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Systematic Review
Oral Medicine

Angina bullosa haemorrhagica: a systematic review and proposal for diagnostic criteria

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Abstract. The aim of this study was to perform a critical review of published data on the epidemiological, aetiological, clinical, histological, biological, and therapeutic characteristics of patients with angina bullosa haemorrhagica (ABH). A literature search was conducted in the PubMed, Science Direct, Web of Science, and Cochrane Library databases. All publications fulfilling the selection criteria were included in the eligibility assessment according to the PRISMA statement. The full texts of 54 retrieved articles were screened. Forty articles published between 1985 and 2016 describing 225 cases of ABH were finally selected. The mean age of the patients was 55.4 years; the male to female ratio was 0.7. The predominant localization was the palate (66%). A third of patients had no medical history. When specified, a triggering event or promoting factor was frequently found (82%). Biological tests were normal. A biopsy was performed on 35% of the patients. Treatment was symptomatic with a favourable outcome. Recurrences were frequent (62%). In conclusion, ABH is poorly documented and only by studies of low-level evidence. This review did not allow any aetiopathogenic association to be made with a general pathology or treatment. On the basis of this systematic review of the literature, diagnostic criteria aiming to improve the care of patients presenting with ABH are proposed.

Key words: angina bullosa haemorrhagica; oral mucosa blisters; diagnostic; systematic review.

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In 1967, Badham described angina bullosa haemorrhagica (ABH) as a pathology causing recurrent haemorrhagic bullae of the oropharyngeal mucosa at sites particularly exposed to trauma[1,2]. This pathology is not limited to the pharynx but may occur anywhere in the entire oral cavity. Many case reports have been published in the literature, but there appears to have been no systematic review on the subject. ABH is poorly understood and is undoubtedly underdiagnosed.

The differential diagnosis includes dermatoses that present mucocutaneous bullous lesions (cicatricial pemphigoid, pemphigus vulgaris, mucous membrane pemphigoid, bullous pemphigoid, amyloidosis, acquired epidermolysis bullosa, linear IgA dermatosis, herpetiform dermatitis, oral bullous lichen planus) and bloodborne diseases (leukaemia, thrombocytopenia, von Willebrand disease)[3–5]. After rupture of the bulla, the differential diagnosis is even wider and includes all pathologies leading to post-bullous erosions. The history of the disease appears to be a major factor in the diagnosis of

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ABH[6–8]; however, there is great variation in the literature on the means of obtaining the diagnosis[9–11].

The objective of this study was to perform a systematic review to identify the epidemiological, aetiological, clinical, histological, biological, and therapeutic characteristics of ABH and to propose diagnostic criteria from the data obtained in order to facilitate the diagnosis.

Methods

A systematic review of the literature on ABH, based on the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[12], was conducted in September 2016 to answer the following research question according to the PICO criteria (population, intervention, control, and outcome): What are the epidemiological, aetiological, clinical, histological, biological, and therapeutic characteristics of patients with ABH?

The key words ''angina bullosa hemorrhagica''; ''angina bullosa haemorrhagica''; ''benign hemorrhagic bullous stomatitis''; ''oral'' AND ''blister'' AND ''hemorrhage'' were applied in the PubMed and Science Direct databases (1950–2016); Web of Science Core Collection (1975–2016); and Cochrane Library (1999–2016) by one review author (U.O.).

If a relevant citation was found in the screened full texts, the full article was also retrieved and included in the selection phase. After the removal of duplicates, the titles and abstracts of the remaining potentially relevant articles were screened by two independent reviewers (U.O. and R.L.) according to the study inclusion and exclusion criteria. The inclusion criterion was all published studies specifically concerning ABH. The exclusion criteria were studies not published in English or French, full text not available in France through inter-university loan, and animal model-based studies.

The full texts of all articles retrieved from the database search and from the manual reference list search were evaluated by the two reviewers considering the following eligibility criteria for inclusion in the final review: studies in which the epidemiological, aetiological, clinical, histological, biological, and therapeutic characteristics were given for at least one patient; original articles published in peer-reviewed journals. There were no discrepancies between the two reviewers with regard to the selection of articles.

An evaluation of the risk of bias and an assessment of the quality of the studies were not performed because of the low level of evidence of the studies identified, which were all observational studies.

Hence, the criteria for considering studies in this review (following the PICO criteria) were: (1) study type, duration, and follow-up: all published studies; (2) participants: all patients with ABH; (3) interventions: positive diagnosis of ABH; (4) outcome measures: epidemiological, aetiological, clinical, histological, biological, and therapeutic characteristics of ABH.

Data from all of the included articles were extracted and summarized independently by the two reviewers (U.O. and R.L.) using the same data extraction form, to obtain all of the characteristics found in Table 1 (number of cases, epidemiological, aetiological, clinical, histological, biological, and therapeutic characteristics), when these were recorded. The readers had previously been trained in the use of this data extraction form. In the case of any discrepancy when comparing the two data extraction forms, consensus between the two reviewers was to be reached systematically following a common reading of the article at the origin of the disagreement. There were no discrepancies between the two readers in this work. When the characteristics of only some patients included in a study were reported, their numbers were recorded in parentheses (Table 1).

Results

The electronic database search was last updated in September 2016 and yielded 207 records: 104 from PubMed, 68 from Science Direct, 35 from Web of Science, and 0 from The Cochrane Library). Six additional records were identified by examining the reference lists of captured articles. Seventy-four records were obtained after the removal of duplicates and these were then screened according to inclusion and exclusion criteria. At this stage 54 articles were considered relevant to the topic (the other 20 studies did not specifically concern ABH). The full texts of these 54 articles were then assessed for eligibility, leading to the inclusion of 40 studies (letters to the editor were excluded). The flow chart of the study selection process adapted from the PRISMA statement is showed in Fig. 1.

Finally, 40 articles published between 1985 and 2016 were retained by the authors, referring to 225 cases of ABH[2,6,8–11,13–46]. The epidemiological, aetiological, clinical, histological, biological, and therapeutic data for each of the 225 patients included in the study were analyzed (Table 1).

Due to the heterogeneity of the available literature and the lack of reported data in numerous studies, the authors decided to limit themselves to a descriptive statistical analysis and not to perform a meta-analysis.

Epidemiological and aetiological features

Age was reported for 76% of the patients ($n = 171$, 39 articles) and averaged 55.4 years. The youngest patient was 13 years old and the oldest 86 years old. Sex was reported in all studies except for that of Stephenson et al. (14 cases)[13]. Of the 211 remaining patients, 88 were male and 123 were female, giving a male to female sex ratio of 0.7.

The medical histories were specified for 43% of the patients ($n = 97$, 31 articles). Of these patients, 33% ($n = 32$) had no known medical history, 22% ($n = 21$) had hypertension, 15% ($n = 15$) diabetes, 9% ($n = 9$) an ischemic cardiopathy, 7% ($n = 7$) asthma, 5% ($n = 5$) cancer, and 27% ($n = 26$) had other various isolated pathologies including thalassaemia, mitral valve prolapse, osteoporosis, hypocholesterolaemia, depression, urticaria, kidney transplant, epilepsy, anaemia, lupus, renal failure, anorexia, liver failure, nephrotic syndrome, haemorrhagic rectocolitis, gout, rheumatoid arthritis, hypothyroidism, and sleeping disorders. Seven percent of patients ($n = 7$) used inhaled corticosteroids as therapy for their asthma and 8% of patients ($n = 8$) had a family history of ABH.

The existence of a triggering event or promoting factor was specified for 66% of patients ($n = 148$, 30 articles). Among these, a promoting factor was found in 82% of the cases ($n = 122$). Mastication was the factor most often found. The onset of symptomatology after a meal was described in 64% of the cases ($n = 95$). This could have been the result of a mechanical (sharp food) or thermal trauma (burn). Other factors were a local trauma (12%, $n = 18$), dental procedures (3%, $n = 5$), shouting, coughing or sneezing (1.5%, $n = 2$), menstrual cycle (0.7%, $n = 1$), or mouthwash (0.7%, $n = 1$). In 18% of the cases ($n = 26$), the lesion appeared without a triggering factor (when one was sought).

Clinical features

The localization was specified for 90% of the patients ($n = 202$, 38 articles) and was strictly oral in 22% of the cases ($n = 44$). The palate was the most frequently affect-

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Table 1. Reported characteristics of angina bullosa haemorrhagica.

Authors	Number of cases	Aetiological and epidemiological features				Clinical features			
		Mean age (years)	Sex, M/F	Medical history	Promoting factor	Localization	Number of lesions	Mean diameter (cm)	Symptoms
Hopkins and Walker, 1985[15]	9	52.8	3/6	NR	Alimentary bolus (7) Dental procedure (1) Cough, sneeze (1)	Reported	NR	3.5	Tingling, pain (low level)
Stephenson et al., 1987[13]	14	64	NR	NR	NR	NR	NR	NR	NR
Stephenson et al., 1987[10]	30	53.9	14/16	NR	Alimentary bolus (15) None (14) Dental procedure (1)	Reported	NR	NR	NR
Daly, 1987[32]	4	69.2	2/2	Reported	Alimentary bolus (3) Local trauma (1)	Reported	Unique (3) Multiple (1)	NR	Tingling (1)
Edwards et al., 1990[18]	3	42.6	0/3	Reported	Alimentary bolus (3) plus shouting (1) or menstrual cycle (1)	Reported	Unique (3)	NR	Tingling (1), pain (1), panic (1)
Higgins and Vivier, 1991[27]	1	37	0/1	Reported	NR	Reported	Unique	>1	Burn
Kirtschig and Happle, 1994[19]	1	70	1/0	Reported	Alimentary bolus	Reported	Multiple	1	Discomfort
Deblauwe and van der Waal, 1994[25]	9	63.3	3/6	Reported (3)	Alimentary bolus (5) None (4)	Reported	NR	>1	Burn, pain (low level)
Ingram, 1995[14]	1	69	0/1	Reported	Alimentary bolus	Reported	Unique	0.8	Asymptomatic
de las Heras et al., 1996[30]	1	67	0/1	Reported	Alimentary bolus	Reported	Unique	2	Burn, dysphagia
Corson and Sloan, 1996[31]	1	31	0/1	Reported	Dental procedure	Reported	Multiple	0.8	Pain (low level)
Von Arx, 1998[11]	1	44	0/1	Reported	NR	Reported	Multiple	2	Asymptomatic
Antoni-Bach et al., 1999[2]	1	58	1/0	Reported	Alimentary bolus	Reported	Multiple	0.5	Tingling
Dominguez et al., 1999[33]	1	52	0/1	Reported	NR	Reported	Unique	2	Pain
Grinspan et al., 1999[6]	54	NR	26/28	Reported (6)	Local trauma (13) NR (41)	Reported	NR	NR	NR
Curran and Rives, 2000[34]	1	74	0/1	Reported	Dental procedure	Reported	Unique	0.6	Pain (low level)
Giuliani et al., 2002[9]	8	39.3	4/4	Reported (3) NR (5)	Alimentary bolus (7) NR (1)	Reported	NR	NR	NR
Roguedas et al., 2002[20]	1	45	0/1	Reported	Alimentary bolus	Reported	Unique	1	NR
Yip, 2003[35]	1	60	0/1	Reported	Mouthwash	Reported	Multiple	NR	NR
Pahl et al., 2004[16]	1	56	0/1	Reported	NR	Reported	Multiple	>1	Pain, dysphagia, dysphonia, salivary incontinence, respiratory distress
Slezák, 2005[36]	14	62.8	5/9	Reported	Alimentary bolus (12) None (2)	Reported	Unique (11) Multiple (3)	NR	NR
Yamamoto et al., 2006[23]	11	54.8	3/8	Reported	Alimentary bolus (7) None (3) NR (1)	Reported	NR	1.6	Pain (mild) (7), discomfort (3), asymptomatic (1)
Kurban et al., 2007[37]	1	24	0/1	Reported	None	Reported	Unique	1	Asymptomatic
Horie et al., 2008[8]	16	50.9	10/6	Reported	Alimentary bolus (16)	NR	Unique	2	NR
Martini et al., 2010[22]	4	50.5	3/1	Reported	Alimentary bolus (4)	Reported	Unique (4)	1.5	Discomfort (2), low pain (1), asymptomatic (1)
Serra et al., 2010[38]	4	59.5	2/2	Reported	NR	Reported	Unique (2)	NR	NR

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Table 1 (*Continued*)

Authors	Number of cases	Aetiological and epidemiological features				Clinical features			
		Mean age (years)	Sex, M/F	Medical history	Promoting factor	Localization	Number of lesions	Mean diameter (cm)	Symptoms
Bertram, 2010[39]	1	67	1/0	NR	Alimentary bolus	Reported	Unique	NR	Asymptomatic
Milin and Fouche, 2011[29]	1	66	0/1	Reported	Dental procedure	Reported	Unique	NR	Asymptomatic
Martins et al., 2012[24]	6	42.6	3/3	NR	Alimentary bolus (6)	Reported	Unique (3) Multiple (2)	NR	Pain (low level) (1), asymptomatic (1) NR (4)
Rai et al., 2012[40]	2	62.5	2/0	NR	Alimentary bolus (1) NR (1)	Reported	Unique (2)	NR	Asymptomatic (1), pain (low level) (1)
Shoor et al., 2013[41]	1	40	0/1	Reported	NR	Reported	Multiple	NR	Pain (low level)
Scully, 2013[26]	1	48	0/1	Reported	Alimentary bolus	Reported	Unique	NR	NR
Kluger and Frances, 2013[42]	1	50	0/1	Reported	Alimentary bolus	Reported	Unique	2	NR
Shashikumar et al., 2013[21]	2	49	1/1	Reported	NR	Reported	Unique (2)	2	Asymptomatic
Shashikala, 2013[17]	1	85	0/1	NR	NR	Reported	Unique	NR	Dyspnoea, respiratory distress
Singh et al., 2013[43]	1	50	0/1	Reported	NR	Reported	Multiple	3	Pain
Beguerie and Gonzalez, 2014[28]	11	64.5	4/7	Reported	Local trauma (4) NR (7)	Reported	Unique	0.5	NR
Reddy, 2014[44]	1	38	0/1	NR	Alimentary bolus	Reported	Multiple	1	Pain (low level)
Patigaroo et al., 2014[45]	1	28	0/1	Reported	None	Reported	Multiple	NR	Discomfort
Lozano-Masdemont et al., 2016[46]	2	45.5	0/2	NR	None	Reported	Unique	1.6	NR

Authors	Number of cases	Histological and biological features					Therapeutic features	
		Platelet count	Coagulation	IIF	Biopsy	DIF	Treatment	Recurrence
Hopkins and Walker, 1985[15]	9	Normal (8) NR (1)	Normal (8) NR (1)	NR	Yes (5) No (4)	NR	NR	Yes (8) No (1)
Stephenson et al., 1987[13]	14	Normal (14)	Normal (5) NR (9)	Neg (11) ? (1) NR (2)	Yes (12) NR (2)	Neg (12) NR (2)	NR	NR
Stephenson et al., 1987[10]	30	Normal (19) ND (11)	NR	Neg (15) ? (2)[a] ND (13)	Yes (17) NR (13)	Neg (11) ? (4)[a] NR (15)	NR	Yes (25) NR (5)
Daly, 1987[32]	4	NR (3) ND (1)	NR (3) ND (1)	NR	Yes (1) ND (3)	Neg	Reported	Yes (2) No (2)
Edwards et al., 1990[18]	3	Normal (3)	Normal (3)	NR	Yes (2) ND (1)	Neg (2) NR (1)	Reported	Yes (3)
Higgins and Vivier, 1991[27]	1	Normal	Normal	NR	Yes	Neg	Reported	Yes
Kirtschig and Happle, 1994[19]	1	Normal	Normal	Neg	Yes	NR	Reported	Yes
Deblauwe and van der Waal, 1994[25]	9	Normal (9)	Normal (9)	NR	Yes (1) NR (8)	NR	NR	Yes (4) No (5)
Ingram, 1995[14]	1	Normal	NR	NR	NR	NR	Reported	Yes
de las Heras et al., 1996[30]	1	Normal	Normal	Neg	Yes	Neg	Reported	Yes
Corson and Sloan, 1996[31]	1	Normal	Normal	NR	NR	NR	Reported	No
Von Arx, 1998[11]	1	ND	ND	ND	ND	ND	Reported	Yes
Antoni-Bach et al., 1999[2]	1	Normal	Normal	Neg	Yes	Neg	Reported	Yes
Dominguez et al., 1999[33]	1	Normal	Normal	NR	Yes	NR	NR	Yes

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Grinspan et al., 1999[6]	54	NR	NR	NR	NR	NR	NR	Yes (16) NR (38)
Curran and Rives, 2000[34]	1	NR	NR	NR	Yes	NR	NR	NR
Giuliani et al., 2002[9]	8	Normal (8)	Normal (8)	NR	Yes (8)	Neg	Reported (1) NR (7)	Yes (2) No (6)
Roguedas et al., 2002[20]	1	NR	NR	NR	Yes	Neg	Reported	Yes
Yip, 2003[35]	1	NR	NR	NR	NR	NR	Reported	NR
Pahl et al., 2004[16]	1	Normal	Normal	NR	Yes	Neg	NR	Yes
Slezák, 2005[36]	14	Normal (14)	NR	NR	NR	NR	Reported	Yes (4) No (10)
Yamamoto et al., 2006[23]	11	Normal (10) NR (1)	Normal (10) NR (1)	NR	NR	NR	Reported	Yes (2) NR (9)
Kurban et al., 2007[37]	1	Normal	NR	NR	Yes	Neg	Reported	Yes
Horie et al., 2008[8]	16	Normal (16)	Normal (16)	NR	NR	NR	Reported	No (16)
Martini et al., 2010[22]	4	Normal (1) NR (3)	NR	NR	Yes (1) NR (3)	NR	Reported	Yes (2) No (2)
Serra et al., 2010[38]	4	Normal (4)	Normal (4)	NR	Yes	Neg	Reported	Yes (2) NR (2)
Bertram, 2010[39]	1	NR	NR	NR	NR	NR	NR	Yes
Milin and Fouche, 2011[29]	1	ND	ND	ND	ND	ND	Reported	Yes
Martins et al., 2012[24]	6	Normal (6)	Normal (6)	NR	NR	NR	NR	NR
Rai et al., 2012[40]	2	Normal (2)	Normal (2)	NR	Yes (2)	NR	NR	NR
Shoor et al., 2013[41]	1	Normal	Normal	NR	Yes	Neg	Reported	Yes
Scully, 2013[26]	1	Normal	Normal	NR	Yes	NR	Reported	Yes
Kluger and Frances, 2013[42]	1	Normal	Normal	NR	Yes	Neg	Reported	No
Shashikumar et al., 2013[21]	2	Normal (2)	Normal (2)	NR	Yes (1) ND (1)	NR	Reported	Yes (1) NR (1)
Shashikala, 2013[17]	1	NR	NR	NR	NR	NR	NR	Yes
Singh et al., 2013[43]	1	Normal	Normal	NR	ND	NR	Reported	NR
Beguerie and Gonzalez, 2014[28]	11	Normal (11)	Normal (11)	NR	Yes (11)	Neg (11)	NR	Yes (2) No (9)
Reddy, 2014[44]	1	Normal	Normal	NR	Yes	NR	NR	Yes
Patigaroo et al., 2014[45]	1	Normal	Normal	NR	ND	ND	Reported	NR
Lozano-Masdemont et al., 2016[46]	2	NR	NR	NR	NR	NR	NR	Yes (2)

F, female; M, male; NR, not reported.
DIF, direct immunofluorescence; IIF, indirect immunofluorescence; NR, not reported; N, normal; Pos, positive; ND, not done; Neg, negative.
[a] ?: non-significant anomaly without diagnosis of autoimmune disease.

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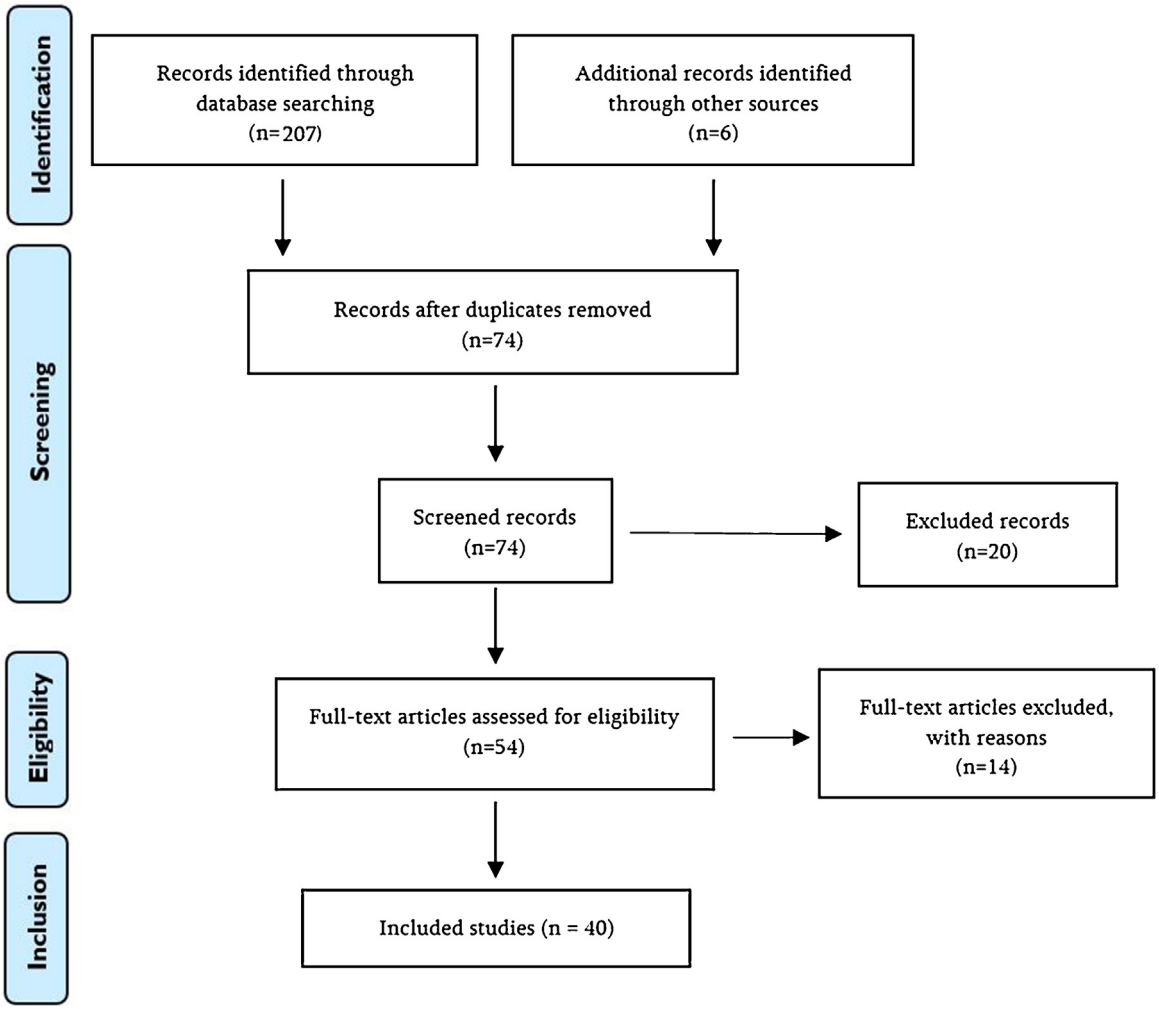

Fig. 1. Flow diagram of the study selection procedure.

ed site (66%, $n = 133$). Of these palatal lesions, 62% ($n = 82$) involved the soft palate; hard palate lesions were much rarer (2%, $n = 3$). The uvula was also slightly affected (3%, $n = 4$), and in 33% ($n = 44$) of the cases, the localization on the palate was not specified.

These lesions affected the tongue (10%, $n = 24$), buccal mucosa (9%, $n = 20$), pharynx (3%, $n = 7$), labial mucosa (2%, $n = 5$), floor of the mouth (2%, $n = 4$), and gingiva (2%, $n = 4$), and could be diffuse across the oral cavity (2%, $n = 4$). Only one case of a cutaneous lesion associated with a palatal lesion was described (Ingram[14]).

The number of lesions was specified for 39% of the patients ($n = 87$, 33 articles), and most of the time, the lesion was single (82%, $n = 71$). The size of the lesions varied from 3 mm to 3.5 cm.

Clinical manifestations were similar amongst most cases. Patients described a haemorrhagic bulla preceded or not by a burning or tingling sensation. This bulla presented an ecchymotic halo and broke after a few minutes or hours to give way to an erosion, which was often painless or even asymptomatic, and that healed without scarring within a few days. The lesions could be impressive and anxiogenic, creating a choking sensation at the time of rupture, causing panic for the patient and prompting an emergency consultation[15]. More rarely, the clinical presentation was more dramatic: two cases of suffocating lesions leading to dyspnoea and respiratory distress were reported in the literature[16,17].

The Nikolsky sign, when sought, was always negative. There was no description of the Asboe-Hansen sign in the reported cases.

Histological and biological features

The platelet count was performed for 63% of the patients ($n = 142$, 32 articles). The value was always normal (150–400 $\times$ 10^9/l), and no thrombocytopenia or thrombopathy was found. A coagulation assessment (prothrombin time, partial thromboplastin time, bleeding time) was performed for 43% of the patients ($n = 97$, 28 articles) and no anomaly was found.

A biopsy was performed for 35% of the patients ($n = 78$, 25 articles). This showed a sub-epithelial haematic bulla associated with a mild to moderate infiltrate of non-specific mononuclear inflammatory cells limited to the lamina propria area. Only Edwards et al. found an intraepithelial bulla[18]. When the biopsy was performed after the bulla had burst and had been replaced by a non-specific ulceration, the lymphocytic infiltrate was then more important[9].

Direct immunofluorescence (DIF) was required with the biopsy in 64% of the cases ($n = 50$, 18 articles) (immunoglobulins IgG, IgM, and IgA, complement C3,

Table 2. Main characteristics of angina bullosa haemorrhagica.

Main characteristics (n = number of reported cases)	Results (% of n)
Average age (n = 171)	55.4 years (range 13–86 years)
Sex ratio M/F (n = 211)	0.7
Medical history (n = 97)	33% without medical history 22% arterial hypertension 15% diabetes
Clinically notable haemorrhagic bulla or erosion with bleeding history (n = 225)	Yes (100%)
Platelet count (n = 142)	Normal (100%)
Coagulation tests (n = 97)	Normal (100%)
DIF (n = 50)	Negative (100%)
Localization (n = 202)	Exclusively oral or oropharyngeal (100%), including soft palate (62%)
Painless lesion, tingling or burning sensation (n = 65)	Frequent (78%)
Presence of a triggering/promoting factor (n = 148)	Yes (82%); including trauma from an a limentary bolus (64%)
Recurrence (n = 139)	Frequent (62%)
Favourable evolution without scar within a few days (n = 122)	Frequent (92%)
Lesion type (n = 87)	Single (82%)
Nikolsky sign (n = 2)	Negative
IIF (n = 34)	Absence of autoantibodies (91%, 9% with equivocal results)
Biopsy (n = 78)	Haematic sub-epithelial bulla and l ight to moderate non-specific inflammatory infiltrate
Treatment (n = 75)	No treatment

DIF, direct immunofluorescence; IIF, indirect immunofluorescence.

and fibrin). Results were negative for all patients, except in the study of Stephenson et al., where the results were equivocal for IgG and/or C3 at the basal membrane[13].

Indirect immunofluorescence (IIF) was only performed in five studies for a total of 34 patients. IgG, IgM, IgA, and C3 were investigated. The absence of circulating autoantibodies was demonstrated in all patients, except three with equivocal results for basal anti-membrane autoantibodies.

Anecdotally, a patch test was performed for two patients[19,20] and a Tzanck cytodiagnosis for one case[21].

Therapeutic features

No treatment was required for some cases (n = 75, 25 articles). Drainage of the bulla was performed for five patients to limit its progression[17,22,23]. A tracheotomy following failure of orotracheal intubation was performed in one of the patients[16]. Martins et al. and Yamamoto et al. described an infection of the erosion that resulted in the prescription of antibiotic treatment for five patients[23,24].

A recurrence was specified in 62% of the cases (n = 139, 33 articles). Of these, 65% of the patients had one or more recurrences (n = 89). The frequency of recurrence was variable and could spread over several years.

The main characteristics found are summarized in Table 2.

Discussion

The epidemiological, aetiological, clinical, histological, biological, and therapeutic features of ABH available in the literature were recorded in this systematic review. All articles were case reports and retrospective studies of small series. A significant number of cases did not include proper documentation of all of the criteria studied.

Epidemiological and aetiological features

No study has reported the incidence and prevalence of ABH. ABH is often described as a rare disease. However, with 225 cases identified through this review, the authors share the impression of Grinspan et al. that this is not an uncommon pathology[6]. It is probably underdiagnosed because of its frequent misunderstanding by physicians, and its rapid and spontaneously favourable evolution.

The localization is not exclusively oropharyngeal or pharyngeal. Moreover, this pathology does not refer to any constriction of the upper aerodigestive tract or to a restriction of the blood flow, and does not give rise to spasmodic, choking, or suffocating pain, pressure, or compression, contrary to the classical definition of angina[47]. Therefore, the term 'angina bullosa haemorrhagica' (ABH) as proposed by Badham[1] has been discussed and other terms have been proposed to define this pathology, without consensus among the scientific community: 'benign haemorrhagic bullous stomatitis'[2], 'stomatopompholyx haemorrhagica'[25], 'localized oral purpura'[26], 'traumatic or recurrent oral haemophlyctenosis'[43]. Furthermore, since this pathology does not involve any inflammation of the lips or mouth, here again the designation of 'benign haemorrhagic bullous stomatitis' proposed by Antoni-Bach et al.[2] does not appear suitable either. The term 'angina bullosa haemorrhagica' (ABH) is the most commonly used to describe this pathology.

The aetiology and pathogenesis of ABH have not yet been elucidated and several hypotheses are found in the literature, as outlined below.

High and Main found a link between the long-term use of inhaled corticosteroids and ABH[48]. Chronic use of corticosteroids may affect the formation of collagen and cause epithelial atrophy (25)[2]. In addition, Higgins and Vivier showed a disorder of the collagenous and elastic fibres of the mucosa resulting in reduced anchoring of the blood vessels, which can cause haemorrhagic lesions following trauma[27].

Horie et al., in a series of 16 cases, found six patients with hypertension (37.5%) and hypothesized an association with ABH[8]. This association is purely speculative, and the hypertension had been treated and was stable in four out of the six patients.

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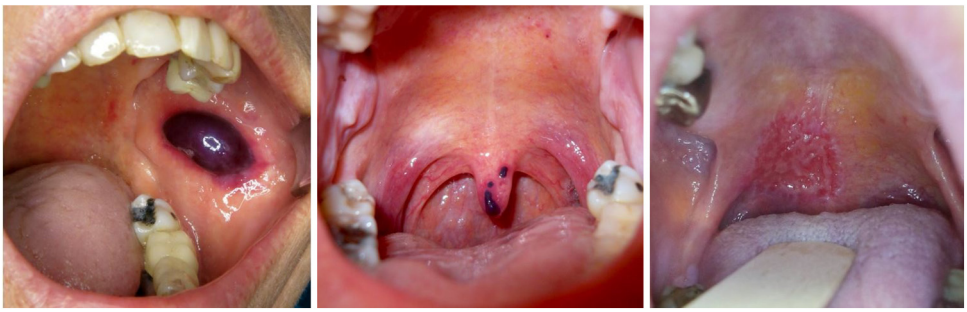

Fig. 2. Left: haemorrhagic bulla of the jugal mucosa; note the ecchymotic halo. Middle: multiple haemorrhagic bullae on the uvula. Right: post-bullous erosion of the soft palate. (Authors' photographic inventory.).

Grinspan et al. reported an association with diabetes, hyperglycaemia, and/or a family history of diabetes in 44% of their 54 cases[6].

In the present review, one third of patients with ABH presented no health problems. In addition, in patients with a medical history, the incidence rates of hypertension (21%), diabetes (15%), and inhaled corticosteroids (7%) were close to, or even lower than those in the general population aged 55 years[49].

On the basis of these arguments, it is impossible to assert a relationship between hypertension, diabetes, or corticosteroid use and ABH. With 3.5% having a family history of ABH, it is also impossible to assert a genetic family trend.

The possible correlation of ABH with dermatoporosis, which associates skin fragility and haematomas, is interesting. Dermatoporosis could be related to a progressive alteration of the dermis extracellular matrix. As for ABH, local and systemic corticosteroids are considered by some authors as an aggravating factor[7]. Nevertheless, as found in the present study, other studies have also failed to find a significant association between dermatoporosis and corticosteroids[50].

The traumatic factor seems more pertinent since it was described in numerous articles and was found in more than 80% of the cases. Mastication was the most incriminated factor (hard, hot, spicy food, etc.). This traumatic factor appears to be associated with a constitutional predisposition, leading to a loss of cohesion between the epithelium and the connective tissue. Vasculature fragility and/or of elastin and/or collagen would favour sub-epithelial haemorrhages[15,18,28]. This hypothesis must be confirmed by a structural study.

Histological and biological features

When performed, the paraclinical examinations were always identical: the biological evaluation was normal and showed no anomaly, whereas the histological examination showed a non-specific ulceration with negative DIF and IIF.

Considerable variability in prescribing practices for complementary examinations was noted across the studies.

Clinical and differential diagnostic features

The diagnosis is clinical. A biopsy and a biological check-up can complete the clinical examination. The appearance of ABH varies according to the stage of the pathology. The diagnosis can be made in the presence of an intact haemorrhagic bulla. However, these bullae break after a few minutes or hours, and it is common for the patient to consult for a post-bullous erosion, making the diagnosis more difficult (Fig. 2). ABH could be considered a superficial haematoma that bursts spontaneously because of its thin surface and the constraints and frictions related to the oral environment. ABH can, however, be differentiated from a post-bite haematoma of the cheek or tongue, because its occurrence is frequently asymptomatic with no patient-reported injury moment at the time of the trauma.

Differential diagnoses are multiple and include (1) cutaneous and mucosal bullous diseases such as mucous membrane pemphigoid, pemphigus vulgaris, bullous pemphigoid, amyloidosis, acquired epidermolysis bullosa, linear IgA dermatosis, herpetiform dermatitis, oral bullous lichen planus, and (2) diseases causing haemostasis disorders such as thrombocytopenia, von Willebrand disease, and leukaemia[28] (Table 3).

Therapeutic features

Treatment is symptomatic; the patient should be reassured. Analgesics for pain and local care (chlorhexidine 0.12–0.2%) can be provided[6,10]. Intact lesions of a large size, especially oral lesions, should be incised and drained to prevent their extension and potential obstruction of the upper aerodigestive tract[16].

Anecdotally, Grinspan et al. suggested that the combination of ascorbic acid and citroflavonoids could prevent recurrences of ABH[6], and Martins et al. proposed antibiotic agents as a strategy for preventing secondary infections in ABH[24]. No studies have yet confirmed these hypotheses.

Diagnostic criteria

Although the diagnosis appears to be based on clinical examination, history, and follow-up of the disease, there is still considerable heterogeneity in the choice of diagnostic criteria and the management of this disease. The diagnostic pathway was found to vary according to the different authors and the complementary examinations they prescribed. This review found that the ordering of complementary examinations was not performed in a systematic way, as the diagnosis is often clinical.

Some authors have considered the context and the clinical aspect as characteristic, requiring no further examinations[11,29], while others have advocated a comprehensive review of the patient[27,30]. Stephenson et al. and Scully stated that the platelet count and a biopsy must be performed as first-line measurements, as well as coagulation tests for patients for whom haemostasis disorders are suspected[10,26]. Giuliani et al. recommended a biological check-up (platelet count and coagulation balance) and a biopsy with DIF[9]. Corson and Sloan considered that a biological assessment is always needed[31].

One of the objectives of this review was to determine from the literature what the diagnostic criteria for ABH should be. The data collected showed that the presence of the following elements is essential: a clinically notable haemorrhagic bulla, an ero-

Table 3. Differential diagnoses of angina bullosa haemorrhagica.

Differential diagnosis	Disease context	Clinical features		Paraclinical features
		Oral symptoms	Skin symptoms	
Mucous membrane pemphigoid	Elderly subjects	No bleeding bullae Unruptured intraoral blood-filled vesicles Erosive or desquamative gingivitis Dysphagia Progressive scarring	Cutaneous and ophthalmic localizations Ocular synechia In most cases, negative Nikolsky sign Erosive, painful, and persistent lesions	Positive DIF IgG and/or C3 at the basal membrane level
Oral amyloidosis	Four types: primitive without associated disease, lymphocytic dyscrasia, secondary to inflammatory diseases, and hereditary	Macroglossia, gingival hypertrophy, xerostomia	Multiple, persistent and small-sized lesions Petechiae or bruising-type skin lesions	Amyloid deposits (Congo Red)
Pemphigus vulgaris	Context of autoimmunity Intra-epidermal bullae on healthy skin or mucosa that quickly break down	Usually starts with oral erosions, often taken for canker sores Dysphagia Painful lesions	Cutaneous bullae of the thorax or the scalp confirm the diagnosis Positive Nikolsky sign	Positive DIF Intra-epidermal bullae by suprabasal acantholysis IIF and ELISA test: autoantibodies linked to desmoglein 1 and 3 of the keratinocytes
Bullous pemphigoid	Elderly subjects Association with neurological diseases	Rare Non-bleeding, large-sized bullae	Sometimes: purely urticarial or eczematiform lesions Symmetrical lesions Negative Nikolsky sign Pruritus	Positive DIF IIF and ELISA anti-BPAG1/2: anti-skin serum antibodies IgE augmentation Hypereosinophilia Dermo-epidermal cleavage
Acquired epidermolysis bullosa	Adult Associated milium cysts	Frequently Canker sores	Skin lesions in friction zones Digestive, ocular, and respiratory lesions, nasal obstruction, epistaxis, etc. Painful lesions	Positive DIF Direct immunoelectron microscopy (IgG) Autoantibodies to type IV collagen Neutrophilia
Linear IgA dermatosis	Children most of the time Drug origin: vancomycin	Rare in children Possible in adults Tense bulla	Tense bulla on healthy or urticarial skin (napkin dermatitis) Prevailing on the lower half trunk, buttocks, perineum, and thighs	Positive DIF Basal membrane IgA
Herpetiform dermatitis	Coeliac disease known or not, children and young adults Pruritus ++: first symptom	Almost never reached	Vesicles or unspecific excoriations Gluten intolerance	Positive DIF IgA deposits Anti-transglutaminase antibodies
Bullous lichen planus	Adults, females (2:1) Emotional ground, anxious, depressive Shock, stress, trauma Lesions often bilateral, symmetrical	Bullous or vesicular eruption in lichenoid zone Gingival erosion Keratotic lesions	Localized papules in flexion areas of the limbs On lichenoid or healthy skin	Negative DIF Lichenoid degeneration, lichenoid infiltrate

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Table 3 (*Continued*)

Differential diagnosis	Disease context	Clinical features		Paraclinical features
		Oral symptoms	Skin symptoms	
Leukaemia	Adults, males Alteration of the general condition	Gingival swelling and hyperplasia Haemorrhage and associated ulcerations Purpura	Pallor, asthenia Fever, lymphadenopathy Petechiae, bruises Erythematous macules	Thrombocytopenia
Thrombocytopenia	Autoimmune origin	Petechiae, ecchymosis Gum haemorrhage Haemorrhage after tooth extraction	Cutaneous haematoma Epistaxis	Thrombocytopenia
Von Willebrand disease	1% of the population	Petechiae, ecchymosis Haemorrhage after tooth extraction	Cutaneous haematoma Epistaxis	Thrombopathy

BPAG, bullous pemphigoid antigen; DIF, direct immunofluorescence; ELISA, enzyme-linked immunosorbent assay; Ig, immunoglobulin; IIF, indirect immunofluorescence.

sion with a history of oral bleeding, and an exclusive oral localization. The presence of a triggering event or promoting factor (mastication), recurrent or isolated lesions of the soft palate, with a favourable evolution in a few days without scars, are in favour of the diagnosis of ABH. The presence of a haemostasis pathology, anti-thrombotic treatment, or a positive DIF can exclude the diagnosis of ABH.

From these observations, the following diagnostic criteria are proposed: (I) clinically notable haemorrhagic bulla or erosion with a history of bleeding in the oral mucosa; (II) exclusively oral or oropharyngeal localization; (III) palatal localization; (IV) triggering event or promoting factor (food intake); (V) recurrent lesions; (VI) favourable evolution without a scar within a few days; (VII) painless lesion, or a tingling or burning sensation; (VIII) normal platelet count and coagulation test results; (IX) negative DIF results.

To validate these criteria, they were tested and applied to each case report retained in this systematic review of the literature that included a sufficiently detailed diagnostic approach and clinical description for each patient. Table 4 provides a summary of the data. The criteria were assessed for 75 patients and the following points were noted: (1) 100% of the case patients fulfilled criteria I and II, (2) 78.7% of the patients ($n = 59$) had normal platelet count and/or coagulation test results, (3) 69.3% of the patients ($n = 52$) presented a favourable evolution without a scar within a few days, (4) 68% of the patients ($n = 51$) had a palatal localization, (5) 66.7% of the patients ($n = 50$) presented a triggering event or promoting factor (food intake), (6) DIF was used as a diagnostic tool for only 16% of the patients ($n = 12$), (7) DIF plus a platelet count and/or coagulation tests was used in the diagnosis in only 13.3% of the patients ($n = 10$).

Consequently, and according to the literature, neither DIF nor a biological check-up appear absolutely indispensable for the diagnosis of ABH. Moreover, the mean number of diagnostic criteria met by the patients in the case reports considered was 5.6. As a consequence, it is proposed that the combination of at least six of the nine diagnostic criteria presented, with criteria I and II being systematically present, should lead to the diagnosis of ABH (Table 5).

In this context, the diagnosis of ABH can be retained on the basis of exclusively clinical criteria. However, DIF and biological check-up results can be taken into account in the case of persistent doubt.

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Table 4. New diagnostic criteria reported in this systematic review.

Authors	I	II	III	IV	V	VI	VII	VIII	IX	Total (Categories I–IX)
	Clinical haemorrhagic bulla or erosion with bleeding history	Exclusively oral or oropharyngeal localization	Palatal localization	Triggering event or promoting factor	Recurrent lesions	Favourable evolution without a scar within a few days	Painless lesion, tingling or burning sensation	Normal platelet count and coagulation tests	Negative DIF	
Edwards et al., 1990[18]	1	1		1	1	1			1	6
	1	1	1	1	1	1		1	1	8
	1	1		1	1	1		1		6
Higgins and Vivier, 1991[27]	1	1	1		1	1	1	1	1	8
Kirtschig and Happle, 1994[19]	1	1		1	1	1		1		6
Ingram, 1995[14]	1	1	1		1			1	1	6
de las Heras et al., 1996[30]	1	1		1	1	1		1	1	7
Corson and Sloan, 1996[31]	1	1		1		1	1	1		6
Von Arx, 1998[11]	1	1			1		1			4
Antoni-Bach et al., 1999[2]	1	1		1	1	1	1	1	1	8
Dominguez et al., 1999[33]	1	1			1	1		1		5
Curran and Rives, 2000[34]	1	1	1	1		1	1			6
Roguedas et al., 2002[20]	1	1	1	1	1	1			1	7
Yip, 2003[35]	1	1	1	1						4
Pahl et al., 2004[16]	1	1			1			1		4
Slezák, 2005[36]	1	1	1	1		1		1		6
	1	1	1	1		1		1		6
	1	1	1	1		1		1		6
	1	1	1	1		1		1		6
	1	1	1	1		1		1		6
	1	1	1	1		1		1		6
	1	1			1	1		1		5
	1	1		1		1		1		5
	1	1	1	1	1	1		1		7
	1	1	1	1		1		1		6
	1	1	1	1		1		1		6
	1	1			1	1		1		5
	1	1	1	1		1		1		6
	1	1		1	1	1		1		6
Kurban et al., 2007[37]	1	1	1	1	1	1	1	1	1	9

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Table 4 (*Continued*)

Authors	I Clinical haemorrhagic bulla or erosion with bleeding history	II Exclusively oral or oropharyngeal localization	III Palatal localization	IV Triggering event or promoting factor	V Recurrent lesions	VI Favourable evolution without a scar within a few days	VII Painless lesion, tingling or burning sensation	VIII Normal platelet count and coagulation tests	IX Negative DIF	Total (Categories I–IX)
Horie et al., 2008[8]	1	1	1					1		4
	1	1	1					1		4
	1	1	1					1		4
	1	1	1					1		4
	1	1	1	1				1		5
	1	1	1	1				1		5
	1	1	1	1				1		5
	1	1	1	1				1		5
	1	1	1	1				1		5
	1	1	1	1				1		5
	1	1	1	1				1		5
	1	1	1	1				1		5
	1	1	1	1				1		5
	1	1	1	1				1		5
	1	1	1	1				1		5
	1	1	1	1				1		5
Martini et al., 2010[22]	1	1	1	1		1	1	1		7
	1	1	1		1	1				5
	1	1	1			1	1			5
	1	1	1	1	1	1				6
Serra et al., 2010[38]	1	1	1			1		1		5
	1	1	1			1		1		5
	1	1	1		1	1		1		6
	1	1	1		1	1		1	1	7
Bertram, 2010[39]	1	1	1	1	1	1	1			7
Milin and Fouche, 2011[29]	1	1		1	1	1				5
Martins et al., 2012[24]	1	1	1	1		1		1		6
	1	1	1	1		1		1		6
	1	1	1	1		1	1	1		7
	1	1	1	1		1		1		6
	1	1		1		1		1		5
	1	1		1		1		1		5
Rai et al., 2012[40]	1	1	1			1	1	1		6
	1	1	1	1	1	1	1	1		8
Shoor et al., 2013[41]	1	1	1		1	1	1	1	1	8
Scully, 2013[26]	1	1	1	1		1		1	1	7
Kluger and Frances, 2013[42]	1	1		1		1	1			5
Shashikumar et al., 2013[21]	1	1	1		1	1	1	1		7
	1	1				1		1		4
Shashikala, 2013[17]	1	1			1					3

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Singh et al., 2013[43]	1		1			1								5	
Reddy, 2014[44]	1		1		1		1							6	
Patigaroo et al., 2014[45]	1		1				1		1			1		6	
Lozano-Masdemont et al., 2016[46]	1		1			1								3	
	1		1			1								3	
Total															
Number	75	75		51	50	31	52		17		59	12			Mean 5.63
%	100	100		68	66.7	41.3	69.3		22.7		78.7	16			

DIF, direct immunofluorescence.

Table 5. Proposed diagnostic criteria for angina bullosa haemorrhagica: six criteria (including criteria I and II) are sufficient for the diagnosis.

I	Clinically notable haemorrhagic bulla or erosion with a history of bleeding of the oral mucosa
II	Exclusively oral or oropharyngeal localization
III	Palate localization
IV	Triggering event or promoting factor (food intake)
V	Recurrent lesions
VI	Favourable evolution without a scar within a few days
VII	Painless lesion, tingling or burning sensation
VIII	Normal platelet count and coagulation tests
IX	Negative direct immunofluorescence

In conclusion, ABH is poorly documented in the literature, with very heterogeneous studies of low-level evidence (case reports or series of cases), with many missing and unreported data. Thus, ABH is a poorly understood pathology and its aetiology remains controversial. Although it is of a benign nature, with a rapid and spontaneously favourable evolution in most cases, it shares some clinical and histological features with more serious pathologies.

The diagnostic procedure must be rigorous to eliminate an autoimmune disease or a pathology that has an impact on the bleeding. The diagnostic criteria proposed according to the results of this review are mainly based on clinical examination and make it possible to establish a diagnosis without systematically performing all of the sometimes-unnecessary complementary examinations, which are invasive and/or costly. A new prospective study should be conducted to validate the proposed diagnostic criteria.

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Competing interests

The authors declare that they have no competing interests.

Ethical approval

This work did not require any ethical approval.

Patient consent

Patient consent was obtained to publish the clinical photographs.

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