بسم اللّٰہ الرحمن الرحیم

مدیریت اختلالات پیگمانتاسیون از منظر طب نوین

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متخصص پوست

اهداف این مقاله

- تبین پاتوفیزیولوژیک اختلالات پیگمانتاسیون به اختصار
- ارایه راهکار های درمانی با تلفیق دستاورد های طب نوین و تجارب و طب سنتی
- تحلیل گزاره های کلامی طب سنتی با یافته های طب مدرن

در طب سنتی در مورد یک فراورده تعدد ادعا بر خلاف طب مدرن وجود دارد در طب مدرن یک فراورده ناظر به درمان یک بیماری و یا دامنه محدودی از بیماریهاست اما ایا یافته های طب مدرن می تواند از نظر تئوری از این حیطه وسیع درمانی حمایت کند

- رزماری با استرس مبارزه می کند،
- رزماری اضطراب را کاهش می دهد،
- رزماری سردرد را تسکین می دهد
- رزماری رشد مو را تحریک می کند،
- رزماری با درد مفاصل مقابله می کند،
- رزماری التهاب را کاهش می دهد
- رزماری گوارش را بهبود می بخشد،
- رزماری از سرطان پیشگیری می کند،
- رزماری پشتیبان سلامت قلب و عروق است.

اما ایا یافته های طب مدرن می تواند از نظر تئوری از این حیطه وسیع درمانی حمایت کند؟

- با مروری بر اختلالات پیگمانتاسیون به عنوان یک الگو نه تنها به پاسخ این پرسش اساسی می رسیم بلکه درمان و مدیریت یک بیماری را با دیدی جامع تر پی ریزی می کنیم
- اختلالات پیگمانتاسیون به دلیل اشکار بودن ان از دیر باز کانون توجه طب سنتی و مدرن بوده است و در نتیجه مبنای خوبی جهت تلفیق نقطه نظرات بوجود می اورد

پیش فرض های منطقی و عقلی ورود به بحث

- در ساختار حیاتی یک موجود زنده توالی واکنش های بیولوژیک وجود دارد
- در این سلسله توالی واکنشی برخی از واکنش ها نقش پایه و اساسی دارد
- ایجاد اختلال در ساختار های پایه که عمدتا ***هموستاز*** بدن به ان وابسته است تنوع علایم علی رغم اختلال واحد ایجاد می کند
- و به عنوان ***نتیجه***
- مداخلات درمانی که تارکت انها واکنش های حیاتی و پایه باشند این قابلیت را دارند که در عین یک فراورده بودن بر روی چندین بیماری موثر باشند
- البته فراورده های طب سنتی به دلیل داشتن چندین عامل در یک فراورده قابلیت اثر چندگانه از این حیث نیز دارند

Vitiligo

- Vitiligo is an acquired disorder characterized by circumscribed depig-mented macules and patches that result from the loss of functional melanocytes.
- A primary challenge is the fact that what is referred to as vitiligo likely represents a heterogeneous group of diseases with different genetic backgrounds and environmental triggers.

pathogenesis

- Intrinsic defects of melanocytes and exogenous triggers may also play a role in vitiligo development.
- In addition, oxidative stress has been investigated as a pathogenic factor that could activate the immuneresponse in vitiligo and underlie impaired WNT signaling that prevents melanoblast differentiation.
- Accumulating data highlight the complexity of vitiligo, with involvement of multiple cell types, including keratinocytes, fibroblasts, and stem cells as well as immune cells
- These hypotheses are not mutually exclusive and the various pathways may converge to induce the disappearance of melanocytes from the skin and hair follicles. However, the exact cascade of events remains to be elucidated.

Clinical Features

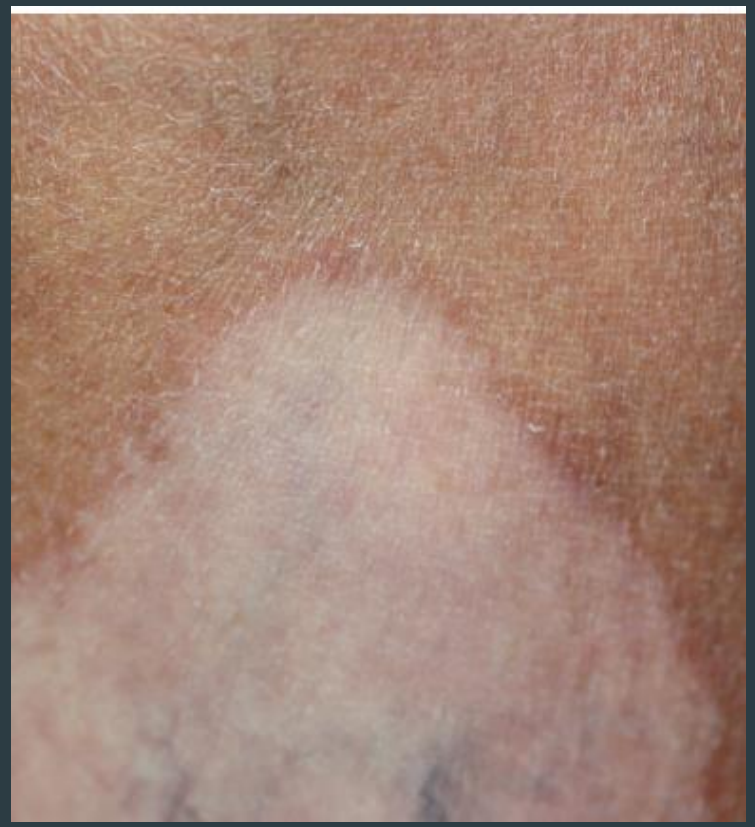
- The most common presentation of vitiligo is totally amelanotic (milk-or chalk-white) macules or patches surrounded by normal skin.
- Well-developed lesions typically have discrete margins and may beround, oval, irregular, or linear in shape.
- The borders are usually convex.
- However, at their onset or when actively spreading, areas of vitiligo may be more ill-defined and hypo- rather than depigmented
- Vitiligo macules and patches range from millimeters to centimeters in diameter and often have variable sizes within an area of involvement.
- In lightly pigmented individuals, the lesions may be subtle orinapparent without Wood's lamp examination or tanning of uninvolved skin.

Clinical Features

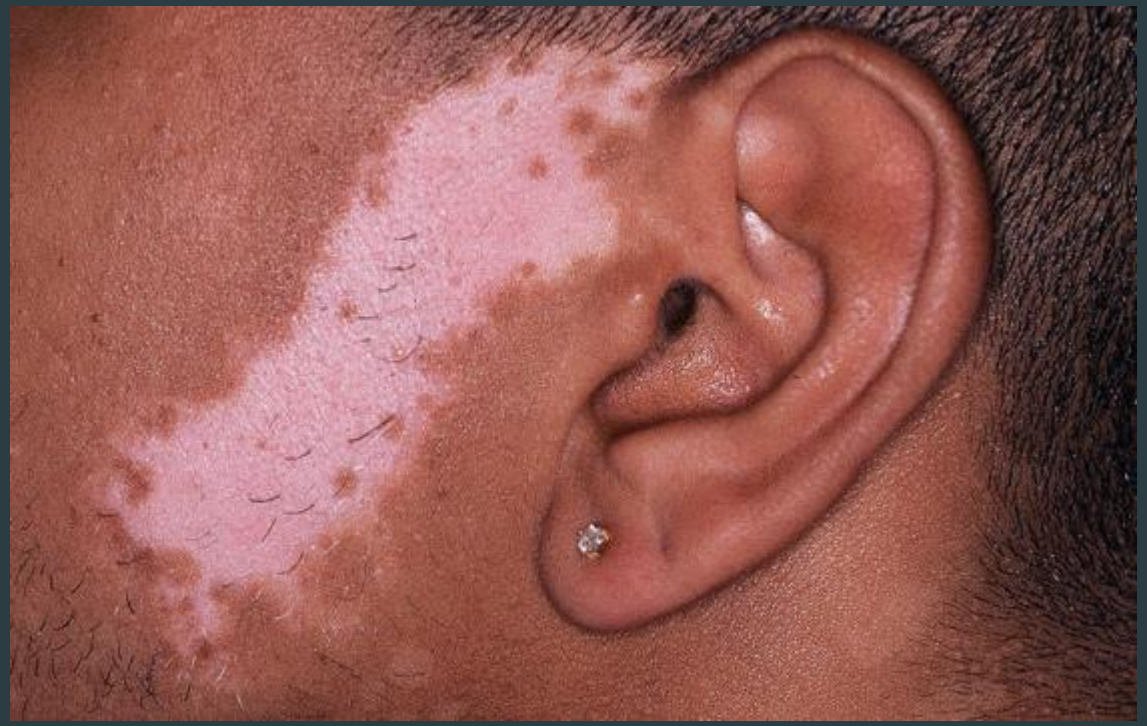
- Vitiligo may develop anywhere on the body.
- Interestingly, it frequently localizes to sites that are normally relatively hyperpigmented, such as the face, dorsal aspect of the hands, nipples, axillae, umbilicus, and sacral, inguinal and anogenital region
- Typically, facial vitiligo occurs around the eyes and mouth (i.e. periorificial), and on the extremities it favors the elbows, knees, digits, flexor wrists,dorsal ankles and shins
- The most common sites of involvement are areas subjected to repeated trauma, pressure, or friction (e.g. in body folds or via contact with clothing).

The incidence of body leukotrichia varies from 10% to >60%, as vitiligo often spares follicular melanocytes.
The occurrence of leukotrichiadoes not correlate with disease ac

Inflammatory vitiligo. An erythematous inflammatory border is evident Such lesions are sometimes misdiagnosed as tinea corporis



Segmental vitiligo. Unilateral band of depigmentation on the face the most common location for segmental vitiligo Note the pigmented and depigmented hairs within the affected area



Course of the disease

- The onset of vitiligo is usually insidious.
- The course of vitiligo is unpredictable.
- Peripheral hypopigmentation and poorly defined borders appear to be predictive of active vitiligo.
- Many patients become aware of the depigmented macules and patches, especially in sun-exposed area
- A spotty pattern of depigmentation may also represent a marker ofprogressive disease.
- The natural course of generalized vitiligo is usually one of slow spread, but it may stabilize for a long period of time orevolve rapidly.
- segmental vitiligo usually reaches it sfull extent within 1–2 years and remains restricted to the initial segmental area.

Associated disorders

- Although most vitiligo patients are otherwise healthy, generalized viti-ligo is associated with a number of other autoimmune diseases, espe-cially in patients with a family history of vitiligo and other forms of autoimmunity.
- Autoimmune thyroid disease occurs in ~15% of adults and ~5–10% of children with vitiligo
- Other less frequently associated conditions include pernicious anemia, Addison disease, lupus erythematosus, rheumatoid arthritis, and adult-onset insulin-dependent diabetes mellitus.

Differential Diagnosis

- When there is complete depigmentation, the differential diagnosis mayinclude chemical or drug-induced (e.g. imatinib) leukoderma,
- post inflammatory depigmentation
- the leukodermas associated with melanoma and scleroderma
- the late stages of treponematosis and onchocerciasis,
- for congenital lesions piebaldism.
- A single circular depigmented lesion on the trunk of a young person may represent a stage III halo nevus
- Early lesions or those with a partial loss of pigment need to be distinguished from postinflammatory hypopigmentation, tinea versicolor, and other cutaneous infections (e.g.leprosy).

Treatment

- The aims are stabilization of the depigmentation process and repigmen-tation.
- Although there is still no therapeutic panacea for vitiligo, available options can lead to satisfactory results.
- The therapeutic regimen depends on the extent, location, and activity of disease as well as the patient's age, skin type, and motivation for treatment.
- In general, aperiod of at least 2–3 months is needed to determine whether a particular treatment is effective.
- The face, neck, mid extremities, and trunk tend to have the best response to therapy, while the distal extremities and lips are the most resistant to treatment.
- Repigmentation initially appears in a perifollicular pattern
- After therapeutic repigmentation, the rate of recurrent depigmentationof vitiligo lesions is ~40%33.

Corticosteroids

- Topical corticosteroids are useful for localized areas of vitiligo.
- A meta-analysis showed that approximately half of patients with vitiligo affecting ≤20% of the body surface area (BSA) achieved >75% repigmentationwith class 1 (superpotent) or 2–3 (high potency) topical corticosteroids;
- cutaneous atrophy was observed in 14% and 2% of these groups, respectively.
- To minimize side effects, class 1 corticosteroids can be used in6–8-week cycles or on a twice-weekly basis, alternating with topical tacrolimus or a less potent topical corticosteroid
- Treatment should be discontinued if there is no visible improvement after 2–3 months.

systemic corticosteroids

- In general, intralesional corticosteroids should be avoided because ofthe pain associated with injection and the higher risk of cutaneousatrophy (≥30%).
- Systemic corticosteroid regimens utilizing high dose pulses, mini-pulses, or low daily oral doses have been reported to arrest rapidly spreading vitiligo and induce repigmentation.
- However,given the potential for serious side effects, the role of systemic corticosteroids in the treatment of vitiligo remains controversial.

Topical calcineurin inhibitors (TCIs)

- Multiple studies have shown that topical tacrolimus 0.1% ointment or pimecrolimus 1% cream applied twice daily can result in repigmentation of vitiligo, with response rates in pediatric patients similar to those achieved with topical corticosteroids.
- The best results are obtained when these agents are used on the face and other sun-exposed areas, suggesting a synergistic effect.
- TCIs can also enhance repigmentation when used in conjunction with narrowband UVB phototherapy or the excimer laser
- Of note, avoidance of UV light is suggested by the package insert for TCIs, and the risk:benefit ratio should be discussed.
- Topical tacrolimus can also be used together with topical corticosteroidson a rotational basis or as maintenance therapy after repigmentation.
- In a recent randomized controlled study, bi-weekly application of tacrolimus 0.1% ointment to sites of previous vitiligo reduced the rate of recurrent depigmentation to 10%, compared to 40% withplacebo40.

Narrowband UVB

- Narrowband UVB (NB-UVB; see Ch. 134) has become the first-linetreatment for adults and children ≥6 years of age with generalized vitiligo
- especially if it involves ≥20% of the body surface area or cosmeti-cally sensitive areas that typically respond to treatment.
- Treatments areB administered 2–3 times per week, but not on two consecutive days.
- NB-UVB can be used in children, pregnant or lactating women, and individuals with hepatic or kidney dysfunction.

Psoralen photochemotherapy

- Psoralen plus UVA involves the use of psoralens combined with UVA light
- The psoralen most commonly used is 8-methoxypsoralen (8-MOP , methoxsalen).
- Psoralens can be administered orally (oral PUVA) or applied topically (topical PUVA),followed by exposure to either UVA light or natural sunlight (PUVASOL).
- Oral PUVA treatments using 8-MOP (0.4–0.6 mg/kg) are typically administered two times weekly.
- For patients with vitiligo, the initial dose of UVA is usually 0.5–1.0 J/cm2, which is gradually increased until minimal asymptomatic erythema of the involved skin occurs.
- To reducethe risk of the Koebner phenomenon, significant erythema (phototoxic-ity) is avoided.
- 5-MOP has about the same response rate as 8-MOP inrepigmenting vitiligo, but a lower incidence of phototoxicity as well as less nausea and vomiting.
- The total number of PUVA treatments required is generally 50–300.

Topical (paint) PUVA

- Topical (paint) PUVA is more difficult to perform because of the high risk of phototoxicity and subsequent blistering or koebnerization.
- A lowoncentration (≤0.1%) of psoralen should be used, which requires diluion of the commercially available preparation.
- Approximately 20–30 minutes after applying the topical cream or ointment onto the lesions,
- the patient should be exposed to initial UVA doses of no more than0.25 J/cm2, with the same fractional increments until mild erythemais achieved in the treated sites.
- PUVASOL (psoralens + natural sunlight) can be used in sunnier climates, utilizing the same principles as for PUVA.
- Less phototoxic oral psoralens such as 5-MOP are preferred in order to avoid phototoxic reactions.

Lasers and related light devices

- Excimer laser and lamp The operational wavelength of the 308 nm excimer laser and lamp is close to that of NB-UVB45.
- The therapeutic benefit of the excimer laser for vitiligo has been investigated in multiple studies, and, overall,20–50% of lesions achieve ≥75% repigmentation
- the excimer lamp appears to have similar efficacy
- Only a few studies have directly compared excimer laser to NB-UVB, and some but not all showed superior results with the former modality.
- Localized patches of vitiligo are treated one to three times weekly with the excimer laser, typically for a total of 24 to 48 sessions;
-

Surgical therapies

- For vitiligo patients who fail to respond to medical therapy, surgical treatment with autologous transplantation techniques may be anoption.
- The general selection criteria for autologous transplantation include stable disease for ≥6 months, absence of the Koebner phenomenon, no tendency for scar or keloid formation, and age >12 years.
- Aminigraft test showing retention/spread of pigment at the recipient siteand no koebnerization at the donor site after 2–3 months can also assistin patient selection.

Combination therapy

- Combination therapy may produce higher rates of repigmentation compared to traditional monotherapies.
- Examples include phototherapy following surgical procedures as well as combining TCIs and/or topical corticosteroids with NB-UVB or excimer laser therapy60–65.
- Althoughtopical vitamin D derivatives are relatively ineffective as monotherapy,these agents may result in additional repigmentation when used inconjunction with phototherapy.

Micropigmentation

- The technique of permanent dermal micropigmentation utilizes a non-allergenic iron oxide pigment to camouflage recalcitrant areas of vitiligo.
- This tattooing method is especially useful for the lips, nipples anddistal fingers, which have a poor rate of repigmentation with currentlyavailable treatments.
- Although the color may not match perfectly with the normal surrounding skin and can fade over time, the result is immediate and can represent a dramatic aesthetic improvement.

Depigmentation

- Depigmentation represents a treatment option for patients who have widespread vitiligo with only a few areas of normally pigmented skin in exposed sites.
- The patients must be carefully chosen, i.e. adults who recognize that their appearance will be altered significantly and who understand that depigmentation requires lifelong strict photoprotection(e.g. sunscreens, clothing, umbrellas).
- The most commonly used agentis 20% monobenzyl ether of hydroquinone (MBEH), applied once to twice daily to the affected areas for 9–12 months or longer.
- MBEH is a potent irritant and allergen, and an open application test can be performed before more widespread application.
- It typically takes 1–3months to initiate a response,.
- Although depigmentation from MBEH is considered permanent,repigmentation (especially perifollicular in areas with pigmented hairs)can be seen following a sunburn or intense sun exposure.

Psychological support

- The impact of vitiligo on quality of life is severe in many affected indi-viduals, and it is critical for physicians to recognize this aspect of the condition and address their patients' psychological needs.
- Although a"magic" treatment is not yet available, there is always something beneficial that can be done for vitiligo patients.
- They first need to know what their skin disorder is.
- Explaining the nature of the disease processand the potential and limits of available therapies is important and more productive than a fatalistic attitude that there is no cure and vitiligo is "only" a cosmetic disorder.
- Even helping patients to conceal the condition so that it is not visible can be part of the management plan.
- The use of support groups and, if indicated, psychological counse lingare important supplementary therapies.

Afamelanotide

- Afamelanotide is an α-melanocyte stimulating hormone (α-MSH) analogue that stimulates melanogenesis and melanocyte proliferation by binding to the melanocortin-1 receptor
- A recent randomized controlled study found that the addition of afamelanotide(monthly subcutaneous implants) to NB-UVB therapy increased the speed and extent of repigmentation compared to NB-UVB alone inpatients with generalized vitiligo, especially those with skin types IV–VI.
- However, afamelanotide-induced excessive tanning of non-lesional skin can increase the contrast with lesional skin, thereby reducing cosmetic acceptance in lightly pigmented patients80.
- Additional studies are needed to determine the indications and limitations of afamela-notide therapy for vitiligo.

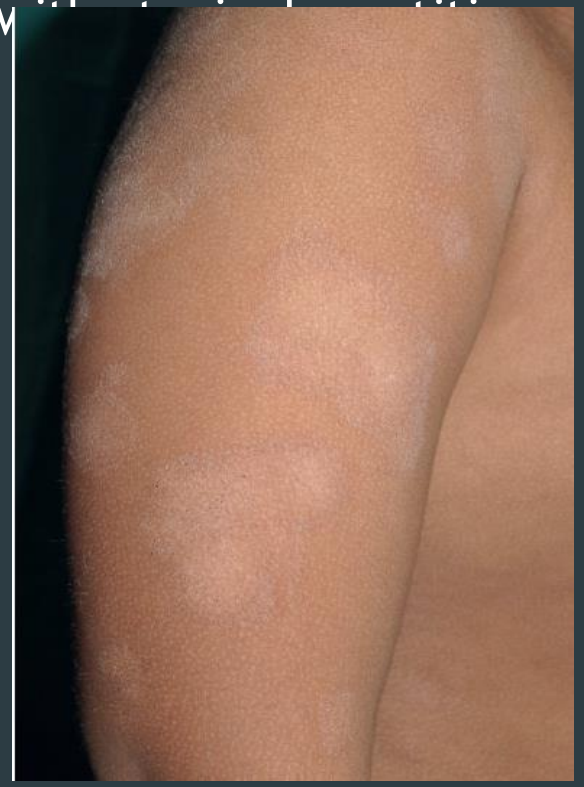
Topical prostaglandins and Janus kinase (JAK) inhibitors

- Preliminary studies have suggested the utility of topical prostaglandinE2 and latanoprost (an analogue of prostaglandin F2) in the treatmentof vitiligo.
- Although interesting, these results require confirmation.
- Administration of the JAK inhibitors ruxolitinib and tofacitinib hasbeen reported to lead to repigmentation of vitiligo.
- Further investigationis needed to determine how approaches targeting the IFN-γ–JAK–STAT1signaling pathway that drives melanocyte destruction can be utilized to treat vitiligo

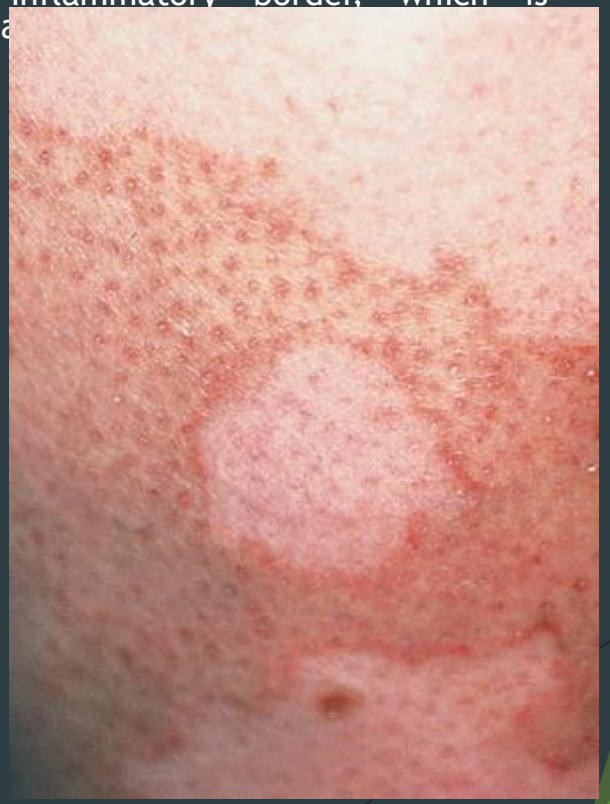
Systemic antioxidant therapy

- The rationale for this approach rests on the hypothesis that vitiligo results from a deficiency of natural antioxidant mechanisms. Although to date not validated by controlled clinical trials, selenium, methionine,tocopherols, ascorbic acid, and ubiquinone are prescribed by somephysicians.

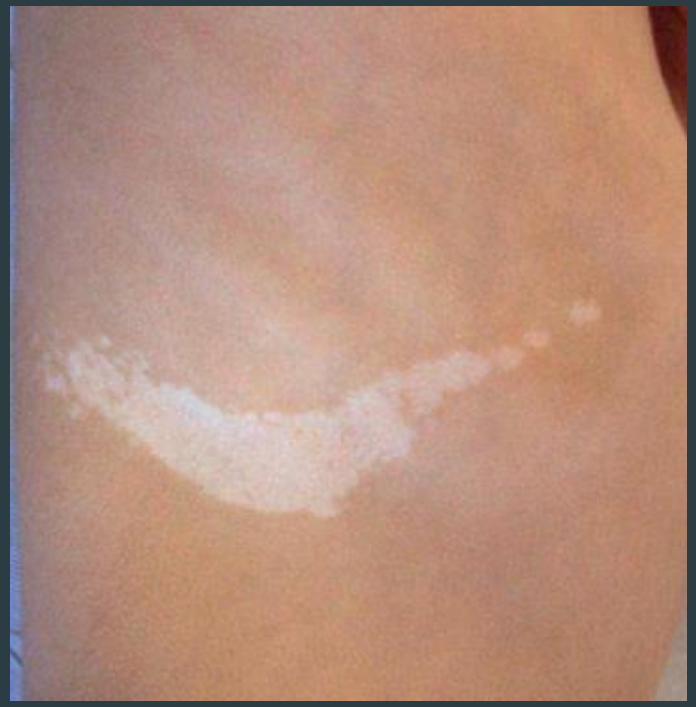
Postinflammatory hypopigmentation in a child w



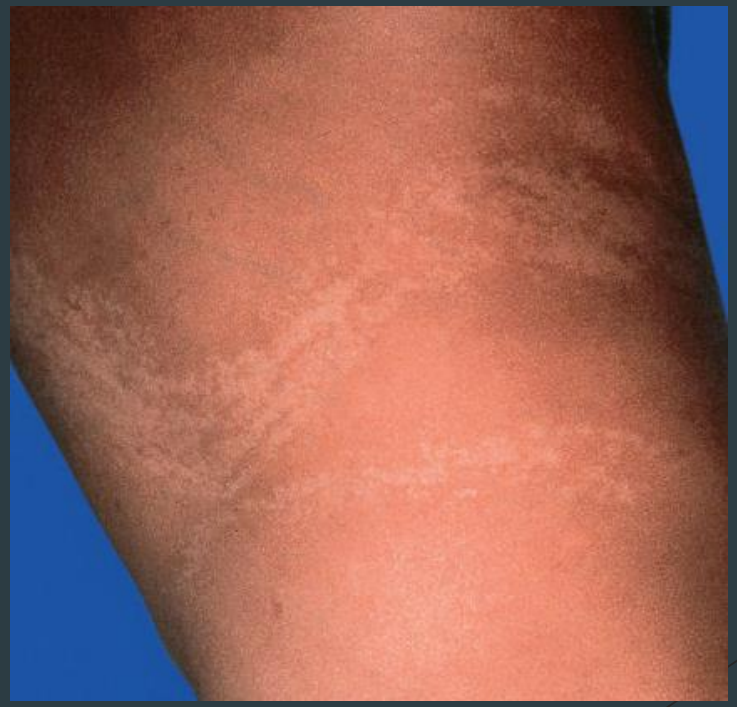
Inflammatory vitiligo There is a figurate outline to the inflammatory border, which is sometimes misdia



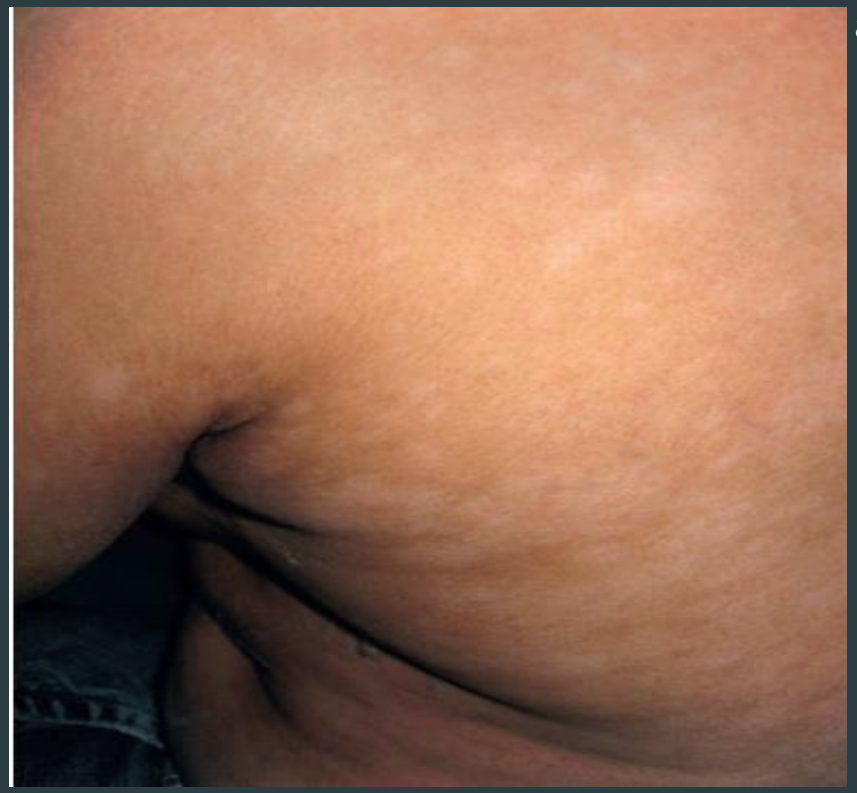
Lichen striatus.Hypopigmented band along the lines of Blaschko



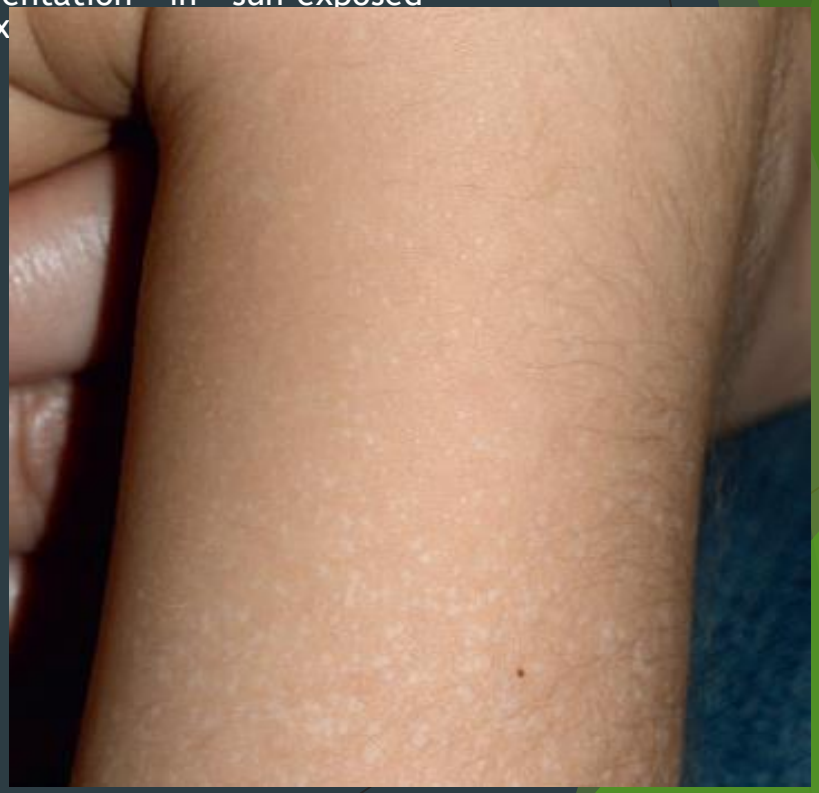
Linear nevoid hypopigmentation.



Hypopigmented mycosis fungoides.

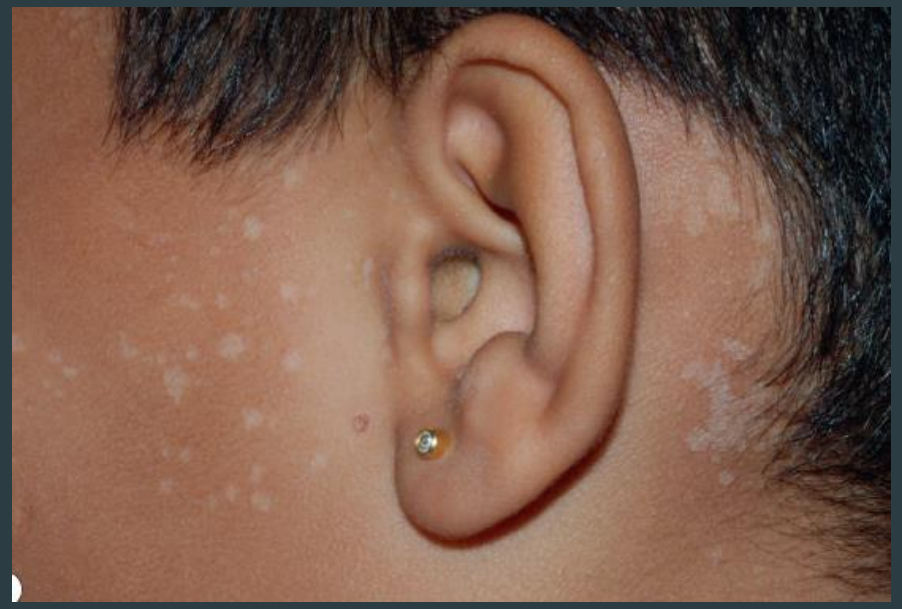


Guttate hypopigmentation in sun-exposed areas on the ex

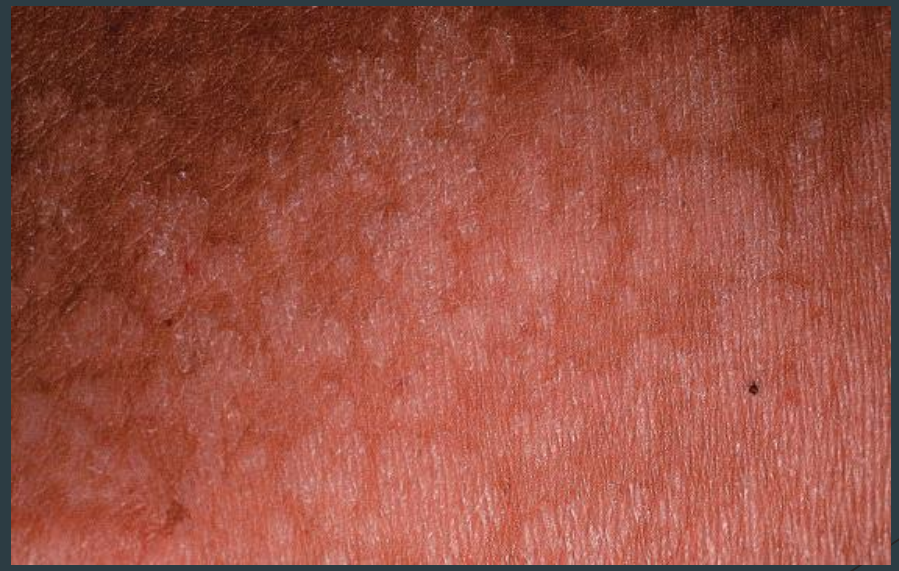


Tinea versicolor

Guttate hypopigmented lesions on the lateral cheek of a child; note the classic scaly lesions in the posterior auricular area



Hypopigmented variant with obvious scale



Associated Diseases

- . Most patients with vitiligo have no other associated findings;
- however, vitiligo has been reported to be associated with
- alopecia areata, autoimmunethyroid disease, Addison disease, pernicious anemia, type1 diabetes mellitus, uveitis, chronic mucocutaneous can-didiasis, rheumatoid arthritis, Guillain–Barré syndrome,the polyglandular autoimmune syndromes, and melanoma.
- Thyroid disorders are the most common and have beenreported in as many as 30% of vitiligo patients.
- In certain populations, such as children andpregnant women, regular screening is warranted.8

Indications for Treatment.

- Treatment is necessary forpatients in whom the disease causes emotional and socialdistress.
- Vitiligo in individuals with fair complexions isusually not a significant cosmetic problem.
- The condition becomes more apparent in the summer months whentanning accentuates normal skin. Tanning may be preventedwith sunscreens that have an SPF of 30 or higher.
- Vitiligois a significant cosmetic problem in people with dark complexions, and repigmentation with psoralens may be worthwhile.

MELASMA

- Key features
- ■ At least 90% of patients are women
- ■ Increased prevalence in individuals who are Hispanic, or of Asian or African descent
- ■ Most common location is the face, followed by the forearms
- ■ Symmetric patches of hyperpigmentation with irregular borders due to increased melanin within the epidermis and/or dermis
- Exacerbating factors include sun exposure, pregnancy, and useof oral contraceptives.

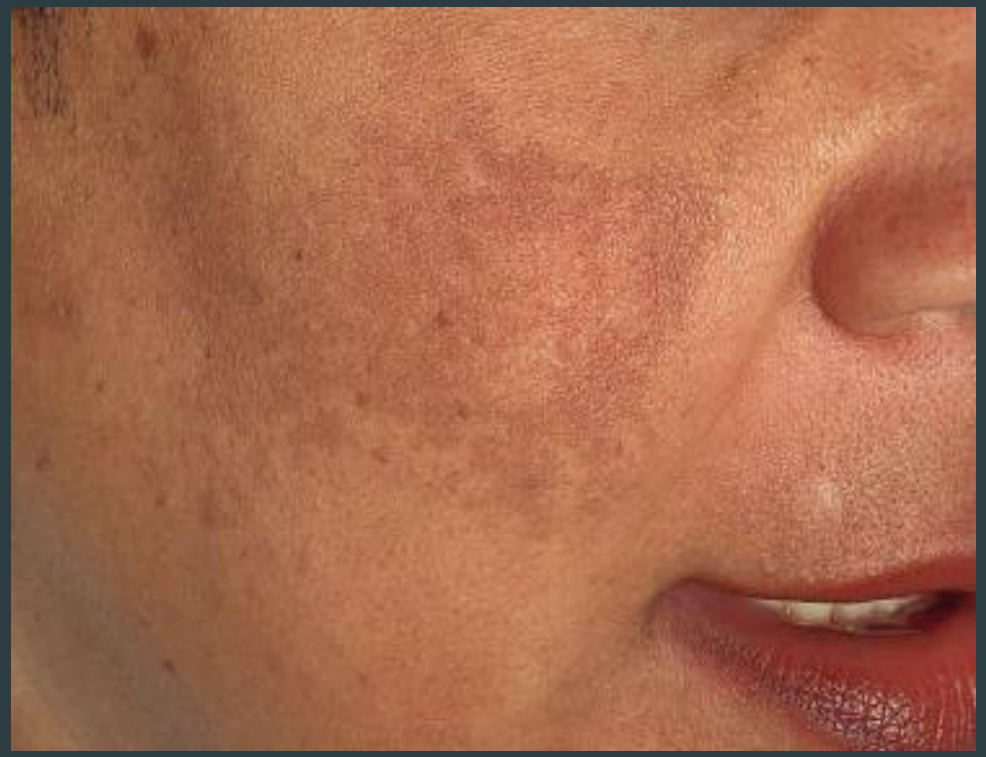
Pathogenesis

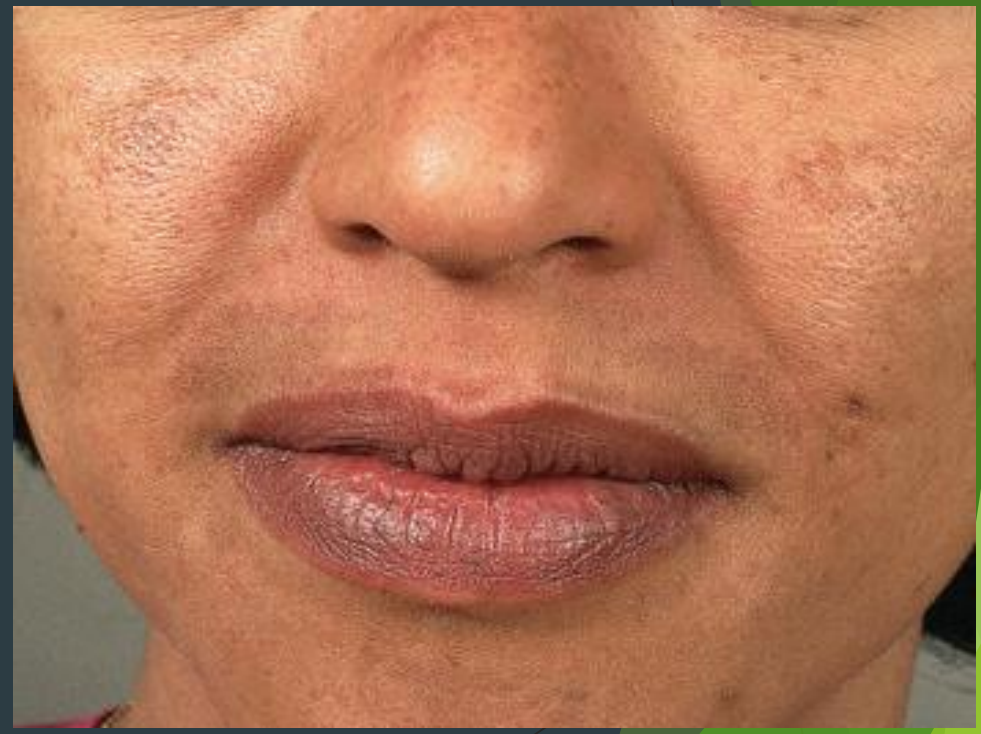
- Although the exact pathogenesis of melasma is unknown, it is hypoth-esized that following exposure to UV irradiation or another inducer, hyperfunctional melanocytes within involved skin produce increased amounts of melanin.
- In addition to oral contraceptive use and hyperestrogenic states, other medications (e.g.phenytoin, phototoxic drugs) and disorders (e.g. autoimmune thyroiddisease) have the potential to aggravate melasma.
- Increased expressionof KIT and stem cell factor within the lesional epidermis and dermis,respectively, may play a role in the hyperpigmentation of melasma.

Clinical Features

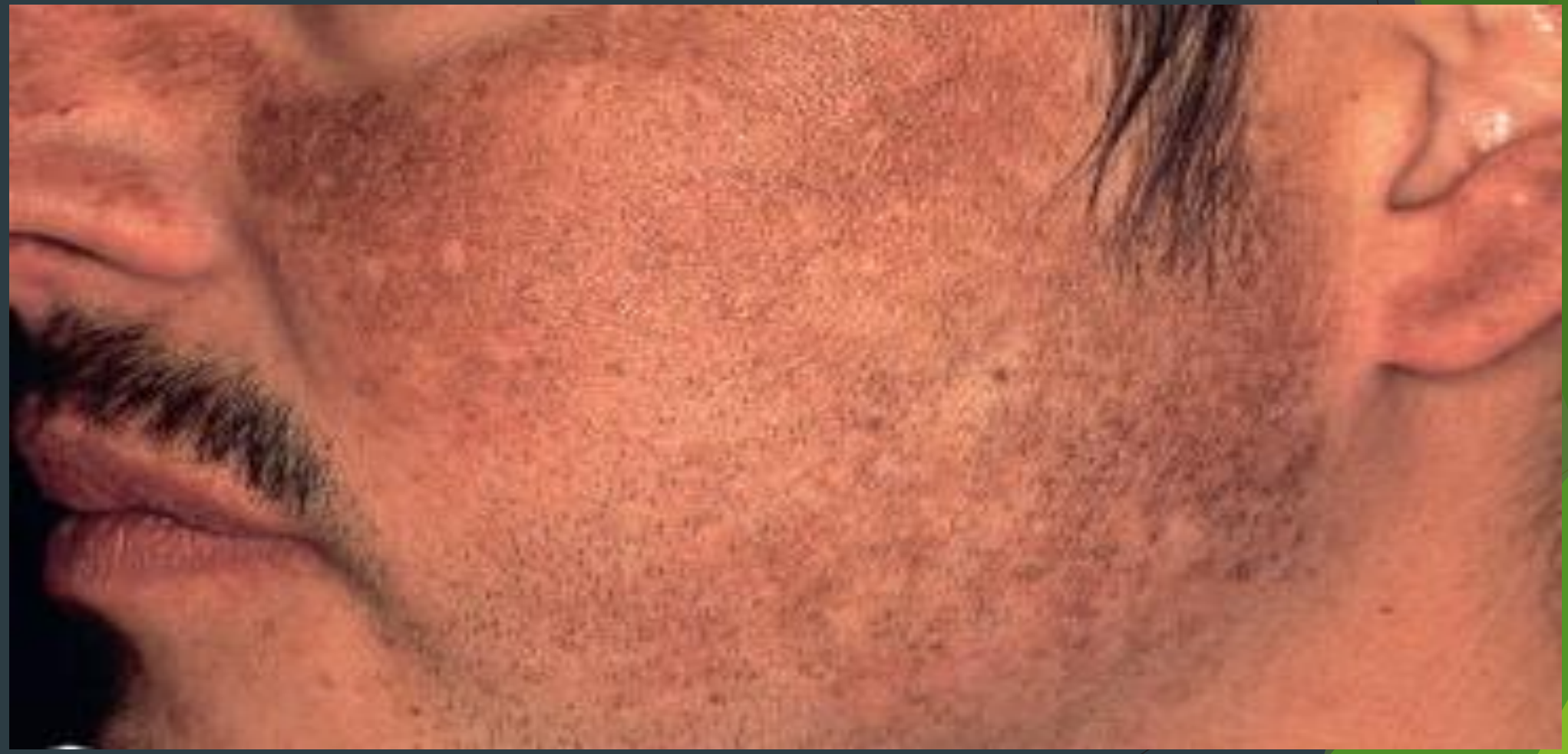
- Light to dark brown or brown-gray patches with irregular bordersappear primarily on the face
- The areas of hypermelanosis are distributed symmetrically in three classic patterns.
- Melasma has classically been subdivided into four types based up on the primary location of the pigment: epidermal, dermal, mixed, and indeterminate (e.g. in patients with very dark skin pigmentation).
- In theory, lesions with increased epidermal melanin are accentuated and those with increased dermal melanin become less obvious (i.e. blendwith uninvolved skin) with Wood's lamp examination.

Clinical Features





Melasma-like appearance in a patient with previous acute cutaneous lupus erythematosus



TREATMENT OPTIONS FOR MELASMA

Recommendations for all patients

- • Avoidance of sun exposure and tanning beds
- • Daily use of broad-spectrum sunscreen (ideally SPF ≥30 with physical blocker such as zinc oxide or titanium dioxide)
- • Sun-protective hats and clothing
- • Camouflage makeup
- • Discontinue oral contraceptives, if possible

Active treatment

First-line topical therapies

- • Triple combination of HQ + retinoid + corticosteroid§ at bedtime
- • 4% HQ daily, typically at bedtime
- • Azelaic acid (15–20%)Adjunctive topical therapies
- • L-ascorbic acid (10–15%)
- • Kojic acid (1–4%)

Second-line therapies

- • Glycolic (start at 30% and increase as tolerated) or salicylic acid peels (20–30%) every 4–6 weeks

Third-line therapie

- • Fractional laser
- • Intense pulsed light (IPL)

Long-term maintenance

- • Continue daily sunscreen and sun-protective measures
- • Topical retinoid
- • Topical α-hydroxy acid (e.g. glycolic acid cream)
- • Other topicals, e.g. L-ascorbic acid (10–15%), azelaic acid (15–20%), or kojic acid (1–4%)