Dermatology Practical & Conceptual

Monitoring of Vitiligo Patches Over Six Months to Validate Dermoscopic Findings of Lesional Stability

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ABSTRACT

Introduction: Previously laid down criteria for lesional stability of vitiligo are inconsistent. Longitudinal data on correlation between dermoscopic features of vitiligo and disease activity is limited.

Objectives: To sequentially determine the dermoscopic features of vitiligo and to assess their association with the dynamic nature of the vitiligo patch.

Methods: Sixty patients with 200 vitiligo patches fulfilling the inclusion criteria on medical therapy were subjected to sequential clinical and dermoscopic examination for 6 months. Baseline lesional photographs, dermoscopy and tracing of the patch was made and repeated at 6 months. The follow up tracing was superimposed onto the baseline tracing. Based on the increase or decrease in size, their outcomes were grouped as responsive, progressive and quiescent. Paired analysis of dermoscopic features was done between baseline, and their follow up after 6 months.

Results: Well defined border was associated with static nature of the vitiligo patch and ill-defined borders and trichrome pattern depicted its dynamic nature. Statistically significant increase in leukotrichia and satellite lesions amongst progressive patches and a decrease amongst responsive patches was observed. Pigment network changes were statistically significant for both responsive and progressive patches. Satellite lesions and micro-Koebner's phenomena was suggestive of progressive disease, while perifollicular pigmentation and perilesional hyperpigmentation was suggestive of re-pigmenting disease and proved to be an early marker for response to therapy.

Conclusions: Repeated dermoscopic evaluation of lesions in a serial manner to assess disease activity helps understand their evolving nature and is a valuable tool in planning appropriate further treatment.

Introduction

Lesional stability in vitiligo is of paramount importance to provide guidance in selecting patients for surgical intervention. Various definitions have been stated to explain disease stability, that are inconsistent and depict conflict amongst one another [1–6]. However, Vitiligo European Taskforce Consensus conference have stated, relying on lesional stability is far better than the overall stability of the disease, as the latter is difficult to define precisely and reliably [7]. Various clinical and experimental studies have tried to assess the lesional stability on the basis of objective biochemical and immunological parameters [8–11]. However, these investigations are not practical, may be invasive and expensive. Off late, dermoscopy has been utilized with respect to the lesional stability of vitiligo.

Some cross-sectional studies have tried to correlate the dermoscopic features with disease activity [12–15]. Results are non-homogenous and even contradictory, as far as association with disease activity/stability is concerned. In these studies, stability was assessed based on patient's history which can be unreliable, and carries a degree of recall bias. Ideally, serial clinical and dermoscopic analysis must be performed to establish lesional stability and there have been paucity of studies achieving the same. This unique study was planned to prospectively document the changes in dermoscopy in vitiligo patches over six months and correlate them with lesional activity.

Objectives

To determine the dermoscopic changes of vitiligo patches sequentially and correlate with its clinical outcome and establish dermoscopic criteria for prognosis of the disease.

Methods

Two hundred vitiligo patches from 60 patients were selected. Study was conducted as a monocenter observational longitudinal study at a tertiary hospital over a period of 18 months from April 2021 to October 2022. The study was approved by the institutional ethics committee.

Inclusion Criteria

1. All patients of vitiligo of any age group.
2. Patients who are willing to give consent and take treatment for the disease.

Exclusion Criteria

Mucosal and scalp vitiligo lesions, close differentials of hypodepigmented lesions, patients on phototherapy, previously surgically treated patches, any changes to primary morphology of lesion like manual excoriation and patches less than 1 cm^2 in size.

Study Data

Detailed patient history and lesional clinical photographs were obtained. Change in size of patches over six months was monitored by tracing the lesion on graph paper with the help of a transparent sheet. The area of the patch was calculated using the point counting method at baseline and at six months. The follow up tracing of the patch was superimposed on the baseline record of the same patch on the transparent sheet. The clinical outcomes of these patches were documented as follows:

1. Responsive-Patch having a minimum of 10% reduction in size from baseline.
2. Progressive-Patch having a minimum of 10% increase in size from baseline.
3. No change, ie quiescent -no variation in size of the patch at baseline and follow up period.
4. Resolved- complete repigmentation achieved within the patch.

Dermoscopy was performed for each vitiligo patch in a clockwise direction, using Dinolite video dermoscope (Model number AF4115ZT) with 20X magnification under polarized light. Pre-defined dermoscopic parameters [16] of border, pigment network, perilesional hyperpigmentation, perifollicular pigmentation, leukotrichia, microkoebnerisation, satellite lesions and trichrome pattern were recorded at baseline and follow-up (Table 1). All patches were treated with tailor-made topical/ systemic therapy based on the patient's subsequent response. The dermoscopic findings and size were documented at baseline and at 6 months. Dermoscopic findings based on their clinical outcomes were analyzed and compared to previously established criteria laid down for the stability of vitiligo.

Statistical Analysis

Data analysis was done using online software of SPSS 23.0. The comparison of two groups was done using one-way Chi Square test. Comparison of mean between two intervals within the group was done using Fischer exact test. A $P < 0.05$ was taken as statistically significant.

Results

Two hundred vitiligo patches from 60 patients were analyzed. Of these, there was a loss to follow-up of three patients (eight patches), and nine patches showed complete resolution; and these were not considered for final analysis. The average age of the patients was 24.21 ± 09.40 years

Table 1. Definition of dermoscopic parameters.

SrNo	Dermoscopic feature	Definition
1	Margins	Ill defined- at least 25% of the margins are ill-defined. Well-defined or ill- defined margins are mutually exclusive.
2	Perilesional Hyperpigmentation	Accentuated pigment network in at least 25% of the perilesional/marginal uninvolved skin of a vitiligo patch
3	Satellite lesions	White structureless areas of size >1mm in diameter in the perilesional skin which may not be apparent on clinical examination
4	Micro-Koebner phenomenon	Linearly arranged areas of depigmentation, which are not easily perceived by naked eye examination
5	Leukotrichia	It is defined as the presence of depigmented hair in at least 25% of total hair follicles.
6	Pigment network changes (interfollicular regions)	At baseline • Absent pigment network refers to no pigment in interfollicular regions. • Reduced pigment network refers to pigment dilution or decreased pigment as compared to the normal skin At follow-up • Initiation of Pigment network refers to onset of new pigmentation on a previously absent pigment network • Well-formed pigment Network -Formation of a reticular pigment network on follow up period. • Status Quo- A patch with absent pigment network at baseline shows the same pigment network on follow up and similarly a patch with reduced pigment network at baseline depicts same findings of pigment network on follow up period as well.
7	Perifollicular Pigmentation	Pigment network around hair follicles, in at least 25% of the hair follicles. Perifollicular re-pigmentation: refers to reappearance of pigment network around hair follicles, which previously had a complete loss of pigment network in at least 25% of the hair follicles.

(range of 05 – 70 years). Of the 183 patches studied, 102 patches (55.73%) were observed in females and the remaining 81 (44.27%) in males. The descending order of involvement of these patches were lower limbs (36.97%), upper limb (33.86%), trunk (15.10%) and 4.69% each for the face, neck and back. At the end of 6 months, 124 (64.58%) patches were responsive, 37 (19.28%) were progressive, and 22 (11.45%) had no change in size from the baseline to the follow-up period.

Dermoscopic Analysis

The changes in border (P = 0.0001) and trichome pattern (P = 0.02) in responsive vitiligo patches from baseline to six-month follow-up were statistically significant. A significant number of patches had ill-defined borders among both responsive and progressive groups. Ill-defined borders were present in 82.2% of responsive patches at their baseline. Of these patches, 98.04% continued to show ill-defined borders at the follow up period. Among progressive patches, 78.38% had ill-defined borders at baseline, of which 100% remained ill-defined at follow up. Well defined borders of quiescent patches (81.82%) showed no change over 6 months (Table 2).

Findings of leukotrichia and satellite lesions decreased from baseline to follow-up in responsive patches, and increased in progressive patches, and the differences seen for both of these parameters were statistically significant (Tables 3 and 4).

There was also a statistically significant increase of perifollicular pigmentation and perilesional hyperpigmentation amongst responsive patches at follow up, and a decrease in the same for progressive patches, when compared to their respective baselines (Table 3). A statistically significant difference in the perifollicular pigmentation were noted in those that had terminal hair versus those that had vellus hair within responsive patches.

Pigment network changes were seen in both responsive and progressive patches, whose differences from baseline to follow up period were statistically significant (Table 5).

Conclusions

In the present study, dermoscopic parameters were studied by observing dynamic changes in a vitiligo patch over a period of 6 months while receiving therapy, to verify the lesional stability.

Table 2. Dermoscopic features – Border and Trichrome pattern according to outcome patients at Baseline and Follow-up of the lesion in the study population.

Dermoscopic features	Responsive(124) N(%)				Progressive(37) N(%)				No change(22) N(%)			
1. Border	Well Defined (Baseline) 22 (17.74)		Ill defined (Baseline) 102 (82.2)		Well Defined (Baseline) 08 (21.62)		Ill defined (Baseline) 29 (78.38)		Well Defined (Baseline) 18 (81.82)		Ill defined (Baseline) 04 (18.18)	
	Well defined (FU) 06 (27.27)	Ill defined (FU) 16 (72.73)	Well defined (FU) 02 (1.96)	Ill defined (FU) 100 (98.04)	Well defined (FU) 01 (12.5)	Ill defined (FU) 07 (87.5)	Well defined (FU) 0 (0)	Ill defined (FU) 29 (100)	Well defined (FU) 18 (100)	Ill defined (FU) 0 (0)	Well defined (FU) 0 (0)	Ill defined (FU) 4 (100)
	p value = 0.0001				p value = 1				p value =1			
2. Trichrome	Present (Baseline) 52 (41.94)		Absent (Baseline) 72 (58.06)		Present (Baseline) 17 (45.95)		Absent (Baseline) 20 (54.05)		Present (Baseline) 02 (9.09)		Absent (Baseline) 20 (90.91)	
	Present (FU) 24 (46.14)	Absent (FU) 28 (53.85)	Present (FU) 07 (9.72)	Absent (FU) 65 (90.28)	Present (FU) 12 (70.59)	Absent (FU) 05 (29.41)	Present (FU) 07 (35)	Absent (FU) 13 (65)	Present (FU) 01 (50)	Absent (FU) 01 (50)	Present (FU) 0 (0)	Absent (FU) 20 (100)
	P = 0.02				P = 0.7004				P = 1			

FU = follow-up.

Table 3. Dermoscopic features of leukotrichia, perifollicular pigmentation and perilesional pigmentation according to outcome of patients at baseline and follow-up of the lesion in the study population.

Dermoscopic features	Responsive (N=124)				Progressive (N=37)				No change (N=22)			
Leukotrichia	Present-Baseline 38 (30.65)		Absent - Baseline 86 (69.35)		Present - Baseline 15 (40.54)		Absent - Baseline 22 (59.46)		Present - Baseline 9 (40.91)		Absent - Baseline 13 (59.09)	
	Present (FU) 18 (47.37)	Absent (FU) 20 (52.63)	Present (FU) 3 (3.49)	Absent (FU) 83 (96.51)	Present (FU) 11 (73.33)	Absent (FU) 04 (26.67)	Present (FU) 08 (36.36)	Absent (FU) 14 (63.64)	Present (FU) 08 (88.89)	Absent (FU) 01 (11.11)	Present (FU) 01 (7.69)	Absent (FU) 12 (92.31)
	P = 0.0001				P = 0.03				P = 0.96			
Perifollicular pigmentation	Present - Baseline 65 (52.42)		Absent - Baseline 59 (47.58)		Present - Baseline 13 (35.14)		Absent - Baseline 24 (64.86)		Present - Baseline 05 (22.73)		Absent - Baseline 17(77.27)	
	Present (FU) 64 (98.46)	Absent (FU) 1 (1.54)	Present (FU) 41 (69.49)	Absent (FU) 18 (30.51)	Present (FU) 08 (61.54)	Absent (FU) 05 (38.46)	Present (FU) 02 (8.33)	Absent (FU) 22 (91.67)	Present (FU) 02 (40)	Absent (FU) 03 (60)	Present (FU) 01 (5.88)	Absent (FU) 16 (94.12)
	P = 0.00001				P = 0.0005				P = 0.67			
Perilesional Hyper-pigmentaion	Present - Baseline 60 (48.39)		Absent - Baseline 64 (51.61)		Present - Baseline 13 (35.14)		Absent - Baseline 24 (64.86)		Present - Baseline 04 (18.18)		Absent - Baseline 18 (81.82)	
	Present (FU) 57 (95)	Absent (FU) 03 (5)	Present (FU) 33 (51.56)	Absent (FU) 31 (48.44)	Present (FU) 05 (38.46)	Absent (FU) 08 (61.54)	Present (FU) 02 (8.33)	Absent (FU) 22 (91.67)	Present (FU) 01 (25)	Absent (FU) 03 (75)	Present (FU) 0 (0)	Absent (FU) 18 (100)
	P = 0.0001				P = 0.02				P = 1			

FU = follow-up.

Table 4. Dermoscopic features of satellite lesions and microkoebnerisation according to outcome of patients at baseline and follow-up of the lesion in the study population.

Dermoscopic features	Responsive (N=124)				Progressive (N=37)				No change (N=22)			
Satellite Lesions	Present - Baseline 36 (29.03)		Absent - Baseline 88 (70.97)		Present - Baseline 13 (35.14)		Absent - Baseline 24 (64.86)		Present - Baseline 03 (13.64)		Absent - Baseline 19 (86.36)	
	Present (FU) 13 (36.11)	Absent (FU) 23 (63.89)	Present (FU) 04 (4.55)	Absent (FU) 84 (95.45)	Present (FU) 10 (76.92)	Absent (FU) 03 (23.08)	Present (FU) 09 (37.5)	Absent (FU) 15 (62.5)	Present (FU) 03 (100)	Absent (FU) 0 (0)	Present (FU) 0 (0)	Absent (FU) 19 (100)
	P = 0.001				P = 0.02				P = 1			
Microkoebnerisation	Present - Baseline 16 (12.90)		Absent - Baseline 108 (87.10)		Present - Baseline 08 (21.62)		Absent - Baseline 29 (78.38)		Present - Baseline 1 (4.55)		Absent - Baseline 21 (95.45)	
	Present (FU) 06 (37.5)	Absent (FU) 10 (62.5)	Present (FU) 04 (3.7)	Absent (FU) 104 (96.3)	Present (FU) 07 (87.5)	Absent (FU) 01 (12.5)	Present (FU) 06 (20.69)	Absent (FU) 23 (79.31)	Present (FU) 1 (100)	Absent (FU) 0 (0)	Present (FU) 0 (0)	Absent (FU) 21 (100)
	P = 0.32				P = 0.0004				P = 1			

FU = follow-up.

Table 5. Dermoscopic features of pigment network according to outcome of patients at Baseline and Follow-up of the lesion in the study population.

Pigment Network		Baseline N (%)	Change	Follow-up (6 months), N(%)	P - Value
Responsive (124)	Absent	88 (70.97)	Absent (SQ)	58(65.91)	0.0001
			IPN	25(28.41)	
			WFPN	05(5.68)	
	Reduced	36 (29.03)	Reduced (SQ)	15(41.67)	
			WFPN	20(55.56)	
			Absent	01(2.78)	
Progressive (37)	Absent	29 (78.38)	Absent (SQ)	24(82.76)	0.0001
			WFPN	0(0)	
			IPN	05(17.24)	
	Reduced	08 (21.62)	WFPN	0(0)	
			Reduced (SQ)	01(12.5)	
			Absent	07(87.5)	
No Change (22)	Absent	20 (90.91)	Absent (SQ)	18(90)	1
			IPN	02(10)	
			WFPN	0(0)	
	Reduced	02 (9.09)	Absent	0(0)	
			WFPN	0(0)	
			Reduced (SQ)	02(100)	

IPN = initiation of pigment network; SQ = status quo; WFPN = well-formed pigment network.

Table 6. Summary of dermoscopic findings of our study.

Dermoscopic finding	Findings of previous studies	Conclusions of our study
Well defined border	Marker of stability [15,19,20]	Marker of static nature of disease which has poor tendency for marginal re-pigmentation
Ill-defined border	Marker of instability [15,17], activity of the disease, poor prognosis [18]	Marker of dynamic nature of the patch which has a potential to re-pigment (upgrade) with treatment. Hence, not necessarily a poor prognostic factor.
Trichrome pattern	Marker of activity/ progressive nature of the disease/ poor prognostic factor [20,23-26]	Marker of both re-pigmentating and progressive vitiligo and not a reliable marker to define prognosis and instability of the condition.
Leukotrichia	Poor prognosis [15,27] Marker of instability	Leukotrichia may reverse after therapy. Patches with leukotrichia may still show re-pigmentation, hence it is not necessarily a poor prognostic factor
Perifollicular pigmentation and perilesional hyperpigmentation	Marker of stability Marker for re-pigmentation [16,21]	Aids in re-pigmentation of patch Marker of response to therapy
Satellite lesion and microkoebnerisation	Marker of activity /unstable nature of the disease [15,16,29,30]	Marker of activity/ progressive nature of vitiligo patch

Lesional stability and the disease stability of vitiligo do not go hand in hand. A patient with unstable vitiligo can have several stable vitiligo patches. Various studies have aimed to define the stability of vitiligo but failed to reach a common consensus. Previous studies have laid down dermoscopic characteristics of "unstable" and "stable" vitiligo with inconsistent conclusions. Dermoscopic parameters of ill-defined borders, trichrome pattern, satellite lesions,

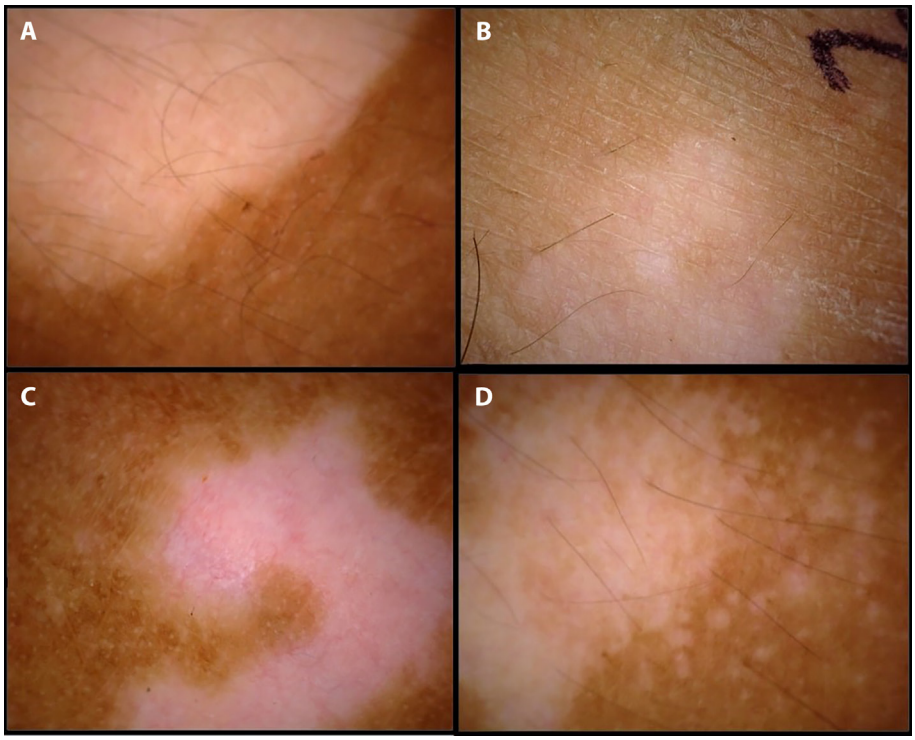

Figure 1. (A) Well-defined border; (B) Ill-defined border; (C) Trichrome pattern; (D) Satellite lesions.

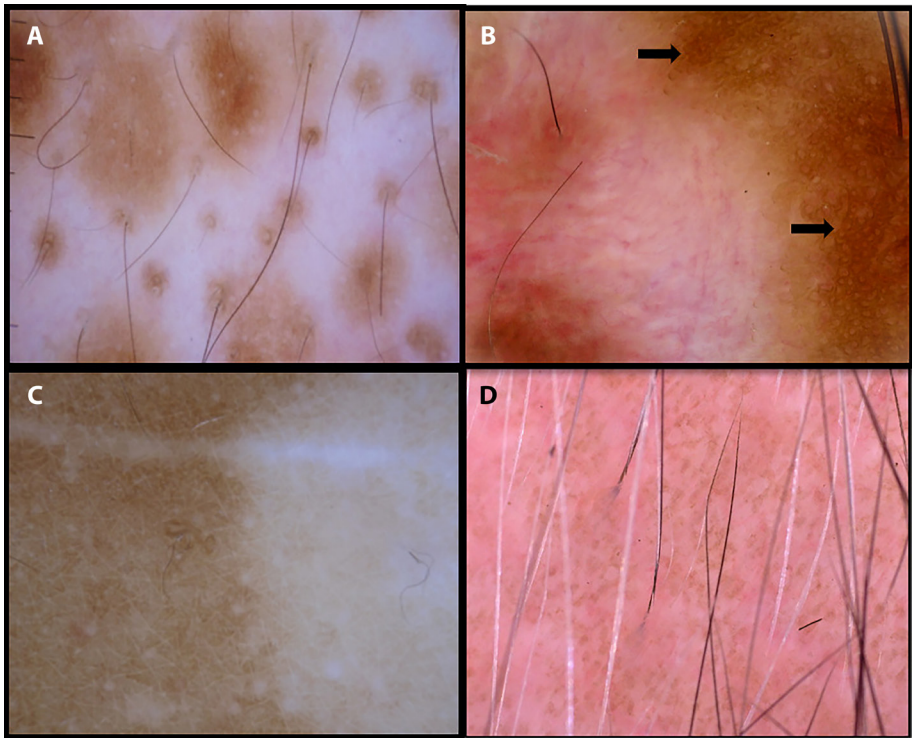

Figure 2. (A) Perifollicular pigmentation; (B) Perilesional Hyperpigmentation (black arrows); (C) Micro-koebnerisation; (D) Leukotrichia.

leukotrichia and micro-koebnerisation were largely linked with unstable vitiligo, and well-defined borders, perilesional hyperpigmentation and an absent/reduced pigment network as positive predictive markers for stability [15,17-19]. They linked the stability of a vitiligo patch to its static nature or a good prognostic factor, and the term "unstable" was synonymous with progressive disease. Dermoscopic features of unstable vitiligo described by previous authors were seen even in the responsive patches. These studies failed to document the dynamic changes of the disease, due to their cross-sectional nature and the results derived were not corroborative.

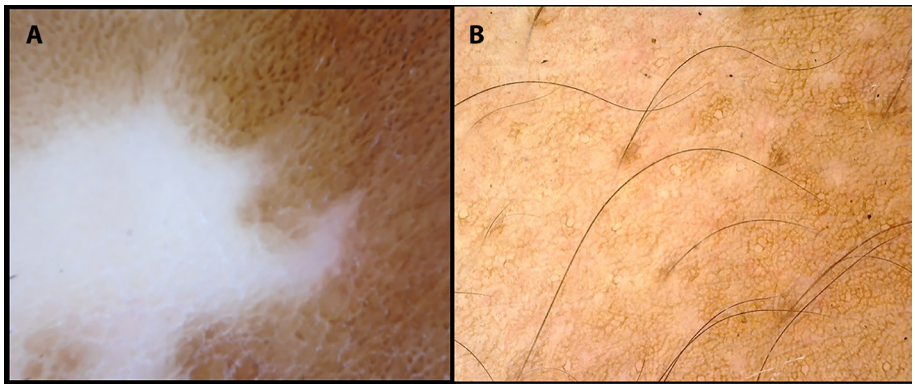

Figure 3. (A) Absent pigment network; (B) Reduced pigment network.

Few prospective studies have tried to assess dermoscopic parameters of vitiligo patches to monitor their therapeutic response [21,22]. However, these studies lacked data on lesional stability. Erichetti et al, checked perifollicular pigmentation, non-follicular pigmentation, leukotrichia and follicular red dots. They found perifollicular pigmentation to be associated with response to NB-UVB phototherapy [21]. Gupta et al analyzed 60 active vitiligo lesions over 12 weeks, on treatment [16]. They found perifollicular re-pigmentation to be a marker for response, and perifollicular depigmentation, satellite lesions micro-koebnerisation to be a marker for activity of the disease and did not draw any conclusion with respect to perilesional hyperpigmentation and disease activity. However, there is paucity of data evaluating lesions over a longer duration with a larger sample size to validate findings of lesional stability.

In various studies, well-defined borders have been reported as a marker of stability or good prognosis of the disease [15,19,20]. The present study confirmed that well defined borders is associated with a static nature of vitiligo patch with low chances of marginal re-pigmentation. Hence, the term "stable" cannot always be used to represent a good prognosis for the disease Ill-defined borders were seen in both responsive and progressive patches and hence it is related to the dynamic characteristic of the patch. Such borders have potential to re-pigment with optimum treatment, and hence it is not necessarily a poor prognostic factor.

Trichrome pattern also reflects the dynamic character of the patch and not a reliable marker to define prognosis and instability of the condition, contrary to the findings of previous studies [20,23–26]. The present study found statistically significant change in trichrome pattern during follow up period amongst responsive patches.

Incidence of leukotrichia from baseline decreased in responsive patches, and increased in progressive patches, with these changes being statistically significant. It has been considered as a poor prognostic factor [15,27] probably because it indicates that the melanocyte reservoir within the hair bulb has been destroyed indicating that the possibility of re-pigmentation is minimal. In contrast, our study revealed reversal of leukotrichia amongst responsive patches. Hence it is not necessarily a poor prognostic factor. Our study found that responsive patches with leukotrichia at baseline exhibited evidence of re-pigmentation, which contributes to the development of pigmentation within the patch. Additionally, it was seen in progressive patches, that the color of pigmented hair disappeared over time (increase in incidence of leukotrichia) along with depigmentation of the skin, which was attributed to the natural progression of the disease.

Overall incidence of perifollicular pigmentation increased in responsive patches from 52.4% at baseline (65 out of 124) to 84.67% (105 out of 124).

Perifollicular pigmentation can be due to two reasons:

1. perifollicular pigment retention in a vitiliginous patch refers to the pigment around hair follicle retained;
2. perifollicular re-pigmentation, refers to appearance of new pigmentation from follicular melanocytes in a vitiligo patch.

These findings can be assessed only when a patch is monitored over a period of time.

Of 65 responsive patches, 64 showed perifollicular pigmentation at baseline and follow up period, ie perifollicular pigment retention. The perifollicular pigmentation of such patches was enhanced and notably darker than at baseline. Of responsive patches that had no perifollicular pigmentation at baseline, 69.5% developed perifollicular pigmentation at follow up period, ie perifollicular re-pigmentation. Increase in findings of perifollicular pigmentation in responsive patches and its decrease amongst progressive patches were both statistically significant. This is consistent with findings from previous studies where perifollicular re-pigmentation was found to be associated with re-pigmenting disease [16,21] but in contrast to few other studies that have claimed perifollicular pigmentation to be a marker of active disease [28,29]. It is merely impossible to comment

on whether perifollicular pigmentation is a marker of active disease on cross sectional observation.

Our study shows that perilesional hyperpigmentation is a marker of re-pigmenting vitiligo in concurrence with a study by Gupta et al [16]. Many cross-sectional studies have stated it to be a marker of stable disease [28,30]. There is paucity of studies observing this finding in a longitudinal manner. Hence, more such studies with larger sample size will help to reach a conclusive statement regarding this finding.

Satellite lesion and micro-Koebner phenomenon reflect similar features of perilesional disease activity. There was a significant increase of these findings at follow-up visits for progressive patches supporting the fact that these findings are considered as markers of active disease [15,16,29,30]. Lesions showing these features clinically or on dermoscopy are expected to progress if left untreated. Changes in pigment network, are consistent with dynamic nature of a patch. We observed that interfollicular pigment network may take longer to appear as compared to perifollicular or perilesional pigmentation while on therapy.

Our study concluded that a well-defined border is associated with the static nature of a vitiligo patch. However, lesions with an ill-defined border and trichrome pattern suggest the dynamic nature of the patch and are not reliable markers to define the prognosis and instability of the condition. Perifollicular pigmentation and perilesional hyperpigmentation are a marker of re-pigmenting vitiligo and can predict the response to therapy. Dermoscopic findings of leukotrichia, satellite lesions and micro-koebnerisation are significantly associated with progressive vitiligo. Leukotrichia may reverse after therapy. Repeated dermoscopic evaluation of lesions in a serial manner to assess disease activity helps understand their evolving nature and is a valuable tool in planning appropriate further treatment.

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