



Oral manifestations of dermatological diseases: A Narrative review of cases in the last ten years.

Dr Shweta Saddu, ¹MDS; Dr Sanjeev Onkar, ²MDS; Dr Swapnali Chaudhari, ³MDS; Dr Aravind Meena Shanmughan, ⁴MDS

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Assistant Professor, Department of Oral Medicine & Radiology, Pandit Deendayal Upadhyay (PDU) Dental College, Solapur, INDIA

Associate Professor, Department of Oral Medicine & Radiology, Pandit Deendayal Upadhyay (PDU) Dental College, Solapur, INDIA

Associate Professor, Department of Oral Medicine & Radiology, Pandit Deendayal Upadhyay (PDU) Dental College, Solapur, INDIA

Assistant Professor, Department of Oral Medicine & Radiology, Amrita School of Dentistry, Kochi, Kerala, INDIA.

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Address for Correspondence:

Dr Shweta Saddu, Assistant Professor, Department of Oral Medicine & Radiology, Pandit Deendayal Upadhyay (PDU) Dental College, Solapur, INDIA

Email id: shwetassaddu@gmail.com

Running Title: Dermatological diseases

Clinical significance: The article provides an update on the skin lesions prevalent in the recent years

ABSTRACT

Background: The skin covering the head and neck may area manifests dermatological lesions that may be in the form of an ulcer, nodule, crack, or an atypical discoloration. There has been no study that focuses on the prevalence of the wide range of oral lesions in patients with skin diseases. This is noteworthy, as skin lesions are strongly associated with oral lesions and, may easily be missed by dentists. Any suspicious lesion should therefore be referred to a dermatologist to enable an early diagnosis and provide a life- saving treatment to the patient.

Aims and Objectives: The aim of this review is to systematically identify and organize the various authenticated published data, reported in indexed journals in the last ten years, relating to the prevalence of oral manifestations of dermatological diseases; to recapitulate the findings of these studies, and to discover selected features that may impact the prevalence estimates. One hundred and twenty four cases matched the inclusion criteria for the review.

Materials and Methods: Studies with original data relating to the prevalence of oral findings in skin lesions (published 2006-2016) were taken-up, by searching the electronic databases, writing to authors and reviewing citations. All articles stating the co-existence of oral lesions in dermatologic diseases were included, where the age of occurrence, sex predilection and the prevalence of oral lesions were given prime importance. Cases of dermatological diseases that were published but which did exhibit oral manifestations were excluded from the study.

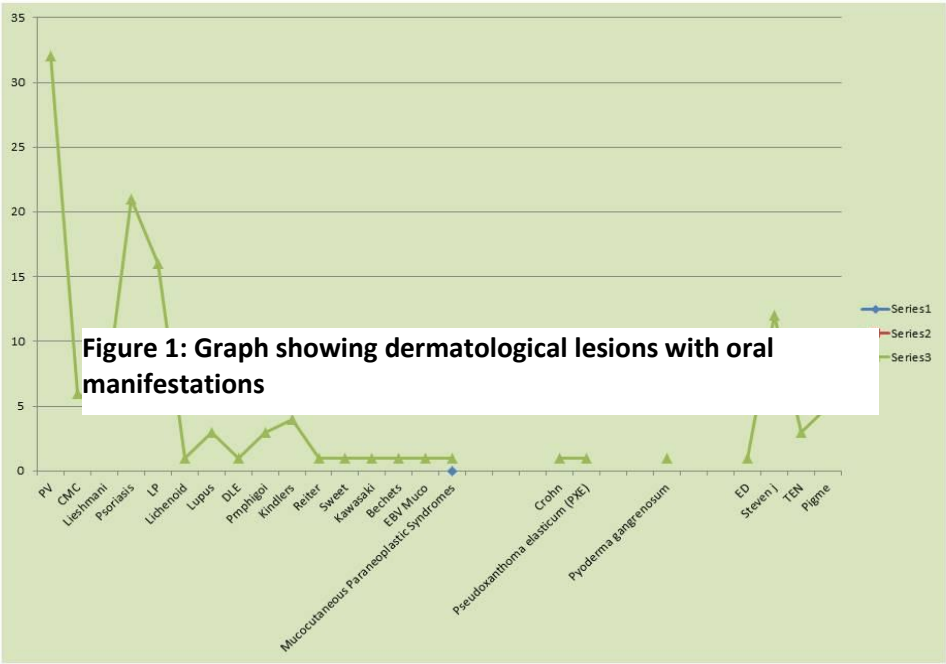
Results: Of the 63 articles, 124 cases reported the occurrence of oral lesions in dermatological diseases. Of them, maximum 32 (26.4%), were of pemphigus and its variants, and the least common were the Sweet's syndrome 0.8%, Bechet's syndrome 0.8%, Kindler's syndrome 0.8%, etc. The mean age of occurrence was 34.3 and the male to female ratio was 2:3. When considering individual diseases, the maximum age of occurrence was 58 years which was seen in case of pyoderma gangrenosum, and minimum was 11 years in case of Crohn's disease. Of the total males, maximum was affected (12.4%) by pemphigus and its variants and in females 9 (7.4%), by the Mucous Membrane Pemphigoid. Only very few articles that were reviewed, laid stress on the site of occurrence in the oral cavity and the mode of treatment of the dermatological cases; hence the prevalence rate for the same were not calculated. Corticosteroids both in the form of topical application and systemic steroids, was reported as the mode of treatment in some articles.

Conclusion: There is a plethora of data available, on the prevalence of mucocutaneous diseases. The available statistics and the inconsistencies found in prevalence appraisal methods could be rectified and that would help in providing a direction for the future hypothesis-driven research.

INTRODUCTION

The oral mucosa is structurally and developmentally similar to that of the skin, and hence, they may be afflicted by a similar set of disorders.¹ The oral lesions may be either an early manifestation of the dermatologic disease; or may be one of the most important feature or the only sign/and or symptom of the disease; or may simultaneously affect the skin as well. Hence, it is likely that the dental surgeon may be the first to observe the dermatological lesion in the primary stages itself. The dentist would therefore be able to diagnose and treat the mucocutaneous disease in collaboration with the dermatologist.²

While scanning through the data,published in the national and international journals of the last ten years, 124 cases of dermatological diseases with oral manifestations were observed.The predominant disease prevalent was pemphigus and its variants 32 (27.1%), followed by psoriasis 21(17.4%), lichen planus 16 (13.2%), and in the descending order of frequency; Steven Johnson syndrome 12(9.1%), Leishmaniasis, chronic mucocutaneous candidiasis and pigmented skin lesions 5(4.1%), mucous membrane pemphigoid, toxic epidermal necrolysis and systemic lupus erythematosus 3(2.5%) and the lichenoid reactions, discoid lupus erythematosus, Kindler's syndrome, Reiter's syndrome, Sweet's syndrome, Kawasaki and Behcet's disease, Epstein Barr virus causing mucocutaneous disease, Mucocutaneous Paraneoplastic Syndromewith chemotherapy, Crohn's disease,



Pseudoxanthomaelasticum (PXE), Pyodermagangrenosum and ectodermal dysplasia 1(0.8%)where a single case each, had been reported during the ten year period.

The predominant site of involvement were the lips and gingiva (8, 7 cases on an average)ajority of cases, and the least affected sites were the soft palate and the faucial pillars (2 cases).Reports of the entire oral cavity being affected in 6 cases were encountered. Some

articles did not mention the site of oral involvement hence this parameter was not included in the statistical study. The clinical manifestations ranged from erosions to ulcers in the vesiculobullous lesions like the pemphigus and its variants; and the mucous membrane pemphigoid,to erythematouseruptions to silvery scales in case of the lichen planus and lupus erythematosus. The desquamative gingivitis was also a predominant complaint of the patients in many of the cases reported.Extensive flat, erythematous vesicular lesions gathered on the midline of the lower lip, some of which had erupted to form ulcers, was a manifestation of the Crohn's disease and multiple asymptomatic wounds; purulent lesions was a manifestation of the Leishmaniasis, largely reported from the developing countries.

Table 1: Shows the age range and male to female ratio of oral manifestations of dermatological cases reported in literature

TABLE 1

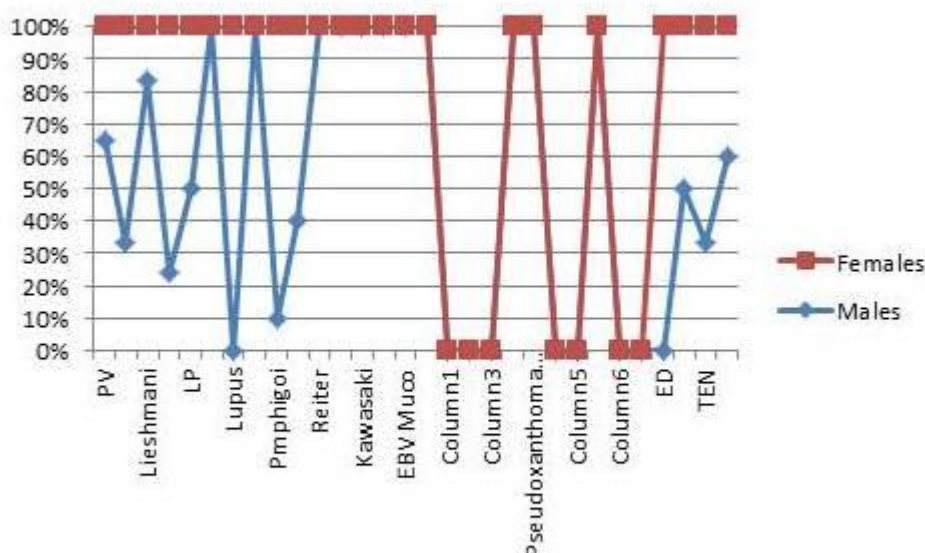
	Age		Sex
Range	Mean	Median	M: F
8-72 Years	34.26	18.9	02:03

Abbreviations for diseases mentioned in Figures 3 and 4:

PV- Pemphigus Vulgaris	CMC-Chronic Mucocutaneous Candidiasis	Lieshmaniasis	PsoriasisKindlers
Syndrome	Reiter Syndrome	Sweet-Sweet Syndrome	Kawasaki disease
Pyoderma gangrenosum	Ectodermal Dysplasia	Steven Johnson	Toxic Epidermal Necrolysis
Lichenoid Reaction	Lupus erythematosus-Systemic	Discoïd Lupus Erythematosus	Lichen Planus
Epstein Bar Virus	Mucocutaneous disease	Mucocutaneous Paraneoplastic Syndromes	Bechets
SyndromeCrohn's disease	Pseudoxanthoma elasticum (PXE)	Hyper pigmentation	

Figure 3

Figure 2: Graph showing the age of occurrence of dermatological lesions with oral manifestaions

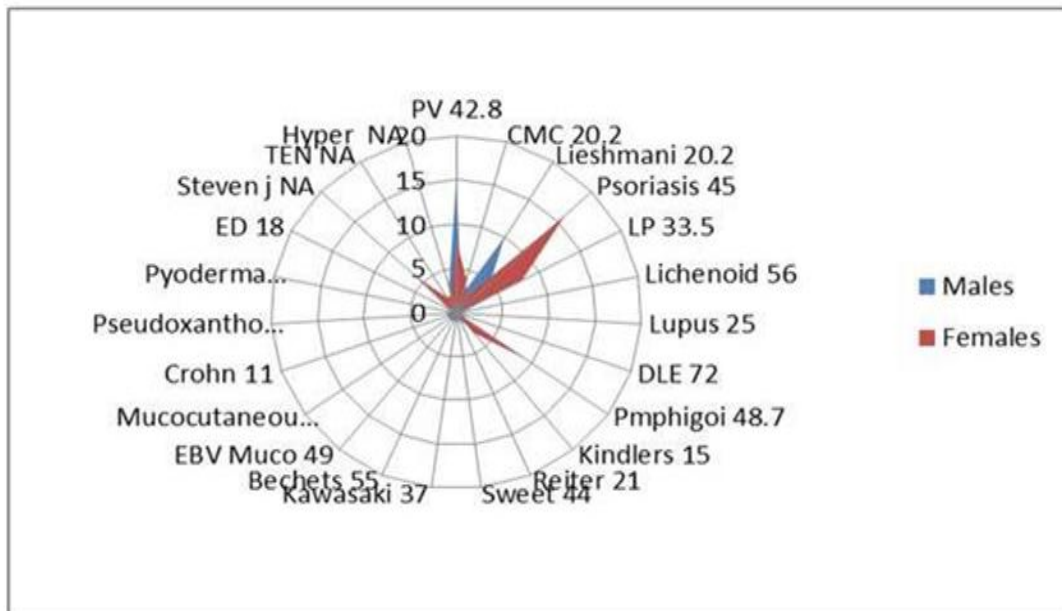


DISCUSSION

Pemphigus: Pemphigus vulgaris (PV) is an autoimmune blistering disease³ in which IgG serum antibodies are formed against the normal desmosomal adhesion molecules that is present on the cell membrane of keratinocytes. In 50-90% cases, the oral cavity shows the initial manifestation of the disease but in the outpatient setting of a dermatology clinic, they are the initial manifestation in only 18% of the cases. In some circumstances they may be the sole symptom of the disease for 2-6 months after which the cutaneous lesions appear, accounting for the importance of the oral features. The roof of the oral blister is thin and they readily rupture due to masticatory forces. This may give rise to a large number of chronic painful bleeding erosions and ulcers that heal with difficulty. The chief complaint of the patient is pain and burning sensation in the oral cavity especially when

taking spicy or acidic food. Any area of the oral cavity is prone to blisters, although the most affected sites are those that are subjected to friction, such as the buccal mucosa, gingiva, soft palate, ventral tongue and lower lip. Our study showed a prevalence rate of 27.1% of pemphigus and its variants, occurring at a mean age of 42.8 years and a male to female incidence of 12.4% to 6.4%; they manifest in the form of erosions and blisters, especially on the gingiva.

Figure 4: Graph depicting the sex predilection and age of occurrence of the recently reported dermatological diseases



Diagnosis:

Nicolsky's sign is a predominant diagnostic test, in which the skin is pressed with a finger, to test for the appearance of a new blister. In case of oral mucosal lesions a Tzanck smear could be useful to prepare for acantholytic cells. Direct immunofluorescence

may be used to detect intercellular deposits of Ig G, A, M and C3 proteins on the skin and around the lesion, thereby confirming the diagnosis of pemphigus; indirect immunofluorescence is used to identify pemphigus antibodies in serum. Other tests like the ELISA, measure the anti-Dsg1 and anti-Dsg3 antibodies in serum using recombinant Dsg1 and Dsg3; and, further confirmation of the diagnosis is done with immunoblotting and immunoprecipitation techniques.

Treatment: Mouthwashes or topical creams containing corticosteroids could be used to temporarily control the disease in case of lesions of the oral mucosa of patients having low titers of circulating antibodies, e.g., 0.1% triamcinolone acetonide in orabase, 0.05% clobetasol propionate, 0.05% fluocinolone acetonide, or 0.05% halobetasol. The lesions could also be injected intralesionally with triamcinolone acetonide (20µg/L) or paramethasone for 7-15 days in cases of refractory lesions. But if the lesions do not heal, the treatment must be stopped after three injections.⁴

Psoriasis: Psoriasis is one of the most common chronic inflammatory skin diseases affecting 2% of the people, manifesting thick and silvery-scaled patches. It is said to occur following disturbance in the inflammatory and immune mechanisms or is said to have a genetic predisposition triggered by stress. Psoriasis can considerably upset the life of the patients. 17.4% prevalence of psoriasis occurring at a mean age of 45 years was identified in our study whereas the study by Azmi MG et al.,²⁴ reported an age occurrence of 32.9±14.8 years and a male to female ratio of 54%:46%. Our study showed M: F ratio of 4.1% to 13.2% and reported the presence of silvery plaques on the gingiva in patients.²⁴

Treatment: Therapeutic approaches include natural light, diet, avoiding stress and drugs, or topical application of creams or lotions and oral or injected drugs. Some of the standard topical treatments along with their side effects include: calcipotriol, anthralin, topical retinoids and immunomodulators (non-steroidal) that may cause side effects such as elevation of serum calcium, skin irritation and reddening or a burning sensation.⁵

Chronic Mucocutaneous Candidiasis: Chronic mucocutaneous candidiasis (CMC) is a tenacious or recurrent/refractory infection of the skin, mucus membrane, nails, and is caused by *Candida albicans*, that can manifest a variety of unrelated clinical conditions that are yet to be identified. They are commonly found associated with primary or secondary immunodeficiencies although there may be different underlying diseases predisposing to CMC. Secondary causes may include HIV infection and other aetiologies. Autosomal dominant and autosomal recessive forms of CMC have also been reported. The prevalence of chronic mucocutaneous candidiasis in our review was 4.1% with a mean age of occurrence of 20.2 years, with 1.7% males and 3.3% females being affected in the past 6 years; most of the cases had been treated by topical corticosteroids. The mean age of occurrence in Leeyaphan C, et al.'s²⁵ study was 63.6 years and the male to female predilection was 1:3 similar to our study.²⁵

Treatment: Azolese.g., clotrimazole, itraconazole, ketoconazole and fluconazole have provided major improvements in the treatment of all variants of CMCs.⁸

Toxic epidermal necrolysis (TEN) and Stevens Johnson Syndrome (SJS): are grave and life threatening cutaneous lesions that arise as drug reactions, majorly involving the skin and mucous membranes. Both the conditions are rare with the TEN and SJS affecting approximately 1 or 2/1,000,000 yearly, and are categorised as medical emergencies due to their potentially fatal outcomes. They exhibit mucocutaneous tenderness, characteristic haemorrhagic erosions, denudation of the skin and may show areas of erythema which occurs as a result of the detachment of the surface of the blisters. Both TEN and SJS are found to differ only in their extent of skin detachment. 6(5%) of males and 6(5%) of females were affected by the Stevens Johnson syndrome and 0.8% of males and 1.7% of females showed the presence of the TENS, according to our study.

Treatment: There is a necessity to understand the severity and outcome of the disease; and the offending drug needs to be promptly withdrawn; an emergency supportive care promptly initiated by providing the "specific" drug therapy. The simultaneous administration of immunosuppressive agents and corticosteroids remains contentious.

Leishmaniasis: The mucocutaneous disease is caused by the protozoan parasite of the genus *Leishmania*, which is carried by the sandfly and is transmitted to humans when they are bitten by them. The prevalence of this lesion in our review was 4.1%. The type of leishmaniasis is dependent on the multifaceted interaction between the type of the species and the immunological response of the host. The disease may or may not be symptomatic; and if symptomatic, it may show a varied set of cutaneous manifestations which may also involve the visceral organs that may turn fatal if not treated on time. Polymerase chain reaction and other molecular diagnostic methods need to be used to detect minute amastigotes. The type of treatment and its success also depends on the infecting species and resistance of the person. Travellers visiting endemic areas need to take preventive measures in avoiding sandfly bites and reducing the susceptibility of leishmaniasis. The disease has been hugely neglected, therefore, no vaccine has been discovered till date.⁷

Our review showed a mean age of occurrence of 20 years whereas Gemaque K, et al.'s study showed a mean age of 45.4 years and there was a huge difference in the male to female ratio of 10:2 in our study and 2:1 in the study by Gemaque K, et al.'s.²⁶

Sweet's syndrome: It is an acute febrile neutrophilic dermatosis that manifests in three clinical settings:

- ✓ Classical (or idiopathic),
- ✓ Malignancy-associated, and
- ✓ Drug-induced.

Classical Sweet's syndrome (CSS) is often preceded by an upper respiratory tract infection and may sometimes be associated with inflammatory bowel disease and pregnancy. It usually affects women in the age range of 30 to 50 years

The malignancy-associated Sweet's syndrome (MASS) commonly occurs as a paraneoplastic syndrome in patients who already suffer from cancer or in undiscovered cases of Sweet's syndrome-related hematologic dyscrasia or solid tumor. The predominant cancer linked to the MASS is the acute myelogenous leukemia and it may precede, follow, or appear together with the patient's cancer. Hence, MASS can be the sign of an undiagnosed visceral malignancy in previously cancer-free persons or an unknown recurrence in a cancer patient. The patient may also manifest with squamous cell carcinoma of the lower lip.

Drug-induced Sweet's syndrome (DISS) mostly occurs in individuals who are undergoing treatment with drugs such as granulocyte colony stimulating factor for cancer mostly, but other medications may also be the cause of DISS.

Our review showed the mean age of occurrence as 44 years and Rochael MC, et al's, study reported a somewhat similar range of 30-60 years. 83% of cases were females in Rochael MC, et al's, study and our findings showed the male to female predilection of 1:0.²²

Diagnosis and treatment: Cytokines have been implicated as an etiologic factor in Sweet's syndrome. The gold standard for treatment of this condition is the systemic corticosteroids.⁹

Kindler's syndrome: Kindler's syndrome affects infants. It is a very rare genodermatosis. It is manifested by acral blistering, poikiloderma, photosensitivity, cutaneous atrophy, and variety of mucosal diseases. Actin-extracellular matrix linker protein gene encoding kindlin-1, mapped to chromosome 20p12.3 has been implicated in Kindler's syndrome. 1.7% was males and 2.5% were females with an average age of occurrence of 15 years in our review.

Diagnosis and Treatment: Diagnostic criteria recently proposed for this condition to facilitate clinical diagnosis⁹ include a

- Major criteria such as infancy and childhood related acral blistering, skin atrophy, poikiloderma, photosensitivity, and gingival friability, and/or swelling.
- Minor criteria proposed such as syndactyly and other mucosal site involvement. Management of this condition is preventive rather than interventional.¹⁰

Kawasaki Disease: Kawasaki disease (KD)/ Kawasaki syndrome, predominantly affects children younger than 5 years of age. It is an acute febrile illness of unknown cause. Clinical signs are mainly rash, swelling of hands and feet, fever, irritation and redness of the sclera, swollen neck glands, and inflammation and irritation of the mouth, throat and lips.¹¹ Mean age of occurrence was found to be 37 years and the male to female predilection was 1:0.

Diagnosis and treatment: Clinical criteria have been used to enable physicians to diagnose Kawasaki disease. Aspirin has been found to successfully treat the disease and has been considered as the treatment of choice.¹²

Crohn's disease: Crohn's disease is an idiopathic inflammatory bowel disease (IBD) showing widespread gastrointestinal tract involvement classically with skip lesions. The extraintestinal features include the mucosal tags, mucogingivitis, deep ulceration, lip swelling, cobblestones, esophageal ulcers, ascars and pyostomatitis vegetans.¹³ Mean age of occurrence was 11 years and male to female ratio was 1:0.

Pseudoxanthoma elasticum (PXE): Pseudoxanthoma elasticum (PXE) is a genetic connective tissue disorder manifesting fragmentation and progressive calcification of elastic fibres of the skin, walls of the arteries and the retina. Prevalence has been projected between 1/25,000 and 1/100,000.¹⁴ 1:2 was the male to female ratio and mean age of occurrence was 55 years.

Pyoderma gangrenosum: Pyoderma gangrenosum (PG) is an uncommon non-infectious neutrophilic dermatosis characterised by initial sterile pustules that rapidly grows to transform into painful ulcers of varying depth and size, having undermined, violaceous borders.¹⁶ The treatment mainly concentrates on long term immunosuppression, predominantly with high doses of corticosteroids or low doses of ciclosporin.¹⁵ Our study

found the mean age of occurrence in pyoderma gangrenosum to be 58 years and the male to female ratio to be 0.8%: 0

Mucous Membrane Pemphigoid: Mucous membrane pemphigoid (MMP) is an autoimmune blistering disorder characterized by subepithelial bullae. Basement membrane zone proteins have been recognized as targets of autoantibodies in MMP. Large variety of clinical manifestations is seen in MMP. Mucous membranes lining the oral cavity, nasopharynx, conjunctiva, esophagus, larynx, genitourinary tract and anus are commonly involved, of which the oral mucosa is most frequently affected, followed by the conjunctiva. The treatment modality is multidisciplinary and the early recognition of this disorder and proper treatment may reduce the disease-related complications.¹⁷ Male to female ratio was 1:9 and mean age at which the lesion occurred was 48.7 years according to our study.

Lupus Erythematosus

Systemic Lupus: Systemic lupus erythematosus (SLE) is a devastating, multifactorial autoimmune disease caused by a bouquet of immunoregulatory, genetic, hormonal, environmental and epigenetic components. Both the innate and adaptive branches of the immune mechanism involving both B and T lymphocytes and also affecting the function of monocytes, macrophages, dendritic cells, and other cellular and humoral components, have been implicated.¹⁸ It is a chronic inflammatory disease affecting multiple systems showing the presence of several autoantibodies.¹⁹ 25 years average age with male to female ratio of 0:2 were found in our study. On the other hand Lourencxo S V, et al's study reported 2.8:1, males to female ratio and a mean age of 41.8 years.²³

Diagnosis and treatment: The antinuclear antibody (ANA) test to look for autoantibodies that react against components of the nucleus is diagnostic for SLE. Antibodies such as anti-DNA, anti-Sm, anti-RNP, anti-Ro (SSA), and anti-La (SSB) are also found to be positive in SLE. NSAIDs, corticosteroids, antimalarials, and immunosuppressives are used in the treatment of SLE.²⁰

Discoid Lupus: Discoid lupus erythematosus is a chronic autoimmune dermatological disease, like mixed connective disease, scleroderma, rheumatoid arthritis and polymyositis, that may lead to hair loss, scarring, and hyperpigmentation in skin if not treated immediately. 72 years was found to be the mean age of occurrence as per our study and the male to female ratio to be 1:0.

Diagnosis and treatment: Clinical features are diagnostic for the disease and in some cases histopathology may be required to verify the diagnosis. The main modality of treatment is the antimalarials and topical steroids. Some cases of discoid lupus erythematosus can be noncompliant to customary therapy; in which case drugs such as the retinoids, topical tacrolimus, thalidomide, offer remedy, as do immunosuppressives like azathioprine, methotrexate, cyclosporine, mycophenolate and mofetil.²¹

The remainder of the lesions showed a prevalence of only 0.8% according to our review, but they must be borne in mind as a likely diagnosis by both the dentists and the dermatologists.

Bechet's Syndrome: Our review found a male to female ratio of 1:0 whereas study found an equal predilection and an age of occurrence between 20-40 years whereas our lone patient was 55 year of age.²⁶

CONCLUSION

The structure and the lining of the oral cavity can manifest features of the systemic disease; especially those that affect the skin, as both these structures are derivatives of the ectoderm. The awareness of these lesions can assume importance in the diagnosis of oral as well as systemic diseases. The oral mucosa may present with a part of the general systemic disease or it may be a component of the cutaneous disease, arising prior to it, or they may be limited to the oral cavity only. The lesions of the oral cavity are more difficult to interpret because of the anatomical and functional peculiarities of the organ. Hence it is significant that the dental specialist be familiar with the oral manifestations of the dermatological diseases, prevalent throughout the world during the recent days, to enable proper diagnosis, and implement early treatment which would ultimately benefit the patient.

Footnotes:

Conflict of interest: The authors declare that there is no conflict with regard to the article

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