Ashy Dermatosis: A Narrative Literature Review

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1. Introduction

Ashy dermatosis (AD) or erythema dyschromicum perstans (EDP) is a pigment disorder of the skin that has no known cause. Pigmentation disorder Ashy dermatosis is characterized by multiple hyperpigmented macular lesions on the trunk and proximal extremities. The incidence of Ashy dermatosis mostly occurs in Caucasians, which is 52% and is most common in Asia and Central and South America. The etiology and pathogenesis of Ashy dermatosis are still not known with certainty. Some studies say that hepatitis C virus infection, human infections immunodeficiency virus (HIV), and whipworm infestation can cause Ashy dermatosis. Environmental influences such as consumption of ammonium nitrate, X-ray contrast media given orally, ethambutol, fluoxetine, chlorothalonil, and omeprazole are also triggers for the occurrence of Ashy dermatosis. The most common clinical manifestation of Ashy dermatosis is hyperpigmented or gray macules with slow progression and pigmentation abnormalities in the inner epidermal layer. The differential diagnosis of Ashy dermatosis is with lichen planus pigmentosus, idiopathic eruptive macular pigmentation, and Riehl's melanosis. Diagnosis of Ashy dermatosis needs to be linked between clinical findings and histopathological examination, other supporting examinations and differentiating it from other differential diagnoses. Management for patients with Ashy dermatosis is with topical or systemic agents. For now, a combination of laser and tacrolimus ointment is recommended.
Definition

The definition of AD was first described by Ramirez in 1957 as asymptomatic pale hyperpigmented macules with slow progression and also referred to as “dermatitis cenicenta” or erythema chronicum figuratum melanodermacum. Ashy dermatosis (AD) or erythema dyschromicum perstans (EDP) is a type of hyperpigmented macules characterized by asymptomatic, gray macular lesions with a symmetrical distribution. Zaynoun et al. classified clinically ashy dermatoses as follows: 1) Ashy dermatosis: Patients with idiopathic hyperpigmented macular eruptions, with or without the presence of interface dermatitis on histopathological examination. 2) Erythema dyschromicum perstans: Patients with lesions similar to ashy dermatosis but have or have had lesions with reddish borders (erythema). 3) Simulator: Dermatological diseases such as lichen planus, post-inflammatory hyperpigmentation, such as pityriasis rosea and erythema multiforme, drug-induced melanoderma, and mastocytosis.

Epidemiology

The incidence and prevalence of macular hyperpigmentation is not known with certainty. Ashy dermatosis almost occurs at all ages, but the average occurs in the 2nd decade of life with less than 30 years of age. Ashy dermatosis most commonly originates from Asia, Central and South America, as most of the published cases originate from these regions. Silverberg et al. reported that the majority of prepubertal patients with Ashy dermatosis were Caucasian (52%) and Hispanic (36%) as well as African American (4%), Asian (4%), and unspecified (4%). Ashy dermatosis is rare in children, but two cases were reported in India of a child with AD. This condition affects both sexes but is more common in women. Besides that, this condition often occurs in individuals with dark skin types.

Etiology

The etiology of ashy dermatosis is still not known with certainty. Special laboratory and radiological examinations are not needed to establish the diagnosis of AD. Consumption of ammonium nitrite, nematode infection, use of radiographic contrast media, cobalt allergy, and exposure to chlorothalonil in farmers can cause AD. Predisposing factors include infections such as intestinal parasitic infections, enteroviruses, HIV seroconversion, chronic hepatitis C as well as adverse environmental conditions such as ingestion of ammonium nitrate, orally administered X-ray contrast media, ethambutol, fluoxetine, chlorothalonil, omeprazole and genetic factors such as HLA-DR4 can cause AD.

Pathogenesis

The pathogenesis of ashy dermatosis or erythema dyschromicum perstans is currently unknown. Parasitic infections, exposure to chemicals such as ammonium nitrate and barium sulfate, and environmental allergens have been reported as triggers for AD. Immunological response to one of the trigger factors can determine the level of inflammation in the lesion based on the genetic profile. A strong inflammatory reaction to a triggering factor can cause EDP, whereas a mild inflammatory reaction causes AD. Baranda et al. in 1997 reported that there is high expression of activated intercellular and adhesion molecules, in addition to class II molecules of the major histocompatibility complex (MHC) (HLA-DR) in the keratinocytes of the basal cell layer. Increased expression of CD36 (thrombospondin receptor) in the spinosum and granulosum layers of active AD lesions is associated with the presence of active lymphocytes in the inflammatory infiltrate in the skin. Expression of CD94 in the keratin cells of the basal cell layer and in the inflammatory infiltrates of the dermis in active AD lesions supports that immunologically genetically predisposes to AD. CD94 expression has also been found to be expressed in several inflammatory processes such as psoriasis, graft-versus-host disease, lichen planus, and other diseases, as well as in keratinized cells of the basal cell layer and in inflammatory dermal infiltrates in active AD lesions. These findings support immunologically that genetics
may be a predisposing factor for AD. Research conducted by Marisol et al. in 2007 in Mexico has a genetic predisposition that the MHC gene is associated with HLA-DR4 (04-7).

**Clinical manifestations**

Clinical manifestations of ashy dermatosis are hyperpigmented or gray macules with slow development where the disorder is deeper than the pigment abnormality in the epidermis (Figure 1A). Ashy dermatosis often occurs in individuals with Fitzpatrick III-V skin types with a predilection most commonly on the neck, trunk, and proximal arms with a symmetrical distribution. However, some AD lesions on the face/neck are sometimes asymmetrical along Blaschko’s line, with typical signs found on the palms, soles, and palms. feet, scalp, and mucous membranes. AD lesions are between 0.5-2.5 cm in size and vary in shape like an oval with the axes following the grooves in the skin, so they are similar to pityriasis rosea (Figure 1B). Macular lesions can slowly increase in width and coalesce to form a patch over several weeks.

![Figure 1](image1.png)

Figure 1. (A) Symmetrical oval brownish hyperpigmented patches on the neck and upper chest in a 51-year-old woman. (B) Erythema passing through dyschromic. Gray-brown macules and oval, polygonal patches are seen on the lower extremities.

AD lesions may disappear spontaneously, especially in prepubertal children (70% in 2-3 years), but in adults, lesions may develop slowly and persist for years. Most of the predilected AD lesions are also present on the face, neck (Figure 2A), and upper trunk without involving the extremities and following the photo distribution of the neck folds (Figures 2B and C). Some AD lesions describe an increased erythematous border on palpation measuring 1-2 mm from the initial phase of the lesion.

![Figure 2](image2.png)

Figure 2. (A) Cheek and neck lesions. (B) The lesion in the neck crease. (C) Neck and upper body lesions.
Differential diagnosis
Macular lesions or hyperpigmented patches may mimic AD and EDP. A significant difference between AD and EDP is the presence of a palpable erythematous border on palpation that is 1-2 mm wide in the initial phase, although it is difficult to assess in persons with dark skin. Several differential diagnoses of skin lesions that resemble AD and EDP include:

Lichen planus pigmentosus (LPP)
Lichen planus pigmentosus is a rare variant of lichen planus (LP) which is characterized by dark brown to gray macules with a predilection for sun-exposed areas such as the face, neck, and flexures. LPP lesions are commonly seen in dark-skinned patients in whom the lichenoid inflammatory response causes pigmentary incontinence. Erythematous surrounding macula in LPP is one of the clinical differences found on physical examination. In the clinicopathological study of 31 cases of LPP and AD, there were 40% of AD cases found, but there was no significant difference on histopathological examination. Histopathological examination of AD and LPP is characterized by vacuolar degeneration of basal cells in the epidermal layer and pigmented macrophages in the papillary dermis. Liquefactive degeneration in the basal layer resulting from separation of the underlying lamina propria is seen on histopathological examination of AD. Histopathological examination of LP and EDP showed a subpopulation of lymphocytes and keratinocytes, but band-shaped infiltrates were only found in LP.

Idiopathic eruptive macular pigmentation
Idiopathic eruptive macular pigmentation (IEMP) is a rare condition characterized by a brownish, confluent, asymptomatic macular eruption with a predilection for the trunk, neck, and proximal extremities in children and adolescents. The two main differences between IEMP and AD are the presence of frequent resolution and hyperpigmentation in the basal layer without degeneration.

Riehl’s melanosis
Riehl’s melanosis, or pigmented contact dermatitis due to cosmetics or textiles, is characterized by satellite perifollicular pigmented macules with reticular pigmentation. It occurs at the site of contact, may be preceded by erythema and pruritus and the patient usually shows positive results on an allergy patch test.

Diagnosis enforcement
The diagnosis of AD is determined based on the history, clinical picture and associated with histopathological examination. Other investigations such as dermoscopy examination can also be used to establish the diagnosis of ashy dermatosis and distinguish it from other differential diagnoses. Clinical diagnosis of hyperpigmented macules is still difficult to enforce. The following algorithms can help to make a diagnosis of hyperpigmented macules:

Histopathological picture
AD histopathological examination did not reveal any pathognomonic signs. The results of a histopathological examination that are commonly found in the epidermal layer show vacuolar degeneration of basal cells, which causes pigment incontinence and accumulation of melanophages in the papillary dermis, that there is edema of the papillary dermis, lymphocytic infiltrates, and histiocytes. The typical histological features of AD lesions depend on the phase of the lesion. Early or active AD lesions may show basal vacuolar degeneration, edema of the papillary dermis, or perivascular lymphocytic infiltration of the epidermis. Inactive lesions show pigment incontinence and melanophage in the dermis (Figure 4).
Figure 3. Diagnostic algorithm with clinical macular hyperpigmentation.

Table 1. Another cause of hyperpigmented macules.

<table>
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<td>Post-kala-azar dermal leishmaniasis</td>
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<td>Post-inflammatory pigmentation (pityriasis rosea, psoriasis, rash virus)</td>
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<td>Malignancy</td>
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<td>Nevus and related conditions</td>
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<td>Reticular and confluent papillomatosis</td>
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<td>Hyperpigmentation after radiotherapy</td>
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Figure 4. Histological picture of AD with HE staining at 20× weak magnification (A) and powerful magnification (B) In the epidermal layer, epidermal atrophy, focal vacuolar changes in basal cells, perivascular lymphoid cell infiltration and melanophage.³

Figure 5. The histological assessment found pigment incontinence and melanophage mainly located in the reticular dermis (dark circles); neither vacuolar degeneration nor lichenoid infiltrate was evident, which is consistent with the diagnosis of ashy dermatitis.²⁰

Immunofluorescent examination directly shows the presence of colloid IgM, which supports the diagnosis of AD.¹⁸ The presence of antigen-positive skin lymphocytes in the basement membrane zone layer indicates that AD can be a response to antigen stimulation.²⁰ In addition, in AD, there is overexpression of intercellular adhesion molecule 1 and HLA-DR in the basal cell layer of the keratinocytes of the lesion ashy dermatosis. AD patients have CD36 (thrombospondin receptor) expression in the spinosum and granulosum layers that is not expressed by normal skin (Figures 4-6).¹⁰,²⁰

Figure 6. Expression of intercellular adhesion molecule 1 in the basal cell layer of keratinocytes and infiltrating lymphocytes in the dermis in active EDP lesions (A). CD36 expression in the spinosum and granulosum layers of active EDP lesions (B).¹⁰
Dermoscopy examination

Dermoscopy examination of AD lesions is not a gold standard diagnosis of AD but it can help rule out other diagnoses. The results of AD dermoscopy are brown to gray dots accompanied by globules on a brown and pink base and a different pattern of blood vessels (Figures 7-12).

Figure 7. Brown to grey dots, which are scattered with a pink base.

Figure 8. Brown to grey dots and globules form an irregular line.

Figure 9. Brown to grey dots evenly distributed on a pinkish brown background.
Figure 10. Brown to grey dots and irregular veins on a skin-colored base.\textsuperscript{17}

Figure 11. Brown dot and lobules spread with combined bases (brown, pink, and skin tone).\textsuperscript{17}

Figure 12. Brown to grey dots, neither a random distribution nor a linear arrangement can be observed. Out-of-focus blood vessels may also be seen. (Dotted vessels: black arrows, circular vessels: red arrows, and irregular linear vessels: white arrows).\textsuperscript{17}

**Management**

The clinical course of AD differs between children and adults. In children, AD usually resolves within two to three years, although some studies report spontaneous resolution occurring in adults. AD lesions in adults are usually persistent and have a chronic course.\textsuperscript{3} Until now, there have been no specific studies and consistently effective treatment options for
the management of AD, such as sun protection, topical corticosteroids, retinoids, vitamin C, chemical peeling, oral antibiotics, vitamin A, dapsone, antimalarials, griseofulvin, and systemic corticosteroids.\textsuperscript{5,22,23} Some of the therapy options that can be given for AD include:

**Topical agent**

1) Cosmetics and camouflage creams: The application or use of cosmetic creams does not remove or reduce the lesions but only improves the appearance in patients with AD. 2) Therapy Narrowband ultraviolet (nB-UVB): Several studies suggest the use of nB-UVB therapy for AD lesions, but there are no studies that clearly state the dose, duration, and rate of improvement in AD lesions. A case study mentions a patient with AD experiencing improvement after receiving nB-UVB therapy at a dose of 4716 Mj/cm\textsuperscript{2} three times a week for four weeks (12 sessions).\textsuperscript{22,24} nB-UVB phototherapy can decrease cell activity, natural killer cells, lymphocyte proliferation and production of immune regulatory cytokines produced by Th1 (IL-2, IFN-\textgreek{g}) and Th2 (IL-10). nB-UVB phototherapy can camouflage clinically by hiding skin pigmentation in the dermis by stimulating pigment production. In addition to hyperpigmentation, nB-UVB phototherapy also induces stratum corneum thickening and T lymphocyte apoptosis. NB-UVB phototherapy can partially fade blue-gray pigmentation and provide a good response in inflammatory lesions.\textsuperscript{24} 3) Tacrolimus ointment. Tacrolimus is a calcineurin inhibitor that binds to the cytoplasmic immunophilin FKBP12 and forms a complex that inhibits the activity of the calcineurin enzyme required for T-cell activation. Inhibition of the calcineurin enzyme prevents dephosphorylation of the cytoplasmic component of T cell activation, which regulates mRNA transcription, namely inflammatory cytokines Th1 and Th2 (IL-2, IFN-\textgreek{g}, and IL-4, IL-10). An abnormal cell-mediated immune response to play a role in the pathogenesis of EDP may be the result of the involvement of cell adhesion and activation molecules (ICAM-1, LFA-1\textalpha) as evidenced by the presence of CD8+ T cells in the dermis, expression of HLA-DR+ and ICAM-1+ in epidermal keratinocytes as well as exocytosis of skin lymphocyte antigen (CLA)+ cells in areas of damaged basal cells. Topical tacrolimus 0.1% is an effective and safe alternative therapy option for AD lesions as an immunomodulator. Mahajan et al. reported that in two patients with erythema, persistent dyschromic, topical tacrolimus 0.1% ointment applied twice daily to the affected area resulted in significant improvement after 3 weeks of therapy (Figure 12).\textsuperscript{25 4} Fractionated laser. Non-ablative 1550 nm fractional laser therapy is not considered effective for the treatment of AD/EDP lesions.\textsuperscript{26} However, laser therapy is a promising treatment modality. Although therapy using a non-ablative fractional laser alone is not effective in treating ashy dermatosis, one case report reported \textgreater75% improvement with eight months of treatment with a non-ablative fractional laser in combination with topical tacrolimus 0.1% ointment.\textsuperscript{26,27} Hyperpigmentation side effects post Laser-induced inflammation may occur, which may exacerbate the cosmetic problem in AD.\textsuperscript{23}

**Systemic agent**

**Clofazimine**

Studies evaluating the effectiveness of clofazimine for AD by administering clofazimine 100 mg tablets daily for 3 months have shown clinically improved responses varying from 66% to 87%. Side effects that appear are discoloration of the skin, cornea and body fluids and gastrointestinal intolerance. Giving clofazimine therapy is not like that recommended for AD as it may cause dyspigmentation in patients.\textsuperscript{3}

**Dapsone**

Dapsone is a class of antibiotic sulfonamide and anti-inflammatory. A case study reported that giving oral dapsone therapy 100 mg per day for 3 months had a very good therapeutic response. Giving dapsone to AD patients must be careful considering the side effects associated with hemolysis and hypersensitivity syndrome.\textsuperscript{28}
Vitamin A

The administration of vitamin A for AD therapy has not been studied further. Research conducted by Bhutani et al. in 1979 regarding the administration of Vitamin A capsules to 140 patients with lichen planus pigmentosus at a dose of 100,000 units per day for 15 days followed by 15 days of rest showed that 9 out of 12 patients showed a good to very good response after 10 or more medication.\textsuperscript{3,29}

Complications

There are no significant complications to the condition ashy dermatosis. Complications that arise in AD are related to clofazimine therapy, namely temporary orange discoloration of the skin and eyes (cornea and conjunctiva). Giving dapsone therapy can cause complications in the form of gastrointestinal disturbances such as nausea, vomiting but will disappear after discontinuation of treatment.\textsuperscript{12}

Prognosis

Although the initial erythematous phase of EDP tends to subside over several months, residual hyperpigmentation remains visible and may expand in size.\textsuperscript{2}

2. Conclusion

Ashy dermatosis (AD) or erythema persistent dyschromic (EDP) is a type of hyperpigmented macular characterized by a gray, asymptomatic macular lesion with a symmetrical distribution. This condition is most common in Asia and Central and South America and occurs most frequently in women and very rarely in children. The etiology and pathogenesis of ashy dermatosis are still not known with certainty. Several predisposing factors include ashy Dermatosis, such as intestinal parasitic infections, bad environments such as consumption of ammonium nitrate, X-ray contrast
media, and genetic factors, such as the HLA-DR4 allele. Clinical manifestations include ashy Dermatosis, namely hyperpigmented or gray macules with slow progression and pigmentation disorders in the inner epidermal layer. Differential diagnosis ashy dermatoses namely with Lichen planus pig mentosus, Idiopathic eruptive macular pigmentation, and Riehl’s melanosis. Diagnosis of ashy dermatosis needs to be connected between clinical findings and histopathological examination, other supporting examinations, and differentiating it from other differential diagnoses. Treatment for sufferers of ashy dermatosis with topical or systemic agents. For now, a combination of laser and tacrolimus ointment is recommended. There are no significant complications to the condition ashy dermatosis but complications associated with clofazimine therapy.

3. References


