

# Confusing Acquired Macular Pigmentation of Unknown Etiology in Children: Retrospective Analysis of 10 Years in Single Tertiary Center

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## Abstract

**Acquired Macular Hyperpigmentation:** Ashy dermatosis (AD), lichen planus pigmentosus (LPP), erythema dyschromicum perstans (EDP), and idiopathic eruptive macular pigmentation (IEMP) are the spectrum of acquired macular pigmentation of unknown etiology (MPUE). The aim of this study is to investigate and reevaluate our pediatric patients who had clinically and histopathologically been diagnosed with aforementioned disorders, in consideration of the global consensus statement on acquired MPUE. **Materials and Methods:** A retrospective chart review of 23 pediatric cases that had applied to the dermatology unit between the years 2007 and 2017 and diagnosed with any of the acquired macular pigmentation was performed. **Results:** Of 23 patients, 16 were diagnosed with AD, 4 with LPP, and 3 with IEMP. In AD patients, major site of presentation at onset was the trunk (13/16) and brownish (15/16) were the most prominent coloring. Dermal melanophages (16/16), perivascular lymphohistiocytic infiltrate (14/16), and pigment incontinence (7/16) were the most prominent features. Upper limbs (3/4) were the most predilection area in LPP patients. Perivascular lymphohistiocytic (4/4), lichenoid infiltration (3/4), basal vacuolar degeneration (4/4), and dermal melanophages (4/4) were observed. The trunk was the major site of presentation (3/3) in IEMP patients. Brownish (2/3) and ashen-gray (1/3) was the coloring of lesions. Basal layer pigmentation (3/3) and dermal melanophages (3/3) were the most prominent findings. No basal vacuolar changes (0/3) were observed. **Conclusion:** Clinical and histopathological distinction between these conditions is challenging. We reevaluated our patients in this context. We predict that we have achieved more accurate terminology with the global consensus statement. Such a terminology might allow that these disorders may be compared with a collective terminology in the literature.

**Keywords:** Ashy dermatosis, erythema dyschromicum perstans, hyperpigmentation, idiopathic eruptive macular pigmentation

## INTRODUCTION

Acquired macular pigmentation of unknown etiology (MPUE) is a new term for acquired macular pigmentation of the skin with unknown etiology in the absence of preceding or concurrent inflammatory lesions. This umbrella term encompasses ashy dermatosis (AD), lichen planus pigmentosus (LPP), erythema dyschromicum perstans (EDP), and idiopathic eruptive macular pigmentation (IEMP).<sup>[1-6]</sup> The overlapping clinical and histological features of these skin disorders identified under the terminology, turn differential, and formal diagnostic stages into a rather challenging process.<sup>[2,5-9]</sup> A consensus on the terminology of these disorders was a long-felt need. This was achieved by the global consensus forum, established after

the 22<sup>nd</sup> International Pigment Cell Conference, in Singapore in 2014. Kumarasinghe *et al.* reported the consensus statement of the forum and reviewed the available literature in 2019.<sup>[3]</sup> Herein, we report 23 pediatric cases of acquired MPUE in consideration of global consensus statement.<sup>[3]</sup>

## MATERIALS AND METHODS

Retrospective review of 23 pediatric cases with acquired MPUE which had applied to the dermatology unit of the children's hospital between 2007 and 2017, was conducted.

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This center provides medical services primarily to Caucasian individuals from the Aegean region but also receives referrals from other parts of Turkey. Patients, histopathologically and clinically diagnosed with acquired MPUE, without any previous or concurrent inflammatory lesions were included in the study. In addition, we re-examined photo documentation of patients whenever possible. Hematoxylin and eosin, crystal violet or Congo-red, and toluidine blue stained archival tissue sections of patients were reevaluated. Hence, mastocytosis and amyloidosis were excluded at the process of differential diagnosis. If there is not erythematous border in the past or current, these conditions were not labeled EDP.

Data regarding clinical location of lesions, presenting symptoms, duration of the disease, sociodemographic characteristics of subjects such as gender, age, history of drug intake, and observed distinct histopathological features were noted.

## RESULTS

In this study, from 23 children, 16 were diagnosed with AD, four with LPP, and three with IEMP, while none of the patients had the diagnosis of EDP. The average age of children was 9, 5 (6 months –16 years). The gender distribution of the cases was 11 females and 12 males. The demographical, clinical, and histopathological features of all cases in the context of diagnosis have shown in Tables 1 and 2.

Children with AD, neither simultaneous erythematous border nor the history of erythematous border were found [Figure 1].

Histories of drug use that might be suspected were noted. (2/ amoxicillin-clavulanate, 1/pyrantel pamoate, 1/nonsteroidal anti-inflammatory drugs, 1/methylphenidate, and 1/ montelukast-desloratadine); summarized in Table 1.

Dermal melanophages (16/16), perivascular predominantly lymphohistiocytic infiltrate (14/16), and pigment incontinence (7/16) were the most prominent features, followed by basal layer pigmentation (5/16) and basal vacuolar changes (5/16) [Table 2 and Figure 2]. Among preliminary diagnoses of the 16 patients, AD/EDP had also been considered.

Of LPP patients, none of the patients had the history of preceding erythema, vesicles, or scaling before the onset of hyperpigmentation or the history of papules of typical lichen planus lesions. Only one patient had had a prior history of medication (naproxen sodium). One of the female patient's lesions was on flexural areas [Figure 3]. Perivascular lymphohistiocytic (4/4) and lichenoid infiltration (3/4), acanthosis (2/4) hypergranulosis (1/4), basal vacuolar degeneration (4/4), and dermal melanophages (4/4) were observed [Table 2 and Figure 2].

In IEMP patients, no erythematous patches had been found, and there was no history of preceding dermatosis and no history of medications [Table 1 and Figure 4]. Basal layer pigmentation (3/3) and dermal melanophages (3/3) were the most prominent findings. No basal vacuolar changes (0/3) were observed [Figure 2].



**Figure 1:** Cutaneous macules in colors with various shades of gray in ashy dermatosis patient

## DISCUSSION

AD, EDP, LPP, and IEMP are potential differential diagnoses.<sup>[1-3,5,6,9-14]</sup> Some authors consider them as a part of the same nosological spectrum of a unique entity, while others argue that they are different diseases. A consensus on the terminology of these lesions with various morphologies was a long-felt need. This was achieved by the global consensus forum, established after the 22<sup>nd</sup> International Pigment Cell Conference in Singapore in 2014. Thirty-nine experts presenting 18 countries participated in the deliberations.

Kumarasinghe *et al.*, in 2019, reviewed the available literature and reported the consensus statement of the forum. In this study, we tried to determine the clinical and histopathological features of 23 children due to this consensus to obtain similar terms.

Many dermatological and medical diseases can cause acquired macular hyperpigmentation as a sequel. In order to be identified as acquired MPUE, it is crucial to prove that encountering pigmented macules do not appear following a known disease, and they do not have any preceding and concurrent prior inflammatory skin lesion.<sup>[1,3]</sup>

Initially described in 1961, Venezuela by Convit, EDP is characterized by asymptomatic, slowly progressing, ashy-gray, expanding macular hyperpigmentations with slightly raised, erythematous border at presentation.<sup>[15]</sup> Yet, Ramirez had reported a novel pigmentary disorder characterized by an eruptive, asymptomatic rash consisting of ash-colored macules without erythematous border, in 1957.<sup>[16]</sup> The same author had reported 139 patients with ash-colored and grayish macules, where some lesions presenting with an easily observable, nonelevated erythematous border, in 1967.<sup>[17]</sup> This disorder had been identified as AD or dermatosis cenicienta.<sup>[5,17]</sup> Henceforth, although some clinical features might slightly differ, many authors and most textbooks have regarded these two as identical conditions.<sup>[5,9]</sup> Zaynoun suggested separate classification to be used for differential diagnoses of EDP

**Table 1: Sociodemographic and illness-specific characteristics of 23 cases with acquired macular pigmentation of unknown etiology**

| Patient number | Age/sex       | Duration | Location                                 | Drug intake/ infection                    | Clinical features  | Most prominent histopathologic features   | Clinical and histological diagnosis |
|----------------|---------------|----------|--|---|--|---|-------------------------------------|
| 1              | 4/male        | 8 months | Trunk, neck, upper limbs                 | +(pyrantel pamoate)/-                     | Ashen-gray brownish, color macula, no erythematous border    | Papillomatosis, increased basal melanocytes in focal areas, dermal melanophages, pigment incontinence   | AD                                  |
| 2              | 7/female      | 1 month  | Upper and lower limbs                    | -/-                                       | Ashen-gray brownish, color macula, no erythematous border    | Focal basal vacuolar changes, eosinophilic colloid body, lichenoid infiltrate, perivascular lymphohistiocytic infiltrate, dermal melanophages, pigment incontinence | LPP                                 |
| 3              | 13/female     | 2 months | Armpit, pupic area, neck, inguinal folds | +(naproxen sodium)/-                      | Brownish, color macula, no erythematous border               | Basal vacuolar changes, perivascular lymphohistiocytic infiltrate, lichenoid infiltrate, dermal melanophages, pigment incontinence                                  | LPP                                 |
| 4              | 11/male       | 8 months | Trunk, lower limbs, back                 | +(montelukast-desloratadine)/-            | Ashen-gray color macula, no erythematous border              | Increased basal layer pigmentation, perivascular lymphocytic infiltrate   | AD                                  |
| 5              | 11/male       | 1 year   | Trunk, upper and lower limbs             | -/-                                       | Brownish, color macula, no erythematous border               | Increased basal layer pigmentation, dermal melanophages, pigment incontinence   | IEMP                                |
| 6              | 6/male        | 6 months | Back of the trunk, upper limbs           | -/-                                       | Ashen-gray brownish, color macula, no erythematous border    | Increased basal layer pigmentation, dermal melanophages, pigment incontinence   | IEMP                                |
| 7              | 16/female     | 2 months | Trunk                                    | -/-                                       | Brownish, color macula, no erythematous border               | Perivascular lymphocytic infiltrate, dermal melanophages, pigment incontinence  | AD                                  |
| 8              | 9/female      | 6 months | Trunk, upper and lower limbs             | -/-                                       | Brownish, color macula, no erythematous border               | Increased basal layer pigmentation, basal vacuolar changes, perivascular lymphohistiocytic infiltrate, dermal melanophages, pigment incontinence                    | LPP                                 |
| 9              | 9/female      | 5 months | Trunk, upper and lower limbs             | +(amoxicillin-clavulanate)/+              | Brownish, color macula, no erythematous border               | Basal vacuolar changes, perivascular lymphocytic infiltrate, dermal melanophages, pigment incontinence  | AD                                  |
| 10             | 9/female      | 1 month  | Trunk, upper and lower limbs             | +(amoxicillin-clavulanate)/+              | Brownish, color macula, no erythematous border               | Dermal melanophages, pigment incontinence, mild lymphocytic infiltrate  | AD                                  |
| 11             | 16/female     | 2 years  | Trunk, upper limbs                       | -/-                                       | Ashen-gray brownish, color macula, no erythematous border    | Basal vacuolar changes, dermal melanophages, pigment incontinence, mild lymphocytic infiltrate  | AD                                  |
| 12             | 12/female     | 1 year   | Trunk, lower limbs, back                 | -/-                                       | Brownish and ashen-gray color macula, no erythematous border | Perivascular lymphocytic infiltrate, dermal melanophages, pigment incontinence, basal vacuolar changes  | AD                                  |
| 13             | 6/male        | 1 month  | Trunk, upper and lower limbs             | +(nonsteroidal anti inflammatory drugs)/- | Brownish color macula, no erythematous border                | Increased basal layer pigmentation, dermal melanophages, pigment incontinence, mild lymphocytic infiltrate  | AD                                  |
| 14             | 9/female      | 5 months | Trunk, upper and lower limbs             | -/-                                       | Brownish color macula, no erythematous border                | Perivascular mild lymphocytic infiltrate, a small number of dermal melanophages   | AD                                  |
| 15             | 13/male       | 5 months | Shoulders, back of the trunk             | -/-                                       | Brownish color macula, no erythematous border                | Perivascular mild lymphohistiocytic infiltrate, a small number of dermal melanophages   | AD                                  |
| 16             | 5 months/male | 4 months | Trunk                                    | Unknown                                   | Brownish color macula, no erythematous border                | Increased melanin in the basal layers, perivascular sporadic melanophages   | IEMP                                |
| 17             | 8/female      | 1 month  | Back of the trunk                        | Unknown                                   | Brownish color macula, no erythematous border                | Increased basal layer pigmentation, perivascular mild lymphohistiocytic infiltrate  | AD                                  |

Contd...

Table 1: Contd...

| Patient number | Age/sex  | Duration | Location                     | Drug intake/ infection | Clinical features  | Most prominent histopathologic features   | Clinical and histological diagnosis |
|----------------|----------|----------|------------------------------|------------------------|--|---|-------------------------------------|
| 18             | 8/male   | 5 months | Trunk, upper and lower limbs | Unknown                | Brownish color macula, no erythematous border                    | Basal vacuolar changes, perivascular mild lymphohistiocytic infiltrate dermal melanophages  | AD                                  |
| 19             | 10/male  | 5 months | Trunk                        | Methylphenidate/-      | Brownish color macula, no erythematous border                    | Basal vacuolar changes, perivascular mild lymphohistiocytic infiltrate, and melanophages  | AD                                  |
| 20             | 12/male  | 1 year   | Trunk, upper and lower limbs | Unknown                | Brownish color macula, no erythematous border                    | Basal vacuolar changes, perivascular mild lymphohistiocytic infiltrate, and melanophages  | AD                                  |
| 21             | 3/male   | 1 month  | Lower limbs                  | Unknown                | Brownish color macula, no erythematous border                    | Basal vacuolar changes, perivascular mild lymphohistiocytic infiltrate, and melanophages  | AD                                  |
| 22             | 9/female | 9 months | Neck, trunk, upper limbs     | Unknown                | Brownish color oval macula, no erythematous border               | Mild lymphohistiocytic infiltrate and melanophages in the superficial dermis  | AD                                  |
| 23             | 8/male   | 1 year   | Trunk, upper limbs           | Unknown                | Brownish, color and mild elevated macula, no erythematous border | Irregular acanthosis of the epidermis, hypergranulosis and sporadic necrotic keratinocytes, basal vacuolar changes, lymphohistiocytic infiltrate in the papillary dermis, pigment-containing melanophages | LPP                                 |

AD: Ashy dermatosis, LPP: Lichen planus pigmentosus, IEMP: Idiopathic eruptive macular pigmentation

and AD.<sup>[5]</sup> Inoue proposed that only cases with marginal erythema be considered as EDP.<sup>[9,18]</sup> Global consensus on acquired MPUE forum reached a consensus on EDP and AD; if there is an erythematous border in the past or current, these conditions should be labeled EDP.<sup>[3]</sup> The erythematous border indicates the presence of an inflammatory process that is caused by T lymphocyte infiltration. Although AD patients in this study had perivascular predominantly lymphohistiocytic infiltrate (14/16), neither prior nor simultaneous erythematous border had been detected [Table 2]. This observation gives rise to the thought that AD and EDP are distinct diseases.

In numerous studies, AD/EDP has shown similar histopathological findings. Prominent histological findings include pigment incontinence and melanophages in the dermis, along with mild-to-moderate superficial perivascular lymphohistiocytic infiltration.<sup>[1,4,5,9]</sup> According to Chang *et al.*, EDP/AD can be subdivided into active and inactive lesions. In active lesions, basal vacuolar degeneration and lymphocytic infiltration, in inactive lesion melanophages, and pigment incontinence are the most prominent findings.<sup>[4]</sup> We observed basal vacuolar changes and also lymphohistiocytic infiltrates in patients with prolonged disease duration of one and 2 years (patients 11 and 12). These findings suggested that the disease could continue with attacks.

The underlying pathomechanism of EDP or AD remains unclear, however, an immunological basis along with possible genetic susceptibility have been suggested. Parasitic infections, human immunodeficiency virus infections, and hepatitis C, exposure to chemicals such as ammonium nitrate, barium sulfate, antibiotics, benzodiazepines, pesticides, and environmental allergens have been as well listed among predisposing factors.<sup>[4,5,9]</sup> In this study, the positive history of

drug use was detected in 6, and the history of infection (upper respiratory infection) was detected in 2 of our AD patients. These factors may be triggers of the aforementioned disease. Therefore, possible triggering factors should be evaluated in addition to the content of this consensus.

IEMP is a rare disease that has been reported mostly in children and young adults.<sup>[6,8,11,19]</sup> In this study, three of the patients had the diagnoses of IEMP. It has been reported initially by Degos;<sup>[20]</sup> however, initial diagnostic criteria for the disorder were defined by Sanz de Galdeano.<sup>[6,8,10,11,21]</sup> In 2007, nine cases that clinically fulfilled the diagnostic criteria for this entity, with comorbid papillomatosis were reported. These lesions had been reported to contain velvety surfaces with prominent papillomatosis, that resembled the presentation of acanthosis nigricans.<sup>[8]</sup> The authors proposed to classify IEMP as an eruptive form of acanthosis nigricans.<sup>[8]</sup> Epidermal hypermelanosis and marked basal cell pigmentation have been regarded as the predominant finding of IEMP, by many authors.<sup>[1,3,6]</sup> Joshi *et al.* have re-evaluated 48 cases identified as IEMP in a total number of 24 case reports.<sup>[6]</sup> They have suggested that IEMP was an epidermal hypermelanotic condition, that sometimes was comorbid with papillomatosis (pigmented papillomatosis).<sup>[6]</sup> The authors have reported 9 cases had been misdiagnosed as IEMP.<sup>[6]</sup> According to the global consensus forum's conclusions; histology of IEMP is characterized by hyperpigmentation of the basal layer of the epidermis and prominent dermal melanophages without visible basal layer damage or inflammatory infiltration. The condition described as IEMP with papillomatosis appears to be a different entity to typical IEMP.<sup>[3]</sup> We proposed the same definition through the histopathology of IEMP patients in



Table 2: Histopathologic examination of 23 cases with acquired macular pigmentation of unknown etiology

| Diagnosis                                      | Acanthosis | Hyperkeratosis | Hypergranulosis | Papillomatosis | Basal pigmentation | Basal vacuolar changes | Eosinophilic colloid body | Perivascular lymphohistiocytic mild infiltrate in the superficial dermis and melanophages in the superficial dermis | Perivascular lymphohistiocytic/lymphohistiocytic prominent infiltrate | Lichenoid infiltrate | Mild infiltrate | Pigment incontinence and dermal melanophages |
|--|------------|----------------|-----------------|----------------|--------------------|------------------------|---------------------------|---|---|----------------------|-----------------|--|
| Ashy dermatosis (n=16)                         | 1          | 4              | 0               | 1              | 5                  | 5                      | 0                         | 12/9  | 0/3   | 0                    | 12              | 7/8  |
| Lichen planus pigmentosus (n=4)                | 2          | 2              | 1               | 0              | 1                  | 4                      | 1                         | 0/1   | 4/0   | 3                    | 0               | 3/4  |
| Idiopathic eruptive macular pigmentation (n=3) | 1          | 0              | 0               | 0              | 3                  | 0                      | 0                         | 0/1   | 0/0   | 0                    | 0               | 2/2  |

this study who had no papillomatosis and no velvety surface clinically of three cases.

Bhutani *et al.*<sup>[16,22]</sup> described LPP lesions with similar pigmentation to that described by Ramirez, some of whom had lichen planus concomitantly in 1974.<sup>[16,22]</sup> These lesions had histopathological findings similar to lichen planus with epidermal vacuolization and lichenoid infiltration. In 2003, Kanwar *et al.* conducted a large study and suggested that LPP, a distinct clinical entity, should be considered in the spectrum of lichenoid disorders as a variant of lichen planus.<sup>[23]</sup> However, mostly, such cases never develop typical lichen planus concurrently or hereinafter. According to the global consensus forum conclusions, it is thought that LPP may not be etiopathologically related to lichen planus. If the hyperpigmentation is limited to areas of previous lichen planus lesions and lesions of lichen planus present, it is best to tend labeling with post-inflammatory hyperpigmentation.<sup>[3]</sup>

LPP involves the head and neck in most cases, the next common area of involvement is the flexures, particularly armpit. With time the upper extremities and upper part of the back and trunk may also be involved. LPP lesions are found on sun-exposed areas as well as nonsun-exposed areas.<sup>[3,23,24]</sup> In our LPP patients, upper limbs (3/4) were the most predilection area, and one of the female patients' lesions was on intertriginous folds.

The most distinctive feature of MPUE is the unknown etiology in the absence of preceding or concurrent inflammatory lesions. Simply post-inflammatory hyperpigmentation due to known conditions may be determined easily, whereas other possible conditions may be challenging. For instance, pigmented contact dermatitis and pigmented cosmetic contact dermatitis that may occur following noneczematous mild inflammatory dermatosis should be kept in mind. The patch test application might be beneficial in such cases. Other causes of pigmentation, such as medicinal drugs, food additives, and food coloring should be carefully excluded as the pigmentation can be insidious.

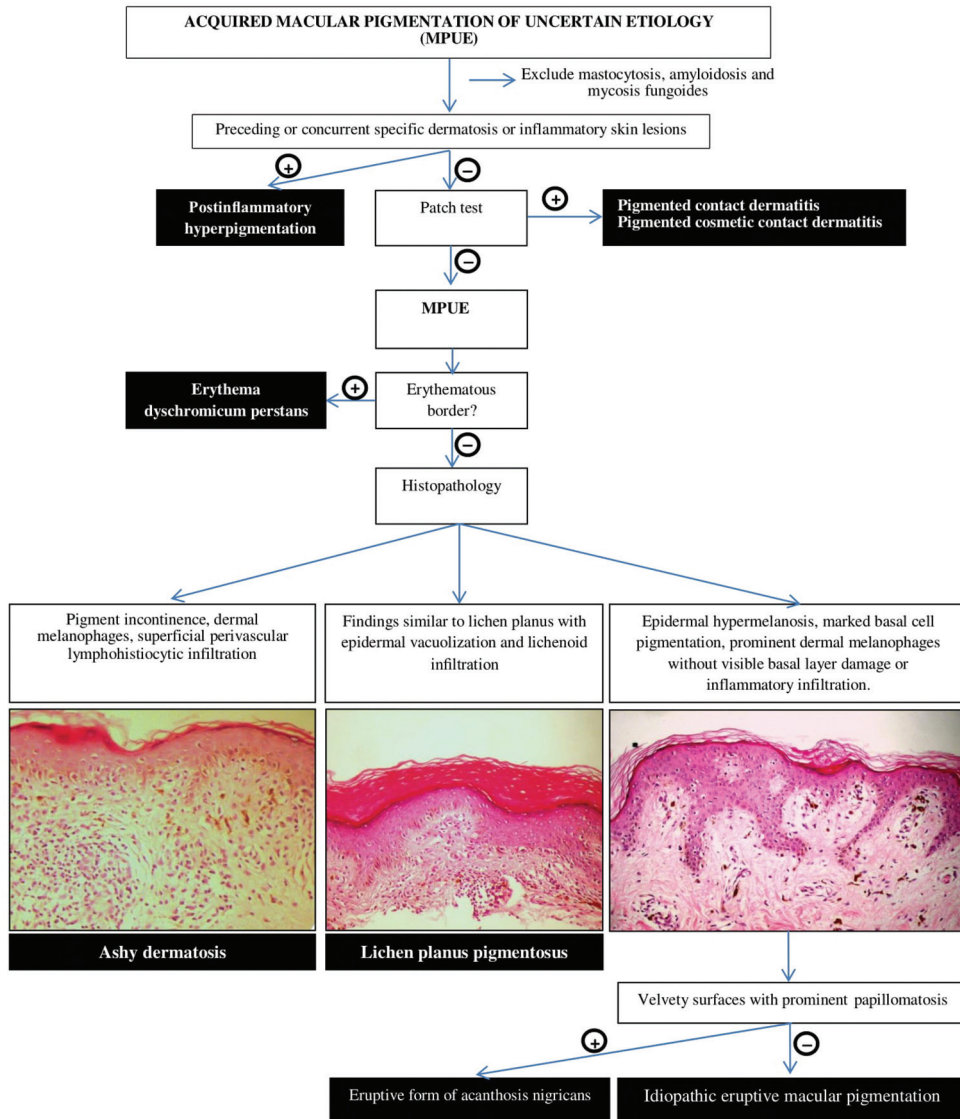
## CONCLUSION

We believe that triggering factors, histopathological examinations, and the novel global consensus classifications reported by Kumarasinghe, need to be taken into consideration throughout formal diagnostic processes.

As a result of this study, we propose a diagnostic algorithm [Figure 2]. Thus, a collective terminology for this disease spectrum could be established in the literature with such a diagnostic consensus.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients' parents have given their consent for patients' images and other clinical information to be reported in the journal. The patients' parents understand that patients' names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.



**Figure 2:** Clinicopathological algorithm of acquired MPUE



**Figure 3:** Cutaneous macules in colors with various shades of brown in lichen planus pigmentosus patient in intertriginous areas



**Figure 4:** Cutaneous macules in colors with various shades of brown in eruptive macular pigmentation patient

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## Conflicts of interest

There are no conflicts of interest.

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