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Review Article

Ocular involvement in oral vesiculobullous diseases: A review on reported cases in the literature

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ABSTRACT

Introduction: Vesiculobullous disorders are a group of autoimmune diseases manifesting as chronic ulcers in the oral cavity. Ocular involvement may accompany oral ulcers and cause various problems for patients. This review summarizes the data regarding ocular involvement in patients with oral vesiculobullous.
Methods: Web of Science, Scopus, PubMed/MEDLINE, and Embase electronic databases were searched according to related keywords. Finally, 58 articles were included, all of which were case reports or series. Characteristics such as the age and sex of patients, location and type of oral lesion, type of ophthalmic injury, the interval between oral and ocular lesion, and treatment of oral and ocular disorders were summarized in tables.
Results: Eye involvement was 1.6 times more prevalent in women, and most patients were between 30 and 60 years old (67.4 %). Pemphigus vulgaris accounted for almost half of the cases (48.4 %), though lichen planus is more prevalent in the general population. The most frequently affected oral site was the buccal mucosa (17.5 %), and oral ulcers usually presented as erythema, erosion, or inflammation (22.7 %). Conjunctivitis was the most common type of eye involvement (18.4 %), and ophthalmic lesions regularly appeared 12–60 months after the development of oral lesions (30.1 %). Blindness was reported in only one case. Corticosteroids and immunosuppressives were the most frequent oral and ocular lesion therapies.
Conclusion: Considering the serious burdens of any ocular injury, monitoring the ocular health of patients with oral vesiculobullous diseases is highly recommended in high-risk cases, especially middle-aged women with oral pemphigus vulgaris.

1. Introduction

Lesions in the oral cavity typically manifest as pigmentations, exophytic lesions, ulcerations, or red-white lesions (Mortazavi et al., 2017). Oral ulcers are one of the most common complaints in the oral cavity (Babu et al., 2017). An ulcer arises due to a defect in either the underlying connective tissue, the epithelium, or both. Oral ulcerative lesions were categorized into three major groups: acute, chronic, and recurrent ulcers, based on the duration of lesions. According to the number of lesions, they were further subdivided into five subgroups: solitary acute, multiple acute, solitary chronic, multiple chronic, and solitary/multiple recurrent. In this regard, vesiculobullous lesions comprise the majority of the multiple chronic ulcer group (Mortazavi et al., 2016).

Vesiculobullous lesions are characterized by the formation of vesicles or bullae; however, in the oral cavity, these vesicles or bullae do not last long because of the high frequency of physical trauma, and the subsequent rupture of these blisters eventually causes ulcers that can impose a great deal of pain and discomfort on patients (Rastogi et al., 2014).

A common pathogenic mechanism of these lesions is the binding of autoantibodies to specific adhesion molecules located in epidermal desmosomes, hemidesmosomes, and, in some cases, within the dermo-epidermal basement membrane zone. As a consequence of circulating autoantibodies binding to target structures and causing an inflammatory

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reaction, adhesion is lost, resulting in the formation of intra- or subepidermal blisters (Rashid et al., 2019).

The most common vesiculobullous diseases in the oral cavity are pemphigoids (cicatricial or benign mucous membrane pemphigoid (MMP) and bullous pemphigoid), pemphigus vulgaris, and lichen planus (Mortazavi et al., 2016).

The most prevalent autoimmune subepidermal blistering condition is bullous pemphigoid (BP), which results from antibodies against two hemidesmosomal proteins: BP180 and BP230 (Moro et al., 2020). However, Mucous membrane involvement is unusual in bullous pemphigoid and is often observed in severe cases (Clapé et al., 2018). Bullous pemphigoid is estimated to occur in 2.4–23 cases per million of the general population each year, but in those over 80, the incidence rises exponentially to 190–312 cases per million (Kridin and Ludwig, 2018).

Cicatricial pemphigoid is a form of subepidermal blistering that affects the mucous membranes and the upper layer of the skin. Clinically, the condition lasts for an extended period of time, and significant scarring can lead to devastating consequences. In vivo, the deposition of antibodies targeting the basement membrane characterizes the disease (Ahmed et al., 1991). Cicatricial pemphigoid affects approximately 1.16 million and 0.87 million people each year in the French and German populations, respectively (Bernard et al., 1995, Zillikens et al., 1995). According to a Greek study, the average age at which cicatricial pemphigoid occurs is 66 years, with a 1.5:1 female preponderance (Tolaymat and Hall, 2022).

Pemphigus vulgaris is a chronic autoimmune disease of the mucocutaneous system that manifests initially as intraoral lesions, eventually spreading to other mucous membranes and the skin. Autoantibodies against substances found between cells are the hallmark of the pemphigus group of diseases (Tamgadge et al., 2011). The incidence of pemphigus vulgaris varies from 5 to 32 cases per million of the general population annually. There is an approximately equal ratio of males to females. There is a wide range of onset ages, but the average is approximately 50–60 years (Ahmed and Moy, 1982, Wilson et al., 1994, Pietkiewicz et al., 2017).

Lichen planus is also a mucocutaneous inflammatory condition characterized by violaceous polygonal flat-topped papules and plaques (Waqas et al., 2020). Nasopharynx, esophagus, larynx, and anogenital are other regions commonly affected by pemphigus vulgaris (Ata-Ali Mahmud and Ata-Ali Mahmud, 2011, Gorouhi et al., 2014, Santi et al., 2019). According to different studies, the prevalence of lichen planus in the general population varies between 0.9 % and 1.2 % and no more than 2 %. Most studies have found that the mean age at the time of diagnosis is around 50–55 years. Women are generally more likely to be affected than men (Lozada-Nur and Miranda, 1997).

These lesions can have important extra-oral complications, one of the most important of which is eye involvement, which can even lead to blindness. The vesiculobullous diseases previously mentioned can cause a variety of symptoms in the eye, from mild irritation and dry eye to severe vision loss, symblepharon, eyelid malposition, chronic conjunctivitis, and ocular surface scarring (Kang et al., 2022).

Regarding the importance of ocular health in general health, early diagnosis and treatment of any ocular injury in patients suffering from vesiculobullous diseases should be appreciated. Therefore, practitioners should be familiar with the traits of eye involvement in oral vesiculobullous disorders.

We aim to evaluate the distribution of ocular involvement among patients with oral vesiculobullous disease. It is also crucial to determine which variation of these diseases causes ocular involvement more frequently. Additionally, we would like to know more about these patients' characteristics so that risk assessment can be carried out more accurately in new patients.

2. Materials and methods

2.1. Literature search

Pubmed/MEDLINE, Scopus, Embase, and Web of Science databases were searched to obtain relevant citations. The electronic search was conducted according to the keywords including, but not limited to, vesiculobullous diseases, pemphigoid, pemphigus, lichen planus, autoimmune blistering diseases, ocular involvement, conjunctivitis, and eye on March 2023. All English studies, regardless of their publication year or status, were selected for appraisal.

2.2. Inclusion and exclusion criteria

At first, two authors independently appraised the title of the obtained citations. Next, the selected citations were evaluated for eligibility by meticulously evaluating their abstract. Finally, full texts of chosen citation were retrieved and assessed to discover if the article satisfies the following requirements: Observational studies reporting one case or cases of oral lichen planus, pemphigoid, and pemphigus vulgaris with ocular involvement were considered eligible. The ocular manifestations could happen after oral involvement or at the same time; also, the studies that did not mention the exact time of ocular involvement were included. However, the cases in which ocular involvement was reported earlier than oral manifestation or was a complication of another systemic disease were excluded. Case reports, case series, and retrospective studies were considered. Studies in which critical information, such as information about patients' conditions or lesion traits, was missed or whose full text was not retrieved were disregarded.

3. Results

3.1. Search outcomes

Fifty-eight studies were finally selected from 1,345 imported citations. Included studies comprised 12 retrospective longitudinal studies or case series and 46 case reports. Fig. 1 illustrates the search flowchart of the current review. The included articles were all published in English.

3.2. Type of vesiculobullous disease

Among 126 cases reported by the included studies, 35 were affected by pemphigoid, 61 by pemphigus vulgaris, and 30 by lichen planus. Table 1 presents an overview of the included studies along with their essential data. Also, Table 2 clarifies the outcomes of combining data from all the studies. Also, Table 3, Table 4, and Table 5 demonstrate a summary of the characteristics of patients with pemphigus vulgaris, pemphigoid, and lichen planus, respectively. The most significant findings are going to be described in the following.

3.3. Demography of patients

According to our findings, oral lichen planus, pemphigus vulgaris, and pemphigoid are all slightly more prevalent in women. Generally, the male-to-female ratio was 1:1.60, but gender difference was most significant among lichen planus cases (Table 5). The average age of reviewed patients was 56.8 for lichen planus, 42.2 for pemphigus vulgaris, 56 for pemphigoid, and 49.5 for all these three vesiculobullous conditions. A 1.6-year-old boy and an 82-year-old woman were the youngest and oldest patients with vesiculobullous lesions, respectively. Over 50 % of the patients that were reported were between the ages of 30 and 60.

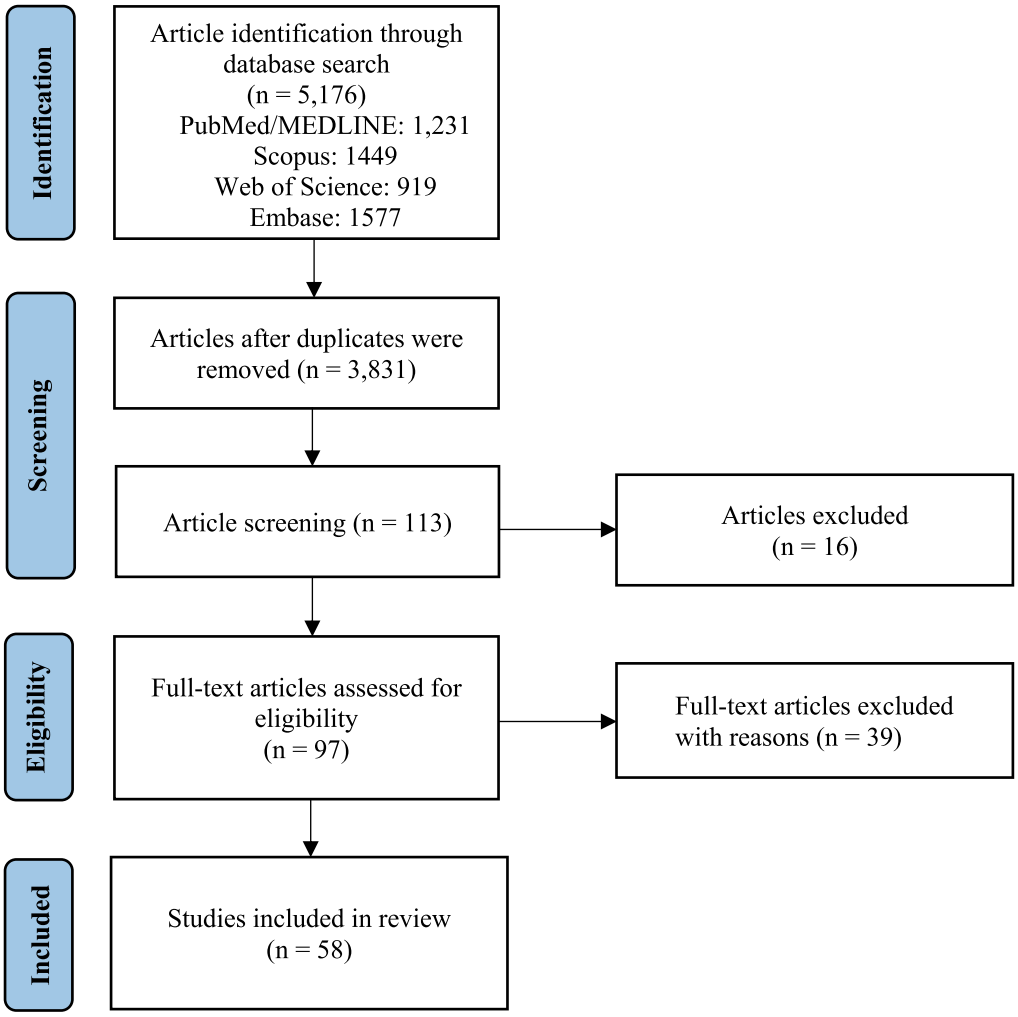

Fig. 1. Search flowchart of the review.

3.4. Oral manifestation

The most common involvement site was the buccal mucosa. The gingiva, palate, and tongue were the other frequently involved sites in that order of prevalence. Although many cases did not report the exact oral clinical presentation, erythema, erosion, and inflammation were the most common clinical presentations among those reporting.

3.5. Ocular manifestation

Most articles did not mention the time of eye involvement, but among those that did, ocular signs and symptoms were most commonly detected 12–60 months after the oral involvement. Eleven patients had eye involvement under six months, and only one patient's eyes were affected under six to 12 months after oral involvement. In 88 patients, eyes were affected bilaterally, and blindness was only reported in one case; however, the blindness was not directly related to the vesiculobullous disorder. Conjunctivitis, erosion, and symblepharon were the most common types of eye involvements in order of prevalence. Symblepharon was the most common manifestation in lichen planus and pemphigoid, but erosion was mainly reported in pemphigus vulgaris.

3.6. Oral lesions treatment

Corticosteroids and immunosuppressive drugs were mainly used for oral lesions in all three conditions. The other frequently mentioned effective treatments were antibiotics and IVIgs.

3.7. Eye lesion treatment

Corticosteroids, immunosuppressives, and artificial tears were the most common treatments for eye lesions. Surgery was done for 18 cases. Other effective treatments include antibiotics, IVIgs, antivirals, and lubricants.

4. Discussion

According to our study and the cases included, patients with oral vesiculobullous disorders with ocular involvement had an average age of 49.5 years. The mean age of patients with oral vesiculobullous diseases has been reported mainly between 41 and 47 years (Sobhan et al., 2016; GonÇAlo et al., 2018). Regarding ocular involvement mainly being observed after 12–60 months of initial vesiculobullous disease, it seems that the age at which patients were affected by the primary disorder does not vary from the overall average, and this condition is mainly observed in middle-aged patients. Although ocular involvement occurs more frequently in older patients, children and adolescents have also been reported to have it. In addition, the male-to-female ratio was 1:1.60, meaning that female patients across all age groups had a higher likelihood of having ocular diseases than male patients. Even though vesiculobullous disorders are generally more prevalent among females (Maharshak and Brenner, 2002; Rosi-Schumacher et al., 2023), the

Table 1
The characteristics of included studies.

Author, year	Number of cases	Average age	Sex	VB disease	Oral site	Oral presentation	Time of eye involvement	Unilateral/ bilateral eye involvement	Type of eye involvement	Blindness	Oral lesion treatment	Eye lesion treatment
Foster and Nally, 1977	2	64.5	F: 2	MMP	Palate, oropharynx, and buccal mucosa	Bullae, ulcer, and blister	N/A	Bilateral	Symblepharon with entropion	No	ACTH	N/A
Kumar et al., 1980	1	51	F	MMP	Gingiva	Erosion and inflammation	N/A	Bilateral	Conjunctival erythema	No	Prednisone	N/A
Nelson and Rennie, 1988	1	53	M	Pemphigus vulgaris	N/A	Ulcers	24 months	Bilateral	Erosion of the lid margin and serous conjunctivitis	No	Prednisolone sodium phosphate and azathioprine sodium	Topical prednisolone drops
Hodak et al., 1990	10	51.6	F: 7 M: 2 N/A: 1	Pemphigus vulgaris	N/A	N/A	N/A	N/A	Hyperemia, mucoid discharge, lower lid margin erosions, irritation, watering, and foreign body sensation	No	Prednisone	N/A
Neumann et al., 1993	1	42	F	Conjunctival lichen planus	N/A	N/A	72 months	Bilateral	Conjunctival cicatrization, foreshortening of conjunctival fornices, conjunctival injection, subepithelial fibrosis, and keratin plaque	No	N/A	Cyclosporine eyedrops
Bystryn et al., 1993	1	60	M	MMP: 1	Buccal mucosa, gingiva, soft palate, uvula, and pharynx	Erosion, bleeding, peeling, swelling, and erythema	Synchronous with oral manifestations	Unilateral	Conjunctivitis and symblepharon	No	Chlorambucil, prednisone, and dapsone,	N/A
Mallon and Wojnarowska, 1994	1	71	F	MMP: 1	Palate	Ulcer, blister	N/A	Bilateral	Gritty eyes	No	Tetracycline, nicotinamide, and minocycline	N/A
Hutnik et al., 1995	1	51	F	Lichen planus	N/A	N/A	N/A	N/A	Refractory keratoconus	No	Steroid, cyclosporine, and dapsone	Cyclophosphamide pulse therapy
Lilly et al., 1995	1	64	F	MMP	Gingiva	Inflammation, bone loss, bleeding	N/A	Unilateral	Loss of vision because of glaucoma, not pemphigoid	Yes	Dapsone, prednisone, and clobetasol	N/A
Buhac et al., 1996	1	57	F	MMP	Tongue and buccal and labial mucosa	Erosion and ulcer	24 months	Bilateral	Conjunctivitis	No	Hydrogen peroxide, dexamethasone elixir, diphenhydramine elixir, fluocinonide gel, triamcinolone acetonide, betamethasone spray lubrication, and fluocinonide ointment	Dapsone and prednisolone sodium phosphate eye drops

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Table 1 (*continued*)

Author, year	Number of cases	Average age	Sex	VB disease	Oral site	Oral presentation	Time of eye involvement	Unilateral/ bilateral eye involvement	Type of eye involvement	Blindness	Oral lesion treatment	Eye lesion treatment
Allbritton et al., 1997	1	57	M	MMP	Palate, buccal mucosa	Ulcer	N/A	Bilateral	Conjunctival infection, loss of fornix, and symblepharon	No	Prednisone and cyclophosphamide	N/A
Uchiyama et al., 2000	1	61	M	MMP	Hard palate, lower lip	Erosion and bullae	6 months	Bilateral	Symblepharon, conjunctivitis, and ankyloblepharon	No	N/A	Betamethasone sodium phosphate, ofloxacin, artificial tear solution, and therapeutic contact lenses
Hahn et al., 2000	4	44	F: 3 M: 1	Paraneoplastic lichen planus	Buccal mucosa, lip	Stomatitis and erosion	2 months	Bilateral	Cicatrizing conjunctivitis	No	Systemic cyclosporin, dexamethasone	Systemic cyclosporin and fluorometholone
Gilmour et al., 2001	1	50	M	MMP	Tongue	Ulcer	12 months	Bilateral	Conjunctivitis, symblepharon, entropion, and lid fibrosis	No	Prednisolone, azathioprine, dapsone, cyclosporin, acyclovir, famciclovir, mycophenolate mofetil, and tetracycline	Cyclosporin, dapsone, and prednisolone
Seo et al., 2001	1	67	F	MMP	Tongue, buccal mucosa	Erosions	N/A	Bilateral	Conjunctival injection and symblepharon	No	Prednisolone and cyclophosphamide	N/A
Leverkus et al., 2001	1	74	M	MMP	Gingiva	Erosion	N/A	N/A	Conjunctivae scarring and impairment of vision	No	IV dexamethasone with cyclophosphamide and fluconazole	N/A
Kurihara et al., 2001	1	45	F	MMP	Gingiva	Bleeding, desquamation	N/A	N/A	Conjunctivitis with burning sensation, irritation, and excess tearing and stye on the eye	No	Systemic and topical corticosteroid	Topical steroids and antibiotics
Tursen et al., 2002	1	34	F	Lichen planus-lupus erythematosus overlap syndrome	Buccal and labial mucosa	White papules with a reticular pattern	2 weeks	Unilateral	Erythematous plaque	No	Hydroxychloroquine	Hydroxychloroquine
Miziara et al., 2002	1	49	F	MMP	Lip	Ulcer	N/A	Bilateral	Conjunctival hyperemia and xerophthalmia	No	Chlorambucil	N/A
Thorne et al., 2003	5	70	F: 5	Lichen planus	Oral mucosa and gingiva	Erosion and blister	Soon after the oral involvement	Bilateral	Foreshortening of lower fornices, nasal symblepharon	No	Prednisone and cyclosporine	Prednisone and cyclosporine
Merchant and Weinstein, 2003	3	15.5	M: 3	Pemphigus vulgaris	Throat, lips, gingiva, palate, tongue, and buccal mucosa	Ulcers and erosions	Synchronous with oral manifestations	Bilateral	Nonpurulent conjunctivitis, corneal ulcers, conjunctival injection with profuse watery discharge, and photophobia	No	IV methylprednisolone followed by prednisone with calcium and vitamin D supplementation. Azathioprine and steroid-sparing therapy.	N/A

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Table 1 (*continued*)

Author, year	Number of cases	Average age	Sex	VB disease	Oral site	Oral presentation	Time of eye involvement	Unilateral/ bilateral eye involvement	Type of eye involvement	Blindness	Oral lesion treatment	Eye lesion treatment
Iaccheri et al., 2004	1	39	M	MMP	Oral mucosa	N/A	N/A	Bilateral	Photophobia, thickened eyelid, conjunctival injection, foreshortening of fornices, symblephara, conjunctivitis, trichiasis, and keratopathy	No	N/A	Topical antibiotic, amphotericin B drop, cyclophosphamide, subcutaneous cytosine arabinoside, IVIg therapy, and prednisone
Seth et al., 2004	1	64	M	MMP	Palate, tongue, throat	Blisters	N/A	Bilateral	Conjunctival ulceration and symblepharon formation	No	Oral steroids on a tapering dose	IV cyclophosphamide
Lifshitz et al., 2004	1	20	M	Pemphigus vulgaris	Buccal mucosa, palate, pharynx, and larynx	Erosions and blisters	N/A	Bilateral	Conjunctival hyperemia, diffuse induration and thickening of eyelids, lid margin erosions in upper and lower lids	No	Oral prednisone, triamcinolone, and azathioprine	Dexamethasone and chloramphenicol drops, antiglaucomatous drops, fusidic acid ointment, and artificial tears
Canizares et al., 2006	5	52	F: 5	MMP	Gingiva, hard palate, and tongue	Erosion	48 months	Bilateral	Dry eye syndrome, symblephara, conjunctival and corneal ulceration, subepithelial erythema, fibrosis, keratopathy, and nuclear sclerosis	No	Dapsone, azathioprine sodium, clobetasol propionate ointment, nystatin, prednisone, etanercept, dexamethasone elixir, and topical fluocinonide gel	IVIg, prednisone, dapsone, clobetasol propionate, nystatin, hydrochlorothiazide, cyclophosphamide, valacyclovir hydrochloride, acyclovir, cyclosporine, and mycophenolate mofetil
Palleschi et al., 2007	3	53	M: 1 F: 2	Pemphigus vulgaris	Palate	Erosion	2 months, synchronous	Bilateral	Erosions of eyelid margins	No	Oral prednisone	N/A
Iovine et al., 2008	1	9	F	MMP	N/A	Ulcer	N/A	Bilateral	Blepharospasm, symblepharon, keratinization of the conjunctiva, scarring of caruncle and puncta, dry eye, corneal leucoma, trichiasis, eyelid edema, conjunctival hyperemia, and corneal perforation.	No	Prednisone, surgery, cyclosporine, and tacrolimus	Ocular plastic surgery and electrolysis
Diniz et al., 2008	1	56	F	Lichen planus	Oral mucosa	N/A	192 months	Bilateral	Cicatricial conjunctivitis, symblepharon, dry eye, corneal infiltration, neovascularization, and thinning.	No	Systemic corticosteroid and cyclosporine	Systemic corticosteroid and cyclosporine

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Table 1 (*continued*)

Author, year	Number of cases	Average age	Sex	VB disease	Oral site	Oral presentation	Time of eye involvement	Unilateral/ bilateral eye involvement	Type of eye involvement	Blindness	Oral lesion treatment	Eye lesion treatment
Olszewska et al., 2008	1	47	M	Pemphigus vulgaris	Oral cavity and esophagus	Erosions, dysphagia, congestion and swelling of esophageal mucosa, and congestion and swelling of the mucosa	N/A	N/A	Conjunctivitis with periodical presence of purulent discharge, photophobia, and burning sensations	No	Prednisone and cyclophosphamide	Repeated lubrication of the eyes and application of diclofenac, naphazoline, and zinc sulfate solutions
Durrani et al., 2008	9	49.5	F: 6 M: 3	Lichen planus	N/A	N/A	N/A	Bilateral	Severe bicanalicular obstruction	No	N/A	Dacryocystorhinostomy, canaliculostomy, and Jones tube
Uchino et al., 2009	1	55	M	MMP	Oral mucosa	Bullae	N/A	Bilateral	Photophobia, subconjunctival fibrosis, partial conjunctivalization, foreshortening of fornices, corneal and conjunctival epithelial defects, and symblepharon	No	Ciclosporin, methylprednisolone, hyaluronic acid, levofloxacin, prednisolone, cyclophosphamide, amniotic membrane transplantation, and IVIg,	Surgery, mitomycin, saline solution, phacoemulsification, and intraocular lenses,
Mehta et al., 2010	1	54	F	Pemphigus vulgaris	Esophagus	N/A	N/A	Unilateral	Necrotizing scleritis and conjunctivitis, redness and irritation in the left eye, conjunctival injection	No	Oral prednisone, transitioning to steroid-sparing immunomodulatory therapy with mycophenolate mofetil, rituximab, and IVIg	IVIg infusions and valacyclovir
Roufas et al., 2010	1	50	M	MMP	Buccal mucosa	Ulcers and inflammation	13 months	Unilateral	Subtarsal scarring, symblepharon/ ankyloblepharon, pyogenic granulomas, papillary conjunctivitis, and mild blepharitis	No	Oral methotrexate and prednisone	N/A
Ahuero et al., 2010	2	50	M: 1 F: 1	Paraneoplastic conjunctival cicatrization	Tongue	Erythema and erosions	Synchronous with oral manifestations	Bilateral	Viral conjunctivitis, eyelid thickening, conjunctival thickening, mucus discharge, symblephara, fornical foreshortening, and corneal desiccation	No	Prednisone, cyclophosphamide, IVIg, rituximab, chemotherapy (carboplatin, paclitaxel)	Ocular surface amniotic membrane grafting and topical lubrication
Kharfi et al., 2010	1	1.6	M	MMP	Gingiva, buccal mucosa, and commisure	Erosion and fibrosis	N/A	Bilateral	Entropion, trichiasis, cicatricial cornea	Yes	Prednisone	Dapsone, topical ocular cyclosporine, surgical correction
Shaikh et al., 2010	1	18	M	Lichen planus	Buccal mucosa,	Ulcer	N/A	N/A	Subepithelial fibrosis and symblepharon	No	N/A	N/A

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Table 1 (*continued*)

Author, year	Number of cases	Average age	Sex	VB disease	Oral site	Oral presentation	Time of eye involvement	Unilateral/ bilateral eye involvement	Type of eye involvement	Blindness	Oral lesion treatment	Eye lesion treatment
					supraglottic area, and laryngeal mucosa							
Brackley and Pagani, 2011	1	43	F	Pemphigus vulgaris	Tongue and buccal mucosa	Ulcers and black spots	2 weeks	Unilateral	Necrotizing scleritis, conjunctival abrasion, and viral pseudomembranous conjunctivitis with burning and discharge, hyperemia, and areas of bulbar erosion	No	Oral prednisone and rituximab	Topical prednisolone acetate 1 %
Fiore et al., 2011	1	33	M	Pemphigus vulgaris	N/A	N/A	N/A	Bilateral	Vegetations on each plica semilunaris	No	Prednisone and methotrexate	Excisional biopsy and topical cyclosporine
Avisar et al., 2011	2	55.5	F: 2	Pemphigus vulgaris	Oral mucosa, pharynx, and esophagus	Ulcer	N/A	Bilateral	Symptomatic eyelid margin mucosal papillomas, ocular irritation	No	Systemic triamcinolone, prednisolone, and azathioprine	N/A
Choi et al., 2011	1	67	M	MMP	Gingival mucosa, hard palate	Erythema, erosion, and white atrophic scars	N/A	N/A	Conjunctival inflammation, symblepharon, neovascularization, and corneal scarring	No	Methylprednisolone, dapsone, and mycophenolate mofetil	N/A
Skorin et al., 2011	1	65	M	MMP	Gingiva	Ulcer	N/A	Bilateral	Dry eye syndrome	No	N/A	Artificial tears
Webber et al., 2012	10	65.1	F: 10	Lichen planus	Buccal mucosa, gingival mucosa, and esophagus	Erosion, fibrous bands	57.6 months	Bilateral: 7, unilateral: 2	Cicatricial conjunctivitis, Punctum scarring, and surgical scar	No	N/A	Eye drops of carmellose sodium and prednisolone sodium phosphate, and bilateral lacrimal duct dilatation
Uludag et al., 2013	1	22	M	Pemphigus vulgaris	Buccal mucosa	Erosions	N/A	Unilateral	Localized conjunctival hyperemia and swelling, lobulated conjunctival tumoral mass associated with conjunctival hyperemia encroaches on the cornea nasally	No	Prednisone and azathioprine	Topical prednisolone acetate
Namba et al., 2013	1	64	M	Pemphigus vulgaris	Tongue, pharynx, and esophagus	Erosions and odynophagia	N/A	Bilateral	Conjunctival giant papillae and photophobia	No	Oral prednisolone, IVIg, and cyclosporine A	Surgical excision
Singh et al., 2014	1	48	M	MMP	Buccal mucosa, vestibule, labial mucosa, floor of the mouth	Ulcer	N/A	Bilateral	Conjunctivitis	No	Topical and intralesional corticosteroids (triamcinolone acetonide, dexamethasone) and chlorhexidine mouthwash	N/A

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Table 1 (*continued*)

Author, year	Number of cases	Average age	Sex	VB disease	Oral site	Oral presentation	Time of eye involvement	Unilateral/ bilateral eye involvement	Type of eye involvement	Blindness	Oral lesion treatment	Eye lesion treatment
Joseph et al., 2015	1	75	F	MMP	Hard and soft palate, alveolar mucosa, buccal mucosa, gingiva	Erythema, ulcer, and vesicle	N/A	Unilateral	Scaring of bulbar conjunctiva and symblepharon	No	Dapsone and prednisolone	N/A
Oyama et al., 2016	1	56	M	Pemphigus vulgaris	Hard palate, buccal mucosa, gingiva, larynx, and esophagus	Erosions and swelling	Synchronous with oral manifestations	Bilateral	Swelling and erosions on the right upper palpebral conjunctiva and pterygium, congestion of the bulbar conjunctiva, conjunctival hyperemia, severe lacrimation, photophobia, and burning irritation of the eyes	No	Oral prednisolone, dapsone, oral cyclosporine, and mizoribine	Topical steroid and tacrolimus eye drops
España et al., 2017	25	49.7	F: 12 M: 13	Pemphigus vulgaris	Oral cavity	N/A	36.4 months	Bilateral: 21, unilateral:3	Conjunctivitis, erosion on eyelids, medial epicanthus, hyposphagma, erosion at eyelid margins, and lacrimal canaliculitis	No	Prednisone, azathioprine, mycophenolate mofetil, rituximab, IVIg, cyclosporine, dapsone photopheresis, and sodium aurothiomalate	Artificial tear drops and topical corticosteroids
Lambiel et al., 2017	1	73	F	MMP	Tongue, buccal mucosa, soft palate, uvula, oropharynx	Ulcer	N/A	Bilateral	Ocular irritation	No	IV dexamethasone, oral prednisone, dapsone, and hormonal therapy	N/A
Temilola et al., 2018	1	54	F	Pemphigus vulgaris	Palate, the floor of the mouth, buccal mucosa, sublingual duct, gingiva	Ulcers, erosions, vesicles, desquamative gingivitis	A few weeks after oral presentations	Unilateral	Diffuse erythema of conjunctiva, left chronic conjunctivitis, with itching, burning, and tearing of the left eye	No	Prednisone	Ocular lubricant and topical corticosteroid
Wijaya et al., 2018	1	50	M	MMP	N/A	N/A	N/A	N/A	Conjunctival symblepharon	No	Corticosteroids, azathioprine, infliximab, rituximab, mycophenolate mofetil, IVIg, and prednisone,	N/A
Bernauer et al., 2018	1	71	M	MMP	N/A	Ulcer and dysphagia	N/A	Bilateral	Cicatrizing conjunctivitis, foreign body sensation, blurred	No	Rituximab, prednisone, and azathioprine	Ganciclovir

(*continued on next page*)

Table 1 (*continued*)

Author, year	Number of cases	Average age	Sex	VB disease	Oral site	Oral presentation	Time of eye involvement	Unilateral/ bilateral eye involvement	Type of eye involvement	Blindness	Oral lesion treatment	Eye lesion treatment
									vision, epithelial defect, dendritic epithelial ulcer, HSV epithelial keratitis, and cataract			
Zeeli, et al., 2019	1	23	M	Pemphigus vulgaris	Soft palate, gingiva, buccal mucosa	Erosions and gingivitis	A few weeks after oral presentations	Unilateral	Anterior nodular scleritis	No	Oral prednisone, mycophenolate mofetil, rituximab, oral indomethacin, and dapsone	N/A
Bosch-Amate et al., 2020	1	70	F	MMP and frontal fibrosing alopecia	Gingiva	Gingivitis	N/A	N/A	Scarring post-surgical changes in the eyelid, conjunctival fornix shortening	No	Dapsone	N/A
Safadi et al., 2021	1	42	F	Lichen planus	N/A	Ulceration	N/A	N/A	Ocular rosacea with blepharitis and dry eye	No	Doxycycline	Cyclosporine and mycophenolate mofetil tobramycin/ dexamethasone eye drops, and doxycycline
Niwa et al., 2021	1	24	F	Pemphigus vulgaris	Lips, tongue, pharynx, and larynx	Ulcers, blisters, and stomatitis	N/A	N/A	Hyperemia and blistering of the bulbar conjunctiva and pseudomembrane formation in the palpebral conjunctiva	No	Prednisolone and Immunoglobulin therapy	N/A
Fageeh, 2022	1	66	F	MMP	Gingiva	Pain, burning sensation, inflammation, and water-filled balloon-like formation	N/A	Unilateral	Conjunctivitis and scar formation	No	Topical corticosteroids, antifungal and antibacterial drugs, and periodontal therapy	Topical corticosteroid, antifungal, and antibacterial drugs
Burningham et al., 2022	1	69	F	MMP	Hard palate, oropharynx, buccal mucosa, and tongue	Ulcer and erosion	N/A	Bilateral	Inflammation and conjunctival scar	No	Topical corticosteroids, prednisone, methotrexate, IVIg, rituximab, zoledronic acid infusion, mycophenolate mofetil, and cyclophosphamide, baricitinib	Voriconazole and amphotericin

VB: Vesiculobullous, F: Female, M: Male, VB, MMP: Mucous membrane pemphigoid, N/A: Not Available, HSV: Herpes simplex virus, ACTH: Adrenocorticotropic hormone, IV: Intravenous, IVIg: Intravenous Immunoglobulin

Table 2
Summary of the included studies reporting eye involvement in patients with vesiculobullous diseases.

Variables	Outcomes	Frequency	Relative frequency (%)
Sex	Female	77	61.1 %
	Male	48	38 %
	N/A[a]	1	0.7 %
Age	Under 30 years old	8	6.3 %
	30–60	85	67.4 %
	Over 60 years old	32	25.3 %
	N/A	1	0.7 %
	Average	49.5	–
Vesiculobullous disease	Pemphigus vulgaris (Table 3)	61	48.4 %
	Pemphigoid (Table 4)	35	27.7 %
	Lichen plan (Table 5)	30	23.8 %
Oral lesion location	Buccal mucosa	31	17.5 %
	Gingiva	28	15.8 %
	Palate	17	9.6 %
	Tongue	13	7.3 %
	Esophagus	10	5.6 %
	Pharynx	9	5.0 %
	Lips	6	3.3 %
	Laryngeal mucosa	5	2.8 %
	Others	12	6.7 %
	N/A	46	25.9 %
Oral clinical presentation	Erythema/Erosion/ Inflammation	36	22.7 %
	Ulcer	21	13.2 %
	Blister/Bulla/Vesicle	11	6.9 %
	Fibrous bands	10	6.3 %
	Swelling	3	1.8 %
	Bleeding	3	1.8 %
	Gingivitis	3	1.8 %
	Others	13	8.2 %
	N/A	58	36.7 %
Time of eye involvement	Synchronous	6	4.7 %
	Under 6 months	11	8.7 %
	6–12 months	1	0.7 %
	12–60 months	38	30.1 %
	Over 60 months	13	10.3 %
	N/A	57	45.2 %
Unilateral/bilateral	Unilateral	18	14.2 %
	Bilateral	88	69.8 %
	N/A	20	15.8 %
Type of eye involvement	Conjunctivitis	57	18.4 %
	Erosion	48	15.6 %
	Symblepharon	24	7.8 %
	Irritation	17	5.5 %
	Hyperemia	16	5.2 %
	Watering	16	5.2 %
	Photophobia	11	3.5 %
	Fornix foreshortening	11	3.5 %
	Scar	9	2.9 %
	Mucoid discharge	9	2.9 %
	Foreign body	9	2.9 %
	Dry eye syndrome	5	1.6 %
	Fibrosis	5	1.6 %
	Ulcer	5	1.6 %
	Erythema	4	1.3 %
	Thickened eyelid	3	0.9 %
	Burning sensation	3	0.9 %
	Trichiasis	3	0.9 %
	Entropion	3	0.9 %
	Others	48	15.6 %
Blindness	Yes	1	0.7 %
	No	125	99.3 %
Oral lesion treatment	Corticosteroid	102	35.1 %
	Immunosuppressive	78	26.8 %
	IVIg-monoclonal Antibody	31	10.6 %
	Antibiotic	19	6.5 %
	Antifungal	4	1.3 %
	Sodium aurothiomalate	4	1.3 %
	Calcium and vitamin D supplementation	2	0.6 %
	Antiviral	2	0.6 %
	Others	15	5.1 %
	N/A	33	11.3 %
Eye lesion treatment	Corticosteroid	47	22 %
	Immunosuppressive	37	17.3 %
	Artificial tear	28	13.1 %
	Surgery	18	8.4 %
	Antibiotic	16	7.5 %
	IVIg monoclonal antibody	12	5.6 %
	Antiviral	4	1.8 %
	Lubrication	4	1.8 %
	Others	13	6.1 %
	N/A	34	15.9 %

[a] Not available.

gender difference observed in patients with lichen planus was noticeable, with a male-to-female ratio of 1:6.25. Pemphigus vulgaris was the primary disorder in nearly half of the cases; however, the incidence and prevalence of lichen planus are much more than that of pemphigus vulgaris (Lavaee et al., 2022). This may suggest that eye injury is relatively more related to pemphigus vulgaris.

The development of autoimmune blistering diseases is thought to be influenced by an array of potentially causative factors, both hereditary and environmental. A growing number of inciting events and agents have been identified in the pathogenesis of these diseases (Patel et al., 2017). There are splits in either the epidermis or dermis that cause vesiculobullous lesions. There are several pathological processes associated with ocular manifestations, including autoimmune-induced conjunctivitis and lid and corneal pathology, that may lead to permanent loss of vision (Laforest et al., 2005).

According to our findings, ocular involvement was generally bilateral. Since the most plausible etiopathologic factor of vesiculobullous disorders is autoimmune antibodies, and regarding that often they present bilaterally in the oral cavity, bilateral involvement of eyes seems rational. Eye involvement is most common 12–60 months after oral clinical presentation. However, it may also occur under six months or simultaneously. It has been reported that ophthalmic involvement occurs mainly when the primary blistering disease has progressed (Laforest et al., 2005; Clapé et al., 2018). Twelve to 60 months may be necessary for the disease to proceed in severity and invade the eyes.

The extent of ocular involvement varies, encompassing mild irritation and dry eye syndrome as well as conjunctivitis, ocular erosions, symblepharon, surface scarring, and profound visual loss. Conjunctivitis and ocular erosions were the most common ocular manifestations observed.

The clinical manifestations of oral vesiculobullous diseases did not occur exclusively at one site of the oral cavity; however, it was found most commonly in the buccal mucosa, followed by the gingiva, palate, tongue, esophagus, pharynx, lips, and laryngeal mucosa. In patients with pemphigus, the buccal mucosa was the most common location, followed by the palate, gingiva, tongue, and lips. Gingiva exhibited the highest frequency of pemphigoid lesions, with the palate, buccal mucosa, tongue, lips, and labial mucosa being the other sites of involvement. The buccal mucosa is most frequently affected by lichen planus, with the gingiva, esophagus, and lips following behind. The common locations of lesions associated with ophthalmic injury did not differ from typical sites affected by diseases (Gupta and Jawanda, 2015; Subadra et al., 2021).

Most oral vesiculobullous conditions are characterized by erythema, erosion, and inflammation. The second most common clinical manifestation of pemphigus and pemphigoid is ulcer, followed by blister, bullous, and vesicle. In contrast, fibrous bands are the second most common clinical presentation of lichen planus in the oral cavity, followed by ulcers and blisters.

Identifying intact vesicles and bullae in the oral cavity is challenging due to the oral mucosa's frequent irritation and friability. If these lesions

Table 3
Summary of the included studies reporting eye involvement in patients with pemphigus vulgaris.

Variables	Outcomes	Frequency	Relative frequency (%)
Sex	Female	33	54.1 %
	Male	28	45.9 %
Age	Under 30 years old	6	9.8 %
	30–60	54	88.5 %
	Over 60 years old	1	1.6 %
	Average	42.2	–
Oral lesion location	Buccal mocosa	7	9.8 %
	Palate	6	8.4 %
	Esophagus	5	7.0 %
	Pharynx	5	7.0 %
	Tongue	4	5.6 %
	Gingiva	4	5.6 %
	Larynx	4	5.6 %
	Lips	2	2.8 %
	Others	3	4.2 %
	N/A[a]	31	43.6 %
Oral clinical presentation	Erosion/Erythema/ Inflammation	9	12.5 %
	Ulcer	6	8.3 %
	Blister/Bulla/Vesicle	3	4.1 %
	Swelling	2	2.7 %
	Gingivitis	2	2.7 %
	Others	5	6.9 %
	N/A	45	62.5 %
Time of eye involvement	Synchronous	4	6.5 %
	6–12 months	0	0 %
	12–60 months	25	40.9 %
	Under 6 months	4	6.5 %
	Over 60 months	11	18.0 %
	N/A	17	27.8 %
Unilateral/ bilateral	Unilateral	10	16.3 %
	Bilateral	40	65.5 %
	N/A	11	18.0 %
Type of eye involvement	Erosion	48	26.2 %
	Conjunctivitis	40	21.8 %
	Irritation	15	8.1 %
	Hyperemia	14	7.6 %
	Watering	12	6.5 %
	Photophobia	9	4.9 %
	Mucoid discharge	8	4.3 %
	Foreign body sensation	8	4.3 %
	Hyposphagma	4	2.1 %
	Others	25	13.6 %
Blindness	Yes	0	0 %
	No	61	100 %
Oral lesion treatment	Corticosteroid	54	37.7 %
	Immunosuppressive	45	31.4 %
	IVIg/monoclonal antibody	22	15.3 %
	N/A	11	7.6 %
	Others	11	7.6 %
Eye lesion treatment	Corticosteroid	42	21.8 %
	Immunosuppressive	35	18.2 %
	Chemotherapy	33	17.1 %
	Artificial tear	25	13.0 %
	Antibiotic	13	6.7 %
	IVIg	12	6.2 %
	Surgery	7	3.6 %
	Others	8	4.1 %
	N/A	17	8.8 %

[a] Not available.

rupture, there will be erosions or ulcerations on the surface. This makes diagnosing vesiculobullous lesions even more challenging since the differential diagnosis includes ulcerative, immunological-mediated, neoplasms, and systemic diseases in addition to autoimmune blistering disorders. Diagnosing vesiculobullous diseases should be based on clinical, histopathological, and immunological characteristics (Rastogi et al., 2014).

Vesiculobullous diseases can be frightening for patients, but they can be managed with medicinal treatments for oral and eye lesions. The

Table 4
Summary of the included studies reporting eye involvement in patients with pemphigoid disorders.

Variables	Outcomes	Frequency	Relative frequency (%)
Sex	Female	19	54.2 %
	Male	16	45.7 %
Age	Under 30 years old	2	5.7 %
	30–60	16	45.7 %
	Over 60 years old	17	48.5 %
	Average	56	–
Type of pemphigoid	Mucous membrane	33	94.2 %
	Paraneoplastic conjunctival cicatrization	2	5.7 %
Oral lesion location	Gingiva	14	20.5 %
	Palate	11	16.1 %
	Buccal mucosa	10	14.7 %
	Tongue	9	13.2 %
	Oropharynx	4	5.8 %
	Lips	2	2.9 %
	Labial mucosa	2	2.9 %
	Uvula	2	2.9 %
	Others	4	5.8 %
	N/A[a]	10	14.7 %
Oral clinical presentation	Erosion/Erythema/ Inflammation	16	30.7 %
	Ulcer	13	25.0 %
	Blister/Bulla/Vesicle	7	13.4 %
	Bleeding	3	5.7 %
	Others	11	21.1 %
	N/A	2	3.8 %
Time of eye involvement	Synchronous	2	5.7 %
	Under 6 months	0	0 %
	6–12 months	1	2.8 %
	12–60 months	4	11.4 %
	Over 60 months	0	0 %
	N/A	28	80 %
Unilateral/ bilateral	Unilateral	5	14.2 %
	Bilateral	24	68.5 %
	N/A	6	17.1 %
Type of eye involvement	Symblepharon	17	16.1 %
	Conjunctivitis	12	11.4 %
	Scar	8	7.6 %
	Fornix foreshortening	5	4.7 %
	Entropion	3	2.8 %
	Fibrosis	3	2.8 %
	Dry eye syndrome	3	2.8 %
	Watering	3	2.8 %
	Trichiasis	3	2.8 %
	Ulcer	3	2.8 %
	Keratopathy	2	1.9 %
	Hyperemia	2	1.9 %
	Erythema	2	1.9 %
	Irritation	2	1.9 %
	Ankyloblepharon	2	1.9 %
	Photophobia	2	1.9 %
	Thickened eyelid	2	1.9 %
	Epithelial defect	2	1.9 %
	Inflammation	2	1.9 %
	Others	27	25.7 %
Blindness	Yes	1	2.8 %
	No	34	97.1 %
Oral lesion treatment	Corticosteroid	40	36.6 %
	Immunosuppressive	25	22.9 %
	Antibiotic	13	11.9 %
	IVIg-monoclonal Antibody	9	8.2 %
	Antifungal	4	3.6 %
	Antiviral	2	1.8 %
	Others	13	11.9 %
	N/A	3	2.7 %
Eye lesion treatment	Immunosuppressive	10	14.9 %
	Corticosteroid	9	13.4 %
	Antibiotic	7	10.4 %
	Antifungal	5	7.4 %
	Surgery	4	5.9 %
	Antiviral	3	4.4 %
	Artificial tear	2	2.9 %

(continued on next page)

Table 4 (*continued*)

Variables	Outcomes	Frequency	Relative frequency (%)
	IVIg-monoclonal Antibody	2	2.9 %
	Lubrication	2	2.9 %
	Contact lenses	2	2.9 %
	Others	5	7.4 %
	N/A	16	23.8 %

[a] Not available.

Table 5
Summary of the included studies reporting eye involvement in patients with lichen planus.

Variables	Outcomes	Frequency	Relative frequency (%)
Sex	Female	25	83.3 %
	Male	4	13.3 %
	N/A[a]	1	3.3 %
Age	Under 30 years old	0	0 %
	30–60	15	50.0 %
	Over 60 years old	14	46.6 %
	N/A	1	3.3 %
	Average	56.8	–
Type of lichen planus	Lichen planus	27	90.0 %
	Paraneoplastic lichen planus	1	3.3 %
	Lichen planus-lupus erythematosus overlap syndrome	1	3.3 %
	Conjunctival lichen planus	1	3.3 %
Oral lesion location	Buccal mucosa	14	34.1 %
	Gingiva	10	24.3 %
	Esophagus	5	12.1 %
	Lips	2	4.8 %
	Others	2	4.8 %
	N/A	8	19.5 %
Oral clinical presentation	Erythema	11	31.4 %
	Fibrous bands	9	25.7 %
	Ulcer	2	5.7 %
	Blister/Bulla/Vesicle	1	2.8 %
	White papules	1	2.8 %
	N/A	11	31.4 %
Time of eye involvement	Synchronous	0	0 %
	Under 6 months	7	23.3 %
	6–12 months	0	0 %
	12–60 months	9	30.0 %
	Over 60 months	2	6.6 %
	N/A	12	40.0 %
Unilateral/ bilateral	Unilateral	3	10.0 %
	Bilateral	24	80.0 %
	N/A	3	10.0 %
Type of eye involvement	Punctum scarring	8	18.1 %
	Canalicular obstruction	8	18.1 %
	Symblepharon	7	15.9 %
	Fornix foreshortening	6	13.6 %
	Conjunctivitis	5	11.3 %
	Dry eye syndrome	2	4.5 %
	Fibrosis	2	4.5 %
	Others	6	13.6 %
Blindness	Yes	0	0 %
	No	30	100 %
Oral lesion treatment	Corticosteroid	8	21.0 %
	Immunosuppressive	8	21.0 %
	Antibiotic	2	5.2 %
	Hydroxychloroquine	1	2.6 %
	N/A	19	50.0 %
Eye lesion treatment	Surgery[b]	7	31.8 %
	Immunosuppressive	6	27.2 %
	Corticosteroid	5	22.7 %
	Antibiotic	1	4.5 %
	Artificial tear	1	4.5 %
	Hydroxychloroquine	1	4.5 %
	N/A	1	4.5 %

[a] Not available.
[b] Lacrimal duct dilation: 2, Stent insertion: 2, dacryocystorhinostomy: 1, canaliculotomy: 1, Jones tube: 1.

treatment usually involves corticosteroids, antibiotics, and immunosuppressives for both oral lesions and eye lesions in order to suppress the immune system and prevent the disease from progressing. It is also possible to use palliative treatments such as artificial tears and lubricants for eye lesions. Systemic corticosteroids should be adjusted by their physician to reduce the chances of adrenal suppression in patients. In all included studies, management and treatment of these conditions were generally agreed upon. Since ocular involvement is directly associated with the severity of primary oral disease and usually follows oral lesions at least a year later (Clapé et al., 2018), managing oral lesions as soon and effectively as possible might be the best preventive approach for ophthalmic involvement in vesiculobullous patients.

This study aimed to provide a comprehensive review of vesiculobullous conditions involving oral and ocular mucosa; however, it is essential to acknowledge a few limitations. Since case reports or series constitute the currently available evidence regarding ocular involvement in vesiculobullous diseases, the etiology and contributing factors of this entity were highly heterogeneous, resulting in a low degree of evidence. It is important to assess the exact pathophysiology of this phenomenon and the associated factors since eye involvement can result in serious problems like blindness. The prevalence of this condition may also be underestimated because some patients may not seek further evaluation and treatment. Therefore, prospective studies regarding this matter are highly recommended.

Based on the current evidence, this study summarized essential findings regarding diagnosing, managing, and treating vesiculobullous conditions with oral and eye involvement. Oral healthcare should pay attention to ocular involvement in patients exhibiting signs and symptoms of oral vesiculobullous diseases, especially in the middle-aged or elderly. As eye involvement usually occurs after oral involvement in this study, it is imperative to control the disease at the stage of oral mucosal involvement and monitor patients' ocular health regularly. There is a good chance that medicinal treatments could control this condition and prevent severe future complications.

5. Conclusions

Within the limitations of the current study, the following conclusions can be drawn:

1. Ophthalmic involvement is most common in patients with pemphigus vulgaris who are in the third to sixth decades of their lives.
2. Ocular signs and symptoms usually emerge 12–60 months after oral involvement, and they frequently appear as conjunctivitis, erosion, or symblepharon.
3. Corticosteroids and immunosuppressives are the treatment of choice for both oral and ocular lesions, and early treatment of oral lesions could be the best approach to prevent future ophthalmic complications.

Ethical statement

Since this study was a review, institutional approval was not needed; however, this review was conducted entirely according to the ethical principles and guidelines.

CRediT authorship contribution statement

Hamed Mortazavi: Conceptualization, Supervision, Writing – original draft, Writing – review & editing. **Parham Hazrati:** Conceptualization, Writing – original draft, Writing – review & editing. **Hediye Koohi:** Writing – original draft, Writing – review & editing. **Termeh Sarrafan-Sadeghi:** Writing – original draft, Writing – review & editing. **Shima Moradian-Lotfi:** Writing – original draft, Writing – review & editing.

Declaration of competing interest and funding

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. Also, this review did not receive any funding.

Appendix A. Supplementary material

All the materials and data used to prepare this review are presented in the article.https://doi.org/10.1016/j.sdentj.2023.12.012

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