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Choroidal thickness, ganglion cell layer and retinal nerve fiber layer: An evaluation in vitiligo patients

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ABSTRACT

Aim: To evaluate the choroidal and retinal structures in vitiligo patients without periocular involvement.
Methods: Choroidal and retinal images of 30 vitiligo patients and 31 healthy individuals were taken using spectral-domain optical coherence tomography (OCT), in this study. The choroidal thickness (CT) was measured at the fovea and at two points 1500 μm nasal and temporal positions to the fovea in a horizontal section.
Results: Subfoveal CT values were significantly lower in vitiligo patients ($p = 0.037$). The differences between the groups in terms of superior quadrant retinal nerve fiber layer (RNFL) and average macular ganglion cell–inner plexiform layer (mGCIPL) values ($p = 0.035$ and $p = 0.004$, respectively) were statistically significant. Vitiligo area severity index (VASI) negatively correlated only with nasal RNFL values ($r = -0.370$). There was no significant correlation between other OCT parameters and VASI values ($p > 0.05$).
Conclusion: CT and mGCIPL were found to be thinner in vitiligo patients. Progressive damage to the melanocytes in vitiligo, which play a protective role in the ocular structure, may result in these findings.

Key words: Vitiligo, optical coherence tomography, choroidal thickness, vitiligo area severity index, pigmentation disorder.

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Introduction

Vitiligo is a pigmentation disorder that causes selective melanocyte loss in genetically susceptible individuals, which is thought to be caused by environmental and immunological factors [1]. The exact pathogenesis of the disease is unclear. The worldwide incidence of vitiligo varies within the range of about 0.5%–2%. Although the lesions usually begin in childhood, they can occur at any age [2]. Various classifications are used for vitiligo based on its spread and localization. According to the commonly used classification, it is classified into three groups: localized, generalized, and universal. The localized type may manifest as focal, segmental, or acrofacial [3]. In addition to the skin, the uveal tissue and retinal pigment epithelium in the eye are rich in melanocytes originating from the neural crest. Pigment cell destruction in vitiligo may contain other tissues than the skin. In biomicroscopic examination, changes that do not generally cause visual impairment including iris, retina and choroidal pigment anomalies and

peripapillary atrophy have been reported in the eyes of these patients [4,5].

Optical coherence tomography (OCT) is quite precious in the diagnosis of retinal nerve fiber layer (RNFL) and chorioretinal diseases [6]. The OCT using enhanced depth imaging (EDI-OCT) ensures comprehensive choroidal imaging and contributes to ascertaining the exact pathophysiology of many ocular diseases. The choroid, one of the tissues with excessive vascularization, has important roles in retinal oxygenation, temperature regulation, and secretion of growth factors [7,8]. Pigmented melanocytes are densely located around the choroidal blood vessels. The melanin synthesized by choroid and retinal pigment epithelium plays an important protective function by being stored in the melanosomes, absorbing light and uptaking of reactive oxygen species [9,10].

Studies that have investigated the retinal structures and choroidal thickness (CT) in patients with vitiligo are limited [4,11,12]. The current study aimed to evaluate the retinal nerve fiber, choroid, and macular ganglion cell–inner plexiform layer (mGCIPL) thickness with spectral-domain OCT in vitiligo patients, and their association with skin involvement of the disease.

Materials and methods

Thirty vitiligo patients and 31 healthy individuals providing written informed consents were included in this cross-sectional study. The study protocol was approved by Ordu University Clinical Research Ethics Committee (Date and number: 2020/172) and conducted following the principles of the Helsinki Declaration.

Patient enrollment: Patients diagnosed with vitiligo in dermatological and histopathological evaluation at the Dermatology Clinic were included. The inclusion criteria of the current study were as follows: age between 19 and 55 years, diagnosis of cutaneous vitiligo without periocular involvement, best-corrected visual acuity (BCVA) of 20/25 or better, and an ocular axial length between 20 and 25 mm. Age- and gender-matched 31 healthy objects were also included as the control group.

Patients with any anterior segment pathologies that may interfere with the OCT imaging, refractive errors of >5D spheric or >3D cylindric, a vertical cup/disc ratio greater than 0.7 or asymmetry in cup/disc ratios greater than 0.3 between two eyes, retinal diseases such as macular degeneration, previous history of ocular surgery, systemic diseases (e.g. hypertension, atherosclerotic disease, or diabetes mellitus), autoimmune diseases, Vogt-Koyanagi-Harada syndrome, glaucoma, optic disc disorders, usage of any ocular or systemic medications, smoking, pregnancy or lactation, and poor OCT images of inner and outer margin of the choroid were excluded.

Study protocol: The patients with vitiligo had not been receiving any systemic treatment within the last 6 months. All individuals underwent a detailed evaluation by the same experienced ophthalmologist, including BCVA using a Snellen chart (converted to the logMAR), slit-lamp biomicroscopy, IOP measurements using Goldmann applanation tonometry, axial length measurements with A-scan ultrasonic biometry (Pac-Scan 300, Sonomed Escalon, NY, USA), and dilated fundus examination. Retinal, RNFL, and CT measurements were obtained with spectral-domain OCT (Cirrus HD-OCT 4000, Carl Zeiss Meditec, Inc., Dublin, CA, USA). All measurements were performed between 09:00 and 12:00 am to exclude diurnal variations. Only the right eyes of the participants were included in the study.

Table 1. Vitiligo disease activity (VIDA) score.

Disease activity	***VIDA score***
Active in the past 6 weeks	+ 4
Active in the past 3 months	+ 3
Active in the past 6 months	+ 2
Active in the past 1 year	+ 1
Stable for at least 1 year	0
Stable for at least 1 year and spontaneous repigmentation	− 1

The activity of disease was specified with the vitiligo disease activity score (VIDA) (Table 1) by the same dermatologist [13]. High scores indicate that the disease is active. To evaluate the extent of the disease, vitiligo area severity index (VASI) values were calculated; lesion width and degree of depigmentation are the parameters evaluated in this scoring [14]. The VASI was determined by the product of the area of vitiligo in hand units (one hand unit was approximately equivalent to 1% of the total body surface area) and the depigmentation extent was expressed by the following percentages: 0, 10%, 25%, 50%, 75%, 90%, or 100%. Then, the VASI score [VASI=Σall body areas (hand unit)×(residual depigmentation)] was calculated by considering the total value of scores of all body areas. Patients were classified as localized, generalized, and universal, according to the extent and spread of the lesions on the body.

All OCT images were taken by the same experienced technician following a pupillary dilation 15 minutes after instillation of 2.5% phenylephrine and 1% tropicamide eyedrops, using an internal fixation target in the OCT device. The OCT scans were performed several times to exclude artifacts until at least two high-quality scans (a signal strength of >7/10) were achieved, and those with the best signal strength were analyzed. The absence of scan and algorithm failures, a clear fundus image during image acquisition, good demarcation of retinal and choroidal structures, absence of artifacts in scans were determined to ensure the quality of the OCT scans used in the study.

Central retinal thickness (CRT, 1-mm diameter circle surrounding the central fovea) and mGCIPL images were obtained using a macular cube protocol (512 × 128 scan pattern). The mGCIPL thickness was measured in a 2.4 mm horizontal and a 2.0 mm vertical radius elliptical annulus (excluding a central elliptical area with a 0.6 mm horizontal and 0.5 mm vertical radius). The measurement points for CT were determined in the horizontal image passing through the foveal center. The CT was

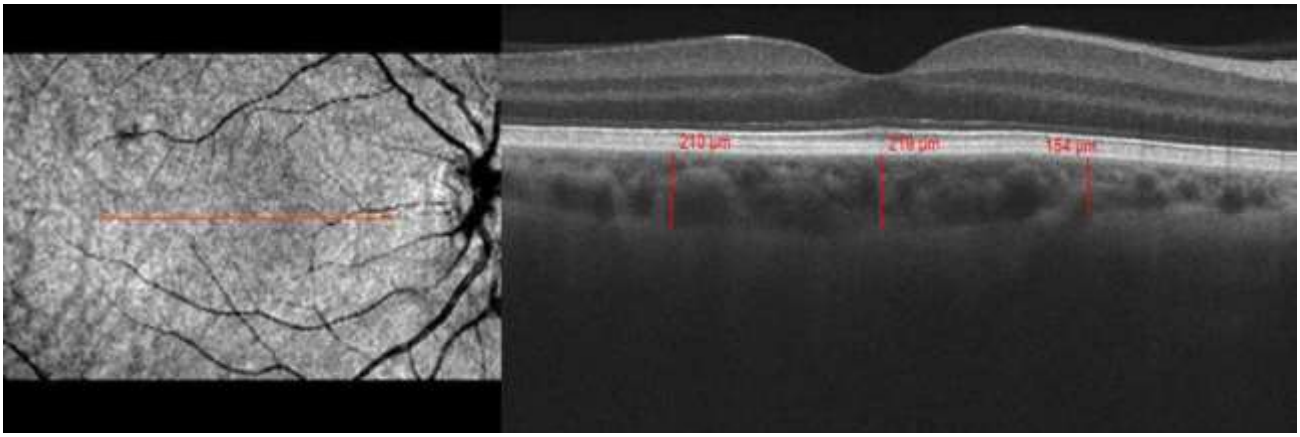

Figure 1. Optical coherence tomography image of the choroidal thickness measurement in a vitiligo patient.

measured at the subfoveal area, and the temporal and nasal segments at a distance of 1500 μm from the fovea. The choroidal images were taken with EDI-OCT. The perpendicular distance from the outer aspect of the hyperreflective layer corresponding to the retinal pigment epithelium, to the inner boundary of the sclera (Figure. 1) was measured manually to determine the CT. All manual measurements were performed using calipers of the device by two experienced ophthalmologists in different sessions (AU and AKS). Optic Disc Cube 200 × 200 scan protocol was used to acquire RNFL thickness. The mean (360°) and superior, inferior, temporal, and nasal quadrant values of peripapillary RNFL thickness calculated by the software were also recorded.

Statistical analysis: The sample size was based on the literature of the change observed in CT in vitiligo patients. A confidence level of 95% and a power of 80% yielded the sample size. All data were analyzed with the SPSS statistical software platform, version 21.0 (SPSS Inc., Chicago, IL, USA). The Kolmogorov–Smirnov test was used to perform a normality check. Normally distributed data were stated as mean and standard deviation and were compared with an independent *t*-test. The non-normally distributed data were compared using Mann–Whitney U test. Categorical variables were expressed as frequency and percent and these variables were compared using the chi-square test. The Spearman correlation coefficient was used to compare the OCT values of patients with the duration of the disease, VASI, and VIDA values. A *p* value of less than 0.05 was accepted as statistically significant.

Results

The demographics and clinical characteristics of the articipants are presented in Table 2. There were no significant differences between the groups in terms of age and gender distribution, spherical equivalent, visual acuity, axial length, and IOP values ($p > 0.05$).

None of the patients with vitiligo had periorbital depigmented patches. No retinal pathology was observed in posterior segment examinations. No retinal or choroidal findings were detected in any of the participants in the control group. When the lesions of vitiligo patients were evaluated, 16 (53.33%) were

Table 2. Demographic and clinical characteristics of the participants.

Characteristics	Vitiligo (*n* = 30)	Control (*n* = 31)	*P* value
Gender (Male/Female)	16/14 (53.3%/46.7%)	15/16 (48.4%/51.6%)	0.573
Age (years)	35.8 ± 12.55	35.0 ± 8.88	0.834
BCVA (logMAR)	0.02 ± 0.04	0.03 ± 0.00	0.260
Spherical equivalent (D)	−0.09 ± 1.08	−0.51 ± 0.91	0.165
IOP (mmHg)	15.67 ± 2.92	15.90 ± 2.56	0.509
Axial length (mm)	23.01 ± 0.66	22.89 ± 0.74	0.337

Data are given as mean ± standard deviation for continuous variables and as frequency (percentage) for categorical variables. BCVA: best-corrected visual acuity; D: diopter; IOP: intraocular pressure.

Table 3. Optical coherence tomography parameters in the vitiligo patients and control group.

Parameter (µm)	Vitiligo (n=30)	Control (n=31)	*P* value*
Subfoveal CT	311.87±74.44	351.32±56.67	**0.037**
Temporal CT	295.63±60.13	320.00±56.97	0.143
Nasal CT	271.50±63.22	295.03±54.15	0.245
Average RNFL	96.80±9.01	94.55±7.79	0.222
Temporal RNFL	65.80±7.41	66.48±6.83	0.707
Nasal RNFL	69.03±9.83	68.35±10.01	0.431
Superior RNFL	124.77±15.76	117.42±14.17	**0.035**
Inferior RNFL	126.83±15.85	126.42±12.09	0.840
CRT	247.70±17.31	254.68±18.86	0.251
Average mGCIPL	83.20±4.21	85.84±3.47	**0.004**

CT: choroidal thickness; RNFL: retinal nerve fiber layer; CRT: central retinal thickness; mGCIPL: macular ganglion cell- inner plexiform layer; Data: mean ± SD; SD: standard deviation. * Independent *t*-test.

localized and 13 (43.33%) were generalized. One (3.33%) patient had the universal type and was not included in the vitiligo subgroup analyses. The mean duration of vitiligo disease was 25.13 ± 33.74 months (range, 1 month–10 years). The mean VASI and VIDA scores were 1.63 ± 1.07 and 3.33 ± 1.37, respectively.

The OCT parameters of vitiligo patients and healthy individuals are shown in Table 3. Subfoveal CT values were significantly lower in patients with vitiligo than those in the control group (p = 0.037; Figure 2). No significant changes in temporal and nasal CT values were observed between the groups (p = 0.143 and p = 0.245, respectively). The differences between the groups in terms of superior quadrant RNFL and mGCIPL values (p = 0.035 and p = 0.004, respectively) were statistically significant. Furthermore, there were no significant differences in CRT and other RNFL values between the groups (p > 0.05).

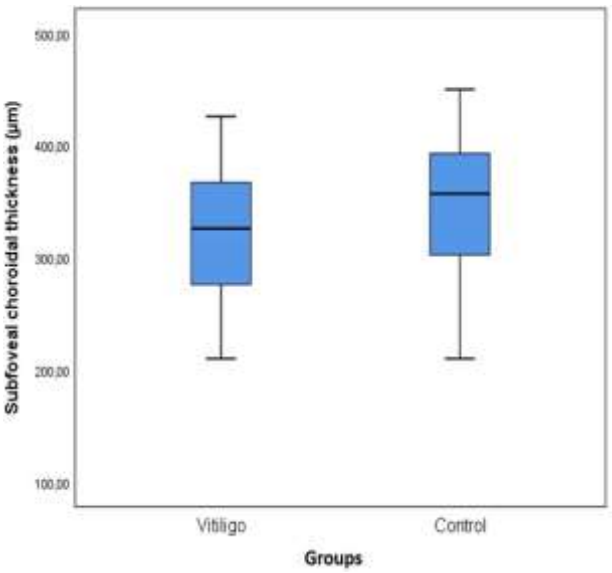

Figure 2. Subfoveal choroidal thickness of patients with vitiligo and control group. The box represents 50% of the sample. A single line inside each box represents the median.

When vitiligo patients were evaluated according to their localized- and generalized type involvement, no significant difference was

Table 4. Optical coherence tomography parameters of the vitiligo subgroups.

Parameter (µm)	Generalized (n=13)	Localized (n=16)	P value*
Subfoveal CT	287.82±80.64	343.31±53.20	0.075
Temporal CT	278.24±61.57	318.38±51.89	0.107
Nasal CT	255.82±71.83	292.00±44.47	0.116
Average RNFL	92.47±7.98	102.46±7.09	**0.001**
Temporal RNFL	63.35±7.80	69.00±5.66	**0.026**
Nasal RNFL	70.29±9.98	67.38±9.78	0.266
Superior RNFL	118.29±14.93	133.23±12.90	**0.011**
Inferior RNFL	117.65±9.64	138.85±14.41	**<0.001**
CRT	242.94±17.24	253.92±15.93	**0.025**
Average mGCIPL	82.35±4.82	84.31±3.09	0.067

CT: choroidal thickness; RNFL: retinal nerve fiber layer; CRT: central retinal thickness; mGCIPL: macular ganglion cell- inner plexiform layer; Data: mean ± SD; SD: standard deviation. * Mann Whitney U test.

found between the groups as regards CT and mGCIPL values (p > 0.05; Table 4). The average, temporal, superior and inferior values of RNFL and CRT were significantly lower in the generalized type (p = 0.001, p = 0.026, p = 0.011, p < 0.001 and p = 0.025, respectively). Whereas no significant difference between the groups as regards the mean VASI (p = 0.107) score was found, the VIDA score was significantly higher in the generalized type (p = 0.041).

A correlation analysis was performed between disease duration, VASI, VIDA values, and OCT parameters (Table 5). There was a positive correlation between the duration of vitiligo and subfoveal, temporal and nasal CT values (r = 0.532, r = 0.500 and r = 0.512, respectively). VASI negatively correlated only with nasal RNFL (r = −0.370). There was also a negative correlation between VIDA score and inferior RNFL (r = −0.478). The correlation between other OCT parameters and VASI and VIDA values was not significant (p > 0.05).

Discussion

In the literature, changes including dry eye, lens changes, transillumination defects in the iris, and uveitis have been reported as ocular findings in patients with vitiligo [5,15,16]. Vitiligo is characterized by chronic and progressive loss of melanocytes, and melanocyte-rich structures including the retina and choroid may also be expected to be affected. We investigated the morphological effects of this disease and subtypes on posterior segment structures. In the current study, we reported that subfoveal CT and mGCIPL were significantly thinner in patients with vitiligo.

Albert et al. [15] were the first investigators to report the ocular findings of vitiligo in a large series of patients. They reported fundus pathologies which included retinal pigment

Table 5. Correlation analysis between clinical characteristics of the vitiligo and OCT parameters.

Parameters		**VASI**	**VIDA**	**Duration of vitiligo**
Subfoveal CT	*r*	-0.251	-0.202	0.532
	*p**	0.182	0.284	**0.002**
Temporal CT	*r*	-0.187	-0.138	0.500
	*p**	0.323	0.468	**0.005**
Nasal CT	*r*	-0.188	-0.290	0.512
	*p**	0.319	0.120	**0.004**
Average RNFL	*r*	0.144	-0.346	0.314
	*p**	0.447	0.061	0.091
Temporal RNFL	*r*	0.343	-0.100	0.121
	*p**	0.063	0.598	0.525
Nasal RNFL	*r*	-0.370	-0.033	0.088
	*p**	**0.044**	0.864	0.642
Superior RNFL	*r*	0.168	-0.281	0.108
	*p**	0.374	0.133	0.571
Inferior RNFL	*r*	0.115	-0.478	0.477
	*p**	0.545	**0.008**	**0.008**
CRT	*r*	0,227	-0.293	0.091
	*p**	0.228	0.116	0.632
Average mGCIPL	*r*	0.101	-0.143	0.128
	*p**	0.596	0.452	0.502

OCT: optical coherence tomography; VASI: vitiligo area severity index; VIDA: vitiligo disease activity; CT: choroidal thickness; RNFL: retinal nerve fiber layer; CRT: central retinal thickness; mGCIPL: macular ganglion cell- inner plexiform layer. *Spearman correlation analysis.

epithelial hypo-pigmentation, chorioretinal scars, and pigment hyperplasia. Karadag et al. [16] evaluated 122 patients with vitiligo. They reported that lens findings and retinal pathologies including peripapillary atrophy, tigroid retina, and choroidal nevus were significantly more common in these patients than those in the control group. They also reported that 20% of the patients had fundus findings. Similarly, Fleissig et al. [4] also reported fundus findings including peripapillary atrophy (3.2%), choroidal nevus (10.32%), and hypopigmented retinal pigment epithelial lesions (6.5%) in patients with vitiligo. In our study, iris pathologies and inflammatory disorders including uveitis were not observed in any patient with vitiligo. Furthermore, none of the patients had choroidal nevus or peripapillary atrophy on fundus examinations.

Although the aetiopathogenesis of vitiligo has not been completely understood, autoimmune mechanisms are determined to be effective. Cytotoxic T lymphocytes are considered to play a role in the pathogenesis of vitiligo. Perilesional $CD8^+$ T cells have been found to induce melanocyte apoptosis and mediate autoimmune destruction [17,18]. Diseases with inflammatory pathophysiology including uveitis and dry eye, reported as ocular findings in vitiligo, suggest that immune processes are effective in the ocular manifestations of this disease. In the literature, based on a similar view, studies showed that there is a strong autoimmune effect and choroidal nevi is more common in patients with generalized vitiligo [4,19].

Retinal and CTs have been evaluated in many diseases with systemic inflammatory pathogenesis, and the choroid has been reported to be thinner in these patients [20-22]. Demirkan et al. [12] evaluated CT in patients with vitiligo and reported that the CT was significantly thinner in the subfoveal, nasal, and temporal quadrants in vitiligo patients than those in the healthy individuals. No correlation was found between CT values and disease duration; however, they showed a negative correlation with VASI. Moreover, they did not find any significant effect of periocular involvement on the CT. Öncül and Ayhan [11] evaluated 51 patients with vitiligo in detail using OCT. They found that the CT was significantly thinner in patients with vitiligo, and no significant differences were found in RPE and RNFL thickness compared to those in the control group. They also reported that periocular involvement had no significant effect on CT.

In our study, no patient had periocular involvement. Similar to the literature, the choroid was thinner in patients with vitiligo, and this difference was significant compared with that in the control group only in the subfoveal area. Furthermore, subfoveal CT values in vitiligo patients were lower compared to the values reported in the healthy population of the same ethnicity [23]. No correlation was found between CT values and VASI and VIDA, which are used as important indicators of activity and severity of the disease. However, a positive correlation was observed between disease duration and CT values. This may be due to the chronic effect of the disease and previous systemic treatments used in the disease.

RNFL may be affected in diseases in which inflammatory processes are involved [22]. Furthermore, reports that a relationship may exist between disease duration and glaucoma development in vitiligo suggest that RNFL and ganglion cells may be affected [24]. Aydin et al. [25] evaluated macular function and morphology with multifocal

electroretinography and OCT in 17 patients with vitiligo and showed that retinal function decreased in patients with vitiligo although the appearance of the fundus was normal. Furthermore, no significant change was found in RNFL and retinal ganglion cell values of the patients with vitiligo compared to healthy individuals. Ornek et al. [26] reported that no significant decrease was found in the RNFL analysis which they performed in a larger patient group. In another study, no significant change was reported in RNFL and retinal ganglion cell values in vitiligo [11]. In our study, superior quadrant RNFL was significantly thicker in patients with vitiligo, whereas no significant differences were found between the groups in average and other RNFL values. This can be explained by the lower density of melanocytes in the optic disc region. Also, unlike reports, mGCIPL was significantly thinner in vitiligo. A negative correlation was found between VASI and VIDA scores and RNFL in only one quadrant. In literature, data with which we can interpret in detail the thickness of the RNFL and ganglion cell layer in vitiligo is limited. These findings, which were obtained without changes in average RNFL and CRT, may be due to the effect of artifacts.

An increased relationship between periorbital skin involvement and ocular findings was reported [5]. Öncül and Ayhan [11] showed that the CT of patients who had the periorbital lesion with universal involvement was thinner than in those with focal involvement. This suggests that the choroid may be more affected depending on the location and extent of vitiligo lesions. In the current study, 16 (53.33%), 13 (43.33%) and 1 (3.33%) patients had localized, generalized and universal types of involvement, respectively. No significant difference between localized- and generalized type involvement of vitiligo as regards mean VASI score was found. The choroid was insignificantly thinner in all quadrants in patients with generalized involvement. Although no patients had periorbital depigmented patches, RNFL significantly decreased in the generalized type and the VIDA score was higher in this group than in the localized group. This suggests that disease activity has an important role in ocular effects such as the extent of the disease and also supports the effect of inflammatory activity on RNFL.

Our study had certain limitations. The first limitation is the limited sample size. Secondly, the number of generalized and universal types of patients was relatively low. The insufficient number of subgroup patients and their unbalanced distribution resulted in limitations in the analyses.

Conclusion

This study evaluated the choroidal and retinal structures using OCT in vitiligo patients without periocular involvement. CT and mGCIPL were thinner in patients with vitiligo. Progressive damage to the melanocytes in vitiligo, which play a protective role in the ocular structure, may result in ocular findings. The choroid being thinner, although not significant, and the decreased RNFL and retinal thicknesses in patients with generalized involvement suggest that a relationship exists between disease severity and ocular effects. The results of the present study demonstrated that disease activity, the extent of the disease, and systemic treatments used should be evaluated as a whole, and patients with vitiligo should be followed up as regards ocular involvement.

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