developing ocular involvement in the whole cohort of patients and according to different ethnicities, based on the presence of variables significantly associated with ocular inflammation over time

Variables associated with ocular involvement	Overall	Arab ethnicity ($n = 60$)	White patients/patients of European descent ($n = 209$)	Turkish origin ($n = 43$)
Overall probability to develop ocular inflammation	11%*	13.4%	4.3%	3.7%
Negative family history	4.6%	9.1%	3.6%	3.5%
Positive family history	20.6%	30.4%	17.7%	17.7%
Presence of major oral aphthosis	22.5%	19.1%	31.8%	36%
One to two concomitant genital ulcers	0.01%	2.4%	0.006%	0.001%
Three to five concomitant genital ulcers	6.1%	5%	6.2%	6.1%
More than five concomitant genital ulcers	~ 0%	100%	~ 0%	~ 0%
Major oral aphthosis + genital aphthosis	16.1%	53.9%	11.1%	7.4%
Pseudofolliculitis + erythema nodosum	18.8%	37.1%	14%	15.6%
Genital aphthosis + pseudofolliculitis + erythema nodosum	17%	37.5%	11.7%	13.2%

Probabilities were estimated from the β coefficients and random effects for Arab and white patients/patients of European descent, derived from the multiple logistic regression models. Both the overall probability calculated from the entire cohort and the probabilities stratified by ethnic group are reported. Subgroup analysis by ethnicity was conducted only for the two most represented groups, namely Arab and white patients/patients of European descent

*The probability was estimated as the ratio between the number of patients who developed ocular involvement over time and those who initially presented with exclusively mucocutaneous manifestations at the onset of Behçet's disease ($36/328 = 0.1098$)

if not adequately managed [5, 9, 10]. Identifying which patients are more likely to develop ocular inflammation is therefore of great clinical importance, especially in those who initially present with only mucocutaneous manifestations, as a substantial proportion of these patients later progress to major organ involvement [3, 4]. Among the variables examined, patient ethnicity emerged as a key determinant. Indeed, Arab ethnicity conferred a significantly increased risk of ocular involvement compared with both white patients/patients of European descent and Turkish patients, with estimated probabilities of 13.4%, 4.3%, and 3.7%, respectively.

With regard to mucocutaneous features, we confirmed previous observations [11] that genital aphthosis was associated with a lower probability of ocular involvement. However, our data suggest that this protective effect may be modulated by the number of concomitant ulcers and by ethnicity. In particular, the presence of more than five genital ulcers was associated with ocular involvement in Arab patients, but not in white patients/patients of European descent or Turkish patients. This finding, although based on a small subgroup, highlights the potential interplay between clinical phenotype and ethnicity in shaping the risk of ocular disease, as also supported by Supplementary Table 1.

Notably, although the mere presence of genital ulcers demonstrated a non-significant but potentially protective odds ratio (as detailed in Table 2), specific mucocutaneous combinations appeared to reverse this protective trend. In particular, the co-occurrence of genital aphthosis with either major oral aphthosis or with the combination of pseudofolliculitis and erythema nodosum was associated with an increased likelihood of developing ocular inflammation. On

one hand, this effect appears to be driven by the presence of major aphthous ulcers, which are significantly associated with ocular involvement, with an increased likelihood of up to tenfold among patients of Turkish origin and more than sevenfold among white patients/patients of European descent. On the other hand, pseudofolliculitis and erythema nodosum, when considered separately, were not significantly associated with the development of ocular affections. However, their combination was strongly and significantly associated with ocular involvement, nullifying any protective effect of genital aphthosis, especially among Arab patients, but also among white patients/patients of European descent and Turkish patients. As illustrated in Table 4, the addition of genital aphthosis to the combination of pseudofolliculitis and erythema nodosum had a negligible impact on the probability of ocular involvement among patients of Arab ethnicity, increasing it only marginally from 37.1% to 37.5%. In contrast, a reduction of approximately one-sixth was observed among white patients/patients of European descent (from 14.0% to 11.7%) and among those of Turkish origin (from 15.6% to 13.2%). Although these latter probabilities may appear modest, they remain approximately 2.7–3.5 times higher than the baseline overall probability of ocular involvement in such populations.

Contrary to previous reports [3, 11], sex was not associated with ocular manifestations in the present cohort. This discrepancy may be attributable to the differing ethnic composition of the study populations—specifically, the absence of Japanese patients in the present cohort—as well as the inclusion criteria, which restricted this study to individuals with exclusive mucocutaneous involvement at BD onset. More notably, a positive family history of Behçet's disease emerged as a strong predictor of ocular involvement, conferring a nearly two- to fourfold increased risk across different populations. The impact of familial history on the risk of ocular inflammation was consistent across ethnic groups, as evidenced by the data provided in Supplementary Table 1. More in details, the variability in the impact of family history on the development of ocular involvement across different ethnicities was minimal, while greater baseline differences in ocular involvement were observed between ethnic groups. However, the majority of the variance in the development of ocular involvement seemed to be driven by factors independent of both ethnic origin and family history.

Ghaleb RM et al. had already reported that the presence of skin lesions increased the risk of ocular involvement by 47-fold in patients with BD [12]. Overall, the findings presented in this study confirm an association between mucocutaneous manifestations and ocular inflammation, while offering more granular insight into the specific mucocutaneous features and their combinations that should alert clinicians to the possibility of future ocular involvement. Nevertheless, certain limitations must be acknowledged. Firstly, although the overall sample size is not particularly small, stratification into multiple subgroups based on the presence or absence of specific clinical manifestations limited the effective size of each subgroup. In some cases, this limit turned out to a high statistical uncertainty, highlighted by a very wide 95% CI. However, although the subdivision into subgroups inevitably reduced the sample size, the use of a mixed-effects model provided more robust estimates than a purely descriptive approach. The results, while to be interpreted with caution, still offer valuable insights into the clinical associations with ocular involvement in BD. In this context, the wide 95% CI and the limited number of statistically significant combinations highlight the exploratory nature of these findings, which should therefore be interpreted as hypothesis-generating. In particular, the association observed between genital aphthosis with more than five concurrent ulcers and ocular involvement among Arab patients was based on a very limited number of cases, which resulted in an extremely wide confidence interval (95% CI 5.8–7497). This highlights the statistical instability of this finding and underscores the need for cautious interpretation. While this result may suggest a possible trend, its confirmation in larger, prospective cohorts will be essential to validate and strengthen the associations suggested by our analysis.

Additionally, potential inclusion bias in the AIDA registry may have influenced the results.

Of note, 11 out of 60 Arabs, 22 out of 209 white patients/patients of European descent, and two out of 43 Turkish patients developed uveitis. While the number of Turkish patients with uveitis is admittedly small, this finding may be the direct expression of the lower tendency of this subgroup to develop ocular involvement when presenting with mucocutaneous-only disease, as highlighted by our analysis. However, the lower probability of developing ocular involvement among patients of Turkish origin could be partly explained by the tendency of Turkish centers to primarily enroll patients with more severe organ involvement from the onset of BD, while potentially underrepresenting cases with exclusive mucocutaneous manifestations. Lastly, the potential positivity of the pathergy test was not included in the statistical analysis, as this test is performed with considerable variability across different countries and clinical centers, which significantly affects its sensitivity and specificity [13–15].

CONCLUSIONS

In conclusion, patients presenting with major oral aphthosis, those exhibiting both erythema nodosum and pseudofolliculitis, with or without genital ulcers, and individuals with a positive family history of BD are at significantly higher risk of developing ocular inflammatory involvement when the disease initially presents with mucocutaneous manifestations only. Patients of Arab ethnicity are at higher risk of developing BD-related ocular involvement; genital aphthosis, which is generally a protective factor, may not confer such protection among Arab patients when aphthous episodes occur with more than five ulcers.

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Declarations

Conflict of Interest. The authors, therefore Antonio Vitale, Valeria Caggiano, Jessica Sbalchiero, Giuseppe Lopalco, Gaafar Ragab, Silvana Guerriero, Ibrahim AlMaglouth, Abdurraham Tufan, Roberto Giacomelli, Haner Direskeneli, Piero Ruscitti, Gülen Hatemi, Francesco Carubbi, Ezgi Deniz Batu, Seza Ozen, Jurgen Sota, Henrique Ayres Mayrink Giardini, Micol Frassi, Petros P Sfikakis, Federica Gatti, Claudia Ammoscato, Amina Maher, Ayman Abdel-Monem Ahmed Mahmoud, Rosanna Dammaco, Hamit Kucuk, Riza Can Kardas, Ibrahim Yahya Cakir, Fatma Alibaz Öner, Gizem Sevik, Martina Gentile, Alican Karakoc, Alessia Alunno, Hulya Ercan Emreol, Francesca Crisafulli, Katerina Laskari, Francesco Ciccia, Maissa Thabet, Naceur Feriel, Serena Bugatti, Alessandra Milanesi, Maria Sole Chimenti, Bendetta Monosi, Matteo Piga, Alberto Floris, Francesco Gavioli, Cecilia Beatrice Chighizola, José Hernández-Rodríguez, Marco Cattalini, Marcello Govoni, Ombretta Viapiana, Adele Civino, Daniela Opris-Belinski, Carla Gaggiano, Rosaria Talarico, Annachiara Alemanno, Annarita Giardina, Giacomo Emmi, Piercarlo Sarzi Puttini, Maria Cristina Maggio, Paola Parronchi, Piero Portincasa, Alejandra De-la-Torre, Laura Daniela Rodríguez-Camelo, Stefano Gentileschi, Angela Mauro, Gian Domenico Sebastiani, Alma Nunzia Olivieri, Ali Şahin, Donato Rigante, Emre Bilgin, Emanuela Del Giudice, Luciana Breda, Amato De Paulis, Alberto Lo Gullo, Şükran Erten, Samar Tharwat, Lampros Fotis, Armin Maier, Antonella Insalaco, Anastasios Karamanakos, Alessandro Conforti, Özgül Soysal Gündüz, Abdelhfeez Moshrif, Francesca Li Gobbi, Stefania Costi, Elena Bartoloni, Patrizia Barone, Serena Guiducci, Andrés Gonzáles-Garcia, Inés Hernanz Rodríguez, Giovanni Conti, Annamaria Iagnocco, Fatos Önen, Sulaiman M. Al-Mayouf, Didar Uçar, Alberto Balistreri, Bruno Frediani, Luca Cantarini, declare that the research was conducted without any commercial or financial relationships that could potentially create conflict of interest. Claudia Fabiani is an Editorial Board member of Ophthalmology and Therapy. She was not involved in the selection of peer reviewers for the manuscript nor any editorial decisions.

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