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Commentary

The Hirsute Hunk-Hairy Leukoplakia

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Preface

Hairy leukoplakia of the oral mucosa is engendered by infection with Epstein-Barr virus (EBV) or human herpesvirus 4 (HHV4) and demonstrates white, confluent zones of fluffy or hairy mucosa. The condition was initially described in1984.

Hairy leukoplakia appears in individuals with significant immunosuppression and is associated with reduced life span. Co-infection with hepatitis B virus (HBV) is accompanied by deteriorating clinical condition with progression into full blown autoimmune deficiency syndrome (AIDS).

Generally, lesions are bilateral and appear along lateral border of the tongue. As the condition emerges in immunosuppressed individuals infected with human immune deficiency virus (HIV), autoimmune deficiency syndrome may appear within 2 years to 3 years.

Disease characteristics

Hairy leukoplakia appears in individuals with human immunodeficiency virus (HIV) infection, infected homosexual males, non infected individuals, immunosuppressed individuals following organ or bone marrow transplantation, severe immunodeficiency or haematological malignancies as leukaemia. Consumption of significant quantities of tobacco in HIV infected individuals appears concurrent with development of hairy leukoplakia [1,2].

Hairy leukoplakia is classified as category B clinical marker indicative of infection with human immunodeficiency virus (HIV) as the condition demonstrates a significant prognostic connotation in subsequent emergence of autoimmune deficiency syndrome (AIDS) [1,2].

An estimated 50% individuals lacking cogent antiviral therapy for HIV infection are prone to develop hairy leukoplakia. Decimated CD4 lymphocyte count is a contributory factor for emergence of hairy leukoplakia [1,2].

The condition is exceptional in immunocompetent individuals. Nevertheless, incriminated immunocompetent individuals may be subjected to long term exposure of inhaled, topical or systemic corticosteroids. Racial or age-specific predilection is absent [1,2].

Additionally, hairy leukoplakia is associated with Behcet's syndrome or ulcerative colitis [1,2].

Disease pathogenesis

Hairy leukoplakia emerges due to an interaction of diverse factors such as coinfection of Epstein- Barr virus along with productive replication, virulence, genetic evolution and expression of specific, latent, viral genes. Aforesaid factors are enhanced by concurrent localized and systemic immunodeficiency with consequent emergence of hairy leukoplakia. Epstein-Barr virus initially infects pharyngeal basal epithelial cells with commencement of a replicative state along and discharge of infectious viral particles into the saliva, a process which perpetuates throughout the lifespan of infected person.

Viral ingress into pharyngeal B lymphocytes consists of a latent phase and persists for an indefinite period [3,4].

Although elimination of Epstein-Barr virus through cytotoxic T lymphocytes remains challenging, the cells abet maintenance of viral infection in latent phase. Reactivation of latent viral particles enclosed within B lymphocytes configures virions [3,4].

Disseminated virions invade circulating monocytes, migrate to oral mucosal lamina propria and subsequently differentiate into macrophages or precursors of Langerhans cell. Macrophages and Langerhans cells migrate and accumulate into basal or parabasal layer of oral squamous epithelium. Viral reactivation is accompanied by migration into keratinocytes within stratum spinosum and stratum granulosum via dendritic processes of Langerhans cells with subsequent viral replication [3,4].

Besides, significant reduction or absence of Langerhans cells may be discerned in tissue specimens of hairy leukoplakia which ensures persistent viral replication and circumvention of immune recognition. Lateral border of tongue is susceptible to mechanical trauma and viral entry into prickle cell receptors may be effortless. Additionally, impaired host immunity along with significant reduction of Langerhans cells contribute to aggregation of Epstein- Barr virus within the oral epithelium [3,4].

Inflammation or infiltration of mononuclear cells within stratified squamous epithelium or lamina propria is absent. Basal epithelial cells are unremarkable. BZLF1 gene is mandatory to ensure intracellular transition from latent viral stage to productive, infectious state. BZLF1 gene is usually confined to cellular stratum spinosum and stratum granulosum in lesions of hairy leukoplakia along with gene Blimp1 which functions as a transcription factor during terminal differentiation of keratinocytes [3,4].

Despite aforesaid indicative histological features, hairy leukoplakia necessitates a definitive demonstration of deoxyribonucleic acid (DNA), ribonucleic acid (RNA) or protein of Epstein-Barr virus within epithelial cells for precise disease determination [3,4].

Clinical elucidation

Frequently, hairy leukoplakia is asymptomatic or emerges as a non tender, whitish plaque along lateral border of the tongue which may spontaneously appear and disappear. Additionally, mild pain, dysesthesia, sensitivity to hot and cold food, altered taste due to modified taste buds and psychological consequences of hideous appearance accompany the lesion [5,6].

Generally, unilateral or bilateral, painless, whitish oral lesions appear upon lateral perimeter of the tongue. Hairy leukoplakia may arise as a smooth, flattened, miniature plaque or an irregular "hairy" or "feathery" lesion with prominent folds or projections [5,6].

The lesion may occur as a contiguous or discontinuous, frequently asymmetrical, bilateral lesion within lateral margin of the tongue. Lesions demonstrate variable magnitude, severity and surface characteristics. Hairy leukoplakia is adherent to superimposed epithelial surface and expungement upon scraping is challenging. Erythema or oedematous alteration of circumscribing soft tissue is absent [5,6].

Hairy leukoplakia may incriminate buccal mucosa, gingiva or diverse surfaces of the tongue and may emerge as a smooth, flattened lesion devoid of typical "hairy" appearance [5,6].

Histological elucidation

Upon microscopy, oral mucosa displays mild papillary acanthosis, hyperkeratosis and significant parakeratosis of superficial layer of stratified squamous epithelium. Superficial layer of hyperkeratotic stratified squamous epithelium may be infected with bacteria or fungi such as *Candida* spp [6,7].

Acanthosis of superficial epithelial layer is engendered by ballooning, koilocyte-like cells. Cellular nuclei depict a homogenous, ground glass appearance along with intra-nuclear inclusions [6,7].

Upon histology, hairy leukoplakia demonstrates hyperkeratosis of superficial stratified squamous epithelial layer wherein squamous cells are imbued with altered keratin. Thickened, hyperkeratotic layer segregates subjacent epithelial cells with appearance of projections and a characteristic "hairy" lesion [6,7].

Superimposed hyperkeratotic stratified squamous epithelium may be superficially infected with bacteria or fungi such as *Candida* spp. Parakeratosis of superficial epithelial layer depicts anomalous persistence of nuclei within the cells indicative of incomplete squamous differentiation. Infection with innumerable fungal hyphae may ensue. Acanthosis of upper stratum spinosum or prickle cell layer delineates aberrant expansion of cells with band of koilocyte-like cells or balloon cells. Nuclei exhibit ground-glass appearance with eosinophilic intranuclear inclusions accompanied by a halo or Cowdry type A intranuclear inclusions [6,7].

Microscopic examination displays stacked, hyperkeratotic stratified squamous epithelium of oral mucosa with intranuclear inclusions. Balloon cells display margination of nuclear chromatin along with nuclear beading. Epstein-Barr viral particles appear accumulated within clear cells of spinous layer. Koilocytes are variable and appear admixed with superimposed fungal organisms of Candida spp. A cogent inflammatory exudate is absent [6,7].

Upon ultrastructural examination, virions of Herpes subtype are observed [6,7].

Differential diagnosis

Hairy leukoplakia requires a segregation from

- Oral candidiasis wherein lesions of hairy leukoplakia are frequently colonised and obscured by organisms of *Candida* spp. Superficial epidermal layer predominantly demonstrates spongiosis, irregular acanthosis and inflammatory alterations. Characteristically, neutrophils appear accumulated within the stratum corneum and upper layers of stratified squamous epithelium. Miniature aggregates of neutrophils configure spongiform pustules, akin to impetigo or psoriasis [2,3].
- Human papillomavirus (HPV) infection wherein koilocyte-like cells constituting hairy leukoplakia simulate cellular infection with HPV. Infection of squamous epithelial cells with HPV demonstrates basaloid features with the absence of squamous differentiation, distinctive foci of keratinization and abundant keratinization. Isolation of Epstein-Barr virus with *in-situ* hybridisation is optimal for segregation [1,2].

Additionally, hairy leukoplakia requires a segregation from oral leukoplakia, white sponge nevus, oral frictional keratosis, smoker's keratosis, proliferative verrucous leukoplakia, lichen planus, lichenoid reactions or condyloma acuminatum [1,2].

Investigative assay

Generally, hairy leukoplakia is a clinical diagnosis supported by histological assessment and discernment of viral deoxyribonucleic acid (DNA), ribonucleic acid (RNA) or protein within squamous epithelial cells. Appropriate categorization of hairy leukoplakia mandates isolation of Epstein-Barr viral ribonucleic acid (RNA), deoxyribonucleic acid (DNA) or protein from incriminated squamous epithelial cells [8,9].

Detection of Epstein-Barr virus may be achieved with techniques such as polymerase chain reaction (PCR), electron microscopy, immunohistochemistry or in situ hybridization [8,9].

An optimal and recommended technique for evaluating hairy leukoplakia is in-situ hybridisation for Epstein- Barr viral ribonucleic acid (RNA), deoxyribonucleic acid (DNA) or protein [8,9].

Tissue sampling is necessitated for assessing ulcerated lesions with unusual morphology or lesions indicative of malignant metamorphosis [8,9].

Therapeutic assay

The benign hairy leukoplakia may resolve spontaneously and is associated with minimal morbidity [8,9]. Therapy is necessitated for relieving clinical symptoms or for cosmetic purposes. Highly active ant- retroviral therapy (HAART) drugs are optimal in decimating lesions of hairy leukoplakia although reoccurrence is observed with decimation of drug dosages [8,9].

Oral or systemic antiviral drugs as acyclovir, valacyclovir or famciclovir are beneficial in resolving the condition within 2 weeks. Nevertheless, latent infection persists and reoccurrence may ensue with weeks following cessation of therapy [8,9].

Topical employment of cytotoxic podophyllin can be adopted to resolve hairy leukoplakia although lesion reoccurrence may ensue with therapeutic cessation. Topical application of podophyllin is associated with pain, discomfort or dysgeusia [8,9].

Topical retinoic acid inhibits viral replication although repetitive lesions may appear. Prolonged therapy is associated with a burning sensation within the tongue [8,9].

Although infrequent, cryotherapy with liquid nitrogen may be adopted to resolve hairy leukoplakia [8,9]. Hairy leukoplakia may be accompanied by occasional superinfection with *Candida* spp with the emergence of glossopyrosis or burning tongue. Altered sensation of taste is observed [8,9].

Figure 1: *Hairy leukoplakia demonstrating whitish, feathery patches upon the lateral border of the tongue [10].*

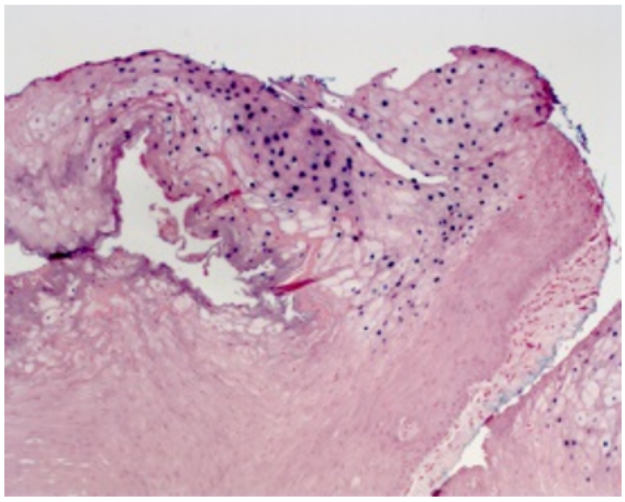

Figure 2: *Hairy leukoplakia enunciating acanthosis, hyperkeratosis and parakeratosis ofthe superimposed stratified squamous epithelium with characteristic, hairy projections and koilocyte-like cells [11].*

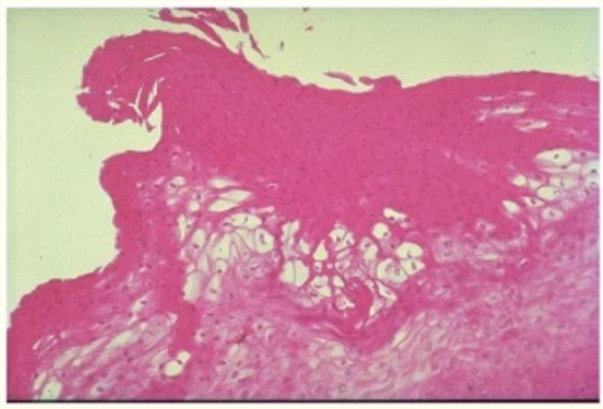

Figure 3: *Hairy leukoplakia delineating hyperkeratosis, parakeratosis and acanthosis of superimposed stratified squamous epithelial layer along with several koilocyte-like cells [12].*

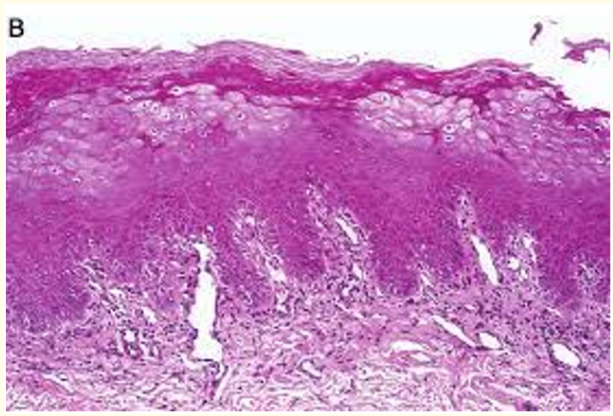

Figure 4: *Hairy leukoplakia exemplifying significant acanthosis, parakeratosis and hyperkeratosis of stratified squamous epithelium with innumerable koilocyte-like cells and upper dermal inflammatory exudate [13].*

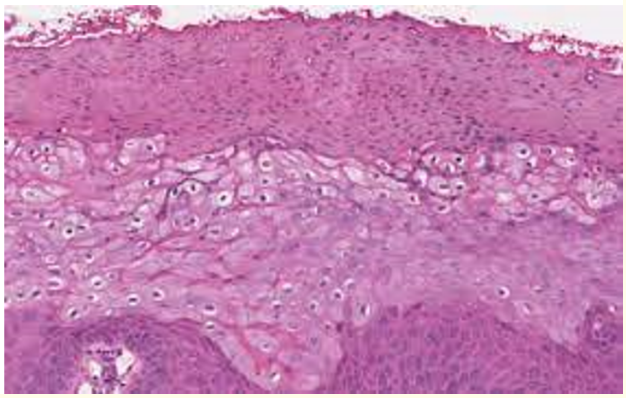

Figure 5: *Hairy leukoplakia depicting marked acanthosis, hyperkeratosis and parakeratosis of stratified squamous epithelium with innumerable koilocyte-like cells [14].*

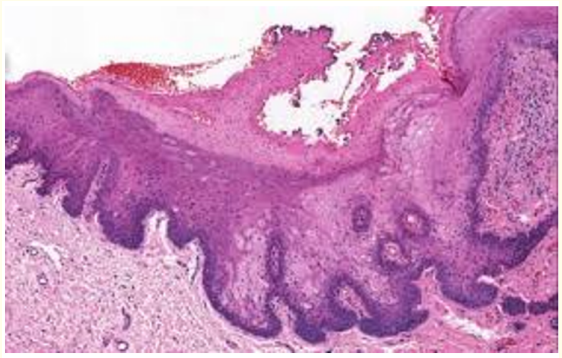

Figure 6: *Hairy leukoplakia demonstrating hairy projections of stratified squamous epithelium with marked acanthosis, hyperkeratosis and parakeratosis [14].*

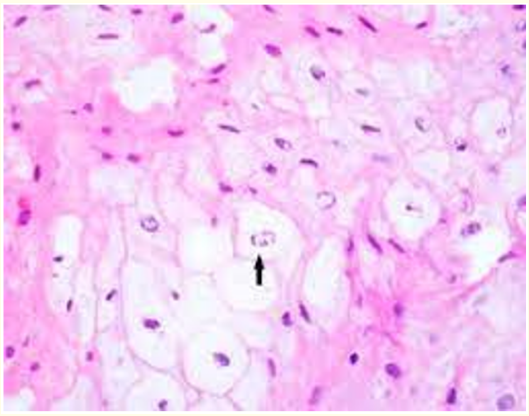

Figure 7: *Hairy leukoplakia exhibiting several koilocyte-like cells with vacuolated cytoplasm and uniform nuclei [15].*

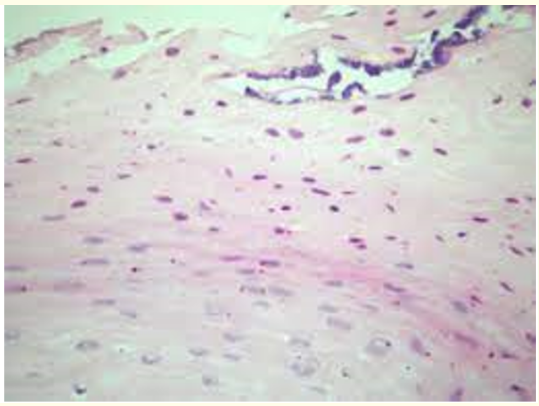

Figure 8: *Hairy leukoplakia displaying acanthosis of stratified squamous epithelium along with significant aggregation of koilocyte-like cells [16].*

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13. Image 4 Courtesy: Oxford academic journals.

14. Image 5 and 6 Courtesy: SAGE Journals.com.

15. Image 7 Courtesy: Science direct.

16. Image 8 Courtesy: Dermnet NZ.

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