



Original Research

Incidence, Histopathological Features and Differential Diagnosis of Cutaneous Graft Versus Host Disease in Allogeneic Bone Marrow Transplantation

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Abstract

Objectives: Hematopoietic stem cell transplantation by allogeneic bone marrow transplantation is a method used in the treatment of various genetic, immunological disorders, hematologic and solid organ malignancies. Graft versus Host Disease is one of the major and fatal complications of allogeneic bone marrow transplantation. It is a systemic disease affecting five main areas: skin, gastrointestinal tract, liver, lung and hematopoietic system. Diagnosis of cutaneous Graft versus Host Disease is made by the correlation between clinical and histopathological findings of the patient. The present study aims to investigate the incidence of cutaneous graft versus Host Disease in allogeneic bone marrow transplantation patients in our center, to discuss the histopathological features and differential diagnosis of cutaneous graft versus Host Disease in the light of the literature.

Methods: The pathology slides of allogeneic bone marrow transplantation patients who were diagnosed as graft versus Host Disease in our pathology department between January 2015 and January 2019 were re-evaluated. Epidermal and dermal histomorphological findings of the disease were classified; the patients' clinical and demographic information was obtained from the files. The incidence of cutaneous Graft versus Host Disease was calculated.

Results: In our center, between January 2015 and January 2019, 273 pediatric and 100 adult patients underwent allogeneic and 181 autologous bone marrow transplantation. Twenty-three patients who underwent allogeneic bone marrow transplantation had cutaneous Graft versus Host Disease whereas 21 patients had gastrointestinal Graft versus Host Disease. The incidence of cutaneous and gastrointestinal Graft versus Host Disease was 16.1% whereas the incidence of cutaneous Graft versus Host Disease was 8.42%. The most common clinical differential diagnosis of cutaneous Graft versus Host Disease was drug reaction (74%). The most common epidermal histomorphologic finding in our cases was keratinocyte necrosis (87%). In our cases, the most common epidermal histomorphologic finding was keratinocyte necrosis (87%). This was followed by vacuolar degeneration in basal keratinocytes (63%), acanthosis and spongiosis (61%), respectively. The most common finding in the dermis was pigment incontinence (59%). Of the patients with Graft versus Host Disease, 56% had transplantation from unrelated donors, whereas 44% of them had transplantation from their relatives.

Conclusion: Cutaneous Graft versus Host Disease is a common complication of allogeneic hematopoietic stem cell transplantation. It is associated with high mortality rates and has a significant negative impact on the patient's quality of life. Dermatological early recognition of the disease; histopathological evaluation and verification with differential diagnosis plays a key role in preventing patient morbidity and mortality.

Keywords: Differential diagnosis, histopathologic, GvHD, Graft versus Host Disease, incidence.

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Graft versus Host Disease (GvHD) is a complication that is one of the most important causes of morbidity and mortality in allogeneic bone marrow transplantation (BMT) recipients. The basic mechanism of GvHD can be summarized as the attack of immunocompetent donor cells against the tissues of the immunocompromised recipient.^[1] GvHD is classified clinically as acute and chronic according to the onset time after BMT. Regardless of clinical findings, it is defined as acute GvHD if followed in the first 100 days after transplantation and chronic GvHD if followed 100 days after transplantation.^[2] GvHD is observed in 40% to 60% of patients undergoing BMT concerning recipient and donor-related factors. Mortality occurs in approximately 15% of affected patients.^[2]

Cutaneous GvHD usually presents as erythematous maculopapular rashes on the face, ears and palmoplantar region. Follicular erythema is one of the earliest signs of acute cutaneous GvHD.^[3, 4] Histopathologic findings of the affected skin are focal or diffuse basal layer epithelial vacuolization in the epidermis (grade I), dyskeratotic keratinocytes adjacent to spongiosis and intraepidermal lymphocytes (grade II), necrotic keratinocytes with eosinophilic cytoplasm, and subepidermal cleavage (grade III), and complete epidermal loss (grade IV).

The suspicion of cutaneous GvHD usually appears with the patient's clinical findings.^[1] Dermatologists undertake an important role in allogeneic BMT patients by assessing the existing rash, suspecting about GvHD and determining the differential diagnosis.^[2] Biopsies can be taken from the patients for the confirmation of the diagnosis.^[1] Additionally, acute cutaneous GvHD can clinically mimic dermatological disorders, such as drug eruption, viral exanthems, acral erythema, toxic epidermal necrolysis, and radiation dermatitis. Histopathological examination has been playing an important role in the diagnosis and treatment of acute and chronic GvHD in determining the pathophysiology of the disease for many years. According to the National Health Institute consensus THE 2014 Pathology Working Group Report on GvHD, minimal criteria for acute GvHD are:

Epidermal/hair follicle outer root sheath/sweat ducts epidermal basal layer±lichenoid inflammation in dermis±lymphocytic satellitosis. The National Health Institute (NIH) recommended final diagnostic categories are: no GvHD, possible GvHD, and likely GvHD.^[5] Treatment usually consists of high-dose steroids and in steroid-resistant cases phototherapy.^[6]

This study aims to calculate the incidence of cutaneous GvHD in patients who underwent BMT between January 2015 and January 2019 and to discuss the demographic and histomorphological findings of the cutaneous GvHD

patients, emphasising the differential diagnosis with the light of the literature.

Methods

The pathology slides of patients who had undergone BMT and diagnosed as cutaneous GvHD in our pathology department were re-evaluated and histomorphological findings were classified; the patient's clinical and demographic information was obtained from the files. The incidence of cutaneous Graft versus Host Disease was calculated. Ethics committee approval of this study was received from science, social and non-invasive health sciences studies ethical committee on 04.03.2019 (no: 2019/3).

Results

In the last four years, 173 pediatric and 100 adult allogeneic and 181 autologous BMT were performed in our center. We determined cutaneous in 23 patients and gastrointestinal GvHD in 21 patients who underwent allogeneic BMT. The overall rate of GvHD in all patients was 16%; the incidence of cutaneous GvHD was 8.42%. Three (13%) of the patients with cutaneous GvHD had GvHD in the gastrointestinal system. Nine patients (42%) had GvHD in the gastrointestinal tract, while 10 patients (48%) had GvHD in the liver. Two patients had GvHD in both the gastrointestinal tract and liver.

Almost all of the cutaneous GvHD patients (n=22; 95.6%) had acute GvHD; one patient was presenting as chronic GvHD. Eight of the patients were male and 15 were female. Six patients were adult and 17 were pediatric BMT patients. KIT was performed in eight patients from relatives and in 15 patients from unrelated donors. The patients developed acute cutaneous GvHD at the earliest 12 and at the latest 400 days with an average of 78 days after BMT. The ages of the patients ranged from two to 61, with a mean age of 19 years (Table 1).

Keratinocyte necrosis was the most common epidermal histomorphologic finding in all of the GvHD cases (87%). This was followed by vacuolar degeneration (63%), acanthosis and spongiosis (61%) in basal keratinocytes, respectively. The most common finding in the dermis was pigment incontinence (59%) (Table 2).

Discussion

The incidence of GvHD in patients undergoing allogeneic bone marrow transplantation varies between 40 and 60%, depending on host and donor factors. GvHD is the cause of mortality in 15% of bone marrow transplant patients.^[2] In our patients, the incidence of GvHD in the cutaneous and gastrointestinal system was 16%. The relationship be-

Table 1. Demographic and clinical information of patients with cutaneous GvHD

Age	Sex	GvHD development time after BMT (days)	Primary disease	Is there a kinship between donor and host?
3	M	150	Beta thalassemia	Yes
4	M	22	Acute lymphoblastic leukemia	Yes
7	M	400	Acute lymphoblastic leukemia	Yes
9	M	15	Acute lymphoblastic leukemia	Yes
17	M	14	Myelodysplastic syndrome	Yes
17	F	90	Acute lymphoblastic leukemia	Yes
18	M	17	Chronic myeloid leukemia	Yes
52	M	30	Myelodysplastic syndrome	Yes
54	F	25	Acute myeloid leukemia	No
2	M	29	Beta thalassemia	No
2	M	40	Juvenile myelomonocytic leukemia	No
4	M	60	Hemophagocyticagositik lymphohistiocytosis	No
5	M	40	Acute lymphoblastic leukemia	No
7	F	26	Acute lymphoblastic leukemia	No
8	M	110	Acute lymphoblastic leukemia	No
9	F	270	Aplastic anemia	No
10	M	30	Beta thalassemia	No
15	M	12	Acute myeloid leukemia	No
15	M	14	Aplastic anemia	No
29	F	210	Acute lymphoblastic leukemia	No
31	F	43	Burkitt lymphoma	No
61	M	60	Acute myeloid leukemia	No
17	F	18	Myelodysplastic syndrome	No

tween donor gender and donor-recipient is a risk factor for GvHD development. The risk of developing GvHD was higher after BMT was performed with male and unrelated donors. In our study, BMT was performed in eight patients from relatives and in 15 patients from unrelated donors.^[7]

⁸⁾ In acute GvHD, skin involvement is one of the most common symptoms and usually occurs before post-transplant day 100, on average two to four weeks after transplantation.^[9] Our patients developed acute cutaneous GvHD at the earliest 12th and at the latest 400th days with an average of 78 days after BMT.

The most common localization of cutaneous GvHD in acute form is maculopapular rash starting from the back and trunk and spreading to the palmoplantar region and face.^[9] When the skin is the only involved organ, both clinical and histopathological features of acute GvHD may be coincided with drug hypersensitivity reactions, viral exanthems, and lymphocyte healing eruptions, making it difficult to reach a definitive diagnosis.^[2]

Involvement of certain body regions may be interpreted in favor of acute GvHD in some cases, excluding other differential diagnoses. In a retrospective study conducted by Byun et al., acute GvHD was determined to have more frequent

facial involvement than drug hypersensitivity reactions.^[10] Additionally, while acute GvHD patients had involvement in the face, palmar and plantar regions, no involvement in these areas was observed in patients diagnosed with drug eruption.^[10] In our cases, the most common type of skin rash was maculopapular rash, in accordance with the literature and the most common localization was trunk with 16 cases (70%). This was followed by the palmoplantar region with six cases (29%). In one case, maculopapular rashes were observed in the whole body.

Chronic cutaneous GvHD has a wider clinicopathological presentation and the most common type is poikiloderma, lichen planus-like eruptions, lichen sclerosus-like lesions, morphea-like plaques and deep sclerosis.^[11] In our chronic GvHD case, morphea-like plaques formed by the combination of hard nodules on the extensor faces of the arms and legs were observed. Histopathological findings included mild fibrosis and melanin incontinence in the papillary dermis and prominent nodular type fibrosis in the deep dermis, together with sparse necrotic keratinocytes in the epidermis (Fig. 1).

Histologically, acute GvHD leads to vacuolar degeneration of the basal layer of the epidermis and formation of the

Table 2. Clinical and histomorphological features of cutaneous GvHD patients

Age	Sex	Clinical differential diagnosis	Clinical findings	Localization	Microscopic epidermal findings	Microscopic dermal findings
17	F	GvHD?	Erythematous maculopapular rash	Trunk	Atrophy in epidermis	Fibrosis, edema, pigment incontinence, perivascular lymphocytic infiltration
61	M	GvHD?	Erythematous maculopapular rash	Trunk	Atrophy in epidermis Basal vacuolar degeneration Necrotic keratinocytes Kerathyaline globules	Fibrosis, edema, pigment incontinence, perivascular lymphocytic infiltration
18	M	GvHD?	Erythematous maculopapular rash	Trunk	Atrophy in epidermis Necrotic keratinocytes	Fibrosis, edema, pigment incontinence, perivascular lymphocytic infiltration
8	F	GvHD?/ Busulphan reaction?	Erythematous maculopapular rash	Trunk	Atrophy in epidermis Basal vacuolar degeneration Necrotic keratinocytes Kerathyaline globules	Pigment incontinence, perivascular lymphocytic infiltration
39	M	GvHD? Urticaria?	Erythematous maculopapular rash	Trunk	Acanthosis Necrotic keratinocytes	Fibrosis, perivascular lymphocytic infiltration
32	F	Drug eruption?	Erythematous maculopapular rash	Trunk	Basal vacuolar degeneration Atrophy in epidermis Necrotic keratinocytes	Fibrosis, perivascular lymphocytic infiltration
54	F	GvHD?	Erythematous maculopapular rash	Palmar region	Necrotic keratinocytes	Pigment incontinence, perivascular lymphocytic infiltration
17	F	GvHD?	Erythematous maculopapular rash	Palmar region	Acanthosis Necrotic keratinocytes	Pigment incontinence, perivascular lymphocytic infiltration
10	M	GvHD?	Erythematous maculopapular rash	Trunk and face	Basal vacuolar degeneration Irregular Acanthosis Hypergranulosis Necrotic keratinocytes	Perivascular lymphoplasmacytic infiltration
9	M	GvHD?	Erythematous papular rash	Whole body	Basal vacuolar degeneration Increased mitotic activity Epidermal thinning Necrotic keratinocytes	Mild fibrosis, pigment incontinence, perivascular lymphocytic infiltration
17	M	GvHD? Drug eruption? Viral eruption?	Maculopapular rash with desquamation	Trunk	Basal vacuolar degeneration Hyperkeratosis, hypergranulosis, irregular acanthosis, spongiosis, basal vacuolar degeneration, dyskeratotic cells	Pigment incontinence, edema, perivascular lymphocytic infiltration
2	F	GvHD? Drug eruption?	Maculopapular rash	Trunk	Hyperkeratosis, hypergranulosis, irregular acanthosis, spongiosis, basal vacuolar degeneration, dyskeratotic cells	Pigment incontinence, edema, perivascular lymphocytic infiltration

Table 2. Cont.

Age	Sex	Clinical differential diagnosis	Clinical findings	Localization	Microscopic epidermal findings	Microscopic dermal findings
4	M	GvHD? Drug eruption?	Violaceous plaques	Palmoplantar region	Hyperkeratosis, hypergranulosis, irregular acanthosis, spongiosis, basal vacuolar degeneration, dyskeratotic cells	Pigment incontinence, edema, perivascular lymphocytic infiltration
8	M	GvHD	Violaceous maculopapular rash	Plantar region	Hyperkeratosis, acanthosis, necrotic keratinocytes	Mild fibrosis, sparse pigment incontinence, perivascular lymphocytic infiltration
2	M	GvHD	Violaceous maculopapular rash	Plantar region	Atrophy in epidermis, hyperkeratosis	Mild fibrosis, sparse pigment incontinence, perivascular lymphocytic infiltration
7	M	GvHD	Violaceous maculopapular rash	Trunk	Hyperkeratosis, acanthosis, Necrotic keratinocytes	Mild fibrosis, sparse pigment incontinence, perivascular lymphocytic infiltration
9	F	GvHD	Violaceous maculopapular rash	Trunk	Hyperkeratosis, necrotic keratinocytes	Mild fibrosis, sparse pigment incontinence, perivascular lymphocytic infiltration
3	M	GvHD	Erythematous maculopapular rash	Trunk	Acanthosis Spongiosis Basal vacuolar degeneration Necrotic keratinocytes	Edema ve perivascular lymphocytic infiltration
29	F	GvHD? Drug eruption? Cutaneous metastasis?	Erythematous maculopapular rash, tending to merge	Palmar region	Hyperkeratosis, acanthosis, spongiosis, dyskeratotic cells, Basal vacuolar degeneration	Pigment incontinence, perivascular lymphocytic infiltration
11	M	GvHD?	Erythematous maculopapular rash	Trunk	Normal findings	Perivascular lymphoplasmacytic infiltration
16	M	GvHD? Sezary syndrome?	Papular rash	Trunk	Acanthosis Spongiosis Basal vacuolar degeneration Sparse necrotic keratinocytes	Pigment incontinence, congestion, fibrosis
15	M	Vasculitis? GvHD?	Violaceous papules and nodules hard on palpation	Trunk and face	Irregular Acanthosis Basal vacuolar degeneration Necrotic keratinocytes	Erythrocyte extravasation, perivascular lymphoplasmacytic infiltration

dyskeratotic keratinocytes. Mild mononuclear superficial perivascular infiltrate are other findings. In later stages, epithelial damage occurs on the rete tips and hair follicles. These findings occur when T lymphocytes attack and destroy activated donor lymphocytes.^[11] In our cases, the most common epidermal histomorphologic findings were keratinocyte necrosis (87%) and vacuolar degeneration in basal keratinocytes (63%), consistent with the literature (Fig. 2). These findings were followed by acanthosis and spongiosis (61%). The most common dermal finding was pigment incontinence (59%) (Fig. 3).

Acute GvHD is histopathologically divided into four grades. Although these degrees are not clinically important, it is important for pathologists to be familiar with all forms of GvHD concerning lesions that may be involved in the differential diagnosis (Table 3).^[8] In our acute cutaneous GvHD cases, one patient had grade 1 and two patients had grade 4 GvHD, while the remaining twenty-two patients had grade 2 GvHD.

In severe drug reactions, such as erythema multiforme and toxic epidermal necrolysis, vacuolization of the basal keratinocytes and necrotic keratinocytes may also be encountered, as seen in acute cutaneous GvHD.^[12] Formerly, it was stated that monitoring a mixed inflammatory cell infiltration in the dermis, including eosinophils, might sometimes help differentiate these entities from GvHD.^[13] However, according to the recent national institutes of health consensus, the presence of tissue eosinophils in a skin biopsy should not be considered as evidence for drug hypersensitivity since they often occur in GvHD.^[5] In a study by Hausermann et al., the authors determined that the lymphocyte/macrophage ratio could help differentiate between toxic epidermal necrolysis and cutaneous GvHD. In cutaneous GvHD, since immunosuppressive therapy is used after the transplantation, the predominant cells are macrophages. If the immunosuppressive regimen fails, there is a predominance of T lymphocytes over macrophages.^[14] Similarly, Nishiwaki et al. noted that many cells in the dermal inflammatory infiltrate in untreated acute GvHD were actually CD163+ macrophages rather than T-cells.^[8]

It should also be kept in mind that drug reactions and GvHD may coexist. Furthermore, reactions due to certain chemotherapeutic agents (e.g., Busulphan) may mimic GvHD histopathologically without GvHD in the patient's clinical picture.^[15] In addition, histopathological findings of GvHD can coincide with diseases, such as viral exanthems, staphylococcal scalded skin syndrome. Therefore, in the differential diagnosis of GvHD, clinicopathological correlation is important as in all other dermatopatholog-

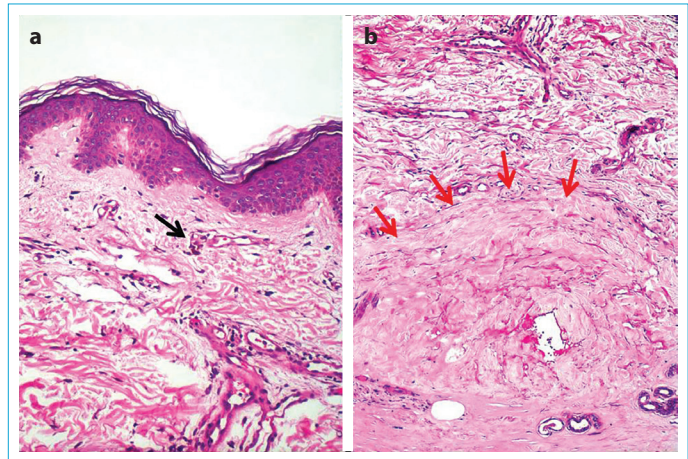


Figure 1. (a, b) Pigment incontinence in papillary dermis (black arrow); prominent, nodular type fibrosis in deep dermis (red arrows) (H&E, 100X, 200X).

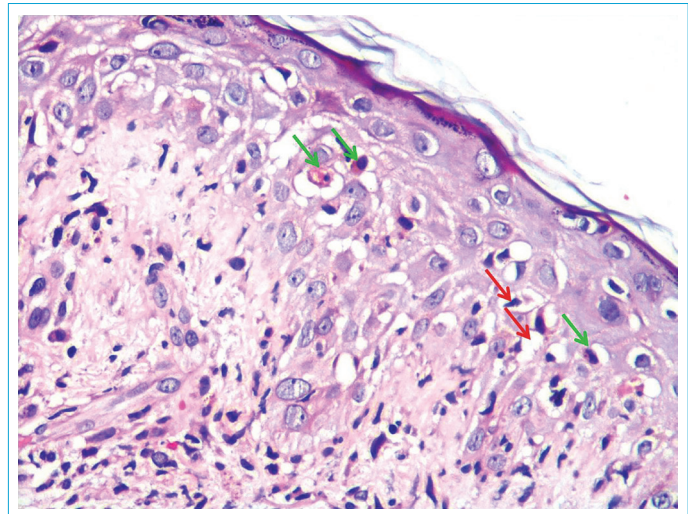


Figure 2. Basal layer vacuolar degeneration (red arrows) and numerous necrotic keratinocytes (green arrows) in the epidermis (H&E, 200X).

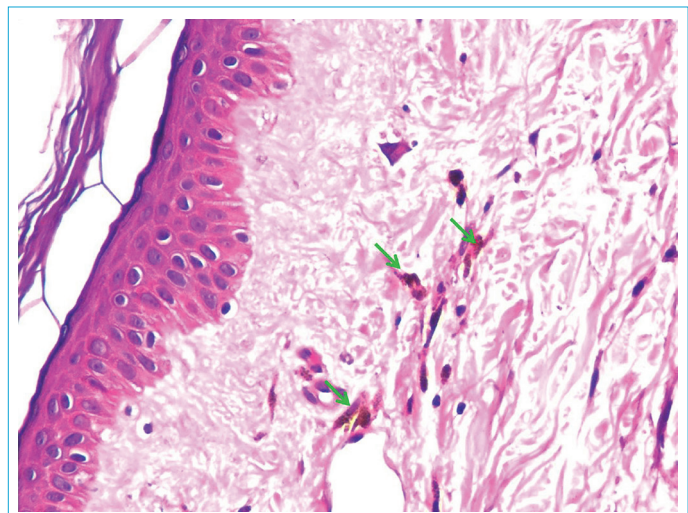


Figure 3. Many melanophages in the dermis, compatible with melanin incontinence (H&E, 200X).

ical diseases. Clinician's approach to the patient, preliminary diagnoses, drugs used by the patient may guide the pathologist in the differential diagnosis. In one of our cases, atrophy in the epidermis, basal vacuolar degeneration, necrotic keratinocytes, keratohyalin globules, as well as severely atypical keratinocytes were observed in the epidermis (Fig. 4). We found that our patient was on Busulphan. Since we had classical histopathological GvHD findings, as well as severe keratinocyte dysplasia, due to the use of Busulphan, we questioned whether the patient had clinical signs of GvHD and reached the correct diagnosis with clinicopathological correlation.

Conclusion

GvHD is one of the most important causes of morbidity and mortality observed in allogeneic BMT recipients. The diagnosis can be made with clinical suspicion and histopathological verification. To reach the diagnosis, the recognition of the early and late histopathological findings and the differential diagnosis by the pathologists together with a clinicopathological correlation is the gold standard.

Table 3. Histopathological grading of acute GvHD

- I. Vacuolar change at dermoepidermal junction
- II. Changes in grade I, dyskeratotic cells, lymphocytic infiltration in dermis.
- III. Changes in grade II, merging of the basal vacuoles and microvesicle formation
- IV. Severe necrosis and denudation of epidermis, dermoepidermal splitting.

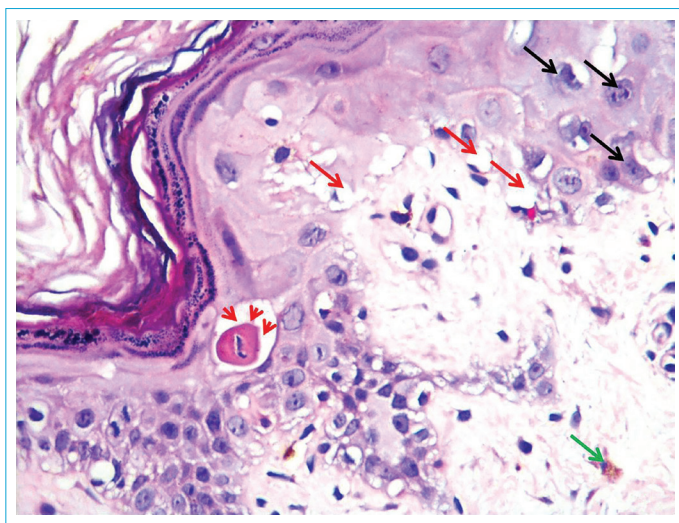


Figure 4. Severe keratinocyte atypia (black arrows), together with basal vacuolar degeneration (red arrows) and necrotic keratinocytes (red arrowheads) in epidermis and melanin incontinence in the dermis (green arrows) (H&E, 400 X).

Disclosures

Ethics Committee Approval: Ethics committee approval of this study was received from science, social and non-invasive health sciences studies ethical committee on 04.03.2019 (no: 2019/3).

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