VESICULOBULLOUS LESIONS

SUBMITTED BY
MANILA UPRETI
BDS 4th Year, Phase I

SUBMITTED TO
DR. SARTAJ SINGH WAZIR (MDS)
Department of OMDR (HOD)

Introduction:

There are a variety of oral lesions which clinically present as vesiculo-bullous (VB) lesion.

Although, the lesions starts as vesicles or bullae, they rupture early and appears as ulcerated or erosive areas. As a result they are better called ulcero-vesiculo-bullous diseases.

Some general features of vesiculo-bullous lesions:

- Vesicular lesions are more common as compared to their bullous counterparts.
- Most vesicular lesions are of infectious nature and present constitutional symptoms such as fever, malaise etc.
- Some bullous lesions can be lethal.
- Most bullous lesions involve both skin and the mucous membrane.
- Vesiculo-bullous lesions may appear singularly or in clusters.

Some general features of vesiculo-bullous lesions:

- Fluid- filled lesions can be intraepithelial or subepithelial in location.
- Small multiple vesicles often coalesce to form bullae.
- Generally vesiculo-bullous lesions are short-lived.
- Vesiculo-bullous lesions rupture leaving erosive, desquamative or ulcerative lesions depending on whether the lesions were located in the intraepithelial or subepithelial region
- Most vesiculo-bullous lesions are painful after rupture.

Causes

- Trauma
- Infection
- Autoimmunity
- Genetic factors

TERMINOLOGIES

- **ULCER**:
- Break in the continuity of the surface epithelium of the skin or the mucous membrane to involve the underlying connective tissue as a result of micro molecular cell death of the surface epithelium or its traumatic removal.
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- **VESICLE**:
- Elevated blister containing clear fluid that is less than 1 cm in diameter.
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- **BULLA**:
- Elevated blister containing clear fluid that is over 1 cm in diameter.
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- **MACULES**:
- These are the lesions that are flush with adjacent mucosa and that are noticeable because of their difference in color from normal skin or mucosa.
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- **PAPULES:**
- These are the lesions raised above the skin or mucosal surface that are smaller than 1 cm in diameter.
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TERMINOLOGIES

- **EROSION**:
- These are red lesions often caused by the rupture of vesicles or bullae, or trauma and are generally moist on the skin.
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- **PLAQUE:**
- These are raised lesions that are greater than 1 cm in diameter, they are essentially large papules.
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- **NODULES:**
- These lesions are present within the dermis or mucosa. These lesions may also protrudes above the skin or mucosa forming a characteristic dome shaped structure.
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- **EROSIONS:**
- Red lesions often caused by rupture of vesicles or bullae, or trauma and are generally moist on the skin.
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- **PUSTULES:**
- These are blisters containing purulent material and appear yellow.

CLASSIFICATION

- **I . Acute and chronic vesiculo-bullous lesion:**
- Acute lesions:
  - Herpes simplex infection
  - Chicken pox
  - Herpes zoster
  - Herpangina
  - Hand foot and mouth disease
  - Erythema multiforme
- Chronic lesions
- Pemphigus
- Bullous pemphigoid
- Cicatricial pemphigoid
- Bullous lichen planus
- Linear IgA disease
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- **II. Based on clinical presentation:**
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- Predominantly vesicular :
  - HSV infection
  - Hand, foot and mouth disease
  - Herpangina
  - Varicella infection
  - Dermatitis herpetiformis
-
- Predominantly bullous :
  - Pemphigus vulgaris
  - Bullous pemphigoid
  - Benign mucous membrane pemphigoid
  - Erythema multiforme
  - Bullous lichen planus
  - Epidermolysis bullosa
  - Bullous impetigo
  - Stevens-johnson syndrome
  - Linear IgA disease
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- **III. <u>Histopathological classification:</u>**
- Intraepithelial bullous lesion:
  - HSV infection
  - Varicella infection
  - Herpangina
  - Hand foot and mouth disease
  - Pemphigus
  - Epidermolysis bullosa
  - Mucosal erythemamultiforme

- Subepithelial vesiculo-bullous lesions:
  Bullous pemphigoid
  Cicatricial pemphigoid
  Linear IgA disease
  Dermatitis herpetiformis
  Dermal erythema multiforme

HSV INFECTION

- The word herpes derived from the Greek word ' herpein ' which literally means to creep i.e. creeping or spreading nature of the skin lesions caused by many of the herpes virus

Herpes simplex virus (HSV 1 and 2)

Varicella zoster virus (VZV)

Cytomegalovirus (CMV)

Epstein-Barr virus(EBV)

Human herpes virus 6 (HHV-6)

Human herpes virus 7 (HHV-7)

Human herpes virus 8 (HHV-8)

Etiopathogenesis:

Viruses replicates in the skin and mucous membrane at the initial site of infection (primary infection)

Migrate up to the neuron and becomes latent in the sensory ganglion cells (latent infection)

HSV-1 latent (trigeminal ganglion)

HSV-2 latent (lumbar and sacral ganglion)

Virus can be reactivated from latent state by inducers like sunlight, hormonal changes, trauma, stress, fever(recurrent infection)

Virus migrate down the neuron

Virus replicates in the skin causing vesicle formation and other lesions.

Types:

- HSV type 1 diseases:

  responsible for causing
- Acute herpetic gingivostomatitis
- Herpetic eczema
- Keratoconjunctivitis
- Herpes labialis

- HSV type 2 diseases:

  responsible for
- Genital herpes
- Uterocervical cancer

HERPETIC GINGIVOSTOMATITIS

- Viral infections of the oral mucous membrane caused by herpes simplex virus-1.
- Usually **herpes simplex virus type 1** and rarely **type 2.**

Clinical feature:

- Age: 6 months - 6 years.
- Site: gingival, labial and buccal mucosa, soft palate, pharynx

Clinical feature:

- Painful severe gingivitis with redness, ulcerations with presence of discrete spherical gray vesicles in initial stage.
- After 24 hours, the vesicles rupture and forms painful small ulcer.
- Elevated halo- like margin with depressed yellowish or grayish – white central portion.
- Fever and lymphadenopathy are common; generalized soreness of the oral cavity.
- Heals without scarring in 10-14 days.

Diagnosis:

- Established from patient history and clinical findings.
- HSV isolation by cell culture is the gold standard.
- Tzanck smear.
- Biopsy and Serological test.

Differential diagnosis:

- Necrotizing ulcerative gingivitis
- Erythema multiforme
- Stevens-johnson syndrome
- Apthous stomatitis

Treatment:

- Careful plaque removal to limit bacterial superinfection.
- In severe cases, including patients with immunodeficiency, systemic use of antiviral drugs such as Acyclovir or valacyclovir is recommended.

VARICELLA ZOSTER INFECTION

- Primary varicella (human herpes virus-3) zoster infection is known as varicella or chickenpox; secondary or reactivated infection is known as herpes zoster and shingles which is an acute inflammatory viral disease. Structurally similar to HSV, the word
- zoster comes from the Latin word which means 'belt' , as the lesion occurs in belt-like distribution.

Pathogenesis:

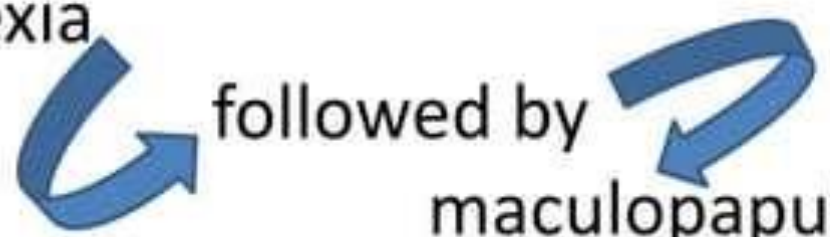
- Transmission is predominantly through the inhalation of contaminated droplets and is highly contagious. Incubation period is of 2 weeks.
- Predisposing factors: immunocompromised patient, HIV infection , leukemia or cancer.

Chickenpox or primary varicella zoster infection:

- It is also known as ' varicella '.
- It is an acute viral disease occurring in children or first two decades of life
- most commonly in winter a spring months

Clinical features:

- Prodromal symptoms-
  headache
  nasopharyngitis
  anorexia



followed by

maculopapular or vesicular eruptions on skin
low grade fever.

Clinical features:

- Site- trunk and spread to involve the face and extremities.
- Onset- development of pruritis, maculopapular rash followed by vesicle.

Clinical features:

- Dewdrop or rose petal - there is classic penetration of centrally located vesicle surrounded by zone of Erythema.
- Healing – the skin eventually ruptures, forming a superficial crust and heals by desquamation.
- Secondary infection- results in formation of pustules which may leave small pitting scar upon healing.
- Complication- cerebellar ataxia, encephalitis, pneumonia, myocarditis, reyes syndrome, sickle cell crisis etc.

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Oral manifestation:

- Site- occasionally involve oral mucosa, tongue, gingival, palate as well mucosa of pharynx.
- Appearance- initially a slightly raised vesicles with a surrounding erythema, ruptures soon after formation and forms a small eroded ulcer with red margins.

Management:

- Analgesics but aspirin is contraindicated as it can leads to reye's syndrome.
- Control pruritis - warm baths with soap or baking soda, application of calamine lotion and systemic Diphenhydramine is also given.
- Antiviral drugs- Acyclovir 800mg five times/day for 5 days, Valacyclovir 1000mg TDS or Famciclovir 500mg TDS for 7 days.
- Varicella zoster immune globulin.
- Local antiseptic prevention by vaccination

. HAND FOOT AND MOUTH DISEASE

The term hand foot and mouth (HFM) disease was used for the first time in 1960 following an outbreak of a relatively mild febrile condition associated with papular and vesicular lesions on the dermis and the oral cavity in Birmingham, England.

Clinical features:

- Age: between 6 month and 6 years.
- Site: hard palate, tongue, buccal mucosa, palms, finger, soles and toes. The oral mucosa and the hand are almost always affected.
- Prodromal symptoms: a sore mouth with refusal to eat, anorexia, low grade fever, diarrhea, nausea and vomiting

- Tongue become red and edematous which may lasts for 3- 7 days.
- Appearance of maculopapular, exanthematous and vesicular lesions of skin, particularly involving the hands, feet, legs, arms and occasionally buttocks

Differential diagnosis:

- Herpetic gingivostomatitis
- Varicella zoster infection
- Herpangina

Management:

- The disease is self limiting and needs to be symptomatically managed.
- Systemic antipyretics (Paracetamol suspension or tablets)
- Topical analgesic mouth rinses (Benzydamine hydrochloride)
- Topical anesthetic agents (2% Lignocaine gel) for fever and sore mouth.

PEMPHIGUS

- Group of autoimmune blister diseases of the skin and the mucous membrane characterized by intraepidermal or intraepithelial vesicle or bulla formation.

Types:

- Pemphigus Vulgaris
- Pemphigus Foliceous
- Paraneoplastic Pemphigus
- IgA Pemphigus
- Drugs induced Pemphigus Vulgaris like lesion.

PEMPHIGUS VULGARIS

Autoimmune mucocutaneous disease that frequently appears first in the oral cavity and can progress to involve other sites.

- **Associated factors:**
- Drugs - Captropil, Penicillamine, Rifampicin, Phenobarbitone, and Phenyl butazone.
- Radiation and surgery.
- Emotion stress, viruses-HHV8
- High level of pesticide exposure, pregnant female diet particularly garlic.
- Certain autoimmune disorders- rheumatoid arthritis, myasthenia gravis, lupus erythematosus.

Pathogenesis:

- Desmosomes forms the predominant components of intraepithelial cell adhesion.
- Desmogleins forming desmosomal components are desmoglein 1, 2 and 3.

Anti-desmoglein antibody

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Activate proteases

↓

Loss of intercellular cement

↓

Lysis of desmosomes

↓

Loss of cell to cell adhesion

↓

Classic suprabasilar bulla

Clinical features:

- Age: 50-60years.
- Sex: male = female
- Site: buccal mucosa, palate, ventral surface of tongue, lips.

Clinical features:

- Classic thin walled bulla containing thin watery fluid developing on otherwise normal skin / mucosa.
- Bulla rapidly breaks, extend peripherally leaving large areas denuded of the skin.
- When pressure is applied to the intact bulla, it enlarges by extension to an apparently normal surface.
- Do not heal and remain there for weeks to months.

- NIKOLSKY'S SIGN-

Pressure to an apparently normal area

Pulling away of the layer of the skin from the basal layer

New bulla formed

Oral manifestation:

- Patient with pemphigus vulgaris (80-90%)
- Precedes 4 months before the skin lesion.
- Classic thin walled bulla on non-inflamed base → shallow irregular ulcers → tissue tags extend peripherally to involve large portion of the oral cavity.

Differential diagnosis

- Pemphigoid
- Erythema multiforme

Diagnosis:

- Biopsy-usually done on intact bulla less than 24 hours.
- Immunofluorescence studies.
- ELISA test

Treatment

- Systemic steroids usually in high doses (1-2 mg/day/kg) mainly Prednisolone.
- For oral lesion-
  - Dispersion of Prednisolone tablet to dissolves in the mouth before swallowing or patent topical steroid creams.
  - Parenteral gold therapy.
  - Dapsone
  - Tetracycline
  - PUVA therapy.
  - Topical therapy:
  - Eroded and crusted, painful skin lesion and the associated foul odor can be effectively managed by 0.01% potassium permanganate solution or 0.5% silver nitrate solution. Chlorohexidine mouth rinses can be used to alleviate discomfort and malodor.

BULLOUS PEMPHIGOID

- Also called as 'para-pemphigus' or 'aging pemphigus'.
- It was first described as a distinct clinical entity by Lever in 1953.
- Is a chronic mucocutaneous bullous disease that usually affects older individual.

Etiopathogenesis:

- IgG autoantibodies against 230 KD and 180 KD antigens, designated respectively as Ag1 and BP 180 Ag2.
- BP 230 is on theintra cellular hemidesmisome plaque and 180BP is a transmembrane glycoproteins, whose extracellular domain goes beyond the lamina lucida on the basemembrane zone.

Clinical features:

- Age: adult above 60 years.
- Sex- affects women slightly more often than men (1.7 : 1)
- Sites: gingival, buccal mucosa, palate, floor of moth and tongue.

Clinical features:

- The oral mucosa is affected in about 20- 40% of cases, usually after skin involvement.
- Gingival lesions consists of generalized edema, inflammation and desquamation with localized area of vesicle formation.
- The oral lesions usually follow cutaneous manifestations and being as bullae that soon rupture, leaving shallow ulcerations.
- Signs: these vesicles and bullae are relatively thick walled and may remain intact for some days.
- Skin lesion: rash commonly on scalp, limb NIKOLSKY'S sign is negative

Differential diagnosis:

- Erosive form of lichen planus.
- Pemphigus.
- Subepithelial bullous dermatosis

Diagnosis:

Clinical diagnosis:

bulla present on skin which does not extend peripherally.

- Laboratory examination: vesicles contains fibrinous exudates admixed with occasional inflammatory cells.
- Indirect immunofluorescence antibody test
- Tzanck smear negative to acantholytic cells.
- Direct immunofluorescence testing and complement fixation test.

Management:

- Advised to maintain oral hygiene.
- Topical treatment: oral paste or ointment or intralesional steroids.
- Systemic steroids: Prednisolone 40-80mg/day.
- Immunosuppressive therapy: Azathioprine 50-100mg/day, Cyclophosphamide 100-200 mg/day or Cyclosporine 5-8 mg/kg.
- Other therapy: Dapsone 50-100 mg/day, Tetracycline 1.5-2 g/day, Niacinamide 1.5g/day and plasmapheresis.

BENIGN MUCOUS MEMBRANE PEMPHIGOID

- Also called as 'cicatricial pemphigoid', the word cicatricial is derived from the word cicatrix meaning scar.
- Chronic, recurrent, autoimmune disease that primarily affects mucous membrane and rarely skin (5- 10%).

Etiopathogenesis:

- Auto antibodies mainly IgG (97%), C3 complement factor (78%) and to lesser degree IgA (27%), targeted to basal lamina of the epithelium.

Clinical features:

- Age: over 50 years
- Sex: female :male - 2:1
- Site: gingival, buccal mucosa, palate, conjunctiva and skin

Oral lesions:

- Blister form first on the gums near the teeth, palate, tongue, lips buccal mucosa, floor of the mouth and throat may be affected, painful and makes it difficult to eat.
- Lesion occurring in the throat (oesophagus, trachea and larynx) can be life threatening.
- Thick walled persist for 24 – 48 hours before rupturing and desquamation.
- Formation of ulcer surrounded by Erythema, erosion on cheek and vesicles on palate with narrower peripheral extensions.
- Gingiva is edematous and bright red, involvement is patchy and diffused, Nikolsky's sign may be elicited.
- Heals without scarring.

Skin lesion:

-
- Blister in the skin develops in 25 -30 % of the patients may be itchy.
- Bleeding may occur if traumatized.

Ocular lesions:

- Subconjunctival scarring leading to blindness in about 15% of the patients.
- Initial lesions may be limited to upper tarsal conjunctiva, where they escape detection if the eyelid is not everted.

Diagnosis:

- Biopsy and hisopathology
- Direct immunofluorescence study
- Indirect immunofluorescence study.

Differential diagnosis:

- Pemphigus vulgaris
- Bullous pemphigoid
- Erythema multiforme
- Lichen planus

Management:

- In case of gingival lesion , flexible mouth guard may be fabricated to use as carrier for corticosteroid medication(0.1 Triamcinolone acetonide, or 0.5 Flucinonide or 0.05 Clobetasol propionate).
- If not successful systemic steroid 30-60 mg/day for 2- 3 weeks than tapered until it is completely stopped and immunosuppressive agent eg. Cyclophosphamide 100-200 mg/day, Azathioprine 100 mg/day.
- Dapsone 50-100mg/day
- Tetracycline 1-2 g/day or Minocycline and Niacinamide 1-2 g/day.

ERYTHEMA MULTIFORME

- Acute self limiting, inflammatory hypersensitivity reaction affecting the skin and mucous membrane that causes verity of skin lesions, hence the term 'multiforme'.

Etiopathogenesis:

- Immune mediated disease
- Deposition of the immune complexes- in superficial microvasculature of skin or mucous membrane
- Cell mediated immunity
- Idiopathic

Predisposing factors:

- Viral infections (HSV)

  ↓

  Present in keratinocytes of skin and mucous membrane

  ↓

  Immune response

- Drugs: NSAIDs, Penicillin, Clotrimoxazole, Radiotherapy, etc.
- Chronic granulomatous infection eg. Crohn's disease, Infection mononuclease, Sarcoidosis.

Types:

- Erythema multiforme minor
- Erythema multiforme major

Clinical feature:

- Age: children and young adults.
- Sex: males
- Site: hands, feet, extensor surfaces of elbow and knees.

Clinical feature:

- Onset: acute or explosive onset with generalized symptoms such as fever and malaise.
- Asymptomatic less than 24 hours, develops self limiting macules and papules in symmetric fashion, measuring 0.5-2 cm in diameter.
- Bull's eye or target lesion: consists of central bulla or pale clearing areas, surrounded by edema and band of erythema.

Oral manifestation:

- Oral lesion starts as bullae on the erythematous base.
- Breaks rapidly into ulcers.
- Large, irregular and deeper and often bleed,
- Lips are generally involved.
- The patient can't eat and swallow, drools blood tinged saliva.
- Healing within 10-14days

Differential diagnosis:

- Viral lesion like primary herpetic gingivostomatitis
- Pemphigus vulgaris
- Mucous membrane pemphigoid
- Recurrent apthous ulcer
- Erosive lichen planus

Diagnosis:

- Clinical diagnosis: mainly clinical and
- Nikolsky's sign is negative. Bull's eye lesion with hemorrhagic crusting of lip.
- Positive serology
- Biopsy of perilesional tissue

Management:

- Supportive care, electrolytes, liquid diet and nutritional support should started as early as possible.
- Removal of cause eg. drugs
- Rehydration

Treatment:

- For milder cases:
  - Supportive (sympotomatic. adequate bed rest)
  - Topical anesthesia mouth washes
  - Soft liquid diet
  - Proper hydration and electrolyte

For moderate cases:

- Short course systemic steroids.
- Dose tapered slowly.

- Immunosuppressant like:
  - Dapsone
  - Thalidomide
  - Azathioprine
  - Cyclosporine
  - For HSV associated erythema multiforme anti-herpetic drugs acyclovir may be used.

BULLOUS LICHEN PLANUS

Andreasen classified oral lichen planus into six types namely reticular, plaque- like, erosive, popular, atrophic and bullous lichen planus.

- Oral lesion are usually seen in women between the 4th and 7thdecades of life.
- Bullous form of lichen planus is the rarest form of the various varieties of lichen planus.

Clinical features:

- Site:

  buccal mucosa especially into posterior

  lateral margins of tongue
- It is clinically characterized by the formation of bullae that soon rupture, leaving painful shallow ulceration.
- The bullae usually arise on the background of papules or striae with typical pattern of lichen planus.
- The lesions vary in size from few millimeters to several centimeters in diameter.

Differential diagnosis:

- Cictricial pemphigoid
- Linear IgA disease
- Pemphigus
- Erythema multiforme

Management:

- Topical or systemic steroids in low doses, in severe cases.
- Azathioprrine, Dapsone, Cyclosporine, Mycophenolate and Retionoids.
- Combination of Tretinoin 0.025% and Triamcinolone 0.1%.

STEVEN - JOHNSON SYNDROME

- Severe form of erythema multiforme that predominantely affects the mucous membranes in which bullous and erosive erythematous lesions are found in the oral cavity.
- Characterized by vesicles and bullae on the skin, mouth, eyes, and genitals.

Clinical features:

- Age: young adults
- Sex: male predilection
- Site: skin, mouth, eyes, and genitals.

Clinical features:

- Oral lesions are usually present, and are characterized by extensive vesicle formation, followed by painful erosions covered by grayish-white or hemorrhagic pseudomembranes.

Clinical features:

- The ocular lesion consists of photophobia, corneal ulceration, panothalmitis, keratoconjunctivitis and even blindness.
- Typical iris-like lesions are presented.

Clinical features:

- Genital lesions shows non- specific urethritis, balanitis or vulvovaginitis, and scrotal erosions.

Treatment:

- Symptomatic treatment is provided with nutritional care and fluid therapy including electrolyte.
- High doses of corticosteroids are recommended and Cyclosporine and Cyclophosphamideare alternative drugs.
- Intravenous immunoglobulin administration to block the process of apoptosis in the skin and plasmapheresis.

CONCLUSION

- Oral soft tissues are affected by numerous pathologic conditions of variable etiology and hence their appropriate management relies on their accurate diagnosis. Clinical identification of intact vesicles and bulla in the oral cavity is really a challenge due to the regular irritation and the friable nature of the oral mucosa. Rupture of these lesions leads to erosion or ulcerations on the surface, hence making the diagnosis of vesiculo-bullous (VB) lesions is even more difficult due to the fact that the differential diagnosis along with VB lesions will also include ulcerative, immunological mediated diseases, neoplasm and systemic disease.

- Hence, knowledge of the clinical presentation of those disorders and the relevant diagnostic procedures is the important not just for dermatologists, but also for general practitioners and dentists.

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