"Ki67 AS A DIAGNOSTIC INDICATOR IN DIFFERENTIATING PSORIASIS FROM PSORIASIFORM DERMATITIS A HOSPITAL BASED STUDY"

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LISTS OF ABBREVIATIONS

SL NO.	ABBREVIATION	EXPANSION
1	ACD	Allergic Contact Dermatitis
2	CD	Contact Dermatitis
3	LSC	Lichen Simplex Chronicus
4	PRP	Pityriasis Rubra Pilaris
5	PBS	Phosphate Buffered Saline
6	UVB	Ultra Violet B
7	PUVA	Psoralen plus Ultraviolet A

ABSTRACT

BACKGROUND: Psoriasis and Psoriasiform dermatitis mimic each other both clinically and histologically thus making it difficult to differentiate them from each other**.** Most studies have observed Ki67 expression in Psoriasis and normal skin, but very few have studied its expression to differentiate Psoriasis and Psoriasiform dermatitis.

AIM: To study Ki67 as an immunohistochemical diagnostic marker to differentiate Psoriasis and Psoriasiform Dermatitis.

METHODS: One-year descriptive study from 1st September 2022 to 1st September 2023 was conducted. Out of the total 40 cases, 23 were Psoriasis and 17 were Psoriasiform Dermatitis. The 10% formalin-fixed and paraffin-embedded skin biopsy specimens were cut into thin sections. Initially, regular hematoxylin and eosin staining was done. Later a primary antihuman antibody against Ki-67 was applied. Tonsillar tissue was used as a positive control.

RESULTS: Of the total 40 cases including 23 Psoriasis and 17 Psoriasiform Dermatitis, the maximum cases were found in the age group of 19-30 years. Auspitzs sign, Silvery scales and nail pits were more predominant in Psoriasis than Psoriasiform dermatitis($p<0.0001$). The histopathological features of parkeratosis, hyperkeratosis, hypogranulosis, suprapapillary thinning, elongated rete ridges, kogoj pustules, munros microabscess and perivascular mixed inflammatory cell infiltrate were more significant in Psoriasis ($p<0.01$). The perivascular lymphocytic infiltrate was seen predominantly in Psoriasiform Dermatitis ($p< 0.0001$). The mean staining of Ki67 was more predominant in Psoriasis as compared to Psoriasiform Dermatitis with a p-value of <0.01.

CONCLUSION: In the present study, Ki67 can be used objectively to differentiate Psoriasis from Psoriasiform Dermatitis in addition to the clinical and histopathological features in optimizing the treatment of Psoriasis and Psoriasiform Dermatitis.

KEY WORDS: Psoriasis; Psoriasiform Dermatitis: Ki67.

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INTRODUCTION

Psoriasis is an inflammatory cutaneous hyperproliferative condition with features of chronicity.[1] In India, Psoriasis accounts for 2.3% of patients visiting dermatology OPD.[1] The worldwide prevalence of Psoriasis is 2% with 11% in Caucasians and Scandinavians and less in Asians.[2] Almost 60 to 90% of cases are hereditary.[3]

Classically Psoriasis presents with silvery scaled erythematous plaques over the extensor surface of upper and lower limbs most commonly.[4,5] Affected sites including the face, genitalia, scalp, nails, palms as well as soles are the ones which take time to get treated completely.[3] The clinical types of Psoriasis are Plaque psoriasis along with Pustular psoriasis, Annular psoriasis, a variety called Erythrodermic psoriasis, and Guttate psoriasis while the most common one being Psoriasis vulgaris.[5] Koebner's phenomenon refers to psoriasis occurring at the site of injury or any trauma.[6]Men show a bimodal peak with the first peak in the third decade of life and the second at the sixth.[7] Similarly, in women, the first peak is between 18-29 years while the second is in the fifth decade of life.[7] The age of onset in women is earlier than in men.[3]Psoriasis has associated morbidities including cardiovascular diseases, psoriatic arthritis, and hepatic diseases.[3] It also has a psychological effect on patients.[3]

The pathogenesis of psoriasis is multifactorial showing genetic predisposition along with dysregulation of inflammation.[5] The primary mechanism of pathogenesis includes cellular proliferation along with improper keratinization.[8] Innate as well as adaptive immunity play a role.[2] The process is autoimmune wherein the autoimmunity is mediated by T-cells.[2]

The proliferation of keratinocytes leading to epidermal proliferation is activated by cytokines released via Th17 cells for example interleukin-17 and interleukin-21.[2] TNF-alpha and Interleukin-23 are also involved in pathogenesis.[2] Thus drugs that act on these targets are used in case of plaque psoriasis.[2]

Histopathologically in Psoriasis, there is hyperkeratosis along with parakeratosis and elongated rete ridges.[9] Munros microabscess are peculiar features seen in Psoriasis.[9] Psoriasis shows increased keratinocyte proliferation due to prolonged inflammation.[2]Inflammation is also seen in the dermis[10].

Psoriasiform dermatitis is a spectrum of diseases which clinically and histopathologically mimic Psoriasis thus making the diagnosis difficult.[4] These include Pityriasis Rubra Pilaris(PRP), nummular dermatitis and Lichen Simplex Chronicus(LSC), with a few others like Pityriasis rosea, Prurigo nodularis and Allergic Contact Dermatitis(ACD).[4,11]

The psoriasiform pattern means the appearance of elongated rete ridges of almost equal length alternating with papillary dermis in between.[12] This pattern contributes majorly to perivascular dermatitis which comes under the inflammatory diseases of skin.[12]

There has always been confusion regarding the histopathological diagnosis due to the relative scarcity of distinctive features of respective skin conditions and further being diagnosed as nonspecific ‘Psoriasiform Dermatitis’. This further affects the treatment and prognosis[13].

World Health Organization mentioned Psoriasis to be a significant disease under the non-communicable category and also stressed problems associated with its improper diagnosis leading to inadequate treatment.[14] In Psoriasis there is high proliferation of cells and shortened turnover time of epidermis from 12 days to 3-4 days.[11] Here comes the role of Ki67 as it is almost always positive in highly proliferating cells and is a proven marker which correlates with the clinical severity of psoriasis[11].The Ki67 activity is found to be more in the inner margins of the lesions and least at the outer margins of the lesion[5,15]. Psoriasiform dermatitis on the other hand shows low Ki67 and thus Ki67 can be used to differentiate psoriasis from psoriasiform lesions.[11]

Also, it was seen that the activated effector memory T cells and natural killer T cells have a role in the pathogenesis of psoriasis and expressed NK receptors along with the Ki67 index showing a significant increase indicating an epidermal proliferation[16].

The treatment of psoriasis includes systemic treatment with steroids, retinoids, methotrexate and others.[17] Other treatments include UV-A, UV-B and narrow-band UVB.[17] Therapy does not stop at the drug treatment but also includes the removal of the triggering agents and making modifications in the lifestyle of the patient.[18]

AIMS AND OBJECTIVE

To study Ki67 as an immunohistochemical diagnostic marker to differentiate Psoriasis and Psoriasiform Dermatitis.

REVIEW OF LITERATURE

Skin is the largest body organ and acts as a barrier protecting the body against external environmental agents.[10] The skin consists of numerous types of cells which play roles such as thermoregulation, innate immunity and metabolism.[10] The two main layers of skin consist of the outermost epidermis followed by the dermis with underlying subcutis. The subcutaneous tissue comprises areolar as well as adipose tissue.[19]

In the histopathology section, the Epidermis comprises stratified squamous epithelium composed of numerous keratinocytes along with a few melanocytes, Merkel cells and Langerhans cells.[19] Rete ridges are the epidermal projections into the epidermis.[19]The epidermis shows the absence of blood vessels along with nerve endings.[19] The basement membrane separates the epidermis from the dermis.[20]

The dermis has a superficial and deep layer. The superficial dermis extends into the epidermis and is called the papillary dermis, and lies adjacent to the basement membrane.[20] The dermis is made up of fine collagen fibres which appear pale eosinophilic.[20]Numerous free nerve endings are seen in the dermis along with Meissner corpuscles.[20] There is the presence of sub-papillary vascular and lymphatic plexuses.[20] Also seen are adnexal structures which maintain thermoregulation and hair growth.[19]

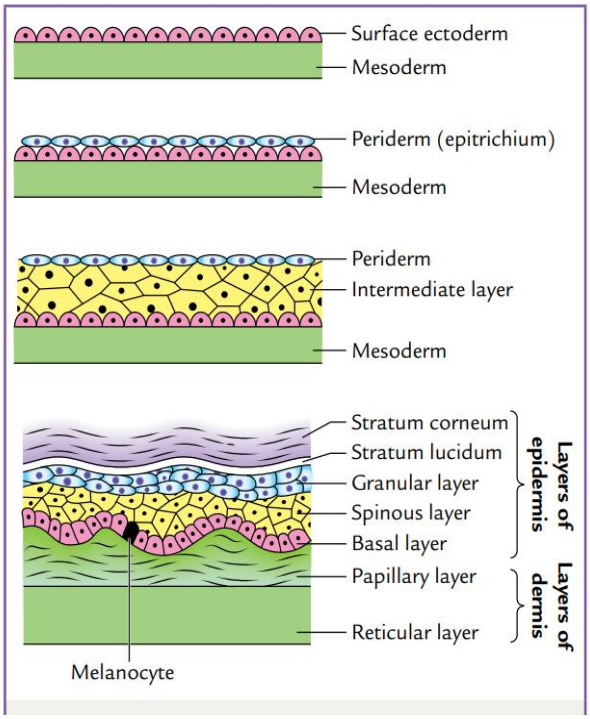
The subcutaneous tissue is made up of fat, a few nerve bundles along with small to medium veins and arteries.[9,20]

EMBRYOLOGY

Epidermis: The surface ectoderm gives rise to the epidermis.[21]A single layer of surface ectodermal cells by the second month proliferates to form a second layer consisting of flattened cells. These cells are called periderm/ epitrichium.[21]The basal layer on proliferation gives a third intermediate layer.[21]The basal layer is also known as stratum germinativum as it is a germinative layer.[21]Four layers of the epidermis are formed by the end of the third month on the proliferation of the basal layer.[21]**(FIGURE 1.1)**

These are:

FIGURE1.1 STAGES OF DEVELOPMENT OF SKIN



SOURCE: VISHRAM SINGH EMBRYOLOGY[21]

I. **Basal layer:** It is the most active layer dividing constantly consisting of columnar cells which divide mitotically and move towards the superficial layer to regenerate the epidermis. This process of movement of the basal cell layer to the skin surface takes about six to eight weeks.[21]

II. **Spinous layer:** The keratinocytes also known as prickle cells have spine-like processes hence the name spinous layer.[21]

III. **Granular layer:** The cells in this layer are arranged in three to four rows of cells with cytoplasm showing keratohyalin granules [21].Just above the granular layer is a homogenous layer of cells having scanty nuclei. This layer on histology appears clear and is called **stratum lucidum**.[4] It is only present in soles and palms along with lips.[21]

IV. Horny layer: This layer has multiple layers of flattened cells which are tough scale and are shed off continuously as residues of cells without nuclei in the form of flakes and die eventually.[21,22]

By the third month, the basal cell layer shows melanoblasts which are neural crest derivatives.[21]

Epidermal Ridges: These are thickenings of the epidermis projecting into the dermis.[21]

Dermal Papillae: These are parts of dermal tissue projecting in between epidermal ridges.[21]

Dermis: The dermis is mesenchymal origin. Mesenchyme lies just beneath the ectoderm and has its derivation from the somatopleuric layer, paraxial mesoderm and neural crest cells[10]. Connective tissue fibres like elastic and collagen fibres are formed from connective tissue cells which are ultimately derived from mesenchymal cells.[21]Dermal papillae are formed in 3rd to 4th month. The dermis divides into two layers superficial layer called the 'Papillary layer' and deeper called the 'Reticular layer' which contains the majority of fatty tissue.[21]Capillary loop plexus are present in the dermal papillae which provide nourishment to the epidermis.[4] By the end of 3rd month dermis shows completion of angiogenesis.[21]

HISTOLOGY

Epidermis

The epidermis is a layered epithelium made of squamous cells producing keratin which undergoes continuous renewal through desquamation. The various types of cells within the epidermis include Keratinocytes along with melanocytes and Langerhans cells. Merkel cells with Toker cells are also present in the epidermis.[23]

The keratinocytes in the epidermis are arranged in 4 distinct layers in an orderly manner from bottom to top. At the base is Stratum Basale followed by Stratum Spinosum, then comes Stratum Granulosum and at the top Stratum Corneum.[23]

The dermo-epidermal boundary shows structures called ‘Dermal Papillae’. The areas within the epidermis that separate these dermal papillae are called ‘Rete ridges.[23]

The epidermis consists of basal cells, responsible for continuous cell division and the formation of new keratinocytes. They are present just above the basement membrane in a single layer of cells. These cells are columnar or cuboidal in shape and have a basophilic cytoplasm. Their nucleus is typically round or oval, displaying coarse chromatin and is inconspicuous.[23]

The **squamous layer** consists of around 5 to 10 layers of cells. These suprabasal keratinocytes are polygonal in shape, with basophilic cytoplasm, and show round nuclei.[23]

As you move towards the more superficial layers, the keratinocytes become larger, flattened, and eosinophilic. These keratinocytes contain one or two distinct nucleoli [23].The squamous layer is often referred to as the spinous layer.[23]

The **granular layer** consists of 1 to 3 layers of flattened cells oriented. These cells contain granules in their cytoplasm that stain intensely basophilic, known as keratohyalin granules which are histidine-rich.[23] The protein filaggrin is produced from histidine.[23]

The **cornified layer** shows a typical basket-weave pattern. Over time, these cells naturally shed off. This is called keratinization, which occurs from basal cells to the cornified layer and typically takes between 20 to 45 days.[23]

PSORIASIS

Psoriasis also known as 'Psoriasis vulgaris' is a long-standing papulosquamous dermatitis showing abnormal epidermal proliferation.[24]While psoriasis can emerge at any age, it is most commonly seen in the 50-69 age group.[14]It can also be seen in the age group below 10 years[25]. It shows two peaks of incidence.[3]

The prevalence varies between 0.09% to 11.4% in Psoriasis. This broad range emphasises the substantial global significance of psoriasis as a significant health concern.[14]

It is a prevalent skin condition in India, exhibiting similar prevalence rates and epidemiological features to those observed in Western populations.[26]In studies comparing twins, it's found that identical twins have a 2 to 3 times greater likelihood of developing psoriasis compared to fraternal twins.[27,28]Regions located at higher latitudes have shown increased occurrence rates, particularly among individuals of Caucasian descent [29].The Psoriasis cases have seen in rise due to increased awareness of the condition among both medical professionals and the general public.[30]

The exact cause of psoriasis is yet to be found. However genetic predisposition can be considered. Researchers are actively investigating the role of immunity in the development of psoriasis. While there is a hypothesis that psoriasis might be an autoimmune disease, a specific autoantigen responsible for it is unknown. Psoriasis can also be triggered by various external and

internal factors, such as minor injuries, systemic infections, certain medications, acute stress and exposure to the sun leading to sunburn.[14]

Continuous exposure to specific environmental elements, such as smoking, along with immediate triggers like psychological stress, can impact the onset and manifestation of psoriasis.[31] Individuals diagnosed with psoriasis exhibit a higher occurrence of cardiovascular risk factors and concurrent health conditions linked to cardiovascular disease[32].

In everyday clinical practice, psoriasis is typically diagnosed on pattern recognition of clinical characteristics, which includes assessing the distribution, pattern, and appearance of skin lesions. The widely accepted gold standard for diagnosis is a clinical assessment performed by a qualified dermatologist along with a histopathological examination might be used for additional confirmation.[14]

ETIOPATHOGENESIS

Psoriasis is caused by both external and internal factors.[33] Genetic predisposition is a significant contributor, particularly in people who develop the disease at a young age, typically under 40 years old.[34] Psoriasis arises from a multifaceted immune response within the skin, characterized by significant inflammation encompassing both innate and adaptive immune mechanisms, alongside irregular proliferation and differentiation of keratinocytes.[35]

Injuries to the body, mental strain, specific medications, various infections such as bacterial Streptococcus along with Staphylococcus, fungal-Candida, metabolic syndrome. Environmental factors that strain the skin barrier can all trigger or worsen the condition by indirectly impacting the internal immune system balance.[36]

Psoriasis is an autoimmune condition where T-cells drive the excessive growth of skin cells. Immunological factors play a significant role in its development. It is now understood as a disorder primarily mediated by T-cells, particularly CD4+ helper lymphocytes, along with CD8+ suppressor cells. These T-cells are activated within psoriatic lesions, expressing markers like HLA-DR and IL-2 receptors. The innate immunity in conjugations with acquired immunity releases various molecules like cytokines, growth factors, and chemokines, contributing to the inflammation observed in psoriatic plaques. While CD4+ T-cells initiate and sustain the psoriatic process, CD8+ T-cells, once activated, become the main driving force behind its progression.[37]

The effective use of cyclosporine A in treating psoriasis patients provided initial clinical support for the involvement of T cells in Psoriasis pathogenesis.[38]

The genetic predisposition for psoriasis is significantly influenced by the MHC region situated at 6p21.[27,39] PSORS1 stands out as the locus most closely linked to psoriasis believed to contribute to about half of the genetic predisposition to the disease.[40–42] The PSORS1 is considered a significant genetic factor in psoriasis.[34] Beta-blockers, lithium, and antimalarial drugs are frequently used medications that can either trigger psoriasis-like skin eruptions or exacerbate existing psoriasis.[34] Psoriasis patients often exhibit low vitamin D levels, but the role of vitamin D in psoriasis remains unclear.[34]

CLINICAL FEATURES

Psoriasis accounts for 90% of all cases.[43,44]The majority of Indian patients suffering from psoriasis commonly report experiencing itching and both Indian and American patients face comparable levels of stress related to cosmetic disfigurement and managing the physical aspects of psoriasis.[45]

Clinically Psoriasis appears as well-delineated papulosquamous plaques which are salmon pink or red and show silvery scales.[44] They are advancing lesions often exhibiting a ring-like appearance, with the active periphery and unaffected skin at the centre.[33] These plaques are symmetrical and are frequently on the outer surfaces of elbows and knees, the scalp, the lower back and the sacral area, as well as around the navel.[33,44] A defining feature of active inflammatory psoriasis is the Koebner phenomenon, wherein new lesions emerge at areas of injury or pressure.[44] It may hold prognostic significance and correlate with the early onset of psoriasis.[46]

There are specific variations of psoriasis vulgaris depending on the location. For instance, flexural (inverse) psoriasis found in skin folds appears shiny, and red and usually lacks scales. Psoriasis vulgaris may encompass several closely related but distinct conditions in terms of appearance and genetic makeup. This diversity could explain the varying responses to treatment, especially when using T-cell-targeted biological therapies.[44]

Early-onset psoriasis, when compared to its late-onset counterpart, often exhibits a higher prevalence of familial cases and an increased frequency of the HLA-Cw6 allele.[36,47] Environmental factors such as exposure to tobacco, obesity or higher body mass index (BMI), and significant life stressors are recognized as potential risks contributing to the onset or exacerbation of the disease.[36,48,49]

Patients have associated Psoriatic arthritis (PsA), a type of inflammatory arthritis characterized by pain and swelling in the joints, which may result in joint damage and chronic disability over time.[50]

Psoriasis is often associated with comorbid conditions such as psoriatic arthritis, depression, hypertension, diabetes, and metabolic syndrome.[51]Further research is urgently required to examine how psoriasis activity and severity independently contribute to the risk of developing metabolic disorders, atherosclerosis, and heart attacks.[51]

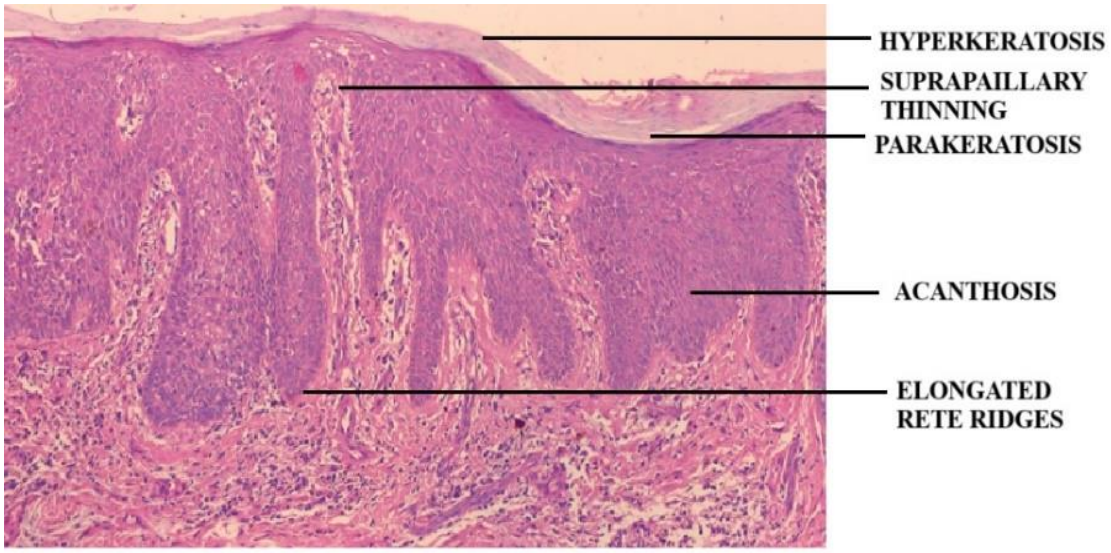
Several genetic regions are identified, like PSORS1 on chromosome 6p21.3, which encompasses gene candidates such as Human Leukocyte Antigen (HLA)-Cw6, CDSN, PSORS1C3, OTF3, TCF19, CCHCR1, LMP, SEEK1, SPR1etc have susceptibility for Psoriasis.[52]

Osteopontin acts through multiple mechanisms, including chronic inflammation and the abnormal proliferation of skin cells associated with Psoriasis. It regulates T-cell-mediated immunity by affecting Th17 and Th1 responses through both its intracellular and secreted variant forms.[53]

HISTOPATHOLOGY OF PSORIASIS

Psoriatic plaques display distinctive features such as distinct parakeratosis, remarkably elongated and slender rete ridges associated with hypogranulosis and thinned suprapapillary plates. The tips of the papillary dermis show the prominence of blood vessels. An associated finding is the presence of superficial perivascular infiltrates mainly consisting of lymphocytes. In acute, guttate, or pustular lesions, there is evidence of characteristic findings such as Kogoj's pustules and the presence of Munro microabscess. The Kogoj's pustules, also referred as spongiform pustules are seen in stratum malpighii are intraepidermal accumulations of neutrophils. Munro microabscesses are seen in the stratum corneum. These are neutrophil aggregates. Neutrophil prominence is not observed within the dermis.[20]**(FIGURE 1.2)**

FIGURE 1.2 HISTOPATHOLOGY OF PSORIASIS



HISTOPATHOLOGY OF PSORIASIS

CLASSIFICATION OF PSORIASIS

Plaque psoriasis: Most psoriasis cases consist of plaque psoriasis, accounting for 80 to 90% of cases and clinically appear as erythematous plaques of size greater than one centimetre which is well-demarcated.[54] The common sites are the extensor surfaces of elbows along with knees.[54] Other areas affected are lumbosacral and umbilical.[55]

Pustular psoriasis: These show clinically apparent pustules hence called as pustular psoriasis.[54]

Guttate psoriasis: These clinically appear as tiny lesions of 1 mm to 10 mm papules which are salmon pink in colour and appear like dew drops and commonly affect age groups less than 30 years of age with the most common sites being the trunk followed by proximal extremities.[54]

Psoriatic arthritis: It is a type of inflammatory arthritis associated with psoriasis and also shows associated enthesitis and dactylitis.[56]

ROLE OF IMMUNOHISTOCHEMISTRY IN PSORIASIS

Dermatologists and pathologists are actively conducting numerous studies to identify additional criteria that could play a significant role in studying the course of the progression of psoriasis and predicting the effectiveness of various treatment approaches. These investigations involve utilizing immunohistochemistry techniques in understanding the molecular aspects of the condition.[57–59]

The expression levels of immunohistochemical markers related to proliferation of cells, presence of vascularization, apoptosis, and inflammation will differ according to the type of psoriasis and the severity of pathological processes. Key markers investigated for their significance include cyclin D1, Ki-67, pRb, p53, Vascular endothelial growth factor (VEGF) and CD31, with differences observed based on the specific form of psoriasis and the extent of the pathological changes.[57–59]

Ki67 IN PSORIASIS

Ki67 is a nuclear protein originally Ki67 which was recognised with the help of a monoclonal antibody produced by L428 cell lines of Hodgkin lymphoma immunized mice.[60,61] Ki67 cDNA was cloned[62,63] and sequenced which brought to notice that the amino acid sequence of Ki67 was unique and thus the antibody encoding the protein was named. The antibodies against this protein were developed in Germany where 'Ki' in Ki67 is derived from the German word Kiel. The "67" was derived from the number of well plates, and the 67th was the well plate for identification of antibody. An approximate of thirty thousand cases were found after sequencing the locus of the gene that encodes Ki67.[60,64] MK167 gene encodes Ki67 in humans.[62]

Regardless of the cell type, various human cell lines exhibit expression of Ki67 in proliferating cells.[60,65,66] Ki67 protein levels peaks during mitosis phase in the late G1 phase of cell cycle.[60,67]

The antigen of Ki-67 is a non-histone type of nuclear protein complex with a molecular weight between 345 and 395 kD.[57] The gene encoding Ki67 has its location on the chromosome number 10.[8] MK167 gene encodes Ki67 protein.[68] Ki67 index of proliferation holds a prognostic value in many malignant tumours.[69] The skin damaged by sun exposure also shows a high Ki67 proliferation index.[69]

The Ki67 expression is analyzed by using Immunohistochemistry and is now a method frequently used to analyse the cell proliferation.[8] It is interpreted by counting the percentage of cells with nuclear positivity.[8] Thus Ki67 can evaluate the growth fraction more reliably and save time.[8]

Ki67 is found to be expressed in the nuclei of all the dividing cells and not just cells of neoplastic origin.[8] In psoriasis, epidermal hyperproliferation involves rapid and irregular maturation of keratinocytes due to intense cell proliferation of the epidermal cells of the basal layer. In normal healthy skin, cell proliferation is limited and only seen in a few basal cells. Psoriasis shows many basal keratinocytes actively dividing. Thus Ki67 can be used as a marker of this improper proliferation and keratinization.[8]

Ki67 protein plays significant role in regulating the cell cycle and serves as the predominant marker for proliferation immunohistochemistry (IHC).[57,70]**(FIGURE 1.3)**

Studies have indicated an elevation in its expression within psoriatic lesions compared to non-lesional skin. However, there is a scarcity of data concerning the comparative expression of this marker in Psoriasis when compared to non-psoriatic dermatitis.[57]

The protein Ki-67 is associated with cellular proliferation and is often used as a marker for assessing the growth fraction of a cell population. In the context of psoriasis, studies have indeed reported higher expression of Ki-67 in psoriatic lesions compared to normal skin or psoriasiform lesions.[57]

Psoriasis shows dysregulation of the normal cell cycle, leading to the rapid turnover of skin cells and plaque formation.[57]The higher expression of Ki-67 in psoriatic lesions supports the notion that abnormal cell proliferation is a key factor in the development and maintenance of psoriasis.[57]

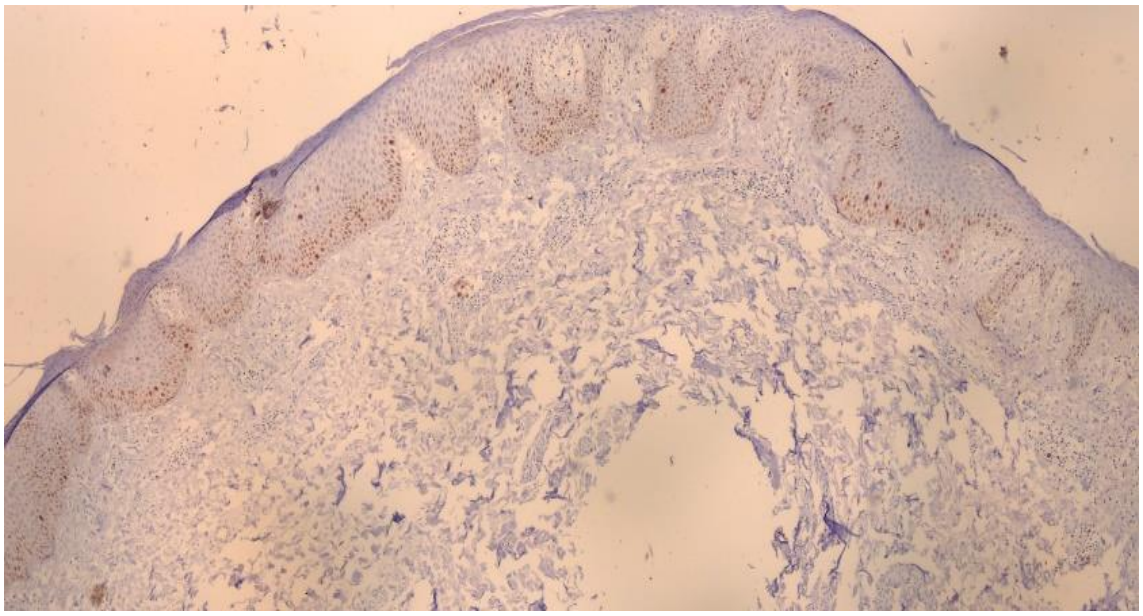
Except in G0 and early G1 phase, the cell cycle shows expression of Ki-67.[8] Maximum expression is seen in G2 and M phase.[8] It is associated with the cell cycle and is related to the proliferative zone of the epidermis.[71] Expression of Ki67 is more evident in Psoriasis in comparison to other Psoriasiform lesions.[4,72]The Ki67 activity is found to be higher in the inner margins followed by the centre of the lesions and least at the outer margins of the lesion.[15]

Also, it was seen that the activated effector memory T cells and NK- T cells have taken part in the pathogenesis of psoriasis. The cells that expressed NK receptors along with Ki67 showed a significant increase indicating an epidermal proliferation.[16]

In Psoriasis there is a high proliferation of cells and the turnover time of epidermis drops from 12 to 3-4 days. This activity is detected by Ki67 and can be used to exclude the diagnosis of Psoriasiform Dermatitis in which there is not much proliferation evident.[59]

In the initial phase of psoriasis, under the effect of TNF alpha, endothelial cell proliferation and angiogenesis occur due to vascular endothelial growth factor (VEGF) that is synthetized by keratinocytes and thus VEGF and TNF alpha can also be employed for the correlation with the proliferation of epidermis.[73]

FIGURE 1.3 KI67 EXPRESSION IN PSORIASIS SHOWING NUCLEAR IMMUNOREACTIVITY(X40)



TREATMENT OF PSORIASIS

The most common treatment protocol for psoriasis includes UVB, PUVA and Methotrexate.[54]PUVA is also used to treat other conditions like prurigo nodularis, eczema, mycosis fungoides and many more.[73]

Acitretin is a retinoid used to treat moderate to severe psoriasis vulgaris. Other drugs like Cyclosporine A and Apremilast are also used.[74]

A study was done by Jesionek and colleagues where they correlated Ki67 expression in the psoriasis lesions after treatment with PUVA but they did not find any significant difference in before and after treatment.[8]

PSORIASIFORM DERMATITIS

Psoriasiform dermatitis (PD) includes various inflammatory skin conditions, many of which exhibit both clinical and histopathological similarities to Psoriasis. The term "psoriasiform" indicates that the lesion resembles psoriasis either in its clinical appearance or in the microscopic examination of skin tissue.[75] This category comprises Pityriasis Rubra Pilaris, Allergic Contact Dermatitis, Pityriasis rosea, Prurigo nodularis and Lichen Simplex Chronicus .[75]

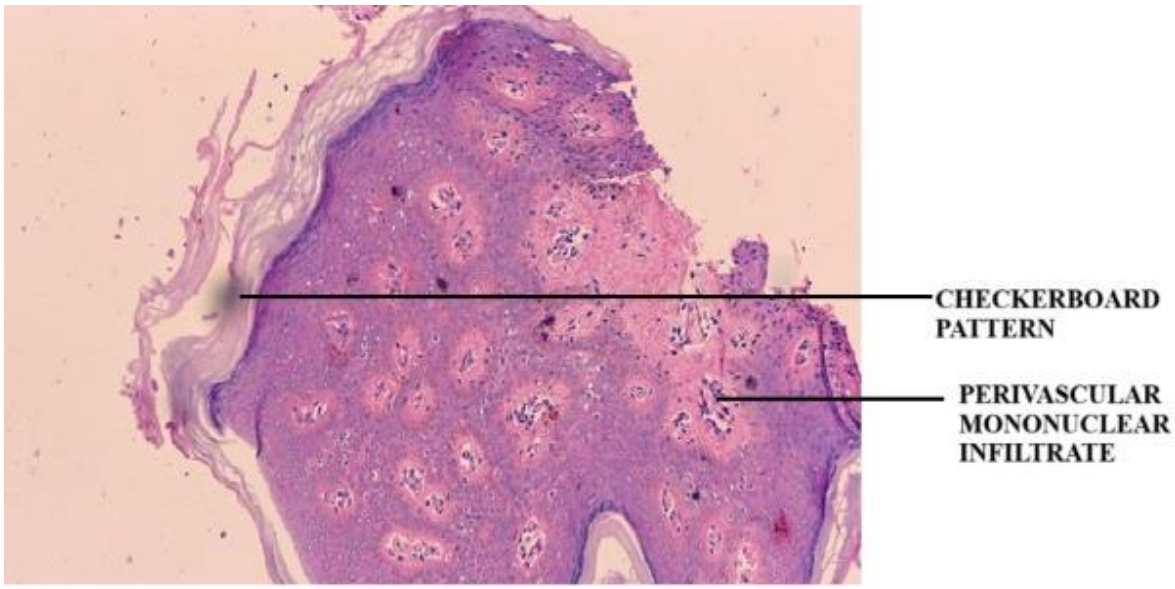
I. PITYRIASIS RUBRA PILARIS

It is a papulosquamous disorder with unknown aetiology.[76] It is rare in its occurrence and presents with cutaneous eruptions comprising hyperkeratotic papules.[77] Clinically these plaques appear orange-red and show islands of normal skin in between affected areas.[78] It can also be seen as secondary to viral infections.[79] It is aggravated by sunlight and is also common in the case of patients treated with phototherapy.[80–82] Predominantly affects the face and can be differentiated from psoriasis clinically by the absence of characteristic nail changes which are present in psoriasis.[83]

On histopathology, the epidermis shows acanthosis. The characteristic feature of this condition is the presence of alternating orthokeratosis and parakeratosis giving a checkerboard pattern appearance. The superficial dermis shows perivascular mononuclear infiltrates comprising of lymphocytes.[77]**(FIGURE 1.4)**

Treatment consists of Phototherapy with narrow-band ultraviolet-B light.[84]

FIGURE 1.4 HISTOPATHOLOGY OF PITYRIASIS RUBRA PILARIS



HISTOPATHOLOGY OF PITYRIASIS RUBRA PILARIS

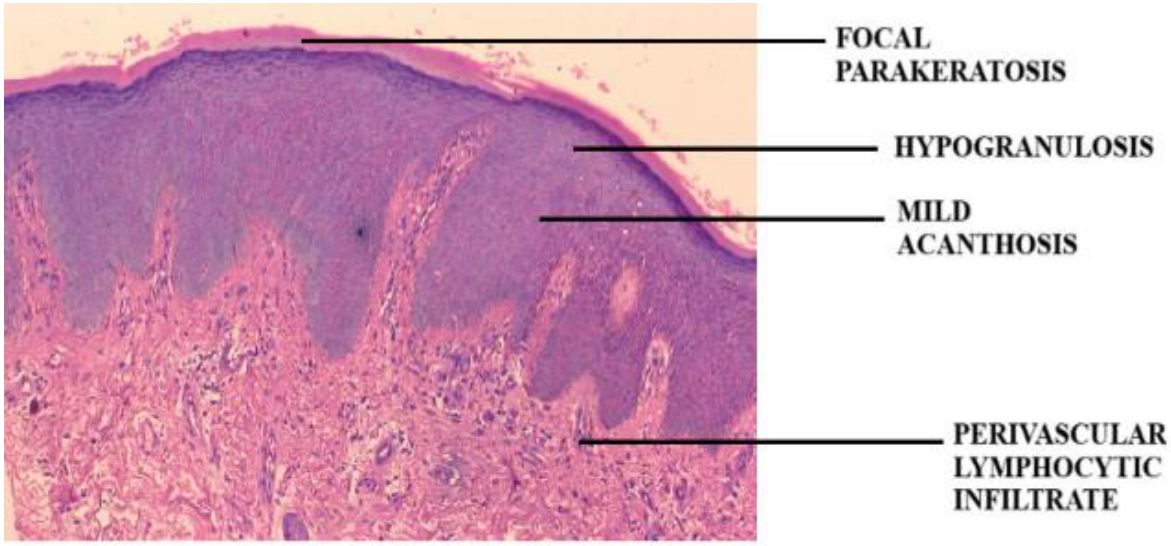
II. PITYRIASIS ROSEA

Pityriasis rosea is a self-limiting papulosquamous disorder.[85,86]It is caused secondary to the reactivation of the human herpes virus.[87] It is seen in individuals between 10 to 35 years[88]. Some cases reported are seen to be associated with respiratory infections.[88,89] Pityriasis rosea characteristically appears as an oval solitary lesion called a 'Herald patch' which is pale and depressed at the centre with finely scaled elevated borders.[90]

Histopathologically, they show focal parakeratosis with mild acanthosis. There is variable spongiosis along with hypogranulosis. Some amount of perivascular lymphocytic infiltrate along with occasional eosinophilic infiltrate is also seen[90]. (FIGURE 1.5)

Treatment consists of steroids, macrolides along with antiviral.[86]

FIGURE 1.5 HISTOPATHOLOGY OF PITYRIASIS ROSEA



HISTOPATHOLOGY OF PITYRIASIS ROSEA

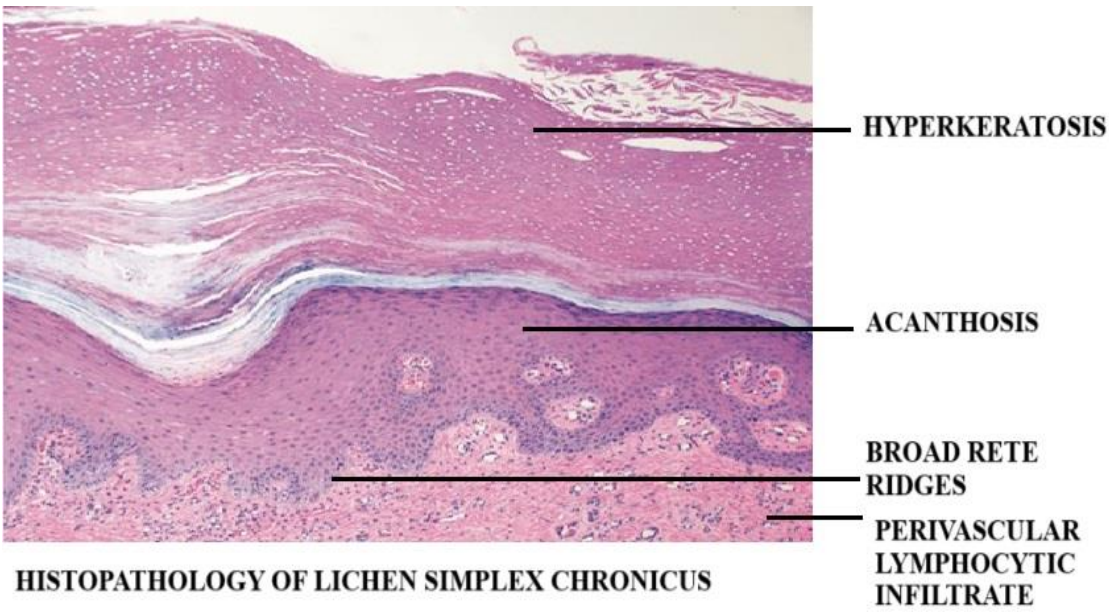
III. LICHEN SIMPLEX CHRONICUS

It is the most common in patients presenting with a long-standing history of chronic itch leading to lichenoid scaly plaques.[91]It occurs either as a primary lesion or secondary to some other skin disorders.[92]

Histopathologically, the epidermis shows hyperkeratosis with marked acanthosis and hypergranulosis. There is parakeratosis which is seen focally. The rete ridges are broadened and elongated. There is mild spongiosis with fibrosis of dermal papillae. The characteristic feature is that the superficial dermis shows collagen bundles which are thickened and oriented vertically. The dermis also shows the presence of perivascular inflammatory cell infiltrate comprising lymphocytes and macrophages, and eosinophils can also be seen.[91] **(FIGURE 1.6)**

Drugs like lubricants, topical aspirin, acetaminophen, etc have been used in the treatment.[91]

FIGURE 1.6 HISTOPATHOLOGY OF LICHEN SIMPLEX CHRONICUS



HISTOPATHOLOGY OF LICHEN SIMPLEX CHRONICUS

SOURCE: WEEDON'S SKIN PATHOLOGY[24]

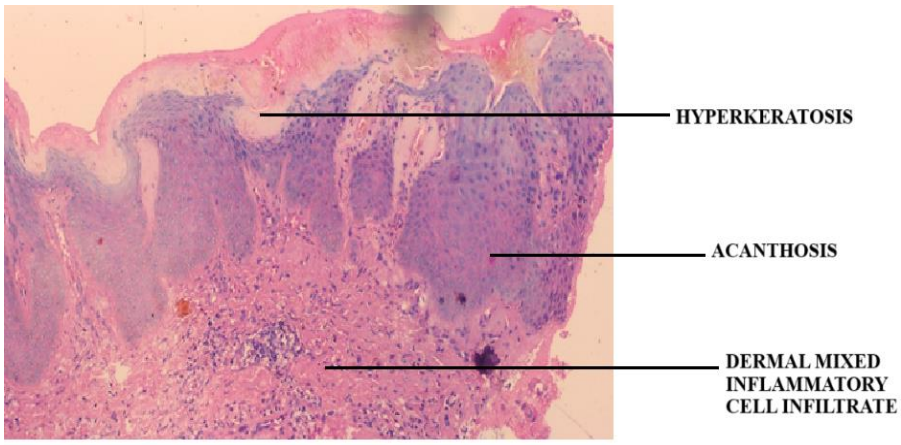
IV. PRURIGO NODULARIS

It is a disorder seen in cases of chronic itch.[93,94].Clinically there is chronic irresistible itch, and associated with a duration of more than 6 weeks of pruritis along with multiple classical lesions.[94,95] Incidence ranges from 1% to 2%.[96]

Recent studies have shown neuropeptides, ion channels, and cytokines along with extracellular proteins and intracellular signalling pathways are involved in the pathogenesis of prurigo nodularis.[97]

Histopathologically, the epidermis shows hyperproliferation along with hyperkeratosis. There is also the presence of acanthosis and hypergranulosis.[102] The dermis shows mixed inflammatory cell infiltrates comprising of neutrophils, lymphocytes, macrophages and sometimes eosinophils.[96]**(FIGURE 1.7)**Treatment includes corticosteroids, antihistamines along with narrow-band UVB.[98]

FIGURE 1.7 HISTOPATHOLOGY OF PRURIGO NODULARIS



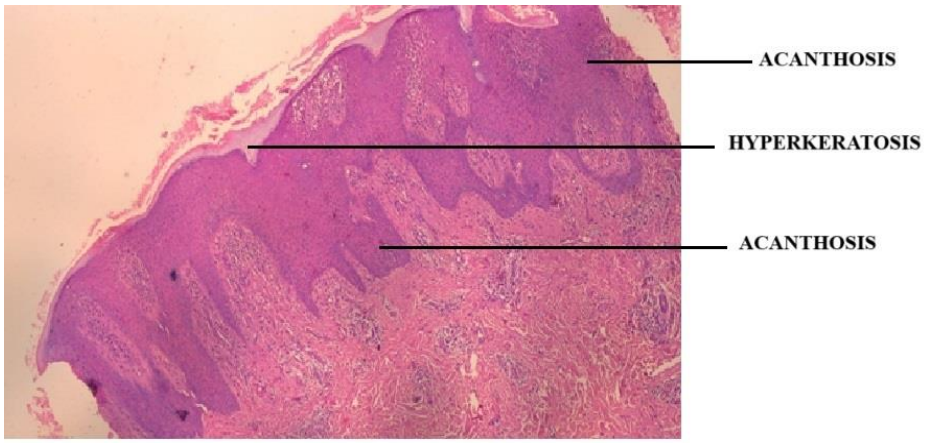
HISTOPATHOLOGY OF PRURIGO NODULARIS

V. ALLERGIC CONTACT DERMATITIS

Allergic contact dermatitis comprises 20% of the cases of CD.[99]Patients present with itchy vesicular rash with blister formation which if present chronically will eventually turn lichenified and hyperpigmented.[100] The causes of allergic contact dermatitis are most commonly contact with detergents, soaps, perfumes, solvents etc.[101] In India, the incidence has increased due to the increase in the usage of cosmetic products and hair dyes.[102] Atopic dermatitis is seen to be a predisposing condition leading to allergic contact dermatitis.[103] It is found as an occupational hazard which affects the quality of life of patients.[104]Topical corticosteroids are the first line of treatment.[105]

Histopathologically, spongiosis along with vesicle formation is seen predominantly in the acute phase. Parakeratosis with acanthosis is also seen. In longstanding cases, hyperkeratosis is accompanied by broad and elongated rete ridges. All the stages show dilated vessels with mononuclear dermal infiltrates.[106]**(FIGURE 1.8)**

FIGURE 1.8 HISTOPATHOLOGY OF ALLERGIC CONTACT DERMATITIS



HISTOPATHOLOGY OF ALLEGIC CONTACT DERMATITIS

Ki67 IN PSORIASIFORM DERMATITIS

Not many studies have been done in past to differentiate Psoriasis from Psoriasiform dermatitis using Ki67 as an IHC marker.

MATERIALS AND METHODS

SOURCE OF DATA:

Patients who attended Dermatology, Venereology and Leprosy OPD KLE'S Dr Prabhakar Kore Hospital and Research Centre, Belagavi with complaints of scaly erythematous lesions.

STUDY DESIGN: This is a Descriptive Study.

STUDY PERIOD: One year of data from 1st September 2022 to 1st September 2023**.**

SAMPLE SIZE:

Calculation of sample size using a sample size formula by Kish Leslie.

Sample size=$\frac{Z^2 \times (p) \times (1-p)}{C^2}$

Where Z=Z value(1.96 for 95% confidence level)

P=Prevalence of disease =2%[11]=0.02

C=Confidence interval expressed as decimal0.05

Sample size=$\frac{1.96 \times 1.96 \times (0.02) \times (0.98)}{0.05 \times 0.05}$

=30

SAMPLING TECHNIQUE: Convenience Sampling.

INCLUSION CRITERIA:

Histopathologically and clinically proven cases who have undergone a biopsy for confirmation. The Psoriasis cases that were included were psoriasis vulgaris, plaque psoriasis and guttate psoriasis which were taken as cases. Psoriasiform dermatitis cases included were Pityriasis rubra pilaris, Lichen simplex chronicus, Pityriasis rosea, Prurigo nodularis and Allergic contact dermatitis were taken as controls.

EXCLUSION CRITERIA:

I. Non Psoriasiform skin lesions.

II. Patients <18 years of age.

III. Inadequate skin biopsies

IV. Patients who are recently diagnosed with Psoriasis and Psoriasiform dermatitis and are already on treatment.

INFORMED CONSENT:

After explaining the motive and the objective of the study in the local language proper informed consent was taken from the participants of the study.

DATA COLLECTION PROCEDURE:

Details pertaining to the age of the patient, clinical features and the site of the biopsy were obtained from the requisition form sent. Punch biopsy was taken in Dermatology, Venereology and Leprosy OPD and sent in 10% formalin to the Department of Pathology. Biopsy was embedded in paraffin blocks after routine fixation and processing. Further thin sections were taken and affixed on the slides and subjected to haematoxylin and eosin staining.

The reporting pathologist then did a detailed microscopic examination of the slides

IMMUNOHISTOCHEMICAL (IHC) STAINING – PROCEDURE

Ki67-M1B1(Clone)- Pathnsitu biotechnology(company) USA

10% formalin was used to fix all the specimens, which was followed by tissue processing and paraffin embedding. 3 to 5mm thickness sections from paraffin-embedded skin biopsy tissues were made. After deparaffinizing the tissue was rehydrated with xylene and graded alcohol respectively. Slides were kept in xylene I followed by xylene II for 5 minutes each. Then they were rehydrated with alcohol I followed by alcohol II for 5 minutes each. 3% hydrogen peroxide was added for 30 minutes which blocked the endogenous peroxide. The slides were then placed in running tap water followed by distilled water for 5 minutes each. To retrieve antigens, the sections were treated with TRIS buffer for 5 minutes two times and then processed in a pressure

cooker before they were washed with phosphate-buffered saline (PBS). The slides were then incubated with a monoclonal primary antibody followed by a polymer HRP-labelled secondary antibody for 40 minutes, with PBS washes after each step. For immunohistochemistry (IHC), 3'-3' diaminobenzidine hydrochloride (DAB) was employed as the chromogen. All the IHC slides were counterstained with alcohol-free haematoxylin for one minute and then rinsed with running tap water.

The keratinocytes showing brown nuclear positivity in the epidermis were counted in 40x and an average was taken of the same and Ki67 proliferating index was calculated. >25% Ki67 index was taken as cutoff.[13]

STATISTICAL ANALYSIS

The analysis of data was done in IBM SPSS (Statistical Package for Social Sciences software) Software version 29.0.2.0. The categorial data was analyzed using Fisher's exact test. The statistically significant p-value was taken as <0.05 to find the expression of Ki67 in Psoriasis and Psoriasiform dermatitis.

RESULTS

TOTAL CASE DISTRIBUTION

A total of 40 cases were studied, out of which 57.5% cases were psoriasis and 42.5% were Psoriasiform dermatitis as controls. **[TABLE 1]**

TABLE 1: TOTAL CASE DISTRIBUTION(n=40)

PSORIASIS	PSORIASIFORM DERMATITIS	TOTAL
57.5%(n=23)	42.5%(n=17)	100%(n=)40

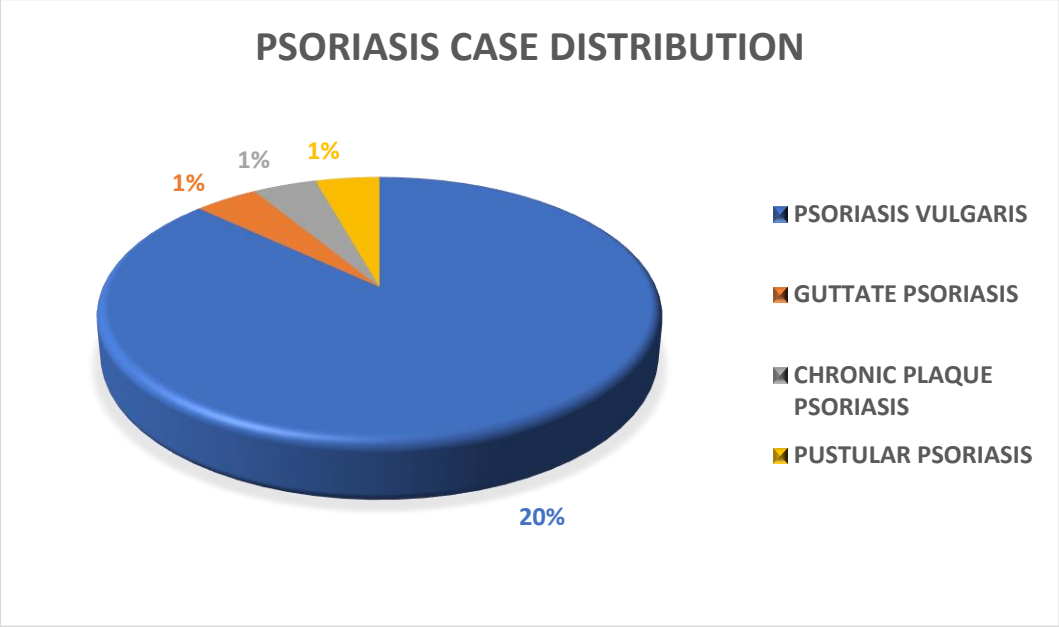
PSORIASIS CASE DISTRIBUTION

Out of 23 psoriasis cases, 87%(n=20) were Psoriasis vulgaris, and 4.3%(n=1) each were Guttate psoriasis, Chronic plaque psoriasis and Pustular psoriasis. **[TABLE 2][GRAPH 1]**

TABLE 2: PSORIASIS CASE DISTRIBUTION

TYPES OF PSORIASIS	NUMBER OF CASES	PERCENTAGE
PSORIASIS VULGARIS	20	87%
GUTTATE PSORIASIS	01	4.3%
CHRONIC PLAQUE PSORIASIS	01	4.3%
PUSTULAR PSORIASIS	01	4.3%
TOTAL	23	

GRAPH 1: PSORIASIS CASE DISTRIBUTION



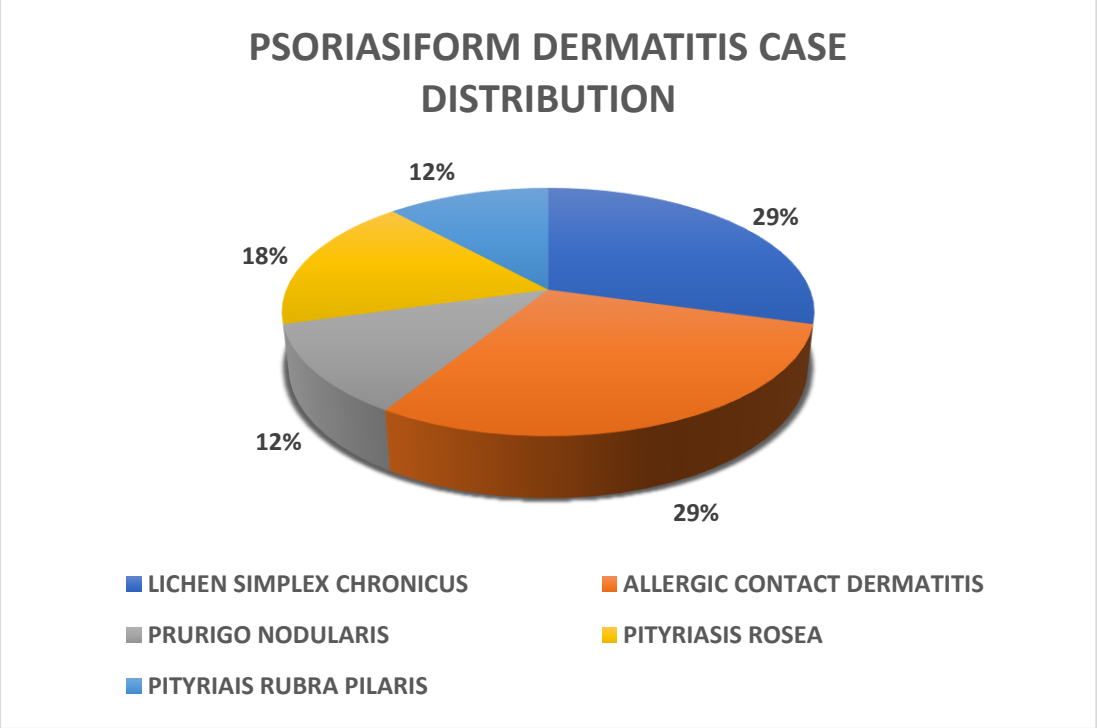
PSORIASIFORM DERMATITIS CASE DISTRIBUTION

Out of 17 psoriasiform cases, 29.4%(n=5) were Lichen Simplex Chronicus and Allergic Contact Dermatitis each. Pityriasis rosea cases were 17.6%(n=3). Prurigo nodularis and Pityriasis Rubra Pilaris were 11.8%(n=2) each. **[TABLE 3][GRAPH 2]**

TABLE 3: PSORIASIFORM DERMATITIS CASE DISTRIBUTION

PSORIASIFORM DERMATITIS	**NUMBER OF CASES**	**PERCENTAGE (%)**
LICHEN SIMPLEX CHRONICUS	05	29.4
ALLEGRIC CONTACT DERMATITIS	05	29.4
PITYRIASIS ROSEA	03	17.6
PRURIGO NODULARIS	02	11.8
PITYRIASIS RUBRA PILARIS	02	11.8
	17	

GRAPH 2: PSORIASIFORM DERMATITIS CASE DISTRIBUTION



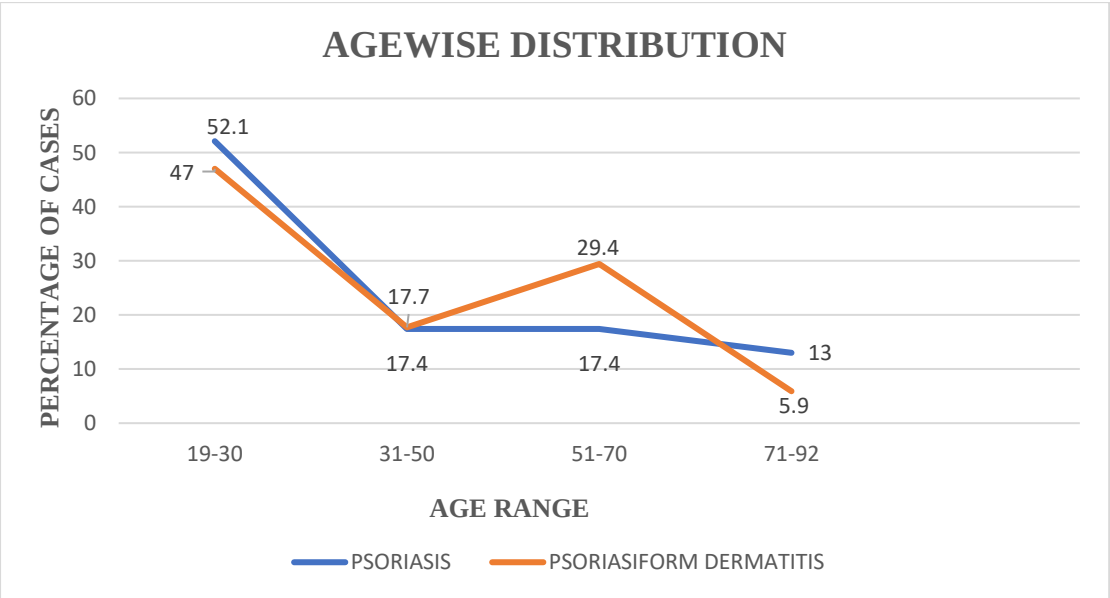
AGEWISE DISTRIBUTION

Both Psoriasis and Psoriasiform Dermatitis showed a maximum number of cases with 52.1%(n=12) and 47% (n=8) respectively in the age group 19-30 years. **[TABLE 4] [GRAPH 3]**

TABLE 4: AGEWISE DISTRIBUTION(n=40)

AGE(YEARS)	PSORIASIS	PSORIASIFORM DERMATITIS
19-30	12(52.2%)	08(47%)
31-50	04(17.4%)	03(17.7%)
51-70	04(17.4%)	05(29.4%)
71-92	03(13.0%)	01(5.9%)
TOTAL	23	17

GRAPH 3: AGEWISE DISTRIBUTION



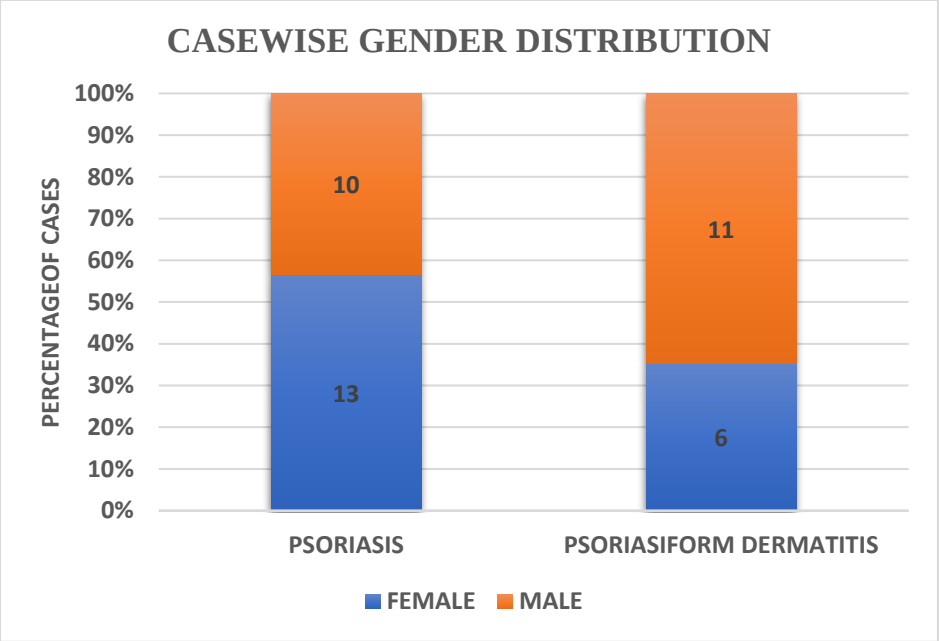
GENDER DISTRIBUTION IN PSORIASIS VS PSORIASIFORM DERMATITIS

Out of the total 23 Psoriasis cases, 56.5% (n=13) were female while 43.5%(n=10) were male, thus a slight female preponderance was seen. While in Psoriasiform Dermatitis 64.7%(n=11) cases were males as compared to females constituting 35.3%(n=6), with male preponderance seen. **[TABLE 5] [GRAPH 4]**

TABLE 5: GENDER DISTRIBUTION IN PSORIASIS VS PSORIASIFORM DERMATITIS

	FEMALE	MALE	TOTAL
PSORIASIS	13(56.5%)	10(43.5%)	23
PSORIASIFORM DERMATITIS	06(35.3%)	11(64.7%)	17

GRAPH 4: GENDER DISTRIBUTION IN PSORIASIS VS PSORIASIFORM DERMATITIS



GENDERWISE MEAN AGE DISTRIBUTION

The mean age in psoriasis for females was 40.6(±23.1) years and for males 38.7(±20) years. Similarly, for psoriasiform dermatitis, the mean age that we found was 50(±26.1) years in females and 36.3(±18) years in males. **[TABLE 6]**

TABLE 6: GENDERWISE MEAN AGE DISTRIBUTION

	FEMALE (MEAN AGE IN YEARS)	**MALE** (MEAN AGE IN YEARS)
PSORIASIS	40.6(±23.1)	38.7(±20)
PSORIASIFORM DERMATITIS	50(±26.1)	36.3(±18)

CLINICAL FEATURES

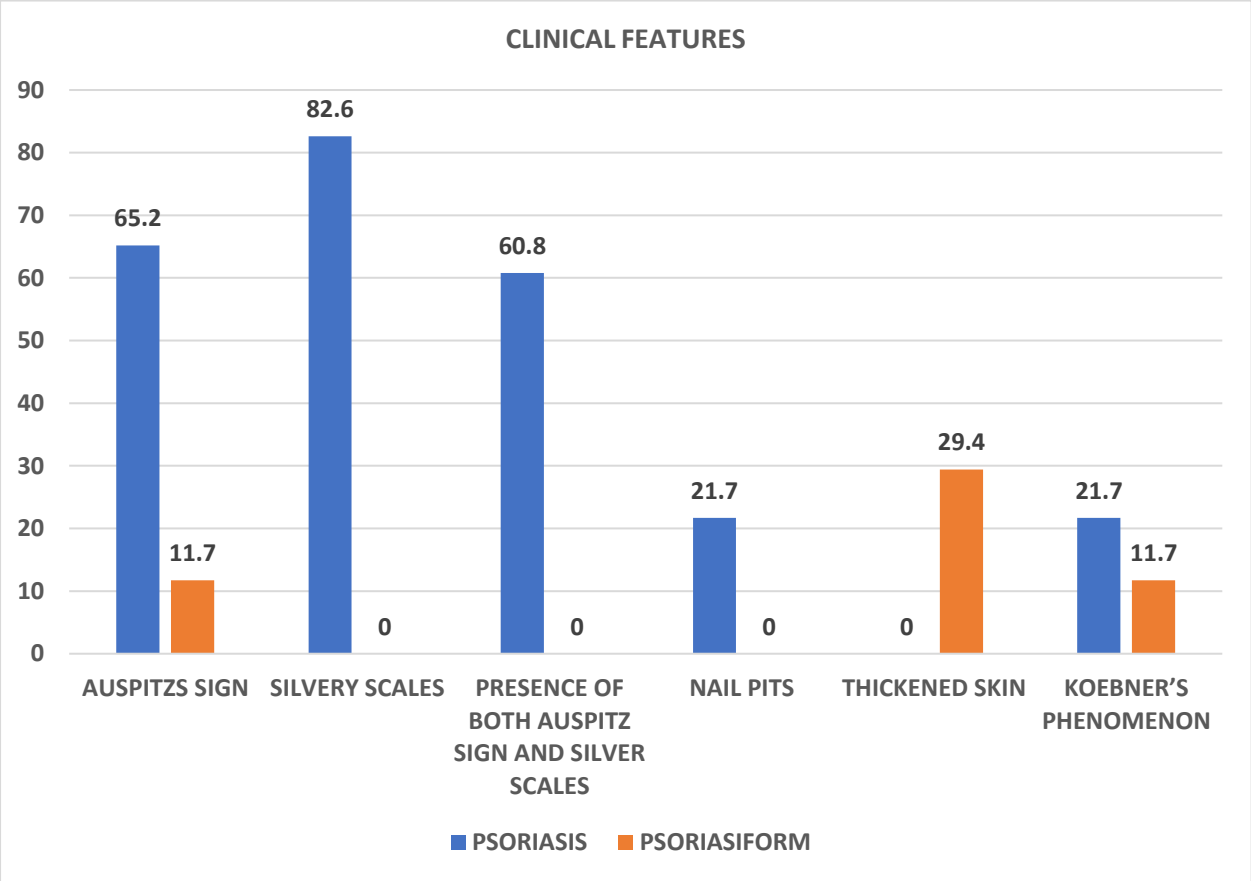
The clinical features of Auspitz sign, Silvery scales, both Auspitz sign and Silvery scales, and Nail pits were seen more in Psoriasis as compared to Psoriasiform Dermatitis and was statistically significant ($p<0.0001$). Thickened skin was only seen in Psoriasiform Dermatitis as was a statistically significant finding ($p<0.0001$). Koebner's phenomenon was seen in both Psoriasis as well as Psoriasiform Dermatitis and thus was not statistically significant ($p=0.08$)

[IMAGE 1-2] [TABLE 7][GRAPH 5]

TABLE 7: CLINICAL FEATURES

CLINICAL FEATURES	PSORIASIS (%) OF CASES	PSORIASIFORM DERMATITIS (%) OF CASES	'P' VALUE
AUSPITZS SIGN	65.2% (15)	11.7% (02)	<0.0001
SILVERY SCALES	82.6% (19)	00	<0.0001
PRESENCE OF BOTH AUSPITZ SIGN AND SILVER SCALES	60.8% (14)	00	<0.0001
NAIL PITS	21.7% (05)	00	<0.0001
THICKENED SKIN	00	29.4% (05)	<0.0001
KOEBNER'S PHENOMENON	21.7% (05)	11.7% (02)	0.0892

Graph 5: CLINICAL FEATURES



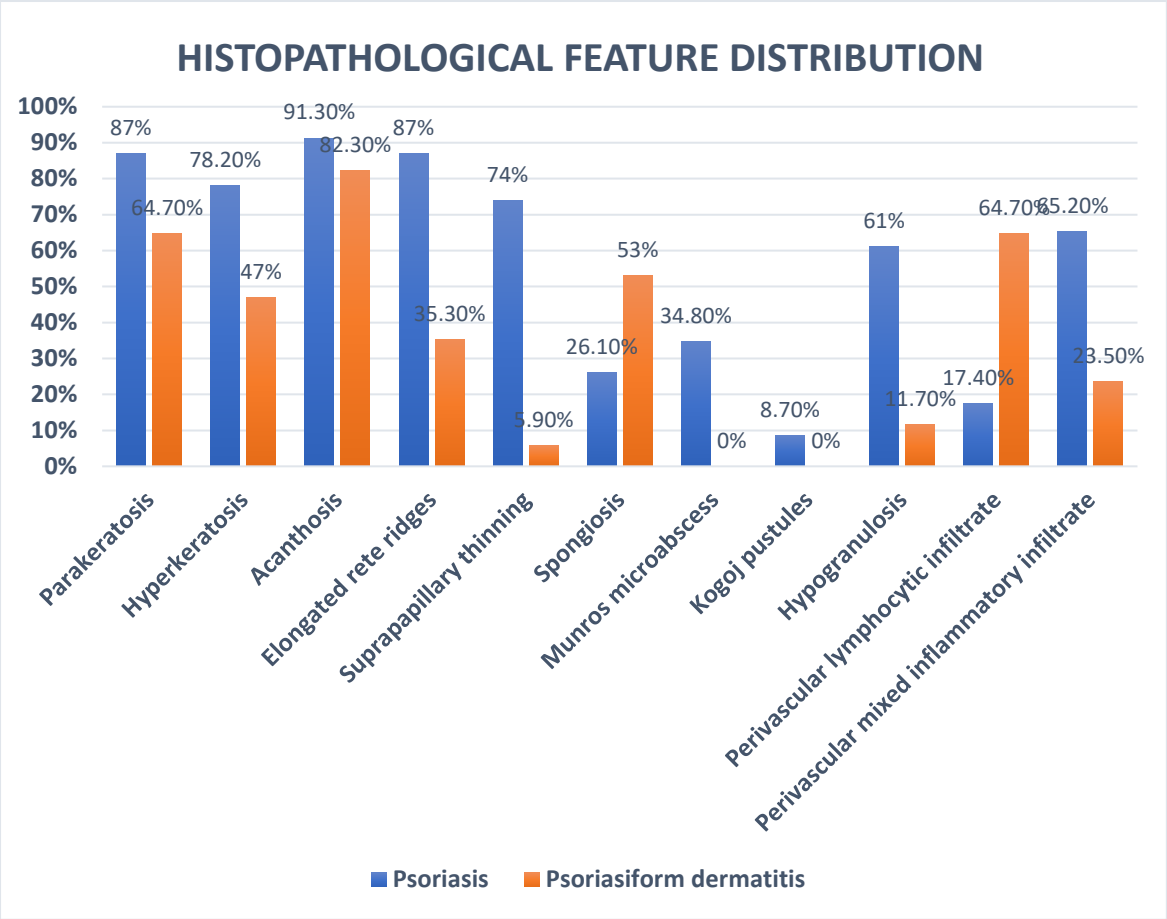
HISTOPATHOLOGICAL FEATURES DISTRIBUTION

Parakeratosis, hyperkeratosis, elongated rete ridges, suprapapillary thinning, spongiosis, Kogoj pustules, Munros microabscess, Hypogranulosis, and perivascular mixed inflammatory infiltrate were predominantly seen in Psoriasis and were statistically significant ($p<0.05$). The perivascular lymphocytic infiltrate was seen predominantly in Psoriasiform Dermatitis and was statistically significant ($p< 0.0001$). Acanthosis was seen in both Psoriasis and Psoriasiform Dermatitis and the difference was not statistically significant ($p<0.0965$)**. [IMAGE 3-10] [TABLE 8] [GRAPH 6]**

TABLE 8: HISTOPATHOLOGICAL FEATURES

HISTOPATHOLOGICAL FEATURES	PSORIASIS (%) OF CASES	PSORIASIFORM DERMATITIS (%) OF CASES	'P' VALUE
PARAKERATOSIS	87	64.7	<0.0001
HYPERKERATOSIS	78.2	47	<0.0005
ACANTHOSIS	91.3	82.3	<0.0965
ELONGATED RETE RIDGES	87	35.3	<0.0001
SUPRAPAPILLAY THINNING	74	5.9	<0.0001
SPONGIOSIS	26.1	53	<0.0002
MUNROS MICROABCESS	34.8	0	<0.0001
KOGOJ PUSTULES	8.7	0	<0.0032
HYPOGRANULOSIS	61	11.7	<0.0001
PERIVASCULAR LYMPHOCYTIC INFILTRATES	17.4	64.7	<0.0001
PERIVASCULAR MIXED INFLAMMATORY INFILTRATES	65.2	23.5	<.0001

GRAPH 6: HISTOPATHOLOGICAL FEATURES



Ki67 IHC staining

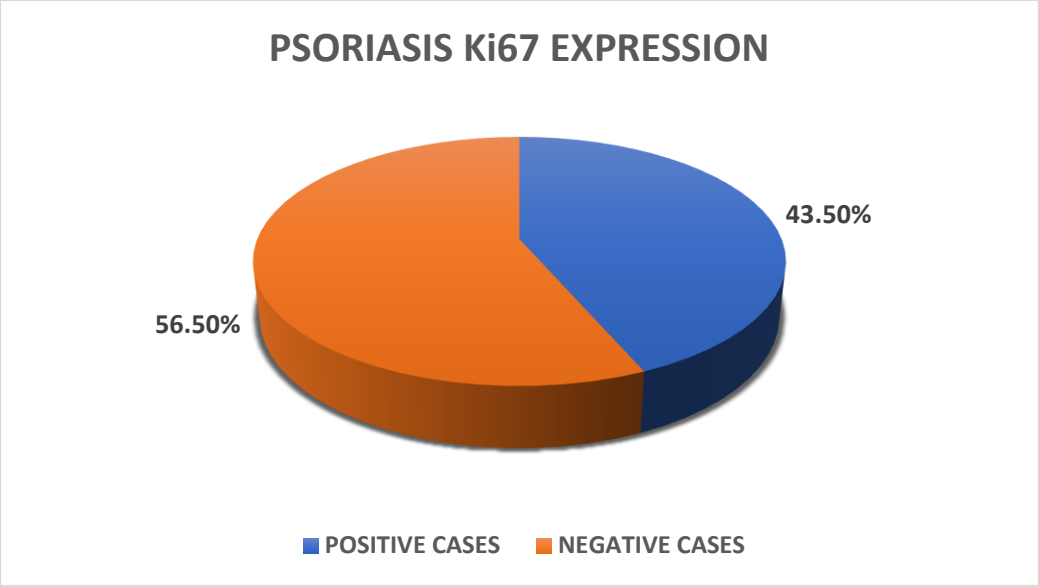
The positive Ki67 expression was assessed by brown-coloured nuclear staining in the epidermal cells. The cutoff taken in the present study was >25%.[13]

Out of the 23 Psoriasis cases, 10(43.5%) were positive for Ki67 expression. The mean Ki67 expression is 24.5% (±19.3). Out of 17 Psoriasiform Dermatitis only 1(5.8%) case was positive for Ki67 expression. The mean Ki67 expression in Psoriasiform dermatitis was 12.7% (±8.1). The expression of Ki67 was more predominant in Psoriasis as compared to Psoriasiform Dermatitis and thus statistically significant ($p<0.01$). **[IMAGE 11-16] [TABLE 9] [GRAPH 7,8]**

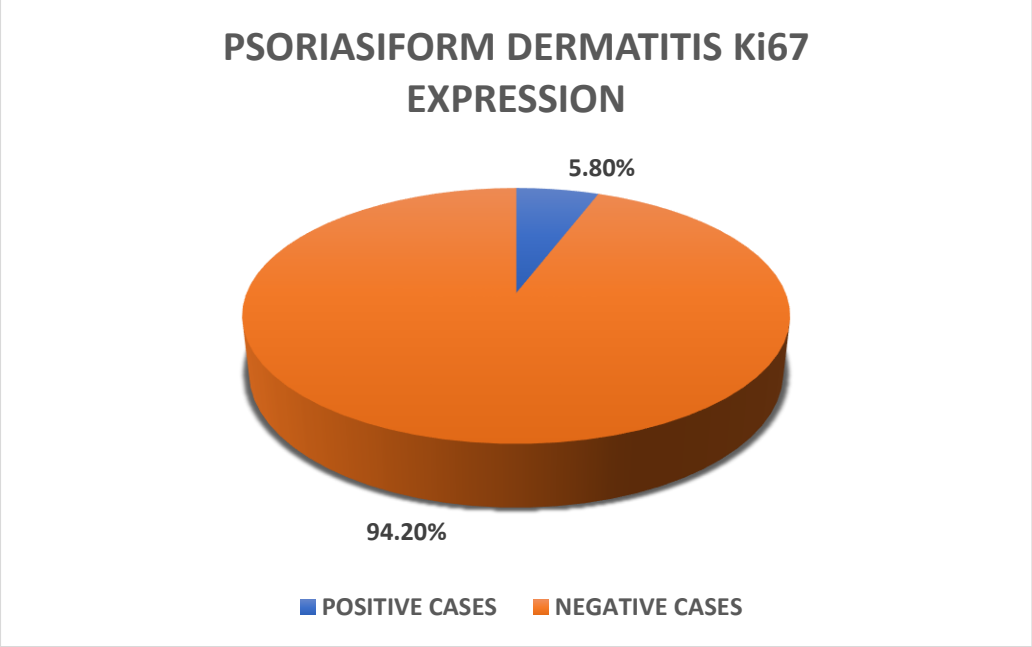
TABLE 9: KI67 IHC STAINING(N=40)

	PSORIASIS		PSORIASIFORM DERMATITIS	
	TOTAL	**PERCENTAGE**	**TOTAL**	**PERCENTAGE**
POSITIVE	10	43.5%	01	5.8%
NEGATIVE	13	56.5%	16	94.2%

GRAPH 7: PSORIASIS KI67 EXPRESSION



GRAPH 8: PSORIASIFORM DERMATITIS KI67 EXPRESSION



DISCUSSION

Psoriasis is a Chronic Inflammatory cutaneous hyperproliferative disorder.[1] Psoriasis and Psoriasiform Dermatitis clinically as well as histologically mimic each other.[13]Hence it becomes difficult to differentiate psoriasis from other psoriasiform dermatitis like Pityriasis rosea, Atopic dermatitis, Seborrheic dermatitis, Lichen Simplex Chronicus and a few others like Eczema, Prurigo nodularis and Pityriasis Rubra Pilaris along with Allergic Contact Dermatitis. [33,75]

This is one of the very few studies being conducted to study the expression of Ki67 in Psoriasis and Psoriasiform Dermatitis in India. A total of 40 cases were studied. Out of these 57.5%(n=23) were of psoriasis and 42.5%(n=17) were Psoriasiform Dermatitis. The Psoriasiform Dermatitis cases included were Pityriasis rubra pilaris, Prurigo nodularis, Lichen simplex chronicus, Pityriasis rosea and Allergic contact dermatitis. Borade S. et al studied 60 cases of an equal number of Psoriasis and Psoriasisform Dermatitis which were matched with gender and age in both groups.[57]Other similar study done by Mazaher Ramezani et al. included a total of 91 cases of which 60 were psoriasis and 31 were psoriasiform dermatitis.[13] Icen et al. studied almost 3105 subjects for 30 years and found out that out of 154 cases, 52.6% were psoriasis while 64.8% were psoriasiform lesions.[107]

Psoriasis is most commonly seen in the age group of less than 30 years.[33] In the present study, maximum cases of 52.1% (n=12) were seen in the age group of 19-30 years. In a study done by NL Gyanchandani et al., similar results of maximum cases of Psoriasis were seen in less than 30 years of age.[33]

In the present study, the mean age of Psoriasis cases was found 39.8 $\pm$ 21.4 years and the mean age of Psoriasiform Dermatitis was found to be 41.1 $\pm$ 21.4 years. Abdelsalam et al. found the

mean age in psoriasis to be 40.2 ± 15.8, and the mean age in psoriasiform dermatitis was 41.9 ± 17.2 and correlated with our findings.[4]

Out of 23 psoriasis cases present study showed 56.5% females while 43.5% were males, thus a mild female predominance was seen in Psoriasis. While in psoriasiform dermatitis 64.7% of cases were males as compared to females constituting 35.3%, with males being more affected in the case of Psoriasiform Dermatitis. Jayalakshmy et al. also found 65% of males in Psoriasiform dermatitis.[75] Studies by Gyanchandani, Dogra and Yadav, Icen et al. and, Abdelsalam et al. findings were not similar. [4,26,33,107]

We found, out of the total 23 psoriasis cases 65.2% clinically presented with Auspitzs sign, 82.6% with Silvery scales, 60.8% with both Auspitzs sign and Silvery scales, and 21.7% presented with nail pits. The p-value for all of these was < 0.0001 and statistically significant. 21.7% of cases of psoriasis presented with Koebner's phenomenon and the p-value for which was<0.0892 and was not statistically significant. None of the psoriasis cases showed thickened skin. Out of the 17 cases of psoriasiform dermatitis in the present study, 11.7% showed Auspitzs sign and Koebner's phenomenon respectively. 29.4% showed thickened skin. None of the cases showed nail pits and silvery scales. Singal et al. found Auspitzs sign, Typical scales and the presence of both typical scales and Auspitzs sign to be statistically significant in Psoriasis and

Gyanchandani et al. and Venna et al. found typical scales and Auspitzs sign to be statistically significant in Psoriasis.[33,108,109] These findings correlated with the present study.

We found 21.7% of Psoriasis cases with nail involvement, particularly nail pitting. Khandpur et al. found nail involvements including mostly nail pitting as well as subungual hyperkeratosis in 41% of the total 154 cases.[110] Another study by Chopra et al. found 23.4% of psoriasis cases with nail involvement. [111] These findings correlated with the present study.

In the present study out of 23 Psoriasis cases on histopathology 87% showed parakeratosis, 78.2% showed hyperkeratosis, 91.3% showed Acanthosis,87% showed elongated rete ridges, 74% showed suprapapillary thinning, 34.8% showed munros microabscess, 61% showed hypogranulosis and 65.2% showed perivascular mixed inflammatory cell infiltrate. Except for acanthosis, all these features had a 'p' value of <0.05 and were statistically significant. Psoriasiform dermatitis in our study included 17 cases of which histopathologically 64.7% showed parakeratosis, 47% showed hyperkeratosis, 82.3% showed acanthosis, 35.3% showed elongated rete ridges, 5.9% showed suprapapillary thinning and 11.7% showed hypogranulosis. 64.7% showed perivascular lymphocytic infiltrate and 35.3% showed spongiosis which were predominant features in psoriasiform dermatitis.

Gyanchandani et al. found munros microabscess and suprapapillary thinning to be statistically significant in Psoriasis ($p<0.05$) as compared to Psoriasiform Dermatitis.[33] Venna et al. found the

presence of suprapapillary thinning, kogoj pustules, munros microabscess and hypogranulosis to be more prominent in Psoriasis as compared to Psoriasiform Dermatitis ($p<0.05$).[109]A study

by Jayalakshmy et al. found acanthosis, parakeratosis, suprapapillary thinning, munros microabscess and hypogranulosis to be prominent in Psoriasis but did not compare the features with Psoriasiform Dermatitis.[75]

In our study, positive Ki67 expression was assessed by brown-coloured nuclear staining in the epidermal cells. The cut-off taken in our study was 25%.[13] Out of the 23 Psoriasis cases, 43.5% were positive for Ki67 expression with the mean Ki67 expression at 24.5% (±19.3). Out of 17 Psoriasiform dermatitis, 5.8% were positive for Ki67 expression with the mean Ki67 expression at 12.7% (±8.1). The Ki67 expression in Psoriasis was more than the Psoriasiform Dermatitis and was statistically significant ($p=<0.05$).

A similar study was done by Ramezani et al. where they studied Ki67, P53, along with CD34 expression in 60 psoriasis and 31 psoriasiform dermatitis in a total of 91 cases. They also used a similar method of Ki67 interpretation wherein they considered the cutoff for positive staining to be >25%. They found that 50% of psoriasis cases showed a positive Ki67 index with a mean Ki67 expression was 21.6 (±10) %. Of psoriasiform dermatitis, 71% showed positive Ki67 expression with a mean of 29 (±11.6) %. They found out that psoriasiform dermatitis showed higher expression of Ki67 as compared to psoriasis cases. [13] In the present study, the sample size was only 40 and also our findings did not correlate with the study by Ramezani et al.

Sezer et al. studied the expression of Ki67 in Psoriasis and Psoriasiform Dermatitis and found Ki67 to be significantly higher in Psoriasis as compared to Psoriasiform Dermatitis. Even though this study supports our study the method of Ki67 used by them to estimate Ki67 expression was not similar. They studied the ratio of Suprabasal to total epidermal cells positive for Ki67 and found the range of Ki67 expression in Psoriasis to be 77.1% - 92.4% and in Psoriasiform Dermatitis 21.0% - 73.3%. Their cutoff for the ratio was 75%.[71]

Abdelsalam et al. studied the Ki67 expression by brown stained nuclei of keratinocytes and counted them per 10 high power fields and then took the median and semi-quantitatively analyzed them by grading them into four groups, from group 0 to 3. The mean Ki67 expression in Psoriasis was 94.4 ± 11 and the range of expression was 75– 121, while the mean Ki67 expression in Psoriasiform Dermatitis was 21.1 ± 5.7 with the range of expression 10 – 28. This study correlated with our study in terms of Psoriasis showing more Ki67 expression as compared to Psoriasiform Dermatitis but the method they followed for Ki67 interpretation was different.[4]

Few of the others have studied the expression of Ki67 in Psoriasis and have compared it with normal skin.

Doger FK et al. studied the expression of Ki67 in psoriasis and normal skin. Ki67 interpretation was done by counting 500 keratinocytes at 40x magnification for three consecutive slides and an average of same was taken. They found Ki67 expression 18.12 (± 12.39) %. Thus, the results

were statistically significant showing Ki67 expression to be more in psoriasis as compared to normal skin.[72]

Prakashiny S et al. studied the clinical and histological correlation with the Ki67 expression. The method of Ki67 interpretation followed by them was the percentage of brown-coloured nuclear-stained keratinocytes which was labelled as positive staining. They found Ki67 expression to be 20.93%. They did not compare with psoriasiform dermatitis.[112]

Another study by Batinac et al. found Ki67 nuclear expression to be statistically significant than in normal skin.[113] Peng et al. found out that the Ki67 expression was higher in psoriasis vulgaris. Here they compared inflammatory linear verrucous epidermal nevus with psoriasis vulgaris, as both these conditions are difficult to differentiate clinically. [114]

LIMITATIONS

The sample size in the present study was less. The cases under each type of Psoriasiform Dermatitis were found to be less so making it difficult to come to the conclusion of expression of Ki67 in the case of Psoriasiform Dermatitis.

CONCLUSION

The present study showed the expression of Ki67 to be more in Psoriasis than the Psoriasiform dermatitis. The findings were statistically significant ($p<0.01$). Aspitzs sign, silvery scales and nail pits were more predominantly seen in Psoriasis than Psoriasiform dermatitis. In addition, histopathological features of parkeratosis, hyperkeratosis, hypogranulosis, suprapapillary thinning, elongated rete ridges, kogoj pustules, munros microabscess and perivascular mixed inflammatory cell infiltrate are more significant in Psoriasis ($p<0.05$). Thus Ki67 can be used objectively to differentiate Psoriasis from Psoriasiform Dermatitis in addition to the above-mentioned clinical and histopathological features in optimizing the treatment of Psoriasis as well as Psoriasiform dermatitis.

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ANNEXURE I

KAHERs

JNMC

BELAGAVI

INFORMED CONSENT FORM

Ki67 AS A DIAGNOSTIC INDICATOR IN DIFFERENTIATING PSORIASIS FROM PSORIASIFORM DERMATITIS A HOSPITAL BASED STUDY.

Name of Student/Principal Investigator:

Name of Guide/Co-Investigators:

Objective: 1. To study ki67 as a diagnostic marker to differentiate Psoriasis from Psoriasiform dermatitis as an Immunohistochemical marker.

2. To study the correlation of Ki67 with the clinical severity of Psoriasis.

Introduction: Psoriasis is a Chronic Inflammatory cutaneous hyperproliferative disorder which has to be differentiated from the spectrum of Psoriasiform Dermatitis as the treatment is different for both conditions.

Explanation of procedure: Under aseptic conditions skin biopsy is taken and then sent to histopathology lab for further evaluation.

Withdrawal from participation in the study: Participation in this study is voluntary. You will be free to decide whether to participate in this study or continue participation once enrolled. In case you decide to withdraw your participation, you are free to do so. However, please convey the decision to the principal investigator.

Possible benefits from participating in the study: You will/will not have nor get any benefits by participating in this study. The data gathered will help the population at large.

Possible risks from participating in the study: There are no risks involved in participating in this study.

Privacy and confidentiality: The information collected from you will be coded, to prevent any person from identifying you. Your identity will never be revealed. The data collected from you will be kept confidential and only processed or aggregated data will be used for publication.

Financial incentives: You will not receive any payment for participating in this study.

Authorization for publication of aggregated data: Results obtained after processing of the aggregated data will be published for scientific purposes and or presented to scientific groups. However, your identity will never be revealed.

Questions: In case of any questions with regard to this study, you are free to contact: "Name of student/PI, mobile number, email ID" If you have any questions or complaints with regard to your right as a study participant you may contact Dr Harsha Hegde, Chairperson, Ethical committee of JNMC, 0831-2473777 Extension 4052.

Legal rights: By signing this consent form, we are not waiving your legal rights.

CONSENT FORM

I voluntarily agree to take part in this study **Ki67 AS A DIAGNOSTIC INDICATOR IN DIFFERENTIATING PSORIASIS FROM PSORIASIFORM DERMATITIS A HOSPITAL BASED STUDY** by signing below. I may withdraw at any time. I am not giving up any legal rights by signing this form. My signature below indicates that I have read, or it has been read to me, this entire consent form and have had all my questions answered.

In case of queries during the study or in future you may contact the following person.

Principal Investigator:

Guide:

Name of the participant:

(signature/thumbprint)

ANNEXURE II-PROFORMA

Name: Case No:

Age: Date:

Address with phone number:

Occupation:

Chief Complaint:

Duration:

Preceding Symptoms before onset:

Clinical diagnosis:

Histopathological findings:

FINDINGS	PRESENT/ABSENT
Hyperkeratosis	
Parakeratosis	
Acanthosis	
Elongated rete ridges	
Suprapapillary thinning	
Spongiosis	
Munro microabscesses	

Spongiform pustules of Kogoj	
Hypogranulosis	
Perivascular lymphocytic infiltrate	
Perivascular mixed inflammatory infiltrate	

IHC findings:

RESULT	
Percentage of IHC positivity	

ANNEXURE III- TISSUE STAINING PROCEDURE

Tissue staining procedure on skin biopsies:

Haematoxylin and Eosin staining is done on the processed skin biopsy sections.

The procedure is as follows:

Chemical composition: Ehrlich's haematoxylin

Eosin 50

HEMATOXYLIN AND EOSIN STAIN – PROCEDURE

The tissue sections were deparaffinised in xylene for 5 to 10 minutes and then subjected to reducing grades of alcohol from 100% to 50%. These slides were then kept for 15 to 20 minutes in haematoxylin and then rinsed with tap water. 1% acid alcohol was used to differentiate (to remove excess of background staining). Bluing was done after placing the slides under tap water for 10 minutes. Counterstaining was done using eosin for 1 to 2 minutes. The slides were again rinsed in tap water. Dehydration was done followed by clearing and finally slides were mounted using DPX (Dibutylphthalate Polystyrene Xylene).

All histopathologically proven cases of psoriasis and psoriasiform dermatitis were subjected to Ki67 immunohistochemical marker staining, to study the presence of epidermal proliferation. The positive and negative controls were also taken into consideration.

ANNEXURE IV- PHOTOGRAPHS

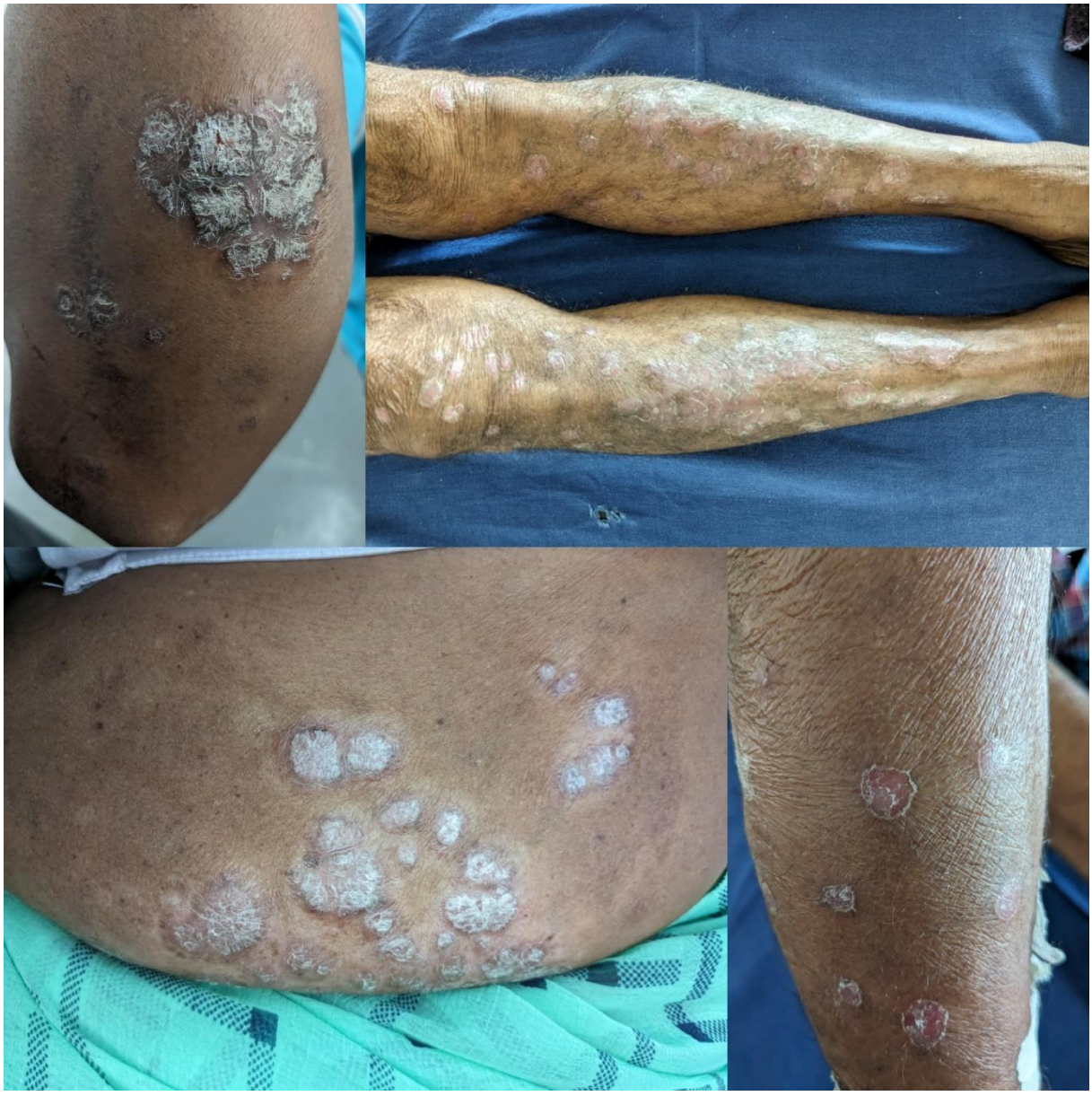

IMAGE 1. PHOTOGRAPH SHOWING CLINICAL PRESENTATIONS OF PSORIASIS CASES.

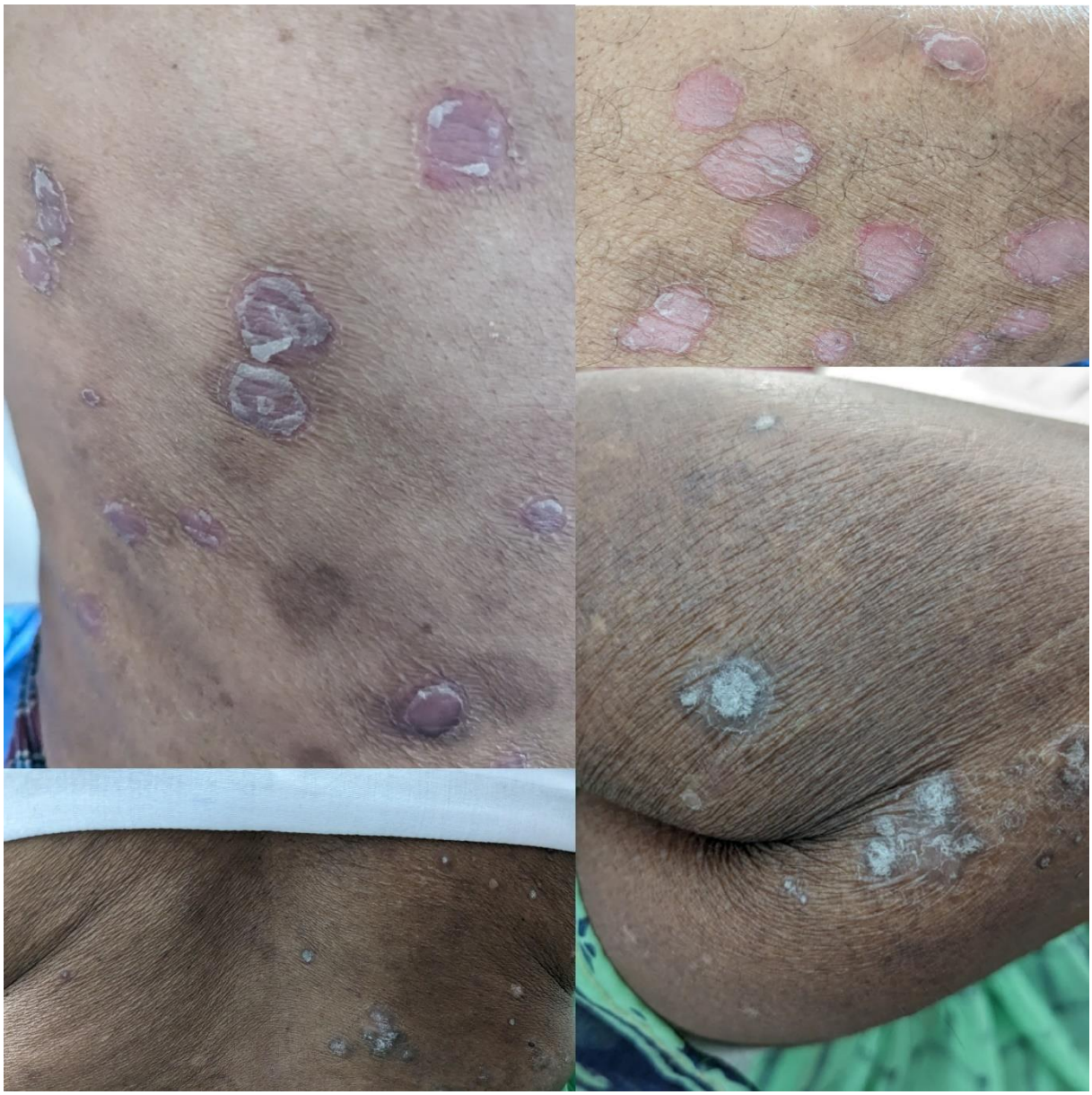

IMAGE 2. PHOTOGRAPH SHOWING CLINICAL PRESENTATIONS OF PSORIASIS CASES.

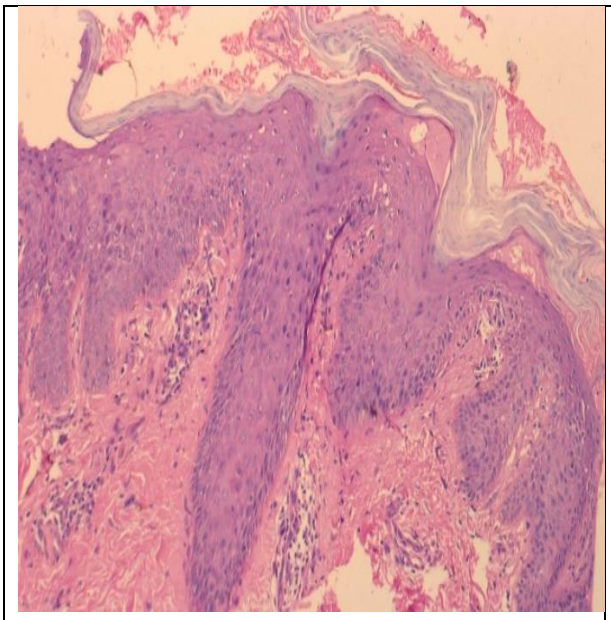

IMAGE 3. HISTOPATHOLOGY OF A CASE OF PSORIASIS (H&E, X100)

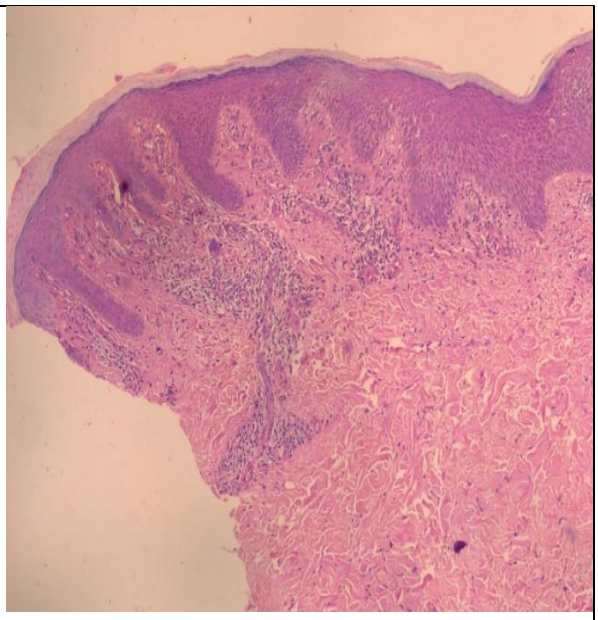

IMAGE 4. HISTOPATHOLOGY OF A CASE OF GUTTATE PSORIASIS (H&E, X40)

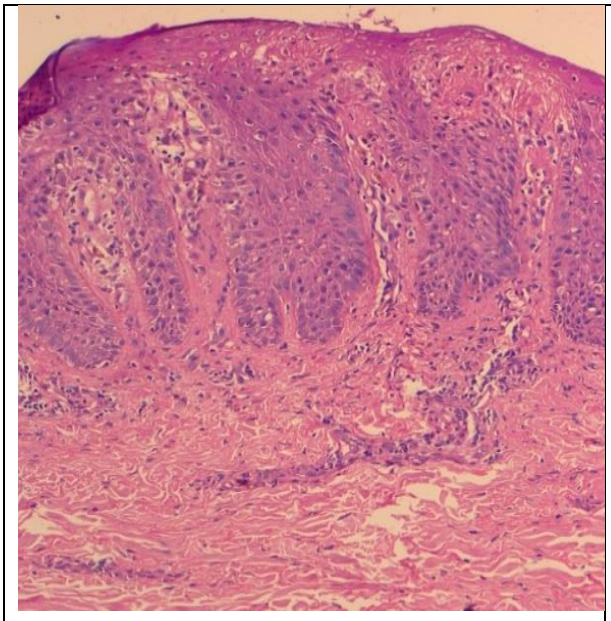

IMAGE 5. HISTOPATHOLOGY OF A CASE OF CHRONIC PLAQUE PSORIASIS (H&E, X100)

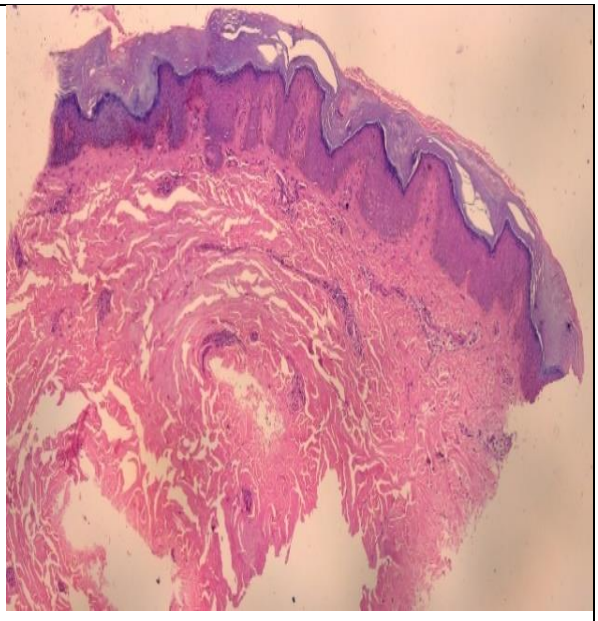

IMAGE 6. HISTOPATHOLOGY OF A CASE OF ALLERGIC CONTACT DERMATITIS (H&E, X40)

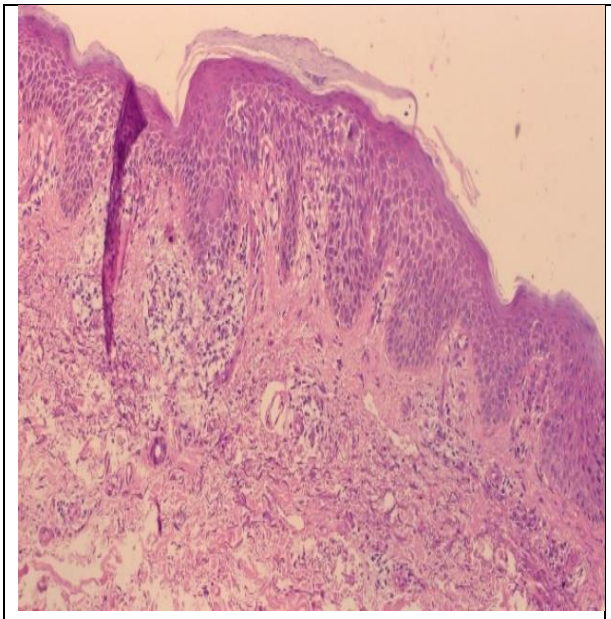

IMAGE 7. HISTOPATHOLOGY OF A CASE OF LICHEN SIMPLEX CHRONICUS (H&E, X100)

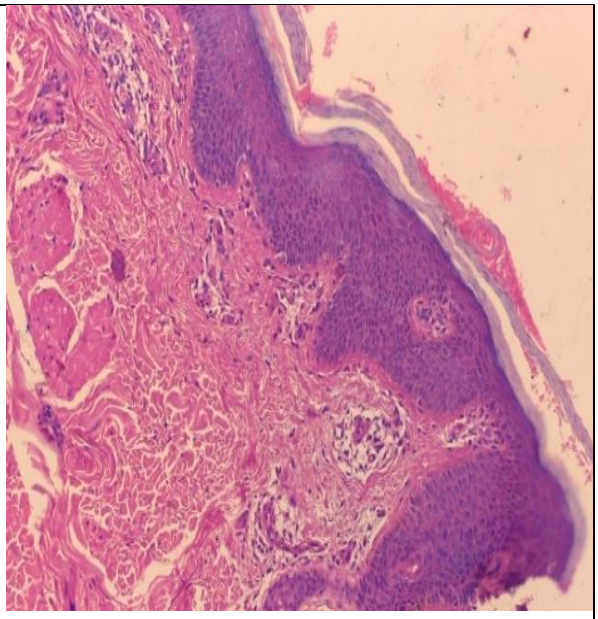

IMAGE 8. HISTOPATHOLOGY OF A CASE OF PITYRIASIS RUBRA PILARIS (H&E, X100)

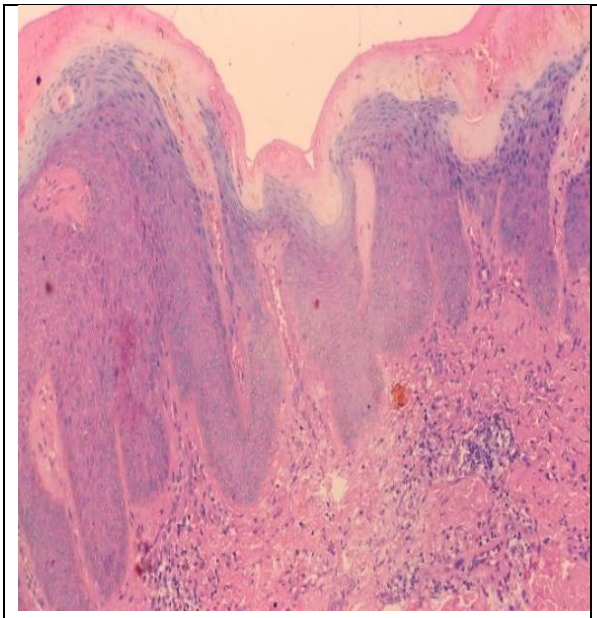

IMAGE 9. HISTOPATHOLOGY OF A CASE OF PITYRIASIS ROSEA (H&E, X100)

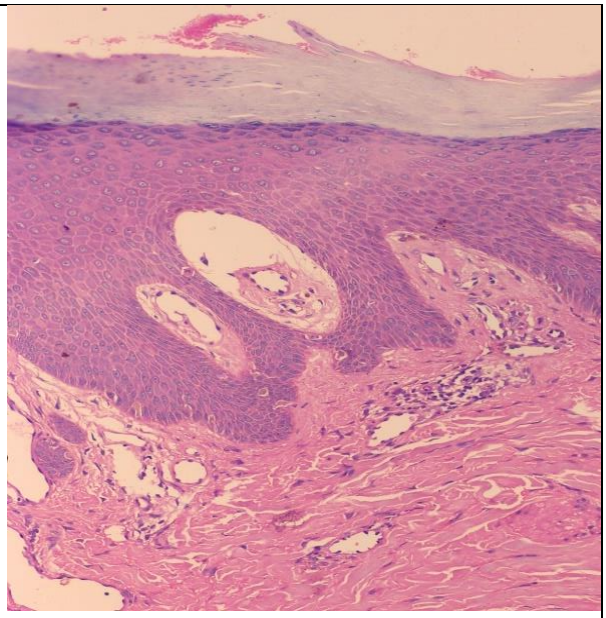

IMAGE 10. HISTOPATHOLOGY OF A CASE OF PRURIGO NODULARIS (H&E, X100)

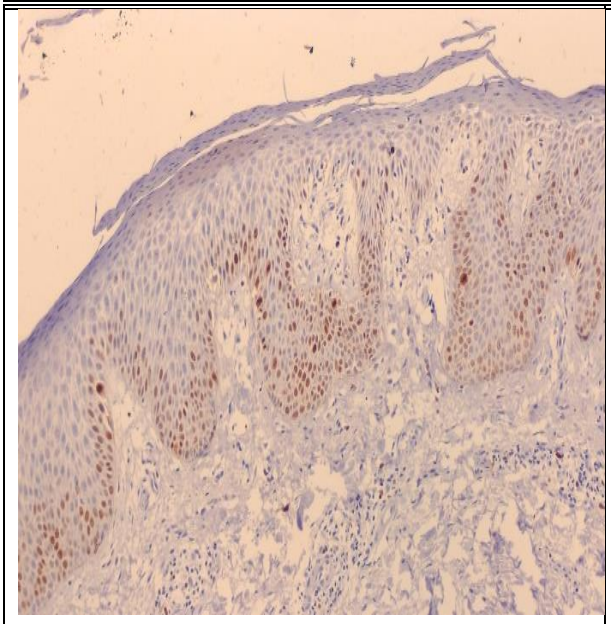

IMAGE 11. A CASE OF PSORIASIS SHOWING KI67 NUCLEAR POSITIVITY(X100)

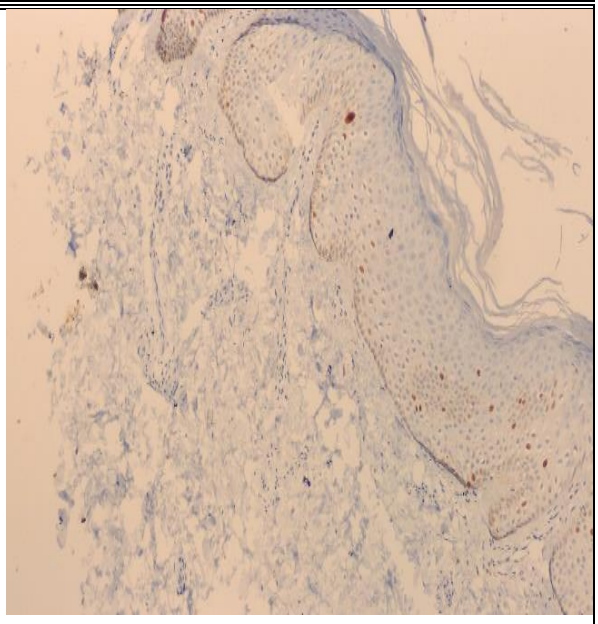

IMAGE 12. A CASE OF PITYRIASIS ROSEA SHOWING KI67 NUCLEAR POSITIVITY (X40)

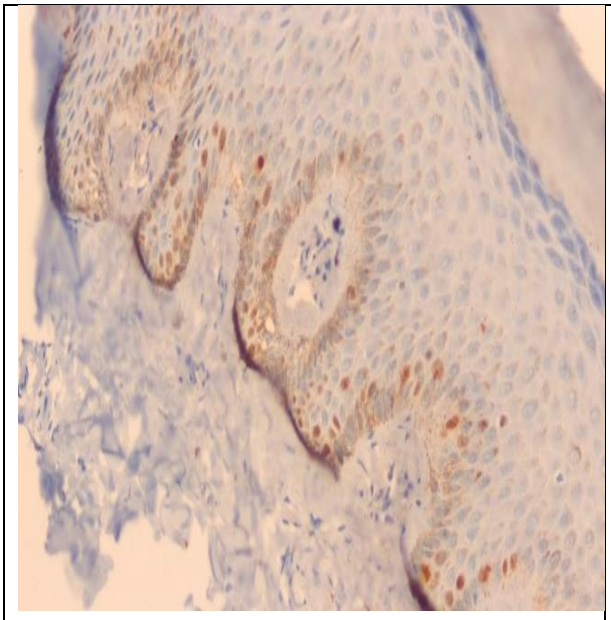

IMAGE 13. A CASE OF LICHEN SIMPLEX CHRONICUS SHOWING KI67 NUCLEAR POSITIVITY(X200)

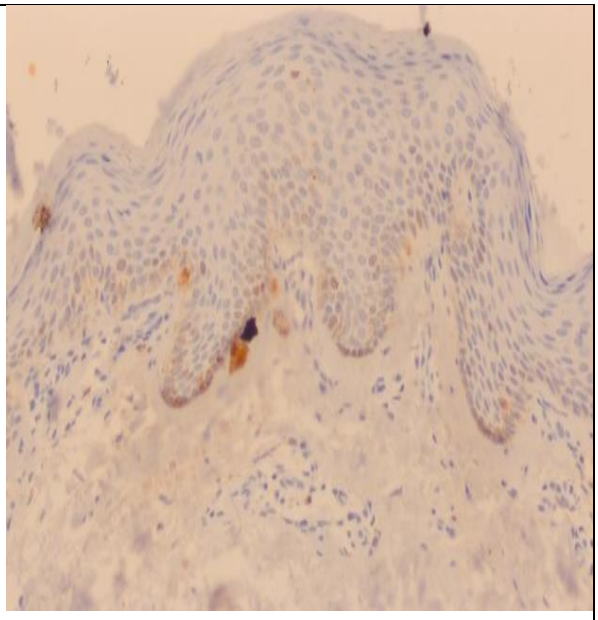

IMAGE 14. A CASE OF PITYRIASIS RUBRA PILARIS SHOWING KI67 NUCLEAR POSITIVITY(X100)

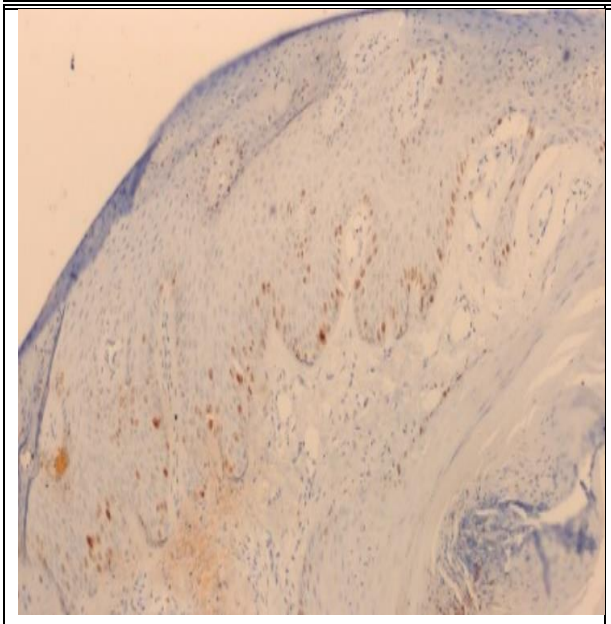	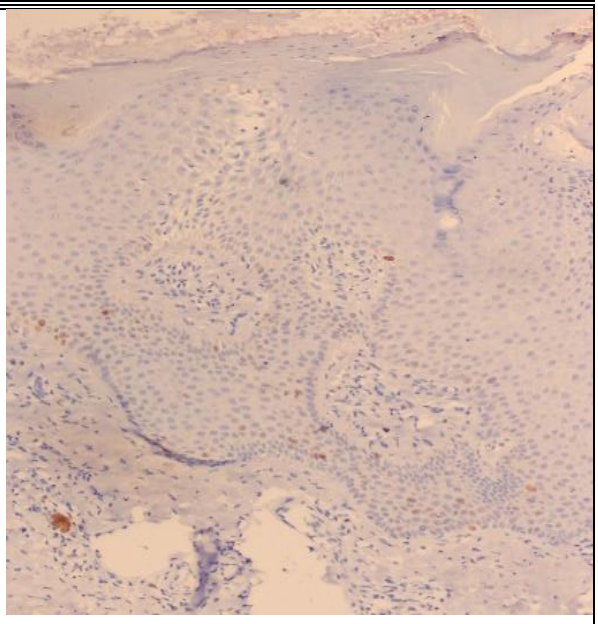
IMAGE 15. A CASE OF PRURIGO NODULARIS SHOWING KI67 NUCLEAR POSITIVITY (X100)	**IMAGE 16. A CASE OF ALLERGIC CONTACT DERMATITIS SHOWING KI67 NUCLEAR POSITIVITY(X100)**

ANNEXURE V-KEY TO MASTERCHART

PSO	**PSORIASIS**
G.PSO	**GUTTATE PSORIASIS**
C.P.PSO	**CHRONIC PLAQUE PSORIASIS**
PUS.PSO	**PUSTULAR PSORIASIS**
LSC	**LICHEN SIMPLEX CHRONICUS**
PRP	**PITYRIASIS RUBRA PILARIS**
P.ROSEA	**PITYRIASIS ROSEA**
PN	**PRURIGO NODULARIS**
ACD	**ALLERGIC CONTACT DERMATITIS**

ANNEXURE VI-MASTERCHART

NO	AGE	GENDER	DIAGNSIS	AUSPITZ SIGN	SILVER SCALES	KOEBNERS PH	BOTH AUSPITZ SIGN AND SILVER	THICKENED SKIN	NAIL PITS	PARA KERATOSIS	HYPERKERATOSIS	ACANTHOSIS	ELONGATED RETE RIDGES	SUPRAPAPILLART THINNING	SPONGIOSIS	CHECKERBOARD PATTERN	MUNRO'SMICRO ABCESS	KOGOJ PUSTULES	HYPOGRANULOSIS	HYPERGRANULOSIS	PERIVASCULAR LYMPHOCYTIC IN	PERIVASCULAR MIXED INFLAMMA	Ki67 EXPRESION(%)	Ki67 IHC INTERPRETATION
1	40	M	P.ROSEA	N	N	N	N	N	N	Y	Y	N	N	N	Y	N	N	N	N	N	Y	N	2	NEGATIVE
2	45	M	LSC	Y	N	N	N	N	N	N	Y	Y	Y	N	N	Y	N	N	N	N	Y	N	15	NEGATIVE
3	25	F	PN	N	N	N	N	N	N	N	Y	Y	N	N	N	N	N	N	N	Y	Y	N	21	NEGATIVE
4	60	M	PRP	N	N	N	N	N	N	Y	N	Y	N	N	Y	N	N	N	N	N	Y	N	6	NEGATIVE
5	22	M	LSC	N	N	Y	N	N	N	Y	Y	Y	Y	N	N	N	N	N	N	N	Y	N	9	NEGATIVE
6	52	F	PSO	Y	Y	N	Y	N	N	Y	Y	Y	Y	Y	N	N	Y	N	Y	N	N	Y	33	POSITIVE
7	19	F	PSO	Y	Y	N	Y	N	N	Y	Y	Y	Y	Y	N	N	N	N	Y	N	N	Y	45	POSITIVE
8	24	M	PN	N	N	N	N	N	N	Y	Y	Y	N	N	N	N	N	N	N	N	N	Y	12	NEGATIVE
9	19	M	PR	N	N	N	N	N	N	Y	N	Y	Y	N	N	N	N	N	Y	N	Y	N	20	NEGATIVE
10	45	F	PSO	N	Y	N	N	N	Y	Y	Y	Y	Y	Y	N	N	N	N	Y	N	N	N	31	POSITIVE
11	19	F	PSO	Y	Y	Y	Y	N	N	Y	Y	Y	N	Y	N	N	N	N	Y	N	N	Y	7	NEGATIVE
12	19	F	G.PSO	Y	Y	N	Y	N	N	Y	N	Y	Y	N	N	N	N	N	N	N	N	Y	48	POSITIVE
13	29	M	PSO	Y	Y	N	Y	N	Y	Y	N	Y	Y	N	N	N	N	N	Y	N	N	Y	49	POSITIVE
14	19	M	PSO	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	N	N	N	N	Y	N	Y	N	35	POSITIVE
15	73	M	PSO	N	N	N	N	N	N	N	Y	N	N	Y	Y	N	N	N	N	N	N	N	57	POSITIVE
16	36	M	PSO	Y	Y	Y	Y	N	N	Y	N	Y	N	Y	N	N	Y	N	Y	N	N	Y	10	NEGATIVE
17	20	F	ACD	N	N	N	N	Y	N	Y	Y	Y	Y	N	Y	N	N	N	N	N	Y	N	2	NEGATIVE
18	53	F	LPC	Y	N	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	Y	N	15	NEGATIVE
19	58	M	PSO	Y	N	N	N	N	N	Y	Y	Y	Y	Y	N	N	N	N	N	N	Y	N	2	NEGATIVE
20	20	M	ACD	N	N	N	N	Y	N	Y	N	Y	N	N	Y	N	N	N	N	N	N	Y	21	NEGATIVE
21	80	F	PSO	Y	Y	N	Y	N	N	Y	N	Y	Y	Y	N	N	N	N	Y	N	N	Y	58	POSITIVE
22	68	M	PSO	Y	Y	Y	Y	N	N	Y	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	49	POSITIVE
23	65	M	LSC	N	N	Y	N	N	N	Y	N	Y	Y	Y	N	N	Y	N	N	N	Y	N	28	POSITIVE
24	58	M	P.ROSEA	N	N	N	N	N	N	Y	N	Y	Y	N	Y	N	N	N	N	N	Y	N	14	NEGATIVE
25	92	F	LSC	N	N	N	N	N	N	Y	Y	Y	N	N	N	Y	N	N	N	N	N	N	2	NEGATIVE
26	33	F	C.PLAQUE.P	N	N	N	N	N	Y	Y	N	Y	Y	Y	Y	N	Y	N	Y	Y	N	N	1	NEGATIVE
27	41	F	PUS.PSO	N	N	N	N	N	N	Y	Y	Y	Y	Y	N	N	N	Y	Y	N	N	Y	3	NEGATIVE
28	20	F	PSO	N	Y	N	N	N	Y	N	Y	Y	Y	N	N	N	Y	N	N	N	N	N	8	NEGATIVE
29	23	M	PRP	N	N	N	N	N	N	N	N	Y	N	N	N	Y	N	N	Y	N	Y	N	20	NEGATIVE
30	19	F	PSO	Y	Y	N	Y	N	N	Y	Y	Y	Y	Y	N	N	N	N	Y	N	N	Y	35	NEGATIVE
31	60	F	ACD	N	N	N	N	Y	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	18	NEGATIVE
32	23	M	ACD	N	N	N	N	Y	N	N	Y	N	N	N	Y	N	N	N	N	Y	N	Y	11	NEGATIVE
33	41	F	PSO	N	N	N	N	N	N	Y	Y	Y	Y	Y	N	N	N	N	N	N	Y	N	18	NEGATIVE
34	52	F	PSO	N	Y	Y	N	N	N	Y	Y	Y	Y	N	N	N	N	N	Y	N	N	Y	7	NEGATIVE
35	88	F	PSO	Y	Y	N	Y	N	N	Y	Y	Y	Y	Y	N	N	N	N	Y	N	N	Y	8	NEGATIVE
36	50	F	ACD	N	N	N	N	Y	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	1	NEGATIVE
37	20	M	PSO	N	Y	N	N	N	N	Y	Y	Y	Y	Y	N	N	Y	Y	N	N	N	Y	15	NEGATIVE
38	26	M	PSO	Y	Y	N	Y	N	N	N	Y	Y	Y	N	N	N	N	N	N	N	N	Y	6	NEGATIVE
39	30	M	PSO	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Y	N	N	Y	N	N	N	N	Y	28	POSITIVE
40	28	M	PSO	Y	Y	N	Y	N	N	Y	Y	Y	Y	Y	N	N	N	N	N	Y	N	Y	12	NEGATIVE