Open Access

Ashy Dermatitis and Lichen Planus Pigmentosus: A Clinico Pathological Study in Republic of Yemen

Mohammed Abdul Qader Almalmi^{1*}

¹Consultant Dermatology and Assistant Professor of Dermatology, Sanaa University Medical School, Alkuiat University Hospital, Doctor AlMalmi Medical Clinic DAMC, Sanaa Republic of Yemen, Alhasabah Zone, Yemen

***Corresponding Author:** Mohammed Abdul Qader Almalmi, Consultant Dermatology and Assistant Professor of Dermatology, Sanaa University Medical School, Alkuiat University Hospital, Doctor AlMalmi Medical Clinic DAMC, Sanaa Republic of Yemen, Alhasabah Zone after Ahasabah Police Station near Alsalueen Mosque Masjed, Yemen; Email: maqma1952@gmail.com

Received Date: 13-01-2021, **Accepted Date:** 13-02-2021, **Published Date:** 20-02-2021

Copyright © 2021 by Almalmi MAQ. All rights reserved under CC BY-NC-ND. This is an open access article distributed under the terms of the Creative Commons Attribution License, which provides freedom to read, share, copy and redistribution of material in any of the medium, provided with the original author and source are credited.

Abstract

Background: Ashy Dermatitis (AD), or Ashy Dermatitis of Ramirez, F. Kerdel-Vegas and Erythema Dyschromicum Perstans (EDP) is a characterized by unknown origin which was reported first in EL-Salvador in 1957, later in Venezuela in 1961 (Latin America) and in the USA in 1966. In Japan it was diagnosed as Lichen Planus Pigmentosus in 1956.

Objective: The objectives of the study are:

1. To assess the clinical and histopathological characteristics of patients with ashy dermatitis and Lichen Planus Pigmentosus and define their differences or similarities of a study populations of 33
2. To find out the relation of socioeconomic status in Yemeni patients with Ashy Dermatitis and Lichen Planus Pigmentosus
3. To compare the prevalence of Ashy Dermatitis and Lichen Planus Pigmentosus in the Republic of Yemen with the other studies carried out in Latin America, North America, Europe, Japan and India

Patients and Methods: Thirty three Yemeni Patients, 11 females and 22 males, 6-70 years old presented with itchy and non-itchy gray-blue dark brown hypo-and hyperpigmented maculo-papular. Skin eruptions in the face, neck, trunk and upper and lower limbs, of several months

Almalmi MAQ | Volume 2, Issue 1 (2021) | JCMR-2(1)-024 | Review Article

Citation: Almalmi MAQ. Ashy Dermatitis and Lichen Planus Pigmentosus: A Clinico Pathological Study in Republic of Yemen. Jour Clin Med Res. 2021;2(1):1-26.

DOI: <http://dx.doi.org/10.46889/JCMR.2021.2102>

duration were studied. Comprehensive blood images, serological tests for syphilis, skin scraping for fungi, Wood's light and rheumatoid factor, stool and urine analyses showed no abnormalities. A skin biopsy with subsequent histopathological examination was done in all selected patients.

Results: The clinical data, investigations and the histopathological findings showed that 23 patients (5 females and 18 males) suffered from Ashy Dermatoses (AD) and 10 (6 females and 4 males) of Lichen Planus Pigmentosus.

Conclusion: 33 patients out of 26,324 dermatology out patients seen during (96-98) presented with Ashy dermatosis or Erythema Dyschromicum Perstans (0.087%) and Lichen Planus Pigmentosus (0.037%) were very rare in Al-Kuwait University Hospital Sana'a City, Republic of Yemen. These two diseases are different clinically but similar histopathologically. This study did not elicit exact etiological factors but racial, nutritional and environmental factors are suspected. Most of those patients were poor and working as farmers and street vendors and by during so were exposed to sunlight.

Keywords

Ashy Dermatoses; Erythema Dyschromicum Perstans; Skin; Yemen

Introduction

Ashy dermatosis (AD) or Erythema Dyschromicum Persians (EDP) is a pigmentary disorder earlier confused clinically and histopathologically with lichenoid reaction, Lichen Planus Pigmentosus. Ashy Dermotosis was first reported in Latin America, USA and Europe [1]. Lichen Planus Pigmentosus was described in Japanese workers/ in India and the Middle East and was known as lichen subtropicus. The etiological factors are not clear and unknown [2]. For the above mentioned reasons it is obvious that there is an overlap between the two diseases.

Ashy Dermatoses (AD)

Clinical features: Ashy Dermatoses or Erythema Dyschromicum Perstans is a chronic, disfiguring, occasionally pruritic and cutaneous hyperpigmentary disorder of an as yet unidentified etiology. No age or sexual predilection seems to exist. Typically, lesions vary in color from slate gray to lead colored and may vary in size from 3 mm to very large confluent patches measuring several centimeters in diameter. Individual lesions may be irregular or even polycyclic in shape and continue to grow slowly in size. Occasionally the lesions are surrounded by an erythematous and slightly elevated 1- 2 mm border and rarely may exhibit a linear distribution. These borders eventually disappear within several months [3]. Lesions also

may be surrounded by a pale halo that serves to accentuate the ashy color of the main body of the lesions, particularly in darker-skinned patients, however this observation is infrequent. The ash-colored maculae of EDP continue to increase slowly in number and although large areas of the body may be affected, the trunk, arms, neck and face are most commonly and symmetrically involved. The palms, soles, scalp, nails and mucous membranes are spared [4].

Laboratory Studies: Routine laboratory studies of the patients with EDP have been normal. These include complete blood and differential counts, erythrocyte sedimentation rate, serum chemistries, liver function tests, Wasserman test, quantitative protein, electrophoresis, serum immunoglobulins and antinuclear antibody titers. Routine chest x-rays, urine analysis, stool for ova and parasites, fungal cultures and rheumatoid factor were performed [5].

Histologic Characteristics: A thin epidermis commonly is observed. Discrete areas of follicular hyperkeratosis decreased basal layer melanin and - alteration of the dermoepidermal junction with melanin incontinence is seen. The accompanying inflammatory lympho-histiocytic infiltrate may be lichenoid or perivascular and is most pronounced in the upper portion of the dermis. Colloid bodies representing extruded degenerated epidermal cells frequently seen. Colloid bodies and melanophages have likewise been found in the clinically normal skin of patients with lichen planus [6].

Immunofluorescence Studies: IgM, IgA, IgC, C3, C4, fibrinogen and fibrin are deposited in the colloid bodies and in the dermo-epidermal junction [5].

Ultrastructural Findings: Electron microscopic findings are individually nonspecific and reflect the inflammatory nature of the condition as seen by light microscopy.

Characteristic Findings: It include desmosomal retraction, extensive keratinocytic alteration, widened intercellular spaces, vacuolar separation at the dermo-epidermal junction, basal laminar discontinuity, abundance of dermal melanophages and melanosomes containing fibroblasts and colloid bodies. Such ultra-structural changes have also been described in lichen planus [7].

Etiology: The cause of the AD or EDP is unknown. Various causes and mechanisms have however been suggested like climatic, alimentary and occupational actors. In the vast majority of cases no ingestants, inhalants or contactants have been implicated. AD showed remission after treatment of concurrent trichuriasis infestation with dithiazine iodide, associated with ammonium nitrate ingestion, environmental pollutants may be affecting predisposing individuals [8]. The histological resemblance between EDP and lichen planus is noteworthy and EDP may be a variant of lichen planus. The typical clinical and histological lesions of EDP were accompanied, preceded or followed by lesions of histologically confirmed lichen planus. Bullous lichen planus of the lower extremities appeared after the onset of the typical lesions of ashy dermatosis and lichen planus pigmentosus would be preferable to EDP. Perhaps the basal cells in these patients of EDP partially overcome the initial changes of the lichenoid reaction

so that in effect the clinical manifestations of EDP may represent an abortive lichen planus [9]. A possible immunologic etiology owing to the findings of a granular deposition of the IgM at the dermoepidermal junction and the lichenoid tissue reaction may reflect an immunologic attack on an abnormal nervoid clone of epidermal cells in a permissive host environmental setting. Clearly further investigation into the etiology and pathogenesis of the EDP reaction pattern is needed to clarify its nature and possible relationships to other disorders [10].

Differential Diagnosis: The most frequent confusion and controversy are with lichen planus pigmentosus/ which is characterized by hyperpigmentation dark brown maculae and a no characteristic distribution that predominates in exposed areas and flexor folds.

Along with the macules, papules and a reticulate pattern can sometimes be seen. Its course is characterized by exacerbation and remissions occasionally accompanied by pruritus. Pinta, in its early stage also Riehl's Melanosis or idiopathic eruptive macular pigmentation, all of which are prevalent in Latin America and which affect mainly lighter skinned people should also be taken into account for the differential diagnosis of ashy dermatosis. Ashy dermatosis also has been confused with confluent and reticulated papillomatosis of Gougerot and Carteaud.

Drug-induced dermatosis with residual hyperpigmentation and occupational dermatosis with exposure to heat or fire (caloric melanosis) must be considered [11].

Treatment: In general treatment of AD or EDP has been uniformly unsuccessful in either halting the progress of the condition or reversing the hyperpigmentation. Among the various modalities that have been tried are avoidance of sun exposure, use of sun blocking agents, chemical peels, broad- spectrum antibiotics, oral and Corticosteroids, oral vitamin therapy, chloroquine, griseofulvin and DMSO. All have been shown to be ineffective. It is recommended that patients however should be reassured of the benign nature of their conditions [12].

Lichen Planus Pigmentosus (LPP): Lichen planus pigmentosus also known as invisible pigmented lichen planus is a condition characterized by hyperpigmented dark brown macules in exposed areas and flexural folds without sex predominance [11].

Clinical Description of LPP: LPP is characterized by hyperpigmented dark macules with a non-characteristic distribution but is predominating in exposed areas and flexural folds. These macules occasionally have papules in a reticulate pattern. Exacerbations and remissions during its course are common and in some cases are accompanied by itching [13].

Histologic Features: Histopathologically LPP shows an atrophic epidermis with vacuolar degeneration of the basal cell layer. The dermis has a scarce lymphohistiocytic or lichenoid infiltrate and pigment incontinence with presence of melanophages can be found [13].

Differential Diagnosis of LPP: The most important differential diagnostic consideration of LPP is AD which affects mainly skin types IV to V, predominates in women and is localized on the

trunk and extremities. It is characterized by blue-gray hyperpigmented macules sometimes with an elevated active red border. It runs a chronic course and is insidious and occasionally shows associated pruritus. Most of the patients with AD are reported from Mesoamerica. Other considerations can be occupational dermatosis with hyperpigmentation, especially argyria, caloric melanosis and drug-induced dermatoses such as fixed drug eruptions or the pigmentary reactions to carbamazepine [14].

Etiology of LPP: The cause of LPP is unknown. However as in lichen ruber planus type XV hyper sensitivity reactions seem to play an important role in its pathogenesis and LPP frequently appears in patients on medications. Indian racial features present in Latin America seem to influence widespread distribution [8].

Treatment: No specific treatment is available for LPP. Multiple drugs have been used such as topical steroids and keratolytics. Some LPP has responded to a 10% aqueous solution of DMSO applied topically. Other drugs used with inconsistent results are griseofulvin, prednisolone, etretinate and chloroquine [15].

Pathogenesis of Ashy Dermatitis and Lichen Planus Pigmentosus as suggested [5,11]

1. Genetic predisposition increase of HLA-B*57:01/ HLA-A*31:01
2. Inborn error of glucose-6-phosphatase metabolism
3. The first epidermal change is an increase in the number of Langerhans cells in epidermis followed by epidermal cell death apoptosis or dropping off leading to formation of colloid bodies and accumulation of dermal cellular infiltrate and epidermal repair with hypergranulosis
4. The mechanism seems to be immunologically mediated. Lichen planus association with other autoimmune diseases as alopecia areata and vitiligo is reported. Many drugs as chloroquine, gold leads to lichenoid lesions. DIF IgM and C in colloid bodies act as filamentous sponge in which immunoglobulins are trapped. LP specific antigen has been demonstrated in st. spinosum and st. granulosum. Lichenoid Graft VS-Host Disease stimulates idiopathic lichen planus
5. The dermal infiltrate is of T-cells mainly helper cells

Literature Review:

The history of Ashy Dermatitis or Erythema Dyschromicum Perstans began in EL- Salvador with Ramirez's observations of several patients with peculiar grayish cutaneous discolorations of unknown etiology. Ashy dermatitis has been confused with confluent and reticulated papillomatosis [16]. The possibility of an underlying single cause of erythema perstans should be elucidated since a simple nosological approach to such a cutaneous disease is inadequate.

However the etiology of most cases remains idiopathic despite careful evaluation. It should always be emphasized that systemic infestations and malignancies have been associated with erythema perstans, particularly erythema chronicum migrans and erythema gyratum repens. Hellerstrom [17-19]. Five cases reported from Venezuela. They suggested classifying the disease as a new variant of Erythema Chromium Figuratum Melanodermicum. He introduced the descriptive term of erythema dyschromicum perstans. This chronic disease progresses slowly and leaves a permanent discoloration [20]. The lesions appear successively with no preceding symptoms. Except for occasional slight itching, they remain symptomless. Pigmented spots vary in color from deep blue-gray to ashy gray and from various shades of medium gray to pale gray, some having less color than normal skin. The lesions show no preference for exposed areas although they have not been observed on the palms, soles or scalp [21]. Early lesions often have slightly elevated margins about 1 to 2 mm in width. Their size may be small or large; their shape is oval, round, or irregular. Growth is by slow peripheral extension/ with coalescence forming large bizarre patterns. Poly cyclic outlines are common. Sometimes both hyperpigmentation and hypopigmentation develop in the same lesions. He demonstrated in to the Detroit Dermatological Society a 29-year- old white woman as a case for diagnosis. She exhibited brownish and blue macules on the trunk and proximal parts of the extremities. These features and the histopathological findings were consistent with that of ashy dermatosis [15]. It occurs frequently in adolescent and young men. Demonstrated a 14-year-old girl with oval, pigmented macules initially these were slightly erythematous. The persistent spots were located on the trunk and arms. The histology is, in their opinion, consistent with that of ashy dermatosis [22,23]. He demonstrated in New York a 7- year-old, girl with widely distributed small, grey color macules in her body. The light- microscopic picture was identical with the cases described above [24]. He described in detail the case of a young German girl with a pigmentary eruption that started with a transient erythematous phase. Histologically it was quite consistent with ashy dermatosis and these authors also found the hydropic degeneration so characteristic of the early lesions. The similarity to ashy dermatosis is discussed in the article/ but the authors were of the opinion that the clinical picture was not quite like that of the American cases [25]. At a conference in Germany demonstrated a 27-year-old man with a slate-gray pigmentary dermatosis quite similar to their 2 cases in their opinion. The pigmentary disorder under consideration is not, to their mind, an infrequent condition among the Indian population and has well-defined clinical and histological characteristics [26]. The fully developed case presents a striking clinical picture and the histological findings are characteristic although not path-gnomonic. In the active phase/ they are represented by vacuolization of cells in the malpighian layers, edema of dermal papillae and variable mild to moderate perivascular infiltration in the upper third of the cutis. This infiltrate consists of small round cells, histiocytes and macrophages filled with melanin granules. The late inactive stage resembles the late stage of incontinentia pigmenti with pigment in dermal macrophages. There are no systemic symptoms or known internal manifestations. The patients' age groups range from childhood and adolescence through

adulthood. The dermatosis affects both sexes and the etiology of erythema dyschromicum perstans is completely unknown [27]. Stated of 139 cases have been discovered so far including 58 from EL-Salvador nine from Venezuela and two from the United States (one American Indian and one Puerto Rican), the remaining cases were from Latin American countries. They had reported a patient from United States of America whose lesions regressed following treatment of a bowel infestation by *trichuris trichuris* (whip-worm) suggesting that patients might be an etiological factor [28]. The macular urticaria pigmentosa in a dark-skinned patient may mimic EDP. When the lesions are rubbed, a negative Darier's sign (absence of urticaria) would make urticaria pigmentosa less likely. Histologically, a relative scarcity of mast cells/when special mast cell stains are used would help to preclude this diagnosis. Mast cells may be nonspecifically found in perivascular infiltrates and mast cell counts may vary from one anatomic site to another in the same individual and with age, sex and race [29,30]. The erythema dyschromicum perstans is a cutaneous pigmentary dermatosis with a characteristic ultra-structural pathology. Changes observed were widening of intercellular spaces, desmosomal retraction, vacuolar changes and membrane- free clear spaces in both basal and prickly cells, discontinuity of the basal lamina and dermal melanophages. These ultra- structural changes, seen separately in various dermatoses, together clearly provide a consistent ultra-structural composite for erythema dyschromicum perstans [7]. They reported 11 cases of EDP more commonly in light-skinned individuals and the lesions are surrounded by an erythematous and slightly elevated 1 to 2-mm border and rarely may exhibit a linear distribution [9,31,4]. Histological features in the epidermis are a degeneration of basal cells, preservation or increase of granular layer orthokeratosis and damage to melanocytes. In the dermis lymphocytic infiltrate with tendency to invade the lower epidermal layers, capillary proliferation and participation, of histiocytes with formation of pigment macrophages are characteristic. His study to the lichenoid and poikilodermatous groups of lesions has added a relatively new subgroup, exemplified by erythema dyschromicum perstans and lichen pigmentosus. The question is raised, whether the recent increase of pigmenting dermatitis of various types is due to the reaction of the skin of predisposed individuals to some as yet unknown environmental contaminant. Tropical lichen planus (lichen planus actinicus) may be sunlight provoked lichen planus or may owe its characteristics to direct epidermal damage by ultraviolet rays. If glucose-6-phosphate dehydrogenase deficiency in lichen planus-prone individuals are confirmed a rational explanation for actinic lichen may be at hand. He noted that the black skinned individuals seemed to be not more than one might expect as post-inflammatory pigmentation from a variety of causes in a patient with a fair amount of natural skin pigment and the deposition of melanin in the dermal macrophages which caused the grayish or gray-blue discoloration [32]. The histological studies indicated that the clinically active lesions were associated with a lichenoid reaction. This reaction seems to subside by time and leave an atrophic epidermis with decreased melanocytic activity. The upper dermis contains significant amounts of melanin that for unknown reasons remains reformed. Direct immunofluorescence studies showed changes that are probably the result of an inflammatory process as in LP [6].

The possibility of sensitization to some membranous or cytoplasmic component during cell damage cannot be ruled out completely since similar antibodies can be detected in patients with extensive burns, toxic epidermal necrolysis and myasthenia gravis [33]. The indirect immunofluorescence in EDP differs from lichen planus by not showing nuclear affinity of immunoglobulins and by showing positive extra nuclear staining of basal cells. Ultra-structural findings were nonspecific, since basal cell vacuolization, colloid bodies and disruption of the basement membrane may be present in any disease in which damage to the basal cells occurs. Langerhans' cells were seen to be increased in number, although counts were not made [34]. The etiology of EDP remains unknown. Presumptive relationships include the fact that one case from Poland was associated with the ingestion of ammonium nitrate. The majority of patients have normal clinical and laboratory tests and no history of medication or ingestion of any chemical [35]. Studied clinically 40 Indian patients with the presence of symptomatic pigment macules; basal cell degeneration inflammatory infiltrates and histologically marked incontinence of pigment, he suggested its close resemblance to lichen pigmentosus as described by the Japanese workers. The finding of colloid bodies and clinical association with more typical varieties of lichen planus in a number of their patients prompted them to regard this entity as a variant of lichen planus and hence the term lichen planus pigmentosus [8]. The history of minimal symptoms coupled with photo-exacerbation of the eruption in their patient was highly suggestive of a disorder seen almost exclusively in Middle Eastern countries termed lichen planus subtropicus [36,37]. They reported two patients with a widespread macular ashy colored eruption. They fit clinically with the erythema dyschromicum perstans (ashy dermatosis). The prime event seems to be injury to the basal membrane zone [38]. Two additional light-skinned, blond individuals of northern European descent with erythema dyschromicum perstans suggesting that this unusual condition may be more widespread than is presently recognized. In fair- complexioned people/ deliberate tanning may lessen the disfigurement [39]. The EDP might be associated with LP and described five cases and compared light and affected skin. The results indicated that erythema dyschromicum perstans was clinically a characteristic disorder with lichenoid reaction in its active phase. This lichenoid reaction leads to a pronounced incontinence of pigment and to decreased numbers of melanocytes and of tyrosinase activity in the involved epidermis. These findings supported the suggestion that erythema dyschromicum perstans and lichen planus pigmentosus are possibly the same entity. Direct immunofluorescence and fine structural studies showed similar findings to lichen planus. Patients had low titer antibodies to extra-nuclear basal components [40,12]. The erythema dyschromicum perstans is a cutaneous pigmentary disturbance originally considered to be a variant of erythema perstans. The nosologic identity of erythema dyschromicum perstans has been changed repeatedly as the number of patients with concurrent EDP-like eruptions and lichenoid disorders had increased. They described women who had EDP for two years before the onset of classic lichen planus. The active lesions of LP gradually evolved into typical ashy-gray macules of EDP. This case provides further support for the

concept that EDP and EDP-like conditions should be classified, in certain instances, as erythema dyschromicum perstans variants of lichen planus [15].

One case of AD with spontaneous disappearance of the cutaneous lesions and associated this with endocrinopathy [24]. There was no identifiable cause even after thorough laboratory evaluation. Age did not appear to be a factor as their patients ranged from 5 to 58 years. Other series may become apparent with larger series of cases but none are evident now. The condition had been observed in American Indians, Latin Americans, whites and Negroes. Very fair skinned relatively non-pigmenting individuals may not be capable of producing the typical ashy gray color and the clinical findings in such individuals were as yet undocumented. The distinctive cutaneous pigmentary dermatosis, erythema adyschromicum perstans, clearly revealed characteristic ultra-structural pathological alterations. The cellular vacuolation, (liquefaction degeneration) seen by light microscopy of the basal cells had an ultra-structural counterpart. Ultra- structurally translucent areas devoid of organelles manifested this feature and they containing membrane bound vacuoles. The dilation of intercellular spaces was a feature observed also [41]. Areas of cellular separation with retraction of normal desmosomes alternatively to one cell or the other [42]. Normal basal cells may contain one or more vesicles thought to be lipid droplets, but the biochemical nature of these vacuoles was not known with certainty [43]. Using experimental vesiculation utilizing collagenases of epidermal cellular alterations induced by ultraviolet irradiation noted the appearance of both single and multiple vacuoles and membrane- free spaces in the cells of the basal and Prickle layers [44]. Basal cellular damage manifested by per-nuclear vacuoles, at times indenting the nuclear envelope. The vacuolar changes/ as well as the widening of intercellular spaces with desmosomal retraction, may represent epidermal cellular response to injury, whatever is its etiology. Melanin granules within dermal melanophages accounted for the hyperpigmentation manifested clinically as an ashy color. The discontinuity of the basal lamina could provide a route of regression for melanin granules from injured epidermal cells into dermal melanophages. The liquefactive degeneration may result in incontinence of pigment [45]. Asymmetric case of EDP was unilaterally affecting the left side of the trunk and left leg. They suggested a possible immunological etiology in their patient due to the fact that they found a granular deposition of IgM at the dermo-epidermal border and a positive rheumatoid factor test. They speculated that the lichenoid tissue reaction might reflect an immunological attack on an abnormal nevoid clone of epidermal cells in a permissive host-environmental setting [10]. The circumscribed dermal hypermelanosis referred to a group of cutaneous disorders with circumscribed blue, blue-gray, slate gray, or blue-black pigmentation, dermal melanocyte deposition (melanocytosis) and melanin in macrophages (melaninosis) were observed histopathologically. This group of disorders could be differentiated clinically from brown epidermal hypermelanosis by examination using Wood's light. The microscopic, his to chemical, immunofluorescent and ultra-structural finding in three cases of erythema dyschromicum perstans supported its classification in the group of circumscribed dermal

melanosis. Damage to epidermal basal cells gives rise to a cascade of events producing the ashy-gray color. The epidermal melanocytes in this disorder were morphologically distinctive and increased in number. Ultra- structurally, a direct interaction between melanocytes and lymphocytes was seen to be resulting in vacuolar degeneration of the dermal-epidermal junction, which resulted in incontinence of pigment. The dermal depth to which the pigment containing macrophages may extend was easily treated more than that found in post-inflammatory hyper pigmentation perhaps because of involvement of the appendageal structures. They classified the circumscribed and diffuse melanocytosis and melaninosis in the following two tables showed below (Table 1 and 2) [46].

➤ **Circumscribed acquired melanoses**

- Erythema dyschromicum prestans
- Lupus erythematosus
- Lichen planus
- Fixed drug eruption
- Incontinentia pigmenti
- Macular amyloidoses
- Pinta
- Riehl, S melanosis
- Facial melanoses
- Minocycline pigmentation
- Chronic nutritional insufficiencies
- Chlorpromazine

➤ **Diffuse acquired melanoses**

- Metastatic melanoma with melaninuria
- Hemochromatosis

➤ **Circumscribed congenital melanocytoses**

- Mongolian spots
- Blue nevus

➤ **Circumscribed acquired melanocytoses**

- Nevus of Ota
- Nevus of Ito
- **Diffuse acquired melanocytoses**
 - Carleton and biggs syndrome
 - Levene, S syndrome

Table 1: Classification of Dermal Pigmentation.

- **Circumscribed acquired hemosiderosis**
 - Stasis hemosiderosis
 - Schaumburg disease
 - Minocycline pigmentation
- **Diffused acquired hemosiderosis**
 - Hemochromatosis
- **Circumscribed acquired heavy metal pigmentation**
 - Mercury
 - Gold
 - Silver
 - Bismuth
- **Diffuse acquired heavy metal pigmentation**
 - Silver
- **Circumscribed acquired drug pigmentation**
 - Quinacrine, chloroquine
 - Chlorpromazine
- **B-Diffuse acquired drug pigmentation**
 - Quinacrine

Table 2: Non -melanin pigmentary disorders.

Ashy dermatosis or erythema dyschromicum perstans was a chronic, disfiguring occasionally pruritic, cutaneous hyperpigmentary disorder of an as yet unidentified etiology. No age or sex

predilection existed. Routine laboratory studies of patients with erythema dyschromicum perstans had typically been normal [5]. Erythema dyschromicum perstans had a lichenoid component, the characteristic lesion of the disease showed no clinical or histopathologic changes indicative of lichen planus in their opinion/ both the ultra-structural and immunofluorescent studies merely indicated that it is a disease in which prolonged injury to the basal layer of the epidermis occurs. Nevertheless, they found the changes observed in erythema dyschromicum perstans more closely related to fixed drug eruption than to lichen planus. They concluded that their female patient had erythema dyschromicum perstans presented by an upper gastrointestinal tract contrast investigation with a radio-dense dye [47]. Ashy dermatosis and lichen planus pigmentosus are two clinically different conditions, the former being found exclusively in specific population with certain similar racial, ecological and nutritional factors, but so far it had not been possible to prove that those factors exert any significant influence on its etiopathology. Lichen planus pigmentosus appears very frequently in patients with racial features other than those present in Latin America, which seems to influence its more wide spread distribution. Finally the histopathological findings in ashy dermatosis were similar with that of lichen pigmentosus. They studied clinically and histopathologically characteristics of 20 patients of ashy dermatosis and 11 patients of lichen planus pigmentosus. They found significant clinical differences between both dermatoses. There may association between ashy dermatosis and allergic contact dermatitis caused by cobalt. Melasma can be misdiagnosed as ashy dermatosis, post-inflammatory hyperpigmentary (history lacking) and caloric melanosis (history of long occupational exposure to heat sources, e.g. (Tortilla cooks)). Riehl's melanosis or idiopathic eruptive macular pigmentation, which are prevalent in Latin America and affect mainly lighter skinned people, should be also be taken into account for the differential diagnosis of ashy dermatosis. The pigmentary problems were one of the most frequent causes of dermatological consultation in the tropics. Their article dealt with diseases seen mostly in tropical countries (ashy dermatosis/ lichen planus pigmentosus) in which a combination of racial/ ecological/ nutritional and social factors all contributes. They observed that Ashy Dermatitis (AD) is clinically characterized by blue-gray hyperpigmented macules with a variable shape and size that sometimes present with an elevated active red border that leaves a residual hypopigmented halo. This dermatosis tends to be symmetrical and commonly affects the face, neck, trunk and extremities. Evolution is chronic, insidious and asymptomatic. The histopathological findings of the Active Border (AD) are a vacuolar degeneration of the basal cell layer, incontinence of pigment and lymphohistiocytic perivascular infiltrate occasionally with colloid bodies. In the active macules the incontinence of pigment predominates whereas the cellular infiltrate and vacuolar degeneration of the basal cell layer may range from minimal to intense. In addition they noted that Lichen Planus Pigmentosus (LPP) was characterized by hyper pigmented dark brown macules with a non-characteristic distribution but predominating in exposed areas and flexural folds. These macules occasionally had papules in a reticulate pattern. Exacerbation and remissions during its course were common and in some cases were accompanied by itching.

The histopathological picture of LPP showed an atrophic epidermis with vacuolar degeneration of the basal cell layer. In the dermis, a scarce lymphohistiocytic or lichenoid infiltrate and pigment incontinence with melanophages can be found [11,13,48].

Patients and Methods

Study Area

This study was performed in Al-Kuwait University Hospital, which lies in the west zone of Sana'a city close to Sana'a University. It has 200 beds for all medical disciplines except for dermatology, which comprises only two Dermatology out Patients Departments (D.O.P.D.). In addition there is main laboratory for the investigations of hematology, microbiology, pathology and serology.

Study Populations

There are two groups: 23 cases of ashy dermatosis (18 males and 5 females, 6-60 years old) and 10 cases of lichen planus pigmentosus (6 males and 4 females, 6-70 years old). The patients coming from two main tribes Hashed and Bakeel. Most Yemeni peoples working in the agricultural sector as farmers and living in small and large houses on the top of mountains built with stones. The non-employers are more than employer and the poverty was limited in which the poors have no cattle and ships or any source of income. Their racial characters belong to the skin Type III.

Study Design

Ashy dermatosis or (EDP) is a chronic disfiguring cutaneous hyperpigmentary disorder. No age or sexual predilection seems to exist; Typically lesions vary in color from slate gray to lead colored and may vary in size from 3mm to very large confluent patches measuring several centimeters in diameter. LPP also known as invisible pigmented lichen planus is a condition characterized by hyperpigmented dark brown macules in exposed areas and flexural folds without a sex predominance.

This study used the descriptive prospective method. The sample size was 33 cases out of 26,324 dermatological cases attended in Al-Kuwait University Hospital (Sana'a). Out of the 33 cases 23 and 10 cases were screened as ashy dermatosis and LPP respectively. Twelve out of 23 patients with ashy dermatosis manifested clinically with blue-gray hyperpigmented macules with active red borders surrounded by a hypopigmented halo. The distribution of these macules is on the face, neck and trunk, upper and lower extremities. These macules are asymptomatic and symmetrical with chronic and insidious course. 10 patients of lichen planus pigmentosus manifested clinically with dark-brown pruritic papules with reticular pattern in the sun-exposed areas. The course was chronic with relapses and remission. The clinical features are shown in the following three tables.

The expected clinical Features seen in patients (n=33) with Ashy Dermatitis and Lichen Planus Pigmentosus [23,10].

Clinical Features	Ashy Dermatitis	Lichen PP
Hyperpigmented macules	Blue gray	Dark-brown popular+/0
Active red border	+/0	0
Residual hypopigmented halo	+/0	0
Reticular pattern	0	+/0
Distribution	Symmetric	Asymmetric
Non characteristic		
Affected areas	Face, neck, trunk upper and lower extremities	Sun exposed areas
Course	Chronic, insidious	Chronic relapses and remission
Associated pruritus	0	+/0
0 = absent; +/- = occasional		

Table 3: Clinical features seen in patients.

Histological Features	Ashy Dermatitis	LPP
Thinned epidermis	+	+
Hyperkeratosis	+	+
Hypergranulosis	0	+
Basal cell vacuolization	+	+
Colloid bodies	+/-	+/-
Lymphohistiocytic perivascular infiltrate	+	+
Lichenoid infiltrate	0	+/-
Scarce / absent cellular infiltrate	C	-
Incontinence of pigment and melanophages	+	+

+ = Present; 0 = absent; +/- = occasional; c = non-active ashy colored area only

Table 4: Histopathological characterized of specimens taken from 33 patients.

Tools and Instruments

Skin scraping is a simple method for investigation by using the scalpel to scrap the scales from the skin lesions. This scraping test was used to exclude a superficial dermatophytosis. Addition of a drop of potassium hydroxide (KOH 20%) preparation was done in all 33 cases on the scales and left in the glass slide for 20 minutes and examined under the light microscope for all the 33 cases. The specimens from the stool, was immersed with normal saline 10% in a glass slides for all the 33 cases and examined under the light microscope. The urine of the 33 cases was put in the glass tubes and centrifuged for five minutes and the precipitates examined under the light microscope. Serological tests for syphilis, either non-specific (Wassermann and venereal disease reagent level) or specific (Treponema pallidum hemoagglutination test) were performed. Those tests were done by addition of the reagent to drops of the blood serum of 33 cases in glass slides and the agglutination noted if occurred after five minutes. The blood sample was taken from the 33 cases and examined for count of red blood cells and the level of hemoglobin. The blood serum of the 33 cases was added to the rheumatoid reagent and examined to detect the rheumatoid factor. Wood's light was used for the detection of a superficial derma tophytosis certain fungi reflect a special color according the type of fungi. This test was used for all the skin lesions of 33 cases. Skin biopsies were done under local anesthesia with 5% xylocaine. The shaving, elliptical incision with scalpels and punch biopsy methods were used. The specimens were put in bottles filled with 20% formaline and sent to the pathological laboratory to be stained with Hematoxylin and Eosin.

Results

Table 5 shows the characteristics of the studied 33 patients: 10 cases of LPP and 23 cases of ashy dermatosis. In regards to the occupation one patient with LPP was an employer. The employer was one case (10%) of LPP. The farmers were 2 cases (20%) in LPP and 10 cases (43%) of ashy dermatosis. The street vendors were 5 cases (50%) of LPP. There were 2 poor cases (20%) of LPP and 10 poor cases (43%) in ashy dermatosis. There were 7 cases of LPP (70%) from Hashed tribe and 3 cases (30%) from Bakeel. There were 13 cases (56%) of AD from Hashed tribe and 10 cases (43%) from Bakeel. The skin scraping for fungi showed no hyphae or spores and Wood's light was normal. The hemoglobin was reduced in one case of LPP (10%) 5 cases of EDP (21%) and red blood cells reduced in one case of LPP (10%) and in 5 cases of EDP (21%). The serological tests for syphilis, rheumatoid factor were normal. The stool analysis revealed no intestinal worms and urine analysis was normal.

Fig. 1 shows that in the 23 cases with ashy dermatosis (EDP), 78% were men (N=18) and 22% women (N=5). Fig. 2 shows distribution per sex; in lichen planus pigmentosus (LPP), six were male patients (60%) and four female (40%). Table 2 shows that the average age of onset was 18 years (range 6-60 years) in AD, in contradistinction to the onset of 47 years (range 12-70 years) in LPP. The P- value is less than 0.001 indicating the high significance with relation to age there is no statistical difference.

Table 7 shows that the analysis of cases with relation to sex shows no significant difference (P-value >0.05) in LPP and AD.

Table 8 shows that the distribution of skin lesions in 23 AD cases. 78% showed a localized distribution (affecting one body area only) and in 22% it was generalized (affecting more than one body area) in 6 cases (22%)/ in the face 2 cases (8%) upper trunk in 1 patient (4%) and neck in 1 case (4%). The lower extremities were affected in only one patient (4%) and upper extremities affected in one case (4%). Distribution of LPP skin lesions was localized in three cases (30%) mainly in the face. In seven cases (70%) with generalized dermatosis, the mainly affected areas were face in two cases (20%). The neck is affected in three cases (30%), upper extremities in two cases (20%) / and symmetrical distribution in ten. cases (100%).

Table 9 shows that ashy - colored macules were observed in 12 cases (52%)/ and in the remaining 11 patients the macules were gray - blue and blackish - brown (48%). Only 11 patients (48%) presented patches with elevated border. In lichen planus pigmentosus/ the macules were black - brown/ in 3 cases (30%) and violet blue in 7 cases (70%) / irregularly shaped, with ill - defined borders and lichenoid papules in 3 cases (30%). All the cases of ashy dermatosis were asymptomatic with a course of 3 - 8 months. The most cases of LPP were pruritic with remission and exacerbation.

Table 10 shows that the histopathological findings of ashy dermatosis which were hyperkeratosis in 12 cases (52%), focal thinned epidermis in 16 cases (70%), focal basal vacuolization 18 cases (78%), focal perivascular infiltrate in 22 cases (91%) and dermal pigmentary incontinence in 23 cases (100%) . In LPP, hyperkeratosis was seen in 10 cases (100%), focal thinned epidermis in 8 cases (80%), focal basal vacuolization in 9 cases (90%) / focal perivascular infiltrate in 9 cases (90%) and dermal pigmentary incontinence in 10 cases (100%).

The data analysis in the Tables 5, 6 was done by SPSS computer program while the data in Tables 5-10 was done manually.

Characteristics	LPP (n=10)	Ashy Dermatitis (n=23)
Occupation		
Employers	-10%	0%
Farmers	-20%	10 (43%)
Street vendors	-50%	-

Almalmi MAQ | Volume 2, Issue 1 (2021) | JCMR-2(1)-024 | Review Article

Citation: Almalmi MAQ. Ashy Dermatitis and Lichen Planus Pigmentosus: A Clinico Pathological Study in Republic of Yemen. Jour Clin Med Res. 2021;2(1) :1-26.

DOI: <http://dx.doi.org/10.46889/JCMR.2021.2102>

Non employers	0%	3 (13%)
Economic status		
Poor	-20%	10 (43%)
Tribes		
Hashed	-70%	13 (56%)
Bakeel	-30%	10 (43%)
Investigations		
Stool	0%	0%
Urine	0%	0%
Serological tests		
For Syphilis	0%	0%
Ruematoid Factor	0%	0%
Wood's light	0%	0%
Blood Count	Normal	Normal
Red Blood Cells	Reduced in 1 Case (10%)	Reduced in 1 Case (21%)
Hemoglobin	Reduced in 1 Case (10%)	Reduced in 1 Case (21%)
Skin Scraping For Fungal elements	0%	0%

Table 5: Characteristics of the study populations.

Diagnosis	N	Mean Age	Standard deviation	SE of Mean	t-value	P value
Ashy Dermatositis	23	18.1	13.3	2.8	-4.3	< 0.001
Lichen Planus Pigmentosus	10	47.7	17.1	5.4		

Table 6: Ashy Dermatositis and Lichen Planus Pigmentosus distribution per age.

Diagnosis	Sex					
	Male	Female	Total	Chi-square	Degree of freedom	P value
Ashy Dermatositis	18	5	23	1.2	1	>0.05
Lichen Planus Pigmentosus	6	4	10			

Total	24	9	33			
-------	----	---	----	--	--	--

Table 7: Ashy Dermatitis and Lichen Planus Pigmentosus distribution per sex.

Localized Type		
Localized+	Ashy Dermatitis (n=23)	Lichen Planus Pigmentosus(n=10)
Face	17/(78%)	3/10(30)
Abdomen	0/23 (0%)	0/10(0%)
Distribution of Disseminated Type		
Dissemination +	Ashy Dermatitis (n=23)	LPP(n=10)
Face	2/23(8%)	2/10(20%)
Neck	1/23(4%)	3/10(30%)
Trunk	1/23(4%)	0/10(0%)
Upper extremities	1/23(4%)	2/10(20%)
Lower extremities	1/23(4%)	0/10(0%)
Symmetrical Type		
Symmetry	Ashy Dermatitis(n=23)	LPP(n=10)
Symmetrical	0/23(0%)	10/10(100%)
Asymmetrical	20/23(80%)	0/10(0%)

Table 8: Distribution of lesions in Ashy Dermatitis and Lichen Planus Pigmentosus.

Findings	Ashy Dermatitis (N=23)	Lichen Planus Pigmentosus (N=10)
Macules (color) Blue gray	12/23(52%)	0
Ashy brown	11 /23(48%)	0
Brown - black	0	3/10 (30%)
Violet- blue	0	7/10 (70%)
Active red border	11/23(48%)	0
Lichenoid papules	0	3 / 10 (30%)
Pruritus	0	5 /10 (50%)

Table 9: Morphology of lesions in Ashy Dermatitis and Lichen Planus Pigmentosus.

Findings	Ashy Dermatitis(N=23)	LPP (N=10)
Hyperkeratosis	12/23(52%)	10/10 (100%)

Focal Thinned epidermis	16/23(70%)	8 / 10 (80%)
Focal Basal Vacuolization	18/23(78%)	9/10 (90%)
Focal Perivascular infiltrate	22/23(91%)	9 / 10 (90%)
Dermal pigmentary incontinence	23/23 (100%)	10/10 (100%)

Table 10: Histopathology of specimens taken from 33 patients with Ashy Dermatitis and Lichen Planus Pigmentosus.

Figure 1: Large Erythematous plaques in the face of old woman Lichen planus pigmentosus.

Figure 2: Small Erythematous plaques in the face of young boy Lichen planus pigmentosus.

Figure 3: Oval well defined Erythematous skin eruption in the face Erythema Dyschromicum Perestans (EDP) Ashy D.

Figure 4: Oval well defined Erythematous skin eruption in the face Erythema Dyschromicum Perestans (EDP) Ashy D.

Figure 5: Oval well defined Erythematous skin eruption in the face Erythema Dyschromicum Perestans (EDP) Ashy D.

Figure 6: Histopathological findings of Lichen Planus Pigmentosus Focal Thinned epidermis, Focal Basal Vacuolization, Focal Perivascular infiltrate and dermal pigmentary incontinence.

Figure 7: Histopathological findings of Ashy dermatosis (Erythema Dyschromicum Perestans) showed Hyperkeratosis, Focal Thinned epidermis, Focal Basal Vacuolization, Focal Perivascular infiltrate and dermal pigmentary incontinence.

Discussion

The patients in ashy dermatosis and lichen planus pigmentosus are working farmers and street vendors. They were exposed to sunlight a long time without protection. The investigations in

this study as stool, urine analysis/ skin scraping/ Wood's light examination, rheumatoid factor/ and serological tests for syphilis are negative and normal. Those characteristics are perhaps related to the racial, nutritional and environmental etiological factors of EDP and LPP. Most authors [1,11] considered the causes of EDP still unknown. In the vast majority of cases no ingestants, inhalants and contact ants have been implicated. One case of AD has been reported, which showed remission of activity after treatment of a concurrent trichuriasis infestation with dithiazine iodide [49]. Another case of ashy dermatosis associated with ammonium nitrate ingestion has been reported [50]. An unidentified set of environmental pollutants may be affecting certain predisposed individuals. The histological resemblance between EDP and lichen planus pigmentosus is noteworthy [51]. An attractive hypothesis proposed that EDP is actually a variant of lichen planus. In nine of the 40 patients they studied the typical clinical and histological lesions of EDP were accompanied preceded or followed by lesions of histologically confirmed lichen planus. In two other patients, bullous lichen planus of the lower extremities appeared within 1 year after the onset of the typical lesions of ashy dermatosis elsewhere on their bodies. These investigators therefore felt that the term lichen planus pigmentosus would be preferred to EDP [52]. Agreeing with the conclusions speculated that, perhaps, the basal cells in these patients partially overcome the initial changes of the lichenoid reaction, so that, in effect, the clinical manifestations of EDP may represent an abortive lichen planus reaction [52,12]. A possible immunologic etiology in their EDP patients owing to the deposition of IgM at the dermoepidermal border and positive of rheumatoid factor. Two factors however may have played a significant role in all cases of. Endocrinal causes in 2 patients the lesions of EDP developed about the time of puberty. The patients developed the condition after an oophorectomy and supplemental estrogen therapy and 6 patients were postmenopausal at the time of onset. Infection or immunization causes: Three patients began developing lesions of EDP approximately two weeks after multiple immunizations. The history of an upper-respiratory tract infection within the preceding five months was also given. Clearly, further investigations into the etiology and pathogenesis of the EDP reaction pattern are needed to clarify its nature and possible relationships to other disorders [53,3,10]. The low prevalence of AD with (0.087%) and LPP with (0/037%) in this study underlines the rarity of those two diseases also in the Republic of Yemen. The authors reported, too, only a few cases of EDP in (skin type II) in USA and Europe. They regarded this disease as rare in those countries. In contradistinction the authors reported many cases of EDP in (skin type III) and they considered this disease as common in Latin America. Reported 41 cases of LPP and EDP in skin type III and also regarded those conditions as rare in India. Reported some cases and called them Lichen Planus Subtropicus (LPP) (skin type III) and they regarded this disease as rare in the Middle East Area. They considered that ashy dermatosis might be a variant of lichen planus that is present only in individuals with skin type III. This may answer to the question why ashy dermatosis is mainly described mainly in Latin America and not in Europe or the United States, where LPP is not uncommon. In this study observed the main features of ashy dermatosis were gray-blue hyperpigmented macules and in its early stages, an elevated red border. Distribution

was mainly symmetrical, affecting face, trunk, upper and lower Extremities, only occasionally (1/23) with a chronic and asymptomatic course. Lichen planus pigmentosus patients presented mainly with violet-blue macules or patches, without an active border, mainly in a disseminated fashion with involvement of neck, face and extremities and often with pruritus running a chronic course. They observed clinical differences between ashy dermatosis and lichen planus pigmentosus [52,54,36,37,13,55]. They noted that no age or sexual preponderance exists in EDP. In this study however there was an average age of onset of 18 years, which was statistically significantly different from the more advanced age of onset of LPP. In regard to sex preferences no statistical difference was found [6,56]. It became obvious that most of the quoted studies and were not comparative between EDP and LPP. They reported the clinical manifestations of their EDP cases, which were similar to the 23 cases of AD and 10 cases of LPP reported in this study. Other studies were however, comparative between EDP and LPP. They found that the EDP and LPP were clinically different. These histological findings include hyperkeratosis or orthohyperkeratosis, focal thinned epidermis, focal basal vacuolization, focal perivascular, lymphohistiocytic infiltrate and dermal pigmentary incontinence. The following reported studies indicated the same histopathological findings for the two diseases starting. They regarded the histopathological findings of EHP and LPP as lichenoid reaction. They considered the histopathological findings of AD and LPP were similar as the histological findings of 33 cases in this study [57-61,52,27,5,7,11,13,49].

Conclusion

Since the appearance of this hypothesis not much has been published the literature and what reported mainly oriented has been oriented towards three aspects:

One group of reports on new cases agrees clinically and histopathologically with this description of EDP. This includes ultrastructural analysis of the lesionated epidermis. Other reported cases do not fulfill clinical and histopathological criteria for EDP, which may account for the confusion relating EDP to lichen planus and its variants (tropical lichen planus, Gougerot invisible lichen planus pigmentosus and Japanese lichen pigmentosus). Other groups of investigators try to relate EDP to previously or recently described diseases. This confusion may be attributed to the lack of clinical experience based on the few cases properly described.

The third group of articles focuses on the concept of lichenoid tissue reaction, which includes distinct disorders of unknown etiology and is linked to genetic disorders, autoimmune disease and influences of the environment. This study had highlighted that the AD and LPP were very confusing clinically and histopathologically. Their histopathological Findings were similar except that hyperkeratosis was only present in 52% of AD cases and always present in LPP cases. I found that 23 cases of AD were clinically different and that AD was asymptomatic and asymmetric while LPP was symptomatic with pruritus.

Ashy Dermatitis (EDP) is reported in Latin America and a few cases in Europe and North America. Lichen Planus Pigmentosus (LPP) is reported in Japanese workers, Indians and in the Middle East area. Some authors regarded the EDP (AD) as a lichenoid reaction, the others studied the AD and LPP have the clinical and histopathological similarities and the others observed that the AD and LPP are similar in the histopathological findings and differ clinically.

References

1. Ramirez CO. Los cenicientos: Problema clinico. Report of the First Central American Congress of Dermatology, San Salvador. 1957.
2. EL -Zawahiry M. Lichen planus tropicus. *Int J Dermatol.* 1965;4:92-95.
3. Ramirez CO. The ashy dermatosis (erythema dyschromicum perstans). *Cutis.* 1967;3:244-7.
4. Palatsi R. Erythema dyschromicum perstans. *Dermatol.* 1977;155(1):40-4.
5. Novick NL, Phelps R, Tom C. Erythema dyschromicum perstans. *Int J Dermatol.* 1985;24:630-3.
6. De La Faille-Kuyper EB, De la Faille HB. An immunofluorescence study of lichen planus. *Br J Dermatol.* 1974;90(4):365-71.
7. Soter NA. Ultrastructural pathology of erythema dyschromicum perstans. *J Invest Dermatol.* 1969;52:155-61.
8. Bhutani LK, Bedi TR, Pandhi RK, Nayak NC. Lichen planus pigmentosus. *Dermatol.* 1974;149(1):43-50.
9. Verbov J, Borrie FF. Ashy dermatosis (erythema dyschromicum perstans). *Br J Dermatol.* 1971;84(2):185-6.
10. Urano-Suehisa S, Tagami H, Iwatsuki K. Unilateral ashy dermatosis occurring in a child. *Arch Dermatol.* 1984;120(11):1491-3.
11. Soto LD, Tomaka TH, Memije EV. Pigmentary problema in the topics. *Dermatologic Clinics:* 1994;12(4):777-85.
12. Tschen JA, Tschen EA, and McGavran MB. Erythema dyschromicum perstans. *J AM Acad Dermatol.* 1980;2:295.
13. Vega ME, Waxtein L, Arenas R, Hojyo MT, Dominguez-Soto LU. Ashy dermatosis and lichen planus pigmentosus: a clinicopathologic study of 31 cases. *Int J Dermatol.* 1992;31(2):90-4.
14. Pozo TR. Liqueo plano pigmentoso: Aportacion de un caso y revision de la literatura. *Actas Dermosifilogr.* 1988;79:681-6.
15. Naidorf KF, Cohen SR. Erythema dyschromicum perstans and lichen planus. *Arch Dermatol.* 1982;118(9):683-5.
16. Gougerot H. Lichens atypiques ou invisibles pigmentogenes reveles par des pigmentations. *Bull Soc Fr Dermatol Syphiligr.* 1935;42:792-4.
17. Hellerstrom S. Erythema chronicum migrans Afzelius with meningitis. *Southern Med J.* 1950;43(4):330-5.
18. Gainmel JA. Erythema Gyrratum Repens. *Arch Derm.* 1952;66:494.
19. Purdy MJ. Erythema Gyrratum Repens. *Arch Derm.* 1959;80:590-1.
20. Convit J, Kerdell-Vegas F, Rodríguez G. Erythema dyschromicum perstans: a hitherto undescribed skin disease. *J Invest Dermatol.* 1961;36(6):457-62.
21. Sulzberger M, Convit J, Kerdell- Vegas F, Rodriguez G. Erythema dyschromicum perstans: A hitherto undescribed skin disease. *J Invest Dermatology.* 1961;36:457- 62.
22. Grekin RH. Case for diagnosis. *Arch Derm (Chicago).* 1961;83:327.
23. Degos R. Pigmentation en taches éruptives de nature indéterminée. *Bull Soc Fr Derm Syph.* 1964;3:296.
24. Shapiro L. Melanoderma of unknown etiology. *Arch Derm (Chicago).* 1968;97:362.
25. Rupec M, Vakilzadeh F. Eine kleinfleckige Pigmentdermatose. *Hautarzt.* 1971;22:337-40.

26. Weidner F. Persistierende exanthematische Melanodermia (casus prodiagnosi). *Z Haut Geschlechtskr.* 1971;47:898.
27. Knox JM, Dodge BG, Freeman RG. Erythema dyschromicum perstans. *Arch Dermatol.* 1968;97(3):262-72.
28. Stevenson JR, Miura M. Erythema dyschromicum perstans (ashy dermatosis). *Arch Dermatol.* 1966;94(2):196-9.
29. Eady RA, Cowen T, Marshall TF, PLUMMER V, Greaves MW. Mast cell population density, blood vessel density and histamine content in normal human skin. *Br J Dermatol.* 1979;100(6):623-33.
30. Mikhail GR, Miller-Milinska A. Mast cell population in human skin. *J Invest Dermatol.* 1964;43:294-5.
31. Peachy RDE. Ashy dermatosis. *Br J Dermatol.* 1976;94:227-8.
32. Pinkus H. Lichenoid tissue reactions: a speculative review of the clinical spectrum of epidermal basal cell damage with special reference to erythema dyschromicum perstans. *Arch Dermatol.* 1973;107(6):840-6.
33. Beutner EH, Chorzelski TP, Jordon RE. Autosensitization in pemphigus and bullous pemphigoid. Thomas; 1970.
34. Stingl G, Katz SI, Shevach EM, Rosenthal AS, Green I. Analogous functions of macrophages and Langerhans cells in the initiation of the immune response. *J Invest Dermatol.* 1978;71(1):59-64.
35. Jablonska S. Ingestion of ammonium nitrate as a possible cause of erythema dyschromicum perstans (ashy dermatosis). *Dermatol.* 1975;150(5):287-91..
36. Dilaimy M. Lichen planus subtropicus. *Arch Dermatol.* 1976;112(9):1251-3.
37. EL -Zawahiry M. Lichen planus tropicus. *Int J Dermatol.* 1965;4:92-5.
38. Holst R, Mobacken H. Erythema dyschromicum perstans (ashy dermatosis). Report of two cases from Scandinavia. *Acta dermato-venereologica.* 1974;54(1):69-72.
39. Byrne DA, Berger RS. Erythema dyschromicum perstans. *Acta Derm Venereol.* 1974;54:65.
40. Kark EC, Litt JZ. Ashy dermatosis--a variant of lichen planus?. *Cutis.* 1980;25(6):631-3.
41. Lever WF. Histopathology of the skin. JB Lippincott Co-Philadelphia. 1967;775. -
42. Ellis FA. Histopathology of lichen planus based on analysis of one hundred biopsy specimens. *J Invest Dermatol.* 1967;48(2):143-8.
43. Odiand GF, Reed TH. Epidermis infrastructure of Normal and Abnormal skin. Lea & Febiger Philadelphia. 1967:54-75.
44. Nix TE. Ultraviolet-induced changes in epidermis. Ultrastructure of normal and abnormal skin. Lea & Febiger Philadelphia. 1967 (pp. 304-319).
45. Kahl FR, Pearson RW. Ultra- structural, studies of experimental vesiculation II collagens. *J Invst Derm.* 1967;49:616.
46. Sanchez NP, Pathak MA. Circumscribed dermal melanosis: Classification, light histochemical and electron microscopic studies on 3 patients on erythema dyschromicum perstans. *Int J Dermatol.* 1985;24:630-3.
47. Lambert WC, Schwartz RA. Erythema dyschromicum perstans. *Cutis.* 1986;37:42-4.
48. Zenorola P, Bisceglia M, Lomuto M. Ashy dermatosis associated with cobalt allergy. *Contact Dermatitis.* 1994;31(1):53-4.
49. Stevenson JR, Miura M. Erythema dyschromicum perstans (ashy dermatosis). *Arch Dermatol.* 1966;94(2):196-9.
50. Jablonska S. Ingestion of ammonium nitrate as a possible cause of erythema dyschromicum perstans (ashy dermatosis). *Dermatol.* 1975;150(5):287-91.
51. Pinkus H. Lichenoid tissue reactions: a speculative review of the clinical spectrum of epidermal basal cell damage with special reference to erythema dyschromicum perstans. *Arch Dermatol.* 1973;107(6):840-6.
52. Bhutani LK, Bedi TR, Pandhi RK, Nayak NC. Lichen planus pigmentosus. *Dermatol.* 1974;149(1):43-50.
53. Convit J, Piquer -Martin J. Erythema dyschromicum perstans. *Int J Dermatol.* 1986;28:168-89.
54. Byrne DA, Berger RS. Erythema dyschromicum perstans. *Acta Derm Venereol.* 1974;54:65.
55. Verbov J, Borrie FF. Ashy dermatosis (erythema dyschromicum perstans). *Br J Dermatology.* 1971;84(2):185-6.

56. Zenorola P, Bisceglia M, Lomuto M. Ashy dermatosis associated with cobalt allergy. *Contact Dermatitis*. 1994;31(1):53-4.
57. Berger RS, Hayes TJ, Dixon SL. Erythema dyschromicum perstans and lichen planus: are they related? *J Am Acad Dermatol*. 1989;21(2):438-42.
58. Convit J, Kerdel-Vegas F, Rodríguez G. Erythema dyschromicum perstans: a hitherto undescribed skin disease. *J Invest Dermatol*. 196;36(6):457-62.
59. Miyagawa S, Komatsu M, Okuchi T, Shirai T, Sakamoto K. Erythema dyschromicum perstans: immunopathologic studies. *J Am Acad Dermatol*. 1989;20(5):882-6.
60. Piquero-Martían J, Pérez-Alfonzo R, Abrusci V, Briceno L, Gross A, Mosca W, et al. Clinical Trial with Clofazimine for Treating Erythema Dyschromicum Perstans Evaluation of Cell-Mediated Immunity. *Int J Dermatol*. 1989;28(3):198-200.
61. Shima T. Supplementative study on lichen pigmentosus. *Jpn J Dermatol*. 1956;66:346-53.