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Diagnostic findings in Various Cutaneous Hypopigmented Disorders: A Scoping Review

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ABSTRACT

Introduction: Medical conditions can cause the skin to become hypopigmented or depigmented, mainly due to decreased production of melanin. Hypomelanosis is mainly benign and rarely malignant. Depigmentation refers to a complete lack of melanin, with the most common cause being vitiligo. Differentiating between these conditions can be difficult. Diagnosis of the condition is primarily based on the patient's detailed history, clinical signs and symptoms, accurate evaluation, and dermoscopy. Repigmentation can occur following early diagnosis and appropriate management.

Aim: To highlight diagnostic findings of various cutaneous hypopigmented macular lesions and patches.

Materials and Methods: PubMed and Google Scholar databases were searched using a mix of terms, including "cutaneous disorders", "dermoscopy", "skin biopsy", and "hypopigmented disorders" for this scoping review, which followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses for Scoping Review (PRISMA-ScR) guidelines. Boolean operators

"AND" and "OR" were used between the keywords. The inclusion criteria consisted of articles with full text availability, articles describing various cutaneous disorders with characteristic morphology, diagnosis, types and subtypes, conditions associated with systemic diseases, histological examination findings, and prognosis of the condition, peer-reviewed papers with a comprehensive diagnosis of cutaneous hypopigmented diseases, histological biopsies. Randomised Controlled Trials (RCTs), review articles, case reports, and articles in the English language were included in this review.

Results: Based on the selection criteria, a total of 12 studies were included in the review, describing various cutaneous disorders with characteristic morphology, diagnosis, types and subtypes, conditions associated with systemic diseases, histological examination findings, and prognosis of the condition.

Conclusion: Knowledge regarding various outcomes from the studies related to diagnostic findings in various cutaneous hypopigmented disorders is essential for dermatologists for awareness, appropriate examination, and adequate treatment.

Keywords: Cutaneous disorders, Depigmentation, Dermoscopy, Histopathology, Hypomelanosis, Repigmentation, Vitiligo

INTRODUCTION

The skin can become hypopigmented or depigmented as a consequence of various medical conditions, with vitiligo being the most common cause of depigmentation worldwide. Approximately 1-2% of the global population, including people of all ethnicities, are affected by this condition [1]. Reduced generation of melanin is the primary reason for hypopigmentation or hypomelanosis, which is caused by problems linked to various mechanisms. These conditions are usually benign, moderately associated with systemic diseases (disorders of the internal organs), and rarely linked to malignancy [2]. In contrast, discolouration refers to the complete lack of melanin due to substantial depletion of melanocytes. In practice, it is difficult to distinguish between depigmented illnesses and hypopigmented conditions [1]. Nearly 1 in 20 individuals, including both adults and children, have diminished pigmentation macules [3].

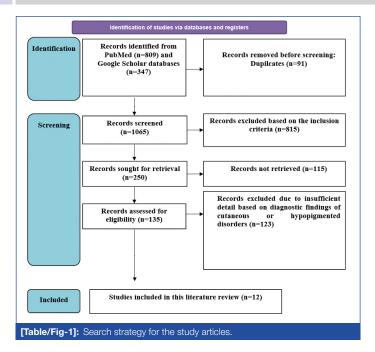
The activity of internal organs may be linked to hypomelanosis, which is frequently benign and rarely malignant. An individual's physical characteristics, which can lead to feelings of anxiety and social shame, particularly for those with darker complexions, make early identification and adequate management of primary importance [4]. Repigmentation may be possible in certain circumstances with proper evaluation and prompt management. Establishing the correct diagnosis is aided by a thorough history, clinical symptoms, appropriate assessment, and dermoscopy, which involves a non invasive procedure [4]. Despite this, skin biopsy histopathology results offer more insight into the pathophysiology, providing a better overview of the condition but involving an invasive procedure. Hypopigmented disorders can cause anxiety in patients and their

families due to social stigma in society. Therefore, this study reviews the common medical problems associated with cutaneous macular lesions and patches.

MATERIALS AND METHODS

The search strategy involved the PubMed and Google Scholar databases, including articles published between 2018 and 2022 to encompass recent findings related to hypopigmented or cutaneous disorders. The keywords used included "cutaneous disorders," "dermoscopy," "skin biopsy," and "hypopigmented disorders." Boolean operators "AND" and "OR" were used between the keywords. The inclusion criteria comprised articles with full-text availability, articles describing various cutaneous disorders with characteristic morphology, diagnosis, types and subtypes, conditions associated with systemic diseases, histological examination findings, and prognosis of the condition. Peer-reviewed papers providing a comprehensive diagnosis of cutaneous hypopigmented diseases, histological biopsies, RCTs, review articles, case reports, and articles in the English language were also included. Articles that did not provide a brief description regarding various cutaneous disorders with characteristic morphology, diagnosis, types and subtypes, conditions associated with systemic diseases, histological examination findings. and prognosis of the condition, along with those that lacked full-text availability and were not published in the English language, were excluded from the study. Based on the aforementioned selection criteria, a total of 12 studies were reviewed [5-16].

The analysis approach was based on PRISMA-ScR, as shown in [Table/Fig-1].



RESULTS

The literature was gathered from pertinent studies and examined for demographic evaluation, methodology, study type, and results, as demonstrated in [Table/Fig-2] [5-16].

DISCUSSION

This review provides information on various cutaneous hypopigmented disorders, focussing on their diagnosis, characteristic morphology, types and subtypes, conditions associated with systemic diseases, histological examination findings, and prognosis of the condition. According to research by Ruggiero JL et al., the typical characteristics of FA comprise weak, undefined macules resembling Café Au Lait Hypopigmented Macules (CALM) that resemble freckles on the skin folds, and macules that are both hypo- and hyperpigmented at the same time. In about 97% of the individuals recruited, cutaneous pigmentary alterations in FA were the most frequent clinical feature related to the disease. 92.5% of patients had CALM, which is a substantial increase from the frequency in the general population (10-20%) [5]. Other conditions similar to the prominent finding of multiple CALM are Neurofibromatosis 1 (NF1), Legius syndrome, tuberous sclerosis, McCune-Albright syndrome, and Noonan syndrome with multiple lentigines. However, the CALM is well-circumscribed in these diseases [5]. The CALM seen in FA patients showed the typical characteristics of having undefined margins and being just slightly darker than the skin closest to it. It was known as "shadow spots" because it was frequently impossible to distinguish them from shadows on the skin [5]. All of these contribute to the confirmed diagnosis of FA, making it a disease-specific sign rather than a late diagnosis interpretation. The research did not examine the longitudinal evolution of skin results because individuals were

S. No.	Author	Study title	Study type	Method	Conclusion
1.	Ruggiero JL et al., (2021) [5]	Cutaneous findings in Fanconi Anaemia (FA)	Cross-sectional study.	A cross-sectional investigation where skin checks were performed on the entire body of people with FA. Individuals with verified genetic or molecular diagnosis of FA were recruited.	Café-Au-Lait Macules (CALM), hypopigmented skin-fold freckle-like macules, and the co-existence of hypopigmented and hyperpigmented macules are among the distinctive morphological features of FA. Practitioners may be able to identify patients more quickly if those symptoms are recognised.
2.	Pruksaeakanan C et al., (2021) [6]	Primary Cutaneous Lymphomas (PCL) in Thailand: A 10-year retrospective study	Retrospective study	Retrospective research included 137 individuals with PCLs identified in the institution between 2008 and 2017. Based on the World Health Organisation-European Organisation for Research and Treatment of Cancer (WHO-EORTC) categorisation system for cutaneous lymphomas, the diagnosis of PCLs was confirmed both clinically and immunohistopathologically. The International Society for Cutaneous Lymphomas (ISCL) and the EORTC proposal from 2007, which was revised in 2011, were used to identify the clinical stages and Tumour-Lymph Node-Metastasis-Blood (TNMB) categorisation of individuals with Mycosis Fungoides (MF) and Sézary Syndrome (SS).	The current analysis showed a larger percentage of Cutaneous T-Cell Lymphomas (CTCL) patients with young ages at the start and a preponderance of females when contrasting with prior Caucasian and Asian investigation. The more frequent CTCL subgroup was MF, which was followed by subcutaneous pannicultis-like T-cell lymphoma. Over 80% of MF individuals had a prompt diagnosis.
3.	Pithadia DJ et al., (2021) [7]	Dermatologic findings in individuals with genetically confirmed Proteus syndrome	Retrospective study	Board-certified dermatologist performed the entire body dermatological examination. A unique restriction-enzyme assay of the afflicted tissue was used for genetic testing on those who exhibited clinical signs of Proteus syndrome in order to identify the existence of the pathogenic mosaic c.49G>A, p. (Glu17Lys) AKT1 variant. For those with the confirmed AKT1 variation, a retrospective review of written medical records and clinical photos from total-body dermatologic tests was carried out.	More mucocutaneous characteristics than initially thought were present in Proteus syndrome patients. These findings could help with early treatment and diagnosis and offer fresh perceptions of the condition's pathophysiology.
4.	Oren-Shabtai M et al., (2022) [8]	Segmental Pigmentation Disorder (SPD): Clinical manifestations and epidemiological features in 144 patients, a retrospective case-control study	Retrospective case- control study.	Two paediatric dermatology clinics in Israel participated in this retrospective case-control research. SPD was present in 144 research participants. The participants recruited were having segmentally distributed hypo- or hyperpigmented patches with a definite midline borders that was initially identified in the early stages of infancy. Data on demographics, clinical features, including the pigmented patch's characteristics and size changes over time, and additional cutaneous and extracutaneous signs were documented.	The research summarises the demographic and clinical characteristics of SPD, indicates that individuals with darker skin tend to exhibit more noticeable cutaneous SPD results, and indicates that there is no chance for the condition to worsen or become more pronounced over time, nor is it associated with extracutaneous morbidities.

5.	Prohaska J et al., (2018) [9]	Scalp sarcoidosis presenting as cicatricial alopecia	Case report	Alopecia and hypopigmented spots on scalp were evident in a 64-year-old lady with a past illness of sarcoidosis. Her upper back was covered in papular sarcoid lesions, and she had previous signs of respiratory illness. Epithelioid granulomas with mild inflammatory infiltration were seen in the biopsy samples. No foreign substance was found in the granulomas when seen in polarised light. Sarcoidosis recurrence was diagnosed based on the presence of papular sarcoidosis on the upper back and hypopigmented cicatricial alopecia of the scalp.	The individual had papular sarcoid lesions on her back, which were a cutaneous diagnostic. This relationship should induce a full skin inspection upon suspicion of scalp sarcoidosis. Patients with scalp sarcoidosis frequently have systemic illness. This discovery of an extensive past of pulmonary sarcoidosis was confirmed by the patient. In order to rule out systemic sarcoidosis, people with scalp sarcoidosis should have an examination for systemic inclusion.
6.	Alshomar KM et al., (2021) [10]	A case of dyschromatosis symmetrica hereditaria with an associated eyelid haemangioma	Case report	During examination, the lesion was found to be pedunculated, measuring 3x6 mm, red in colour, and shaped like a cauliflower. It was also firm in consistency and involved the medial aspect of the margin of the right lower lid. There was no damage to the skin or eyelashes found. Because of her identified disease, the skin of her face, neck, and dorsal extremities was seen to have a mottled look with regions of hypo- and hyper-pigmented skin. There was no evidence of skin or eyelash damage. The results of the histological analysis showed a spherical skin lesion with papillomatosis, an ulcerated and noticeably inflammatory epidermis covering a cavernous haemangioma and mixed capillary with a lobular pattern and prominent hamartomatous capillary proliferation.	Although the pathophysiology of DSH is not well known, past reports of cerebral haemangiomas and the recent reports of cutaneous vascular lesions would suggest that heredity and variable expression may play a part, particularly when Cutaneous Lupus Erythematosus (CLE) is present concurrently. This may call for more research into the causes of DSH.
7.	Choi MJ et al., (2018) [11]	Acquired brachial cutaneous dyschromatosis in a middle aged male	Case report	On either forearms, an inspection of the body revealed mixed hyper- and hypopigmented macules, as well as localised atrophy and telangiectasia. On the outside of the forearm, the hyperpigmented macule was subjected to a punch biopsy. Histopathologic examination revealed blunted rete ridges and epidermal atrophy. The Fontana Masson stain, which detects melanin, highlighted the remarkable darkening of the basal layer.	Histological analysis revealed numerous telangiectatic arteries in the upper dermis, elevated basal layer pigmentation, and epidermal atrophy. The solar elastosis was average. Acquired Brachial Cutaneous Dischromatosis (ABCD) was diagnosed based on the individual's symptomatic and histopathologic characteristics. The potential aetiology of ABCD include melasma, acquired bilateral telangiectatic macules, poikiloderma of Civatte, and other pigmentary disorders.
8.	Luo Y et al., (2020) [12]	MFs and variants of MFs: A retrospective study of 93 patients in a Chinese population at a single centre	Retrospective study	Between October 2012 and January 2018, a retrospective analysis of people diagnosed with MF and its variants was conducted. The 2018 revision of the WHO-EORTC primary cutaneous T-cell lymphoma categorisation system was used to diagnosis MF, combined with TNMB staging. Patients were classified as having hypopigmented skin lesions (hMF), ichthyosiform skin lesions (ichthyosiform MF), or poikilodermatous skin lesions (poikilodermatous MF) based on the results of their biopsy diagnosis.	In China, hMF influences younger individuals than traditional MF and has an improved outcome than the initial stages of MF.
9.	Singh AK et al., (2021) [13]	Mixed cutaneous infection caused by leishmania and dermatophytes: A rare coincidence or immunological fact	Case report	There are several lesions that are hypopigmented, round, or ovoid in shape. Sharp marginations and occasionally elevated erythematous scaly margins are present in these annular lesions. The lesions propagate centrifugally, leaving behind a centre clearing and light residual scaling; this gives rise to the term "ringworm" because it resembles a "ring." In order to screen for leishmania species, procedures included skin scraping, followed by skin slit biopsy, fungal culture, lacto phenol cotton blue stained microscopy, biochemical test, Rk39 fast immunechromatographic test, skin slit smear, giemsa stained microscopy, and polymerase chain reaction test. Based on the aforementioned investigations, tinea corporis with Post-Kala-Azar Dermal Leishmaniasis (PKDL) was diagnosed.	The cause of the co-infection was presumably a combination of acquired dermatophytic infection, which is common and linked to a decreased CD4+ T-cell count, skin abruptions, and depressed cellular immunity.

10.	Friedman BJ et al., (2018) [14]	Association of clinical, dermoscopic, and histopathologic findings with gene expression in patients with Balloon Cell Melanoma (BCM)	Case study	Dermoscopy in the two subjects under consideration revealed dull yellow globules, an asymmetrical brown atypical pigment network, and a transparent white-gray veil covering a sizable portion of the injuries. On dermoscopy, irregular black patches with scalloped edges and uneven periphery streaks were seen in case 2.	Diagnostic and dermoscopic characteristics of BCMs might be observed. Findings from an adjuvant gene expression profile analysis may offer extra helpful medical data in circumstances when the histology is unclear. Finding the molecular causes of BCMs can increase the precision of diagnosing and predicting prognosis in individuals with these uncommon neoplasms.
11.	Sultan M et al., (2019) [15]	Unique clinical spectrum with distinguishing diagnostic features in Vogt-Koyanagi-Harada Syndrome (VKHS)	Case report	A slit-lamp examination of the eyes revealed sporadic cells in the anterior chamber without any keratic precipitates or iris nodules, and an eye test confirmed visual acuity of 20/200 in both eyes. Hyperaemic discs and bilateral multifocal exudative retinal detachment were observed by optical coherence tomography and funduscopy. Diffuse pinpoint leakage was shown by fundus fluoresce and late pooling at exudative detachment locations in angiography. Using indocyanine green angiography, several hypofluorescent spots that were indicative of choroidal granulomas were seen.	To avoid vision issues, the right course of intervention was necessary, and systemic corticosteroids combined with immunosuppressive medication regimen demonstrated a considerable improvement in eyesight at follow-up. Despite the whole regimen, cutaneous symptoms remained resistant.
12.	Geller S et al., (2020) [16]	Outcomes and prognostic factors in African American (AA) and black patients with MFs/SS: Retrospective analysis of 157 patients from a referral cancer centre	Retrospective study	Dermatopathologists and dermatologists who have confirmed the clinical and histological diagnosis of MF/SS in 157 cases were included. In addition to demographic information, the shape of the lesion, MF clinical variant, and clinical and TNMB classification stage were documented. At the time of presentation, the following laboratory results were noted: absolute lymphocyte count, White Blood Cell count (WBC), absolute Eosinophil Count (EOS), and serum Lactate Dehydrogenase (LDH). Large Cell Transformation (LCT), folliculotropism, and the Immunohistochemistry (IHC) staining status of CD4+ and CD8+ T-cell phenotype on skin biopsies were examined in the initial pathology reports.	Black and African American (AA) people with MF/SS have a wide range of symptoms and prognoses. While clinical variables may aid in the classification of the likelihood of disease growth and shortened longevity, enabling personally customised therapy approaches, socioeconomic and demographic variables do not appear to have a predictive impact.

[Table/Fig-2]: Review of the included studies [5-16].

DSH: Dyschromatosis symmetrica hereditaria; FA: Fanconi anaemia; WHO-EORTC: World health organisation- European organisation for research and treatment of cancer; CALM: Café-au-lait macules; PCLs: Primary cutaneous lymphomas; CTCL: Cutaneous T-cell lymphomas; MF: Mycosis fungoides; SPD: Segmental pigmentation disorder; CLE: Cutaneous lupus erythematosus; ISCL: International society for cutaneous lymphomas; TNMB: Tumour-lymph nodes-metastasis-blood; ABCD: Acquired brachial cutaneous dischromatosis; DSS: Disease-specific survival; PKDL: Post kala-azar dermal leishmaniasis; BCM: Balloon cell melanomas, and SS: Sézary syndrome

only evaluated once [5]. Therefore, it may be considered for the future scope of the study with a large patient population.

According to research presented by Pruksaeakanan C et al., a greater percentage of onset of Cutaneous T-Cell Lymphomas (CTCL) was observed in younger individuals and more commonly in the female population. The most frequent CTCL subtype was MF, subsequent to a T-cell lymphoma that resembled subcutaneous panniculitis. More than 80% of MF patients had an early diagnosis because of these features [6]. The introduction of modern laboratory methods, such as genetics and molecular biology, as well as the present increase in knowledge regarding Primary Cutaneous Lymphomas (PCL) among dermatologists and pathologists, may provide benefits in the initial identification of the disorder. The primary limitations of the study were the single-centre retrospective study methodology, absence of histopathology examination, and exclusion of instances where hospital pathologists failed to verify the diagnosis [6].

The variety of mucocutaneous characteristics seen in Proteus syndrome is much wider than initially believed, according to the research presented by Pithadia DJ et al., [7]. These results could help with early treatment and diagnosis and offer fresh perceptions of the condition's pathophysiology. Nearly all of the Proteus syndrome patients in this cohort had genetic confirmation and dermatologic abnormalities that were not sufficient for the diagnosis in comparison to cutaneous symptoms. Both the non cerebriform and cerebriform morphologies of the Connective Tissue Nevi (CTN) were noted, and confluent, hypopigmented papules and nodules were often seen on the palms and soles, which are a sign of cerebriform CTN [7].

Therefore, it could be feasible to diagnose the condition sooner in young infants by performing a biopsy and genetic testing on tissue prior to its development into a cerebriform state. Due to the study's retrospective observational methodology and insufficient long-term monitoring of the progression of numerous mucocutaneous characteristics, there were some drawbacks. Upcoming histologic and molecular studies are needed to more fully understand the pathophysiology of Proteus syndrome and its less often reported dermatologic features [7].

Segmental Pigmentation Disorder (SPD) is more likely to be experienced by patients with a dark complexion, based on research by Oren-Shabtai M et al., [8]. This might be due to the findings of prior research indicating that the majority of the people studied in that series were of Sephardic background [8]. The research demonstrated that SPD frequently affects the torso, which was consistent with earlier research that determined that SPD most frequently affected the back, chest, and belly [8]. The retrospective design of the study was considered as the major limitation. Additionally, there was bias as only part of the information was gathered through a questionnaire [8].

According to a case study by Proshaka J et al., there are very few cases of sarcoidosis affecting the scalp. When it does occur, it usually causes scarring alopecia [9]. The existence of additional sarcoidal lesions, such as those on the head or upper back, is one confirmatory indicator for scalp sarcoidosis [9]. A systemic workup should be started as soon as a scalp sarcoidosis diagnosis has been made because the majority of patients are accompanied by systemic illness, mainly involving the lungs or lymph nodes.

Dyschromatosis Symmetrica Hereditaria (DSH) or Reticulate acropigmentation of Dohi is a rare pigmentary genodermatosis disorder with autosomal dominant inheritance, according to a case study published by Alshomar KM et al., [10]. The disorder starts in early childhood and ends with puberty, characterised by mixed reticular hyper- and hypopigmented macules on the extremities, and freckle-like pigmented macules on the palms, cheeks, and soles [10].

Furthermore, the case study by Choi MJ et al., case study showed an upper dermis full of telangiectatic veins, displaying epidermal atrophy and enhanced basal layer pigmentation. Clinical and histopathological characteristics of the patient supported and confirmed the Acquired Brachial Cutaneous Dischromatosis (ABCD) diagnosis [11]. In a similar study, Hu SW et al., observed telangiectasia, solar elastosis, basal layer hyperpigmentation, and epidermal atrophy in the superficial dermis of a pigmented lesion resulting from ABCD [17].

Additionally, a case study presented by Singh AK et al., showed that the dermatophytic infection obtained, which is common and linked to a reduced CD4+ T-cell count, was likely the cause of co-infection due to skin abruptions, weakened cellular immunity, and infection. The patient's home consisted of stone and mud, and they also had a cow shed in their yard, all of which created favourable circumstances for sand fly reproduction, as earlier documented [13]. According to a case study by Friedman BJ et al., understanding the genetic basis of Balloon Cell Melanoma (BCM) will increase the precision of diagnosis and prognosis. The accuracy of the procedure in identifying the biological makeup of histopathologically ambiguous tumours was one of its main shortcomings. The longitudinal follow-up of a cohort of biopsy patients is the only way to validate this or comparable tests through a comparison of what was expected with the actual results [14].

Another cutaneous lesion, Vogt-Koyanagi-Harada syndrome (VKHS), has been linked with different autoimmune diseases and cancers; consequently, its association with ulcerative colitis is exceedingly rare and could be linked to their shared pathophysiology and Human Leucocyte Antigen (HLA) [15]. Sultan M et al., also showed that VKHS has been linked to various autoimmune diseases and cancers [15]. The diagnosis of VKHS involves eye examinations to confirm the diagnosis. The goal of medical intervention for VKHS in its acute form is to prevent problems that might be life-threatening to vision by lowering ocular inflammation, for which prompt and vigorous use of corticosteroids predicts positive results [15].

According to retrospective research by Luo Y et al., the initial stage MF in Chinese patients had a more favourable outcome than latestage MF and hMF, which influences younger individuals than classic MF and has restrictions including a limited sample size and a single centre's experience. Despite its limitations, this research is important since it sheds light on Chinese patients' MF and their variations [12]. Additionally, MF/SS symptoms and prognosis in African American (AA) and black individuals are varied, according to prior retrospective research by Geller S et al., [16]. While medical parameters may aid in the classification of the likelihood of disease growth and reduced survival, permitting self-intervention approaches, socio-economic and demographic variables are not enough to have a predictive function [16]. The findings are in line with the body of evidence that indicates a high incidence of CD8+ MF in AA and Black people and an indolent course for the CD8+ variant of MF. While some clinicopathologic characteristics were substantially related to survivability and advancement, demographic and socioeconomic variables had little bearing on prognosis. Considerations regarding the handling and management of MF/SS should not

only be focussed on racial or demographic characteristics, but should also focus on particular clinical and pathological prognostic markers [16].

Limitation(s)

The limitation of the present scoping review was the inclusion of articles that were only written in the English language and that were present with full-text availability, which may have limited the amount of literature to be included. Thus, the results may not reflect all the current literature on diagnostic findings of various cutaneous hypopigmented macular lesions and patches.

CONCLUSION(S)

This review briefly describes various cutaneous disorders, including their diagnostic findings, characteristic morphology, types and subtypes, conditions associated with systemic diseases, histological examination findings, and prognosis of the condition. The conditions discussed include CALM in FA, CTCL in which MF is more common followed by subcutaneous panniculitis, mucocutaneous characteristics in Proteus syndrome, SPD in people with dark skin, scalp sarcoidosis, concurrent presence of DSH and CLE, ABCD, leishmania and dermatophytes consisting of hypopigmented rashes, BCM, and VKHS. Understanding these disorders may help in early and precise diagnoses leading to adequate management and care; hence, it is crucial for dermatologists to be aware of such illnesses to provide appropriate counselling to patients and to promptly refer them for examination and treatment.

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