ACQUIRED HYPOMELANOSIS

Vitiligo

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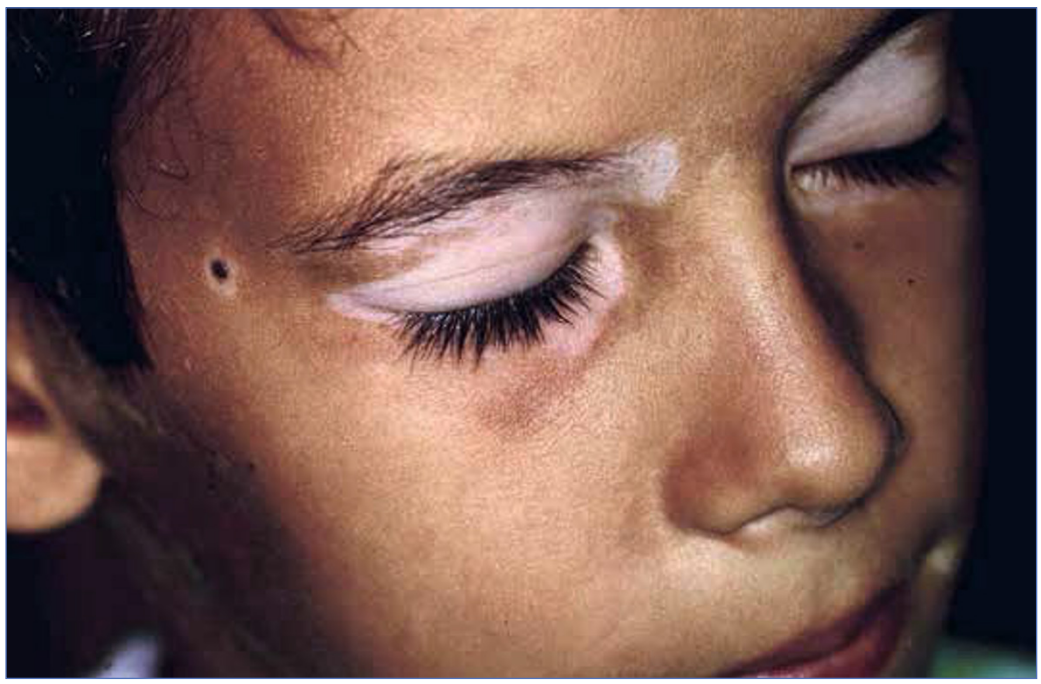
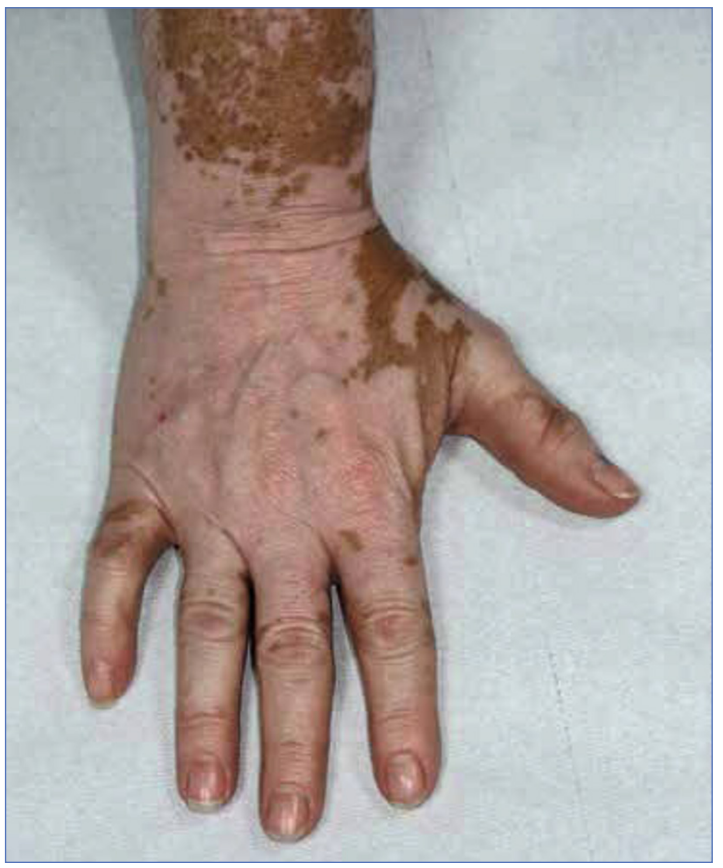
T. Passeron and J.-P. Ortonne, *Atlas of Pigmentary Disorders*, DOI 10.1007/978-3-319-10897-1_4

VITILIGO



Vitiligo of the face. note the presence of halo nevus.



Vitiligo of the hand.

EPIDEMIOLOGY

The worldwide prevalence of vitiligo is 0.5 to 1%.
The frequency of vitiligo in siblings of affected individuals is increased to 4 to 8%.
Men and women are equally affected.
No apparent difference in rates of occurrence according to skin type and race.
The age of onset is usually in the second or in the third decade of life in non-segmental vitiligo, but all ages are concerned. Most of segmental vitiligos begin during childhood.
Congenital vitiligo exists, but it is extremely rare, and Piebaldism or Waardenburg syndrome have to be first ruled out in front of congenital achromic patches.

PATHOPHYSIOLOGY

Vitiligo is a polygenetic disorder characterized by incomplete penetrance, multiple susceptibility loci, and genetic heterogeneity associated with nongenetic factors. It is characterized by a substantial loss of functional melanocytes in the epidermis and sometimes in hair follicles.
Genome-wide linkage studies of multiplex generalized vitiligo families have revealed several susceptibility genes involved in melanogenesis and in immune regulation.
Subtle defects in melanocyte catabolism, in defense against oxidative stress, or in melanocyte antigen presentation, might trigger the immune response against melanocyte and lead to their disappearance.

CLINICAL DERMATOLOGICAL PRESENTATION

Vitiligo is characterized by acquired achromic patches that appear completely white under Woods' lamp examination
The lesions are asymptomatic but pruritus can occur, especially in active phase of the disease.
Segmental and non-segmental forms of vitiligo have to be individualized.

Segmental vitiligo

The depigmentation is restricted on a unilateral segment of the body. Leukotrichia is frequently associated.
Most cases occurs during infancy and the lesions are less evolving, but their response to medical treatment is lower as compared to non-segmental vitiligo.

Non-segmental vitiligo

The achromic lesions are often symmetric and usually increase in size over time. Face, extremities, periorificial areas and bony prominences are the most affected localizations. Hair (leukotrichia) and mucosal areas can be involved. Koebner phenomenon is frequently observed.
Several types of clinical presentations are described.

- Acrofacial vitiligo: lesions restricted on the face, hands and feet.
- Inflammatory vitiligo: with erythematous, sometimes squamous or hyperpigmented borders.
- Vitiligo punctate: achromic macules of 1 to 5 mm in diameter.
- Mucosal vitiligo: achromic lesions restricted to the mucosal areas.
- Polychrome vitiligo: classical achromic macules associated with hypopigmented patches harboring different intensities of depigmentation. Mostly observed in dark-skinned patients.
- Hypochromic vitiligo (also called vitiligo minor): rare and misleading form of vitiligo presenting with hypochromic patches. Achromic lesions can be associated but may be lacking.

On the face, the localization often has a seborrheic distribution. Only reported so far in dark-skinned individuals.

- Vitiligo universalis: the depigmentation concerns all or almost all the body surface and only few pigmented areas remain

The association of segmental and non-segmental vitiligo is called mixed vitiligo.
Occupational vitiligo is a form of vitiligo induced by chemicals that are typically derivatives of hydroquinone. In most cases the exposure occurs during the professional activity.
The depigmentation then extend beyond the initial site that was exposed to the chemical.

EXTRACUTANEOUS SIGNS

Auto-immune disorders are associated to vitiligo in 25 to 30% of cases. Auto-immune thyroiditis are by far the most frequent. Ocular and auditory involvement has been reported. Up to 30% of vitiligo patients have choroidal abnormalities but clinical symptoms are rare.

HISTOPATHOLOGY

Loss of melanocyte with absence of pigmentation in the epidermis. In hypochromic vitiligo the number of melanocytes and the melanin contained are decreased but some remain.
The rest of the epidermis is usually normal. Slight lymphocytic infiltrate can be observed on the borders of active lesions.

DIFFERENTIAL DIAGNOSIS

- Piebaldism.
- Waardenburg syndrome.
- Melanoma-associated vitiligoid depigmentation.
- Discoid lupus, mycosis fungoides, atopic dermatitis, pityriasis alba, leprosy.

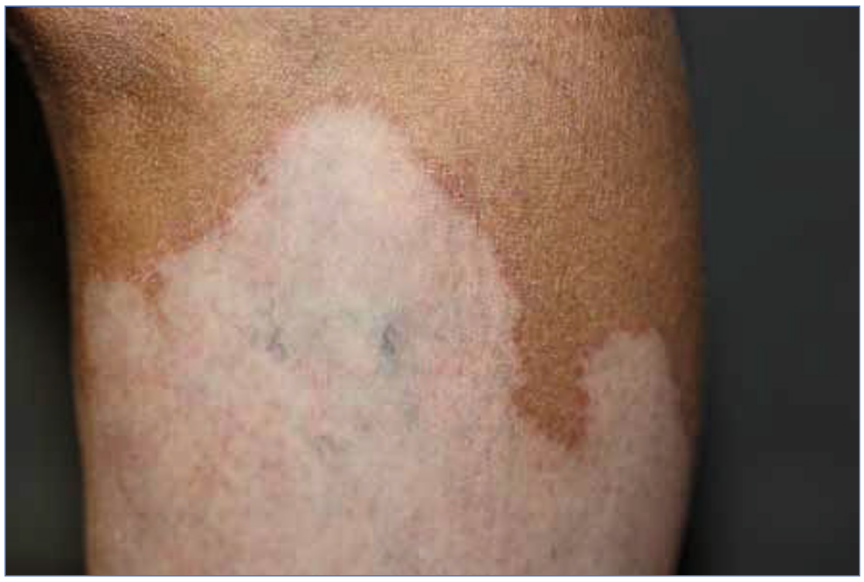
TREATMENT

Topical steroids or calcineurin inhibitors are the first line option for localized forms. Excimer laser or lamps can be proposed in second line.
Phototherapy (preferentially narrow band UVB) is the best option for generalized forms. Association with topical treatment is required for improving results.
Surgical approaches with grafts are good option for segmental vitiligo and for stable localized forms of non-segmental vitiligo
Depigmentation of the remaining pigmented skin can be proposed for vitiligo universalis. Q-switched lasers have to be preferred to depigmenting agents.
Camouflaging, self-tanning creams and psychological support can be useful.

KEY REFERENCES

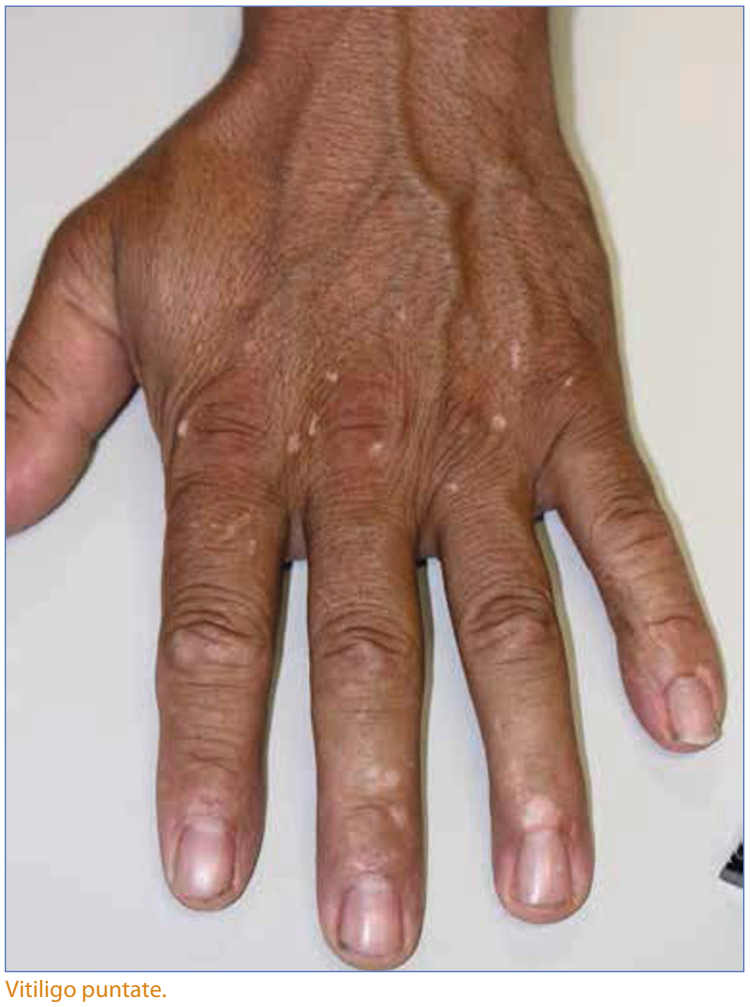
- Activation of the unfolded protein response in vitiligo: the missing link? Passeron T, Ortonne JP. J Invest Dermatol. 2012;132:2502-4.
- Taïeb A, Picardo M; VETF Members. The definition and assessment of vitiligo: a consensus report of the Vitiligo European Task Force. Pigment Cell Res. 2007;20:27-35.

VITILIGO

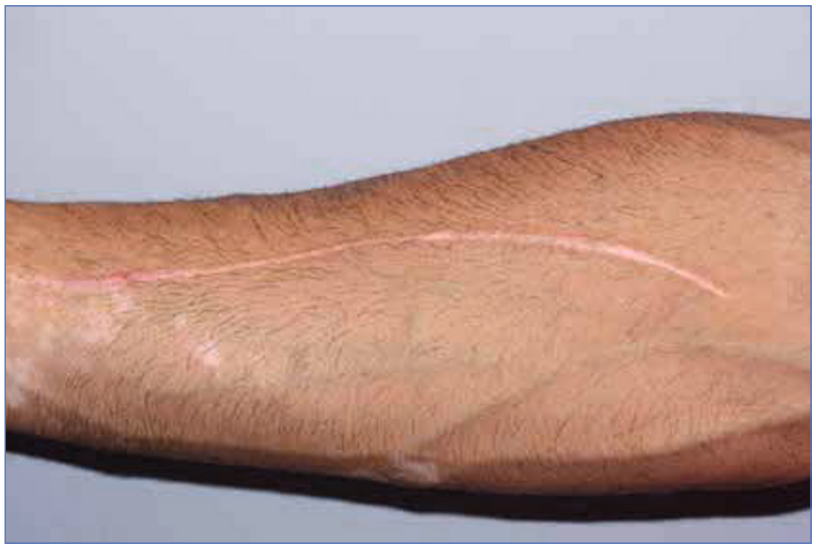


Inflammatory vitiligo. Note the erythematous and squamous borders.

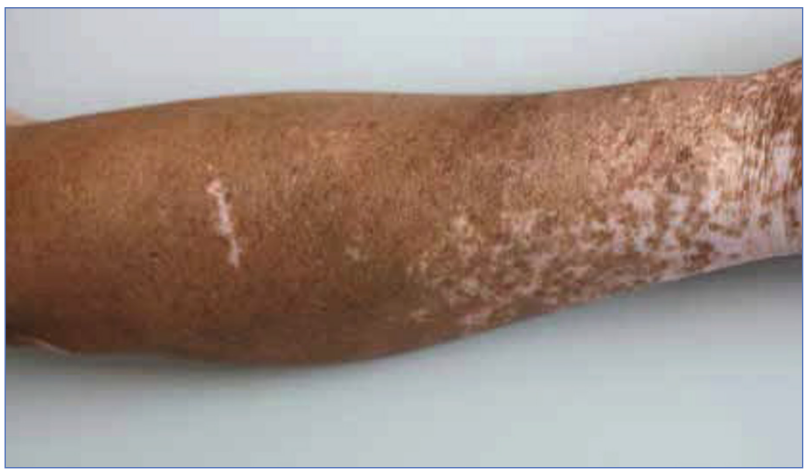
Plantar involvement in a patient with vitiligo.



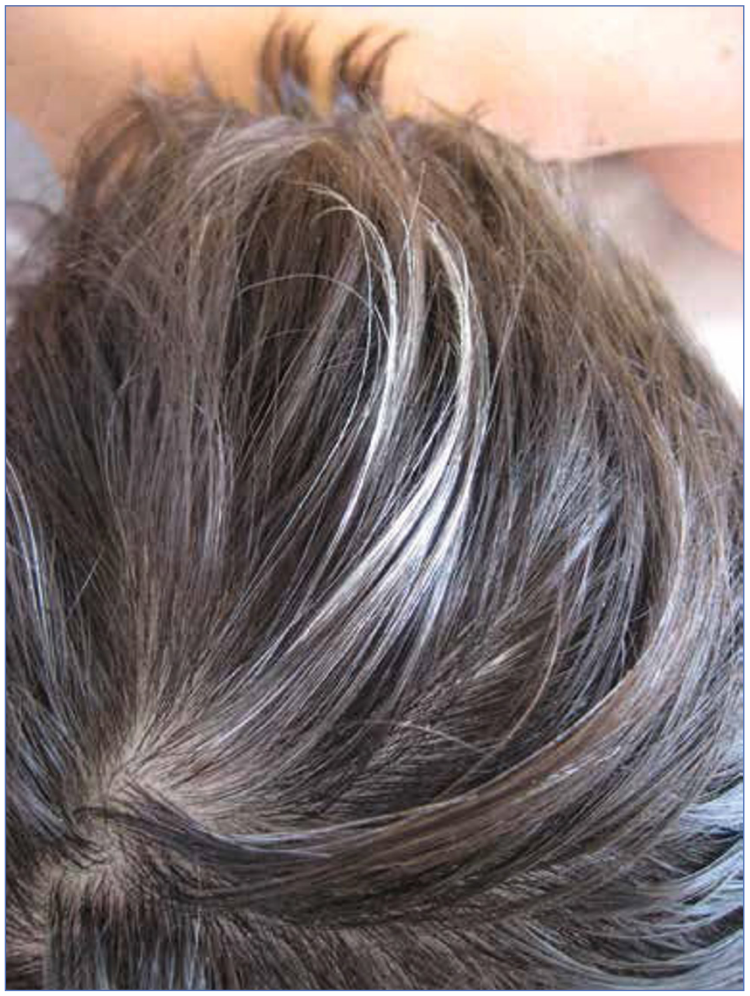
Vitiligo puntate.



Koebner phenomenon with localization of vitiligo on a recent scar.

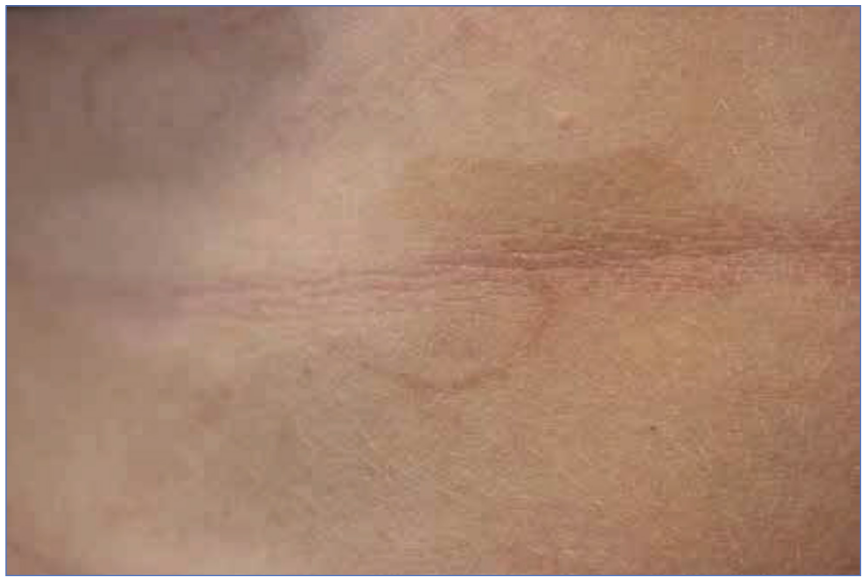


Vitiligo of the arm with koebner phenomenon.



Depigmentation of the hairs in a patient with generalized vitiligo.

VITILIGO

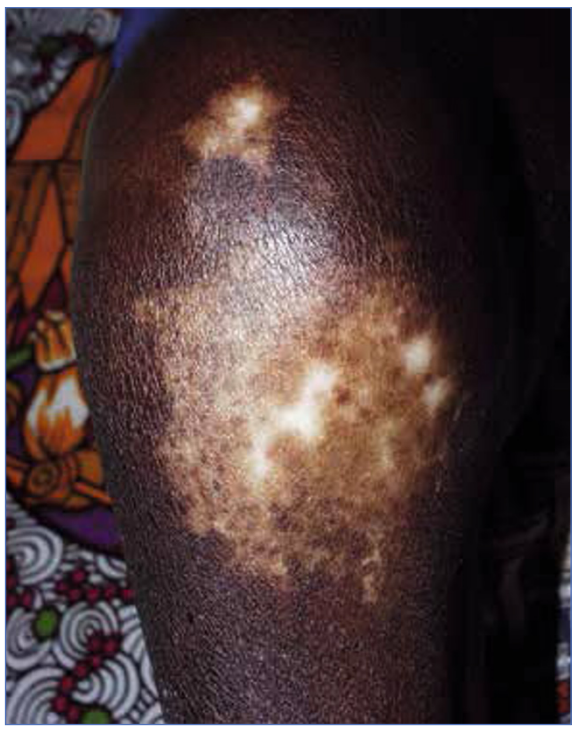


A. Vitiligo with slightly inflammatory active borders.

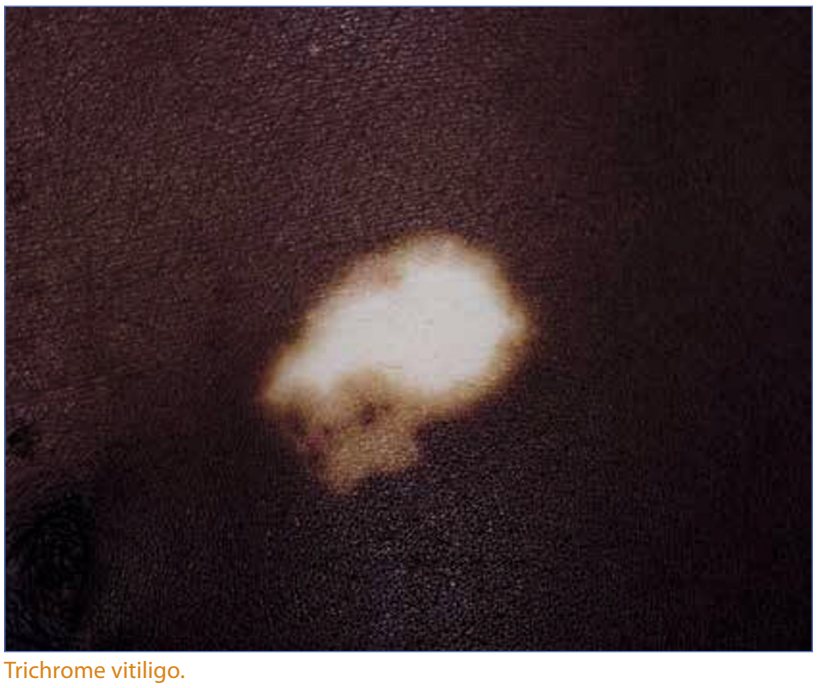
B. Aspect under Woods' lamp examination. The recent lesions are still hypopigmented while the former ones appear completely white.

Leukotrichia of the eye lashes in a patient with segmental vitiligo.

Mucosal vitiligo.

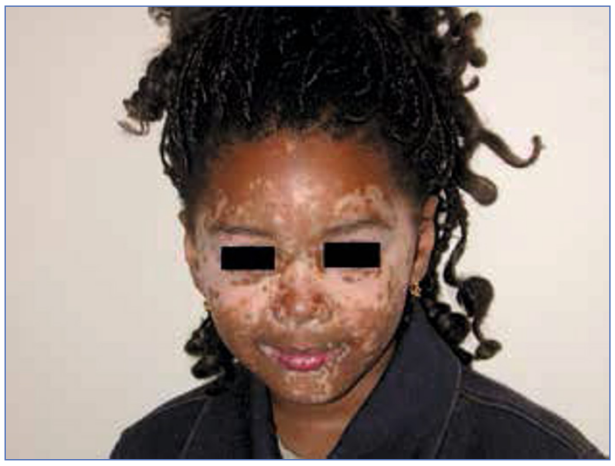


Multichrome vitiligo.

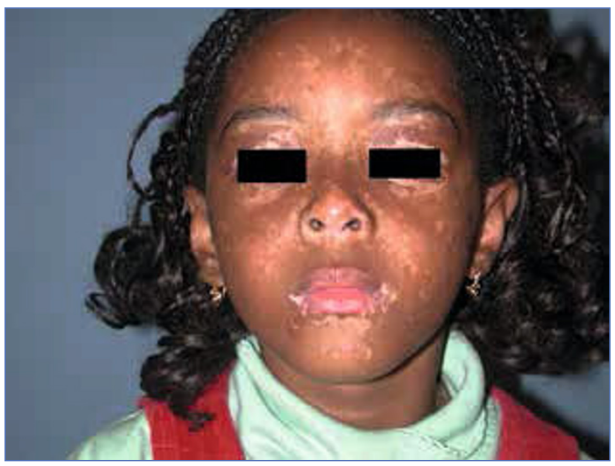


Trichrome vitiligo.

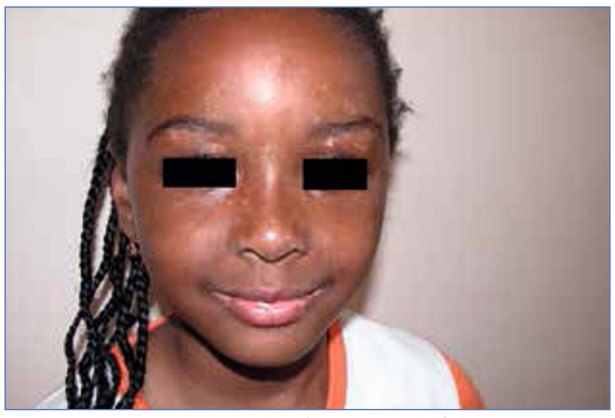
VITILIGO



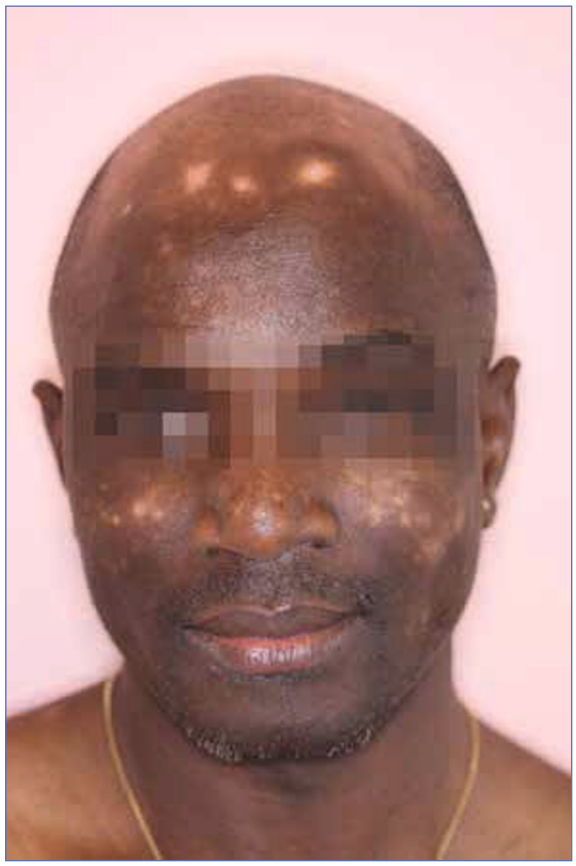
A. Vitiligo in a young girl.



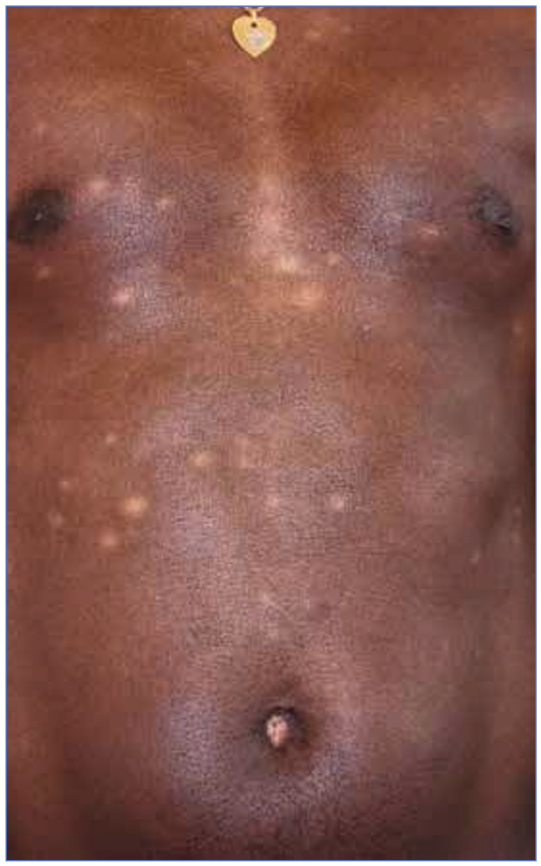
B. Almost complete repigmentation after 40 sessions of excimer laser.



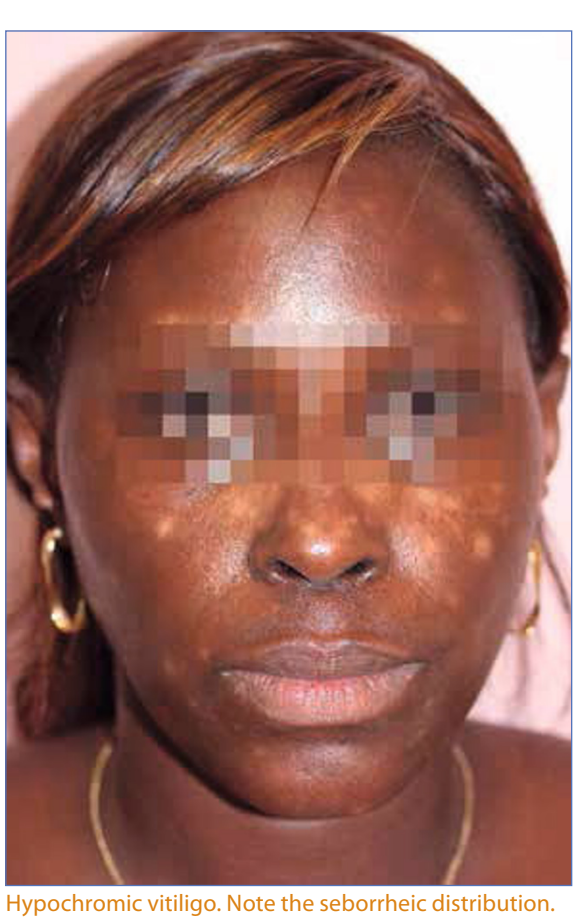
C. Clinical aspect 18 months after the end of the treatment.



A. Hypochromic vitiligo. Note the seborrheic distribution. The presence of achromic macules on the vertex is helpful for the diagnosis.

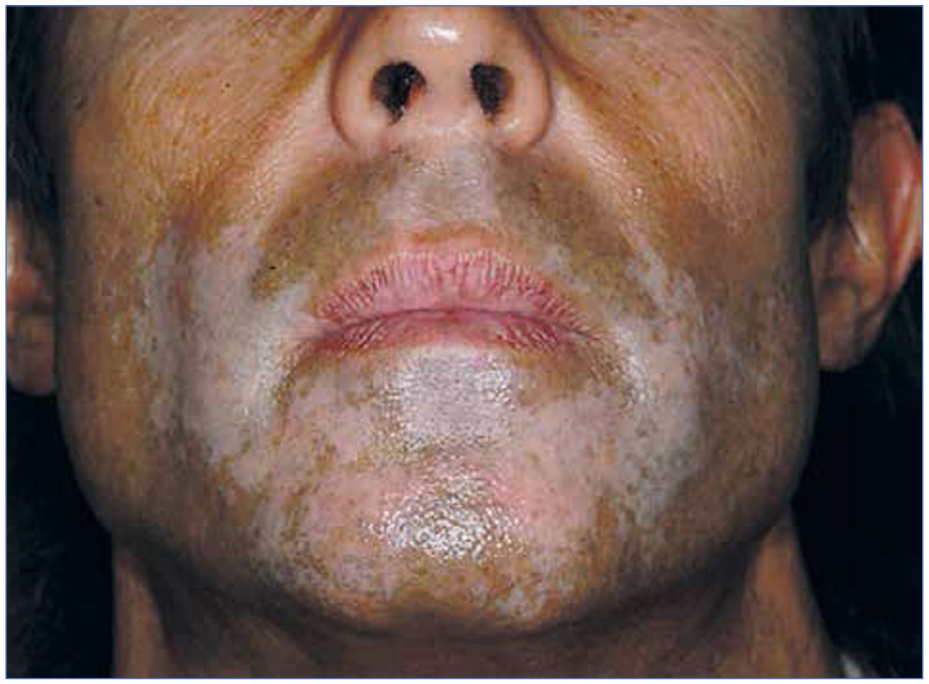


B. Hypochomic vitiligo (same patient on the trunk).

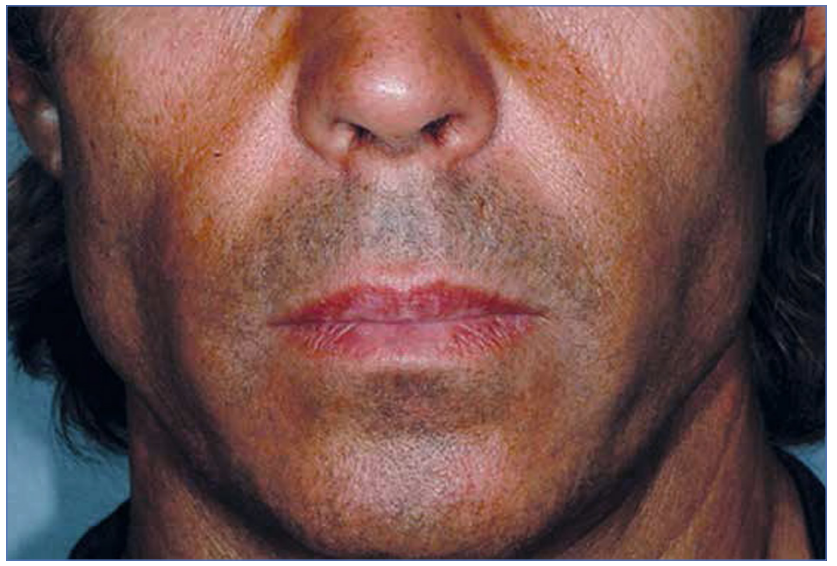


Hypochromic vitiligo. Note the seborrheic distribution.

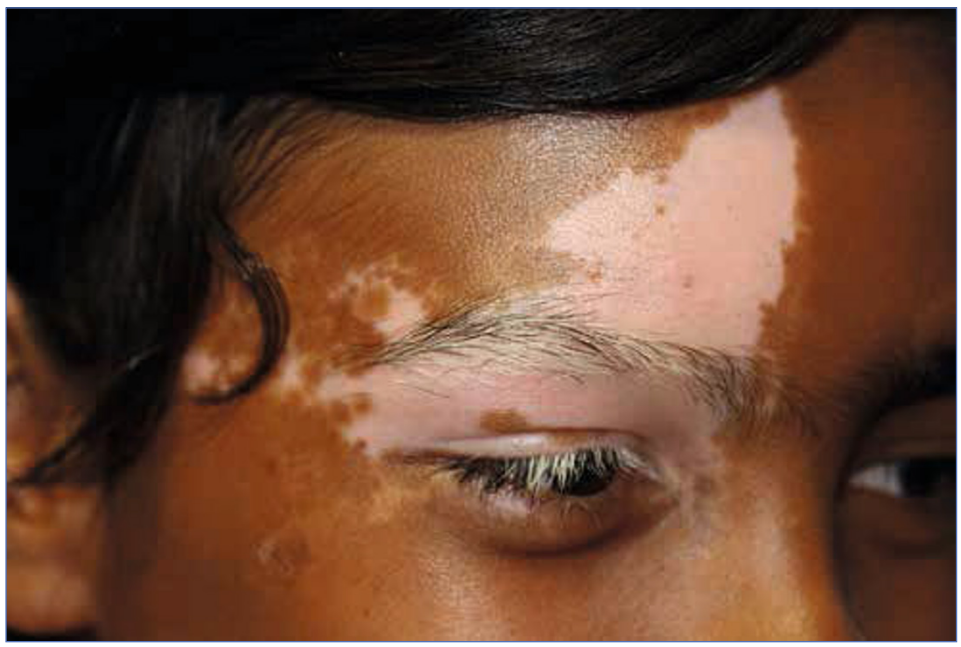
VITILIGO



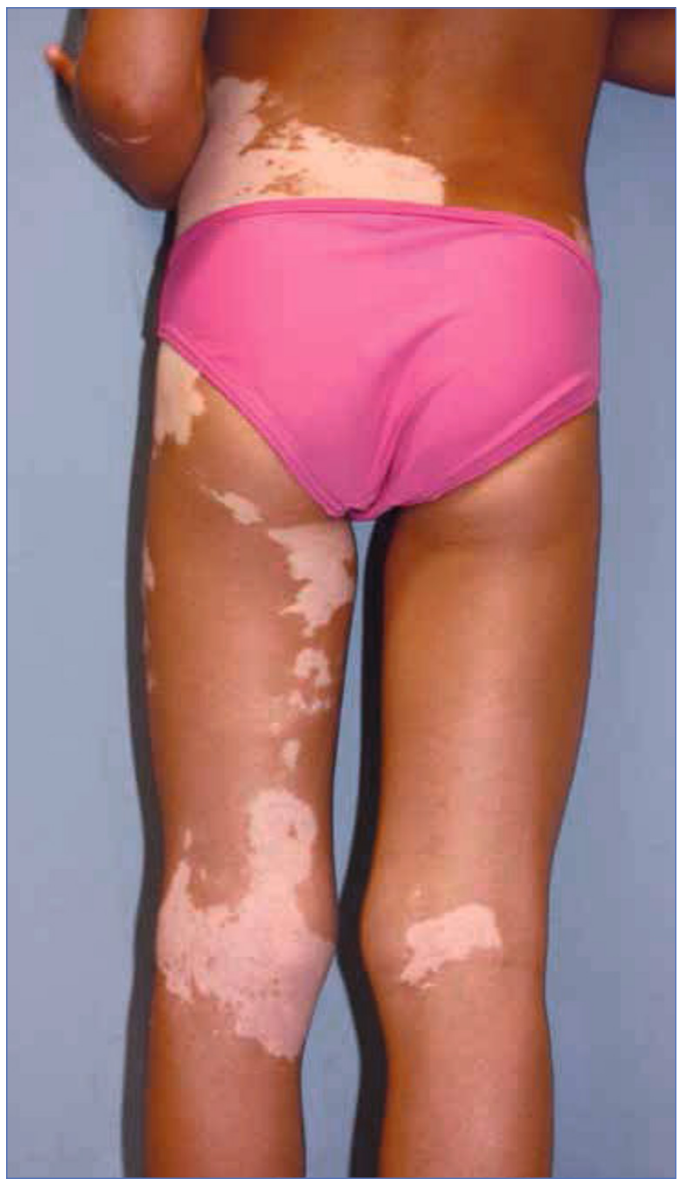
A. Vitiligo of the face.



B. Complete repigmentation after 15 sessions of excimer laser combined with twice-daily applications of 0.1% tacrolimus ointment.

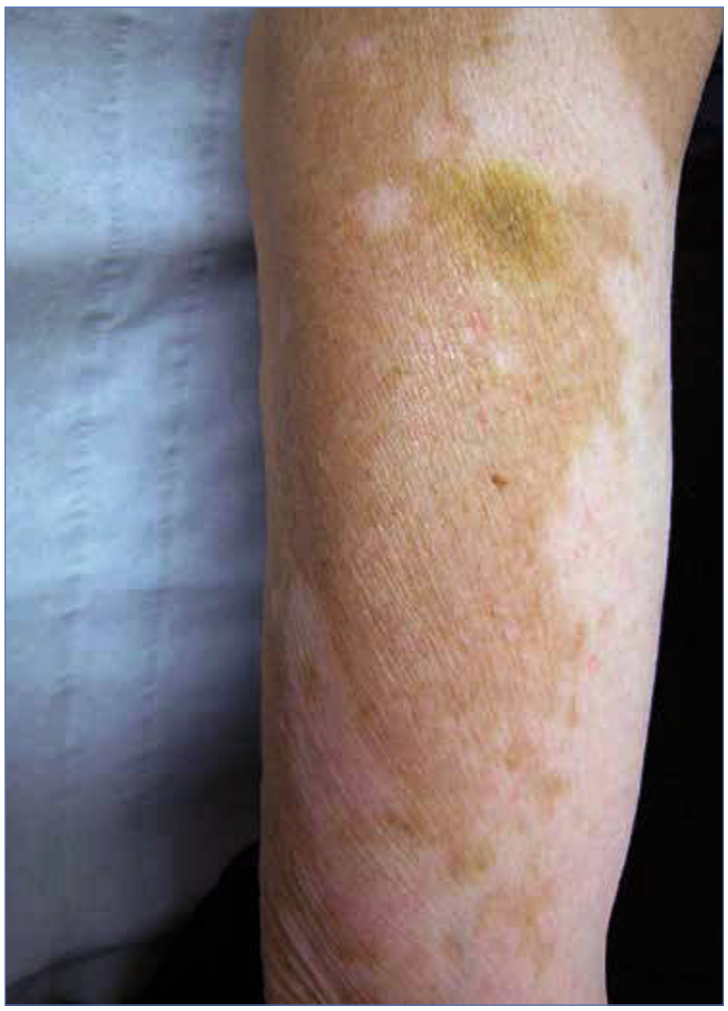


Segmental vitiligo.

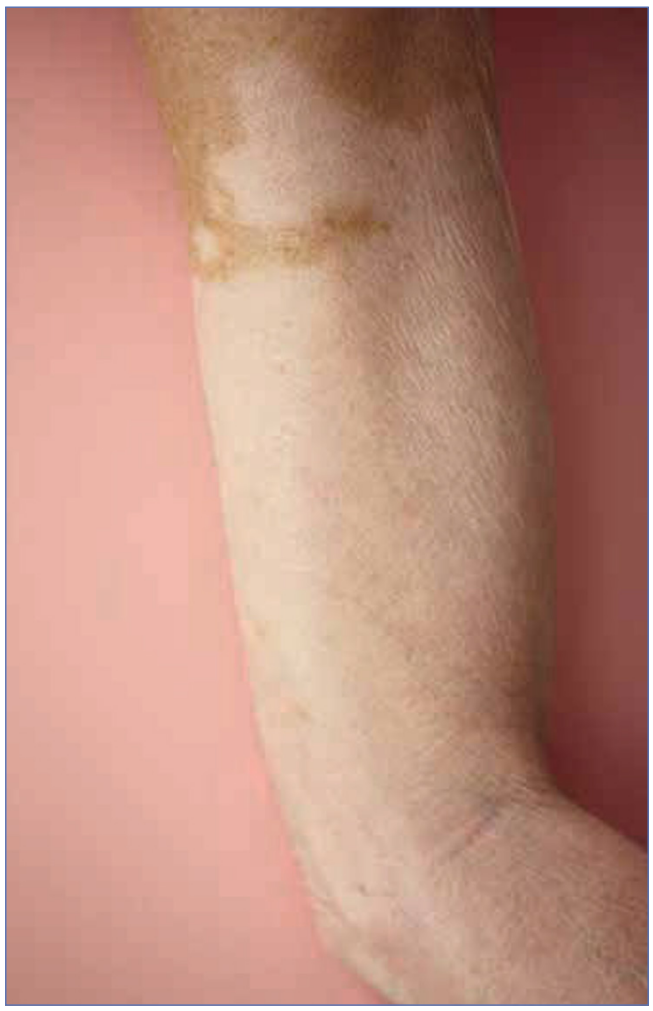


Mixed vitiligo.

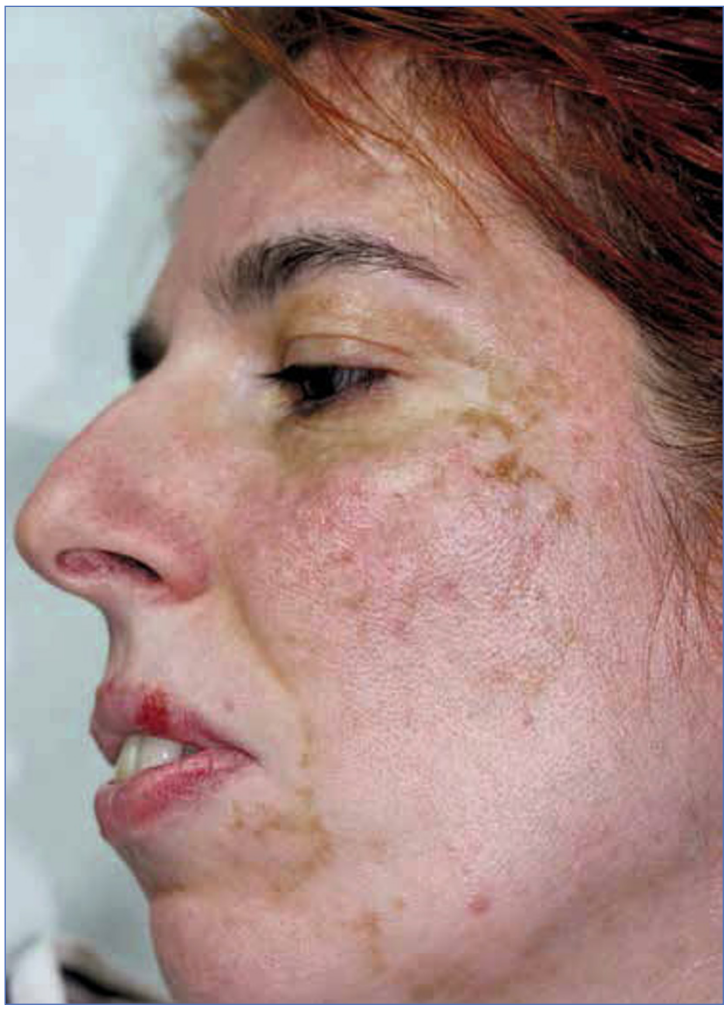
VITILIGO



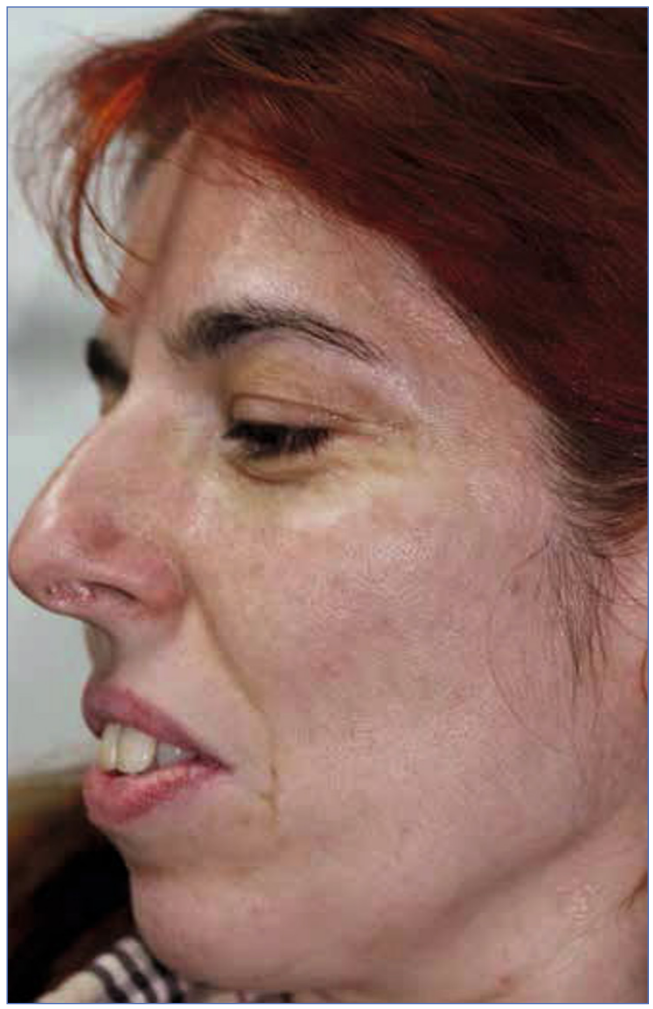
A. Widespread vitiligo with remaining pigmented skin on the arm. After failure of repigmenting approaches the patient wanted to depigment the lower part of the arm so she could wear T-shirts.



B. Clinical aspect two years after two sessions of alexandrite Q-switched laser. The demarcation between treated and untreated area is obvious.



A. Vitiligo universalis with almost complete depigmentation of the face.

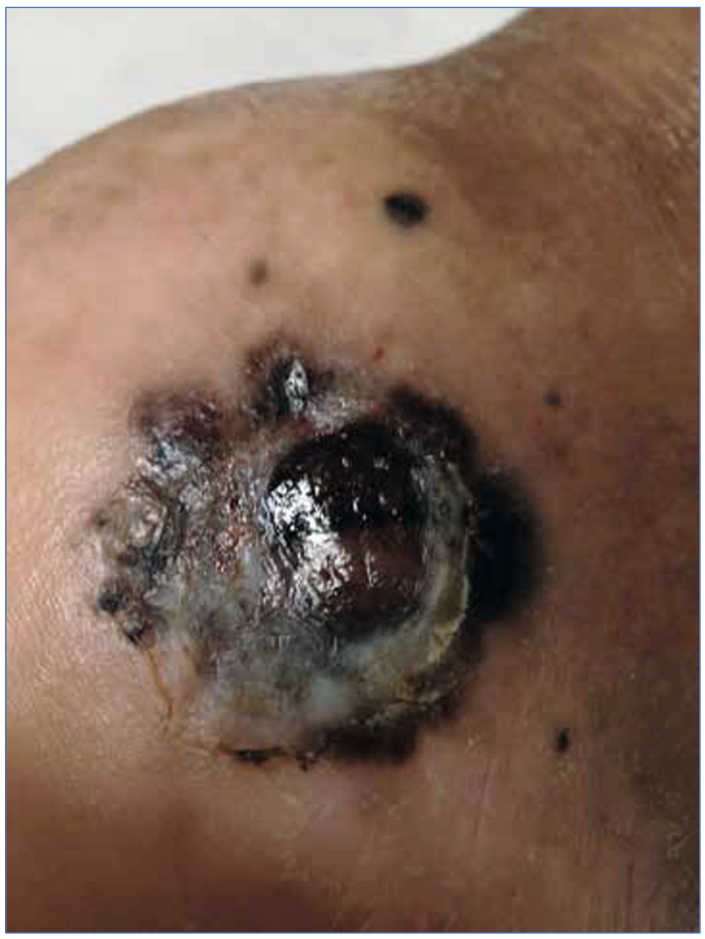


B. One session of alexandrite Q-switched laser allowed removing the remaining pigmented areas.

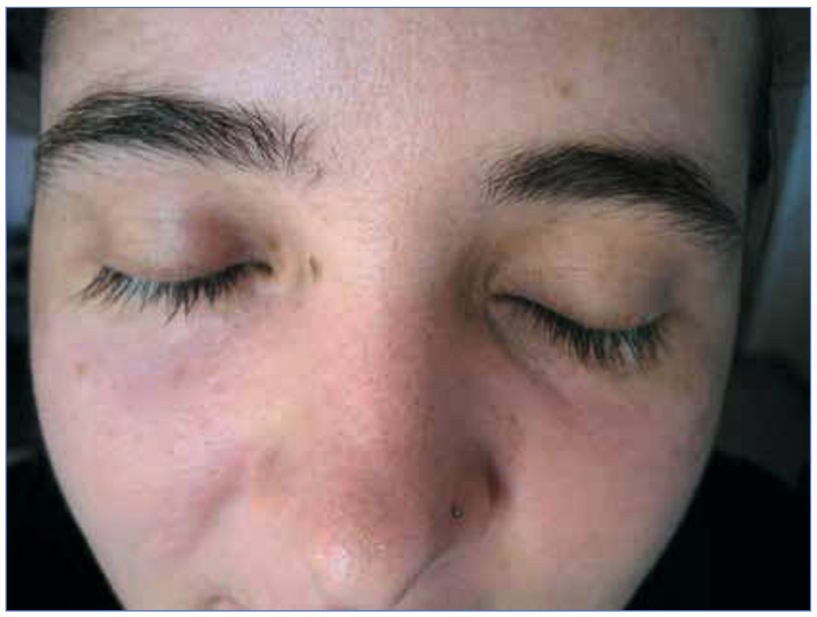
ACQUIRED HYPOMELANOSIS

Melanoma associated-vitiligoid depigmentation

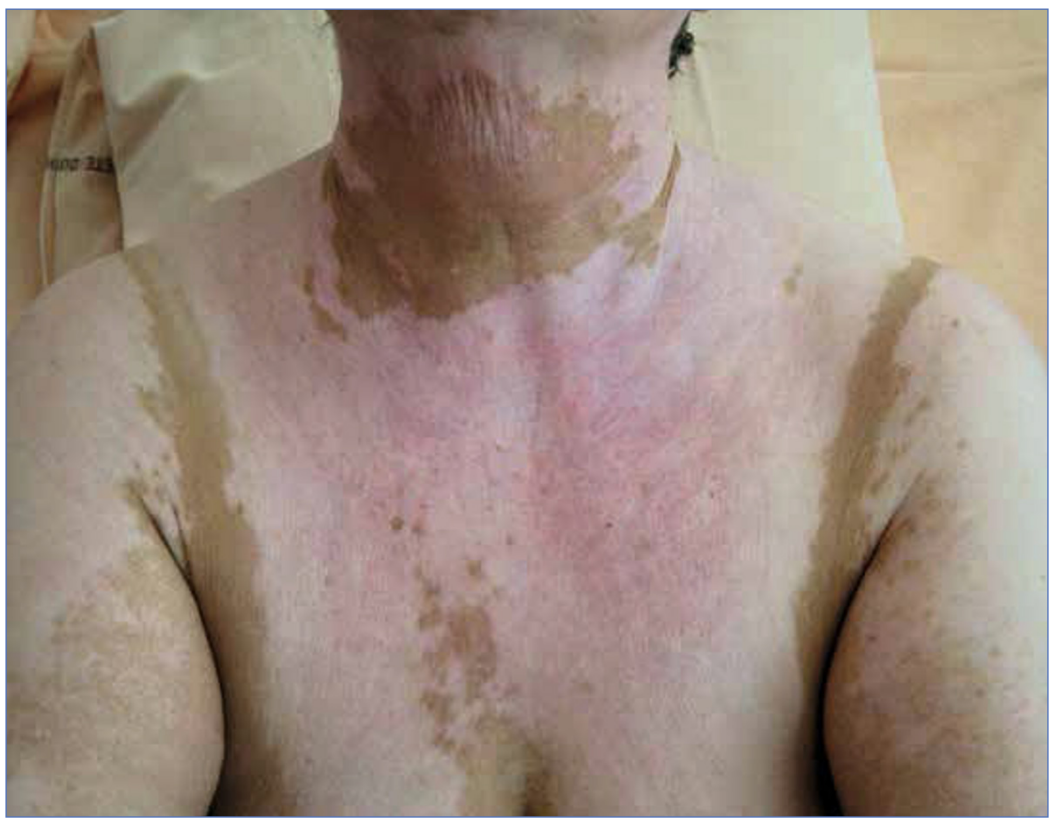
MELANOMA-ASSOCIATED VITILIGOID DEPIGMENTATION



Depigmentation within primary melanoma developed on a congenital melanocytic nevus (coll. Thomas Paulo).



Depigmentation of the eyelashes in a woman with metastatic melanoma.



Widespread vitiligoid depigmentation in a patient with metastatic melanoma.

EPIDEMIOLOGY

Melanoma-associated vitiligoid depigmentation occurs in 2 to 16% of melanoma patients.
Occurrence after treatment is more frequent than spontaneous depigmentation.
Depigmentation appears more frequently in younger patients and females.
Personal history of autoimmune disorders and familial history of vitiligo predispose to vitiligoid depigmentation in melanoma patients.
Melanoma-associated vitiligoid depigmentation appears to be associated with a better prognosis.

PATHOPHYSIOLOGY

Depigmentation-associated with melanoma reflects the immune reaction against melanocytic cells.

CLINICAL DERMATOLOGICAL PRESENTATION

Several types of leukoderma have been described in patients with melanoma:

- Depigmentation within melanoma: depigmented areas within the melanoma lesion corresponding to the progressive replacement of the tumor with fibrous stroma. Complete regression of primary melanoma has been described but remains rare.
- Melanoma-associated depigmentation: appearance of white patches in sites distant from the primary tumor, arising either spontaneously or following immunologic-based treatments such as BCG therapy, interferon alpha, interleukin 2 or ipilumumab. The depigmentation usually begins on the neck, upper back and the chest and can take a confetti-like presentation.

The depigmentation is asymptomatic.

EXTRACUTANEOUS SIGNS

Uveitis can be associated.

HISTOPATHOLOGY

Absence of melanin and melanocyte in depigmented area.

DIFFERENTIAL DIAGNOSIS

- Vitiligo.

TREATMENT

Treatment of the melanoma.

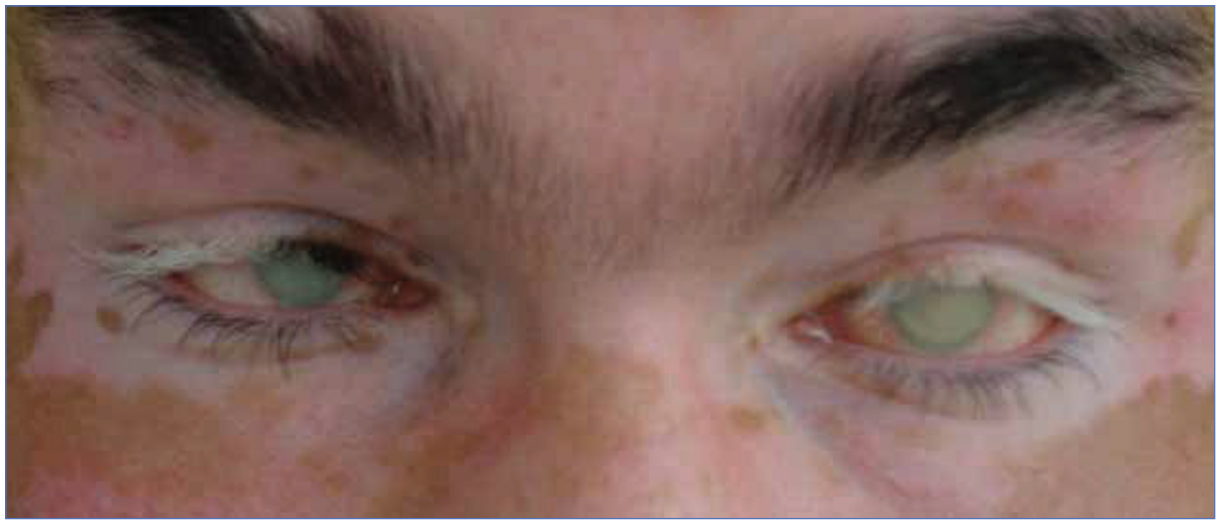
KEY REFERENCES

- Koh HK, Sober AJ, Nakagawa H, Albert DM, Mihm MC, Fitzpatrick TB. Malignant melanoma and vitiligo-like leukoderma: an electron microscopic study. J Am Acad Dermatol. 1983;9:696-708.
- Naveh HP, Rao UN, Butterfield LH. Melanoma-associated leukoderma - immunology in black and white? Pigment Cell Melanoma Res. 2013;26:796-804.

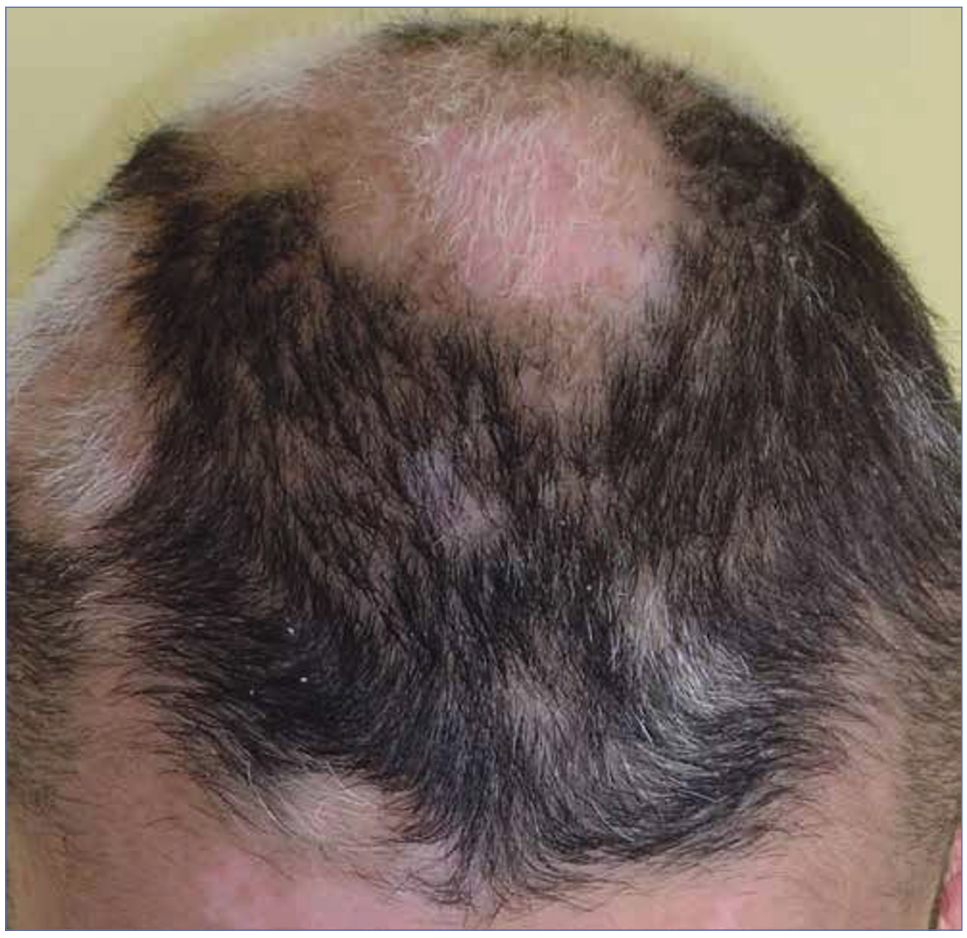
ACQUIRED HYPOMELANOSIS

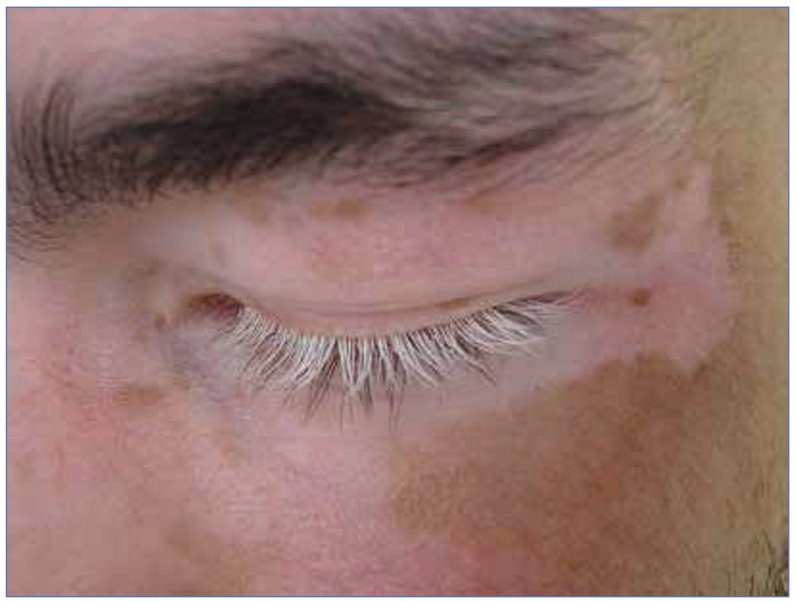
Vogt-Koyanagi Harada syndrome

VOGT-KOYANAGI HARADA SYNDROME



Sequelae of severe bilateral panuveitis (coll. P Berbis).





Poliosis of the lashes and vitiligoid depigmentation (coll. P Berbis).

Vogt-koyanagi-harada disease with vitiligo lesions, poliosis and areas or alopecia (coll. P Berbis).

EPIDEMIOLOGY

Rare disease occurring more frequently among people with dark skin types.
Asians, Native Americans, and Hispanics are most frequently affected.
Male:female ratio: 1:2.
Onset usually between 20 and 50 (mostly in the third decade of life) but may be observed at any ages.

PATHOPHYSIOLOGY

Multisystemic autoimmune disease directed against the melanocytes of the eye, inner ear, meninges, and skin.
The exact pathophysiology remains unclear.
Genetic predisposition with association with HLA DR4/DR53. Association with HLA DR1 and HLA-DRB1*0405 have been also reported.
The immune response is mediated by lymphocytes. Th1, Th17 and regulatory T cells are involved.
Infection (especially viruses) might trigger the immune response in patients with genetic predisposition.

CLINICAL DERMATOLOGICAL PRESENTATION

Vitiligo.
Poliosis.
Alopecia.
Localization: mostly on head, face and trunk.

EXTRACUTANEOUS SIGNS

Chronic bilateral panuveitis characterizes Vogt-Koyanagi-Harada disease.
Clinical course in three stages:
Stage1: headache, fever, photophobia, nausea (less frequently vertigo, orbital pain, tinnitus) during a few days.
Stage 2: bilateral uveitis, hypoacusis, meningitis, and cutaneous involvement (focal neurological signs such as cranial nerve palsies or hemiparesis can be observed).
Stage 3: convalescence stage with evolution during weeks ormonths. Sometimes remain chronic.

DIFFERENTIAL DIAGNOSIS

- Vitiligo.
- Piebaldism.
- Alopecia areata.
- Other causes of uveitis including Behcet's disease, tuberculosis, sarcoidosis, and syphilis.

TREATMENT

Systemic corticosteroids 1 to 2 mg/kg/d (sometimes pulse high-dose of steroids for the first days of treatment) for 6 to 12 months. Association with immunosuppressants.
Anti-tumor necrosis factor-alpha (TNFα) agents (infliximab or adalimumab), or intravenous immunoglobulin might be useful in recalcitrant forms.

KEY REFERENCES

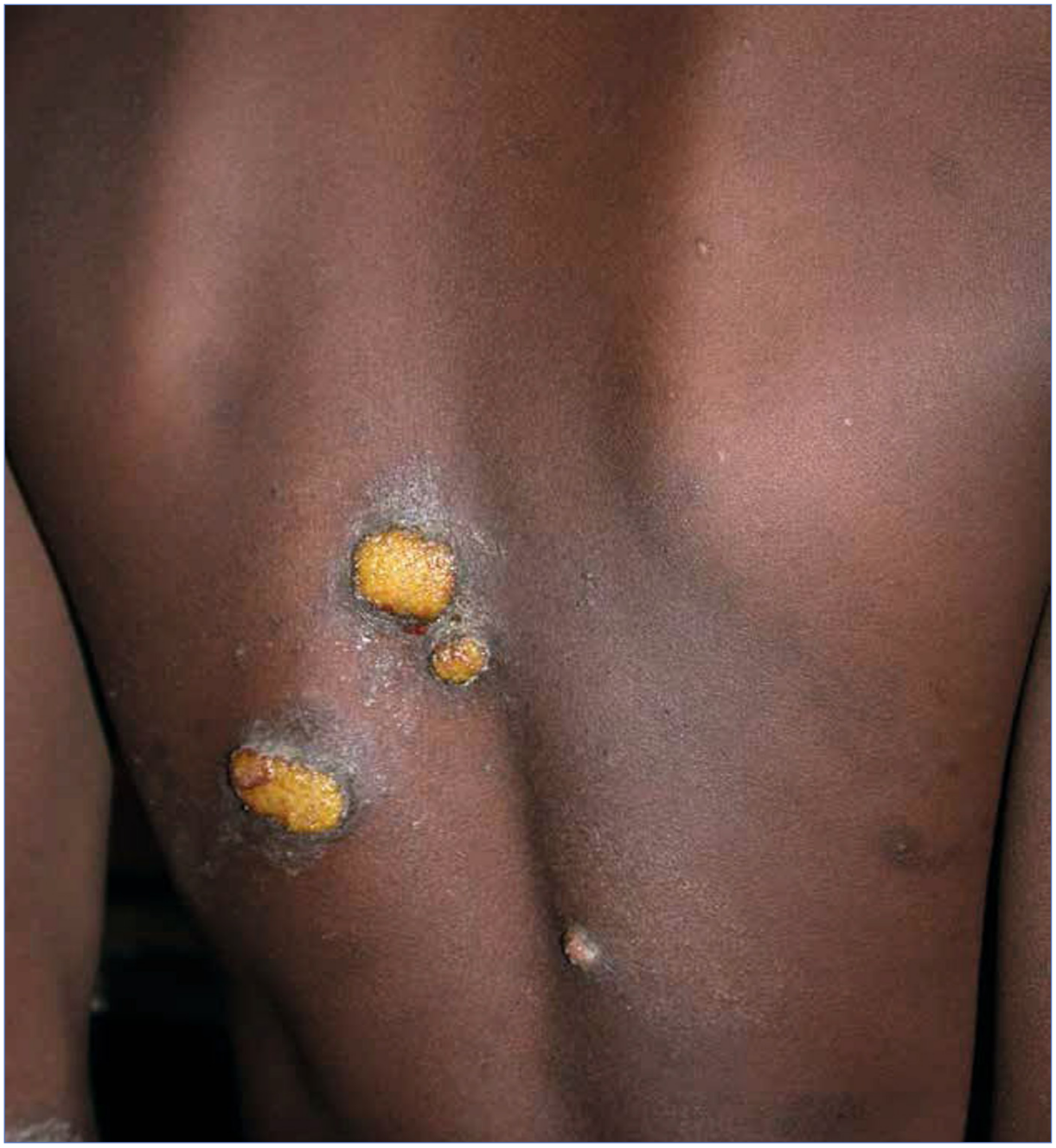
- Greco A, Fusconi M, Gallo A, Turchetta R, Marinelli C, Macri GF, De Virgilio A, de Vincentiis M. Vogt-Koyanagi-Harada syndrome. Autoimmun Rev. 2013;12:1033-8.
- Read RW, Holland GN, Rao NA, Tabbara KF, Ohno S, Arellanes-Garcia L, et al. Revised diagnostic criteria for Vogt-Koyanagi-Harada disease: report of an international committee on nomenclature. Am J Ophthalmol. 2001;131:647-52.

ACQUIRED HYPOMELANOSIS

Infectious hypomelanosis

ENDEMIC TREPANOMATOSES (PIAN, BEJEL, PINTA)

Jean-Jacques Morand



Yaws at an inhabitant of the ivory coast (coll J.J. Morand)

EPIDEMIOLOGY

- Bejel (endemic syphilis, firjal) (*Treponema pallidum* spp endemicum), which is prevalent in the dry Sahel region of Africa.
- Yaws (pian, framboesia, parengi, paru and bouba) (*T. pallidum* spp pertenue), arising in humid tropical or equatorial regions worldwide.
- Pinta (caraté, mal del pinto, puru-puru) (*T. carateum*), which is now extremely rare but still occurs in some areas of Central and South America.

PATHOPHYSIOLOGY

Non-venereal infections caused by spirochetal organisms.

CLINICAL DERMATOLOGICAL PRESENTATION

- Bejel: mucosal eroding lesions and plaques, genital and peri-anal pseudo-condylomatous lesions and annular patches.
- Yaws: polymorphous condition mainly affecting the tegumentum and soles of the feet therefore mimicking a variety of papular, squamous and keratotic disorders (atmospheric humidity influence the oozing or vegetating nature of the lesions).
- Pinta: acral dyschromias.

EXTRACUTANEOUS SIGNS

Osteoperiostitis in yaws and bejel: bone demineralization and incurvation of tibia and femur, dactylitis, hypertrophy of the nasal bone (Goundou), gumma, juxta-articular nodules and/or painful osteolytic damage, destruction of the nasal cartilage and perforation of the palate potentially leading to mediofacial mutilation (gangosa).
No central nervous and cardiovascular involvement.

HISTOPATHOLOGY

Serology: venereal disease research laboratory test (VDRL), *T. pallidum* haemagglutination assay (TPHA).
No specific histology; presence of plasmocytes.

DIFFERENTIAL DIAGNOSIS

- Bejel: syphilis, condylomas.
- Yaws: pemphigus, sickle-cell anaemia, pyodermatitis.
- Pinta: secondary syphilis.

TREATMENT

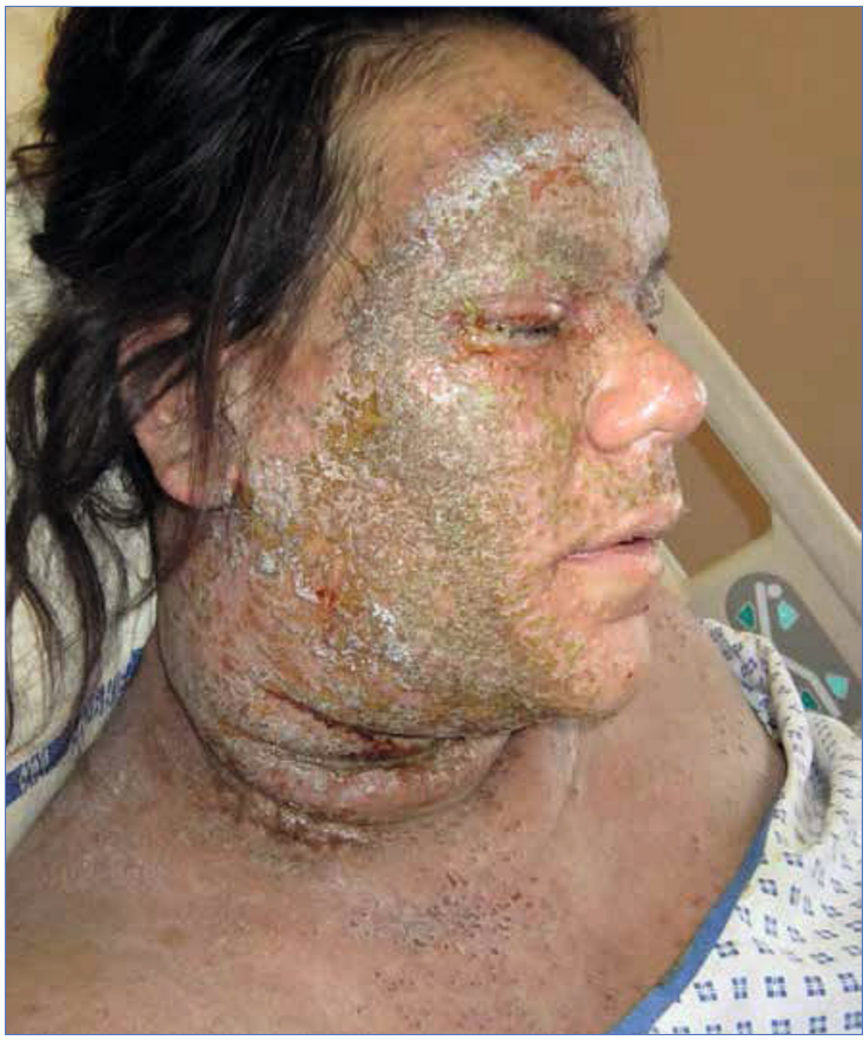
Benzathine penicillin (Extencilline®) : single intramuscular injection of 2.4 million units for adults and 0.6 to 1.2 MU in children; second injection recommended for the delayed onset forms.

KEY REFERENCE

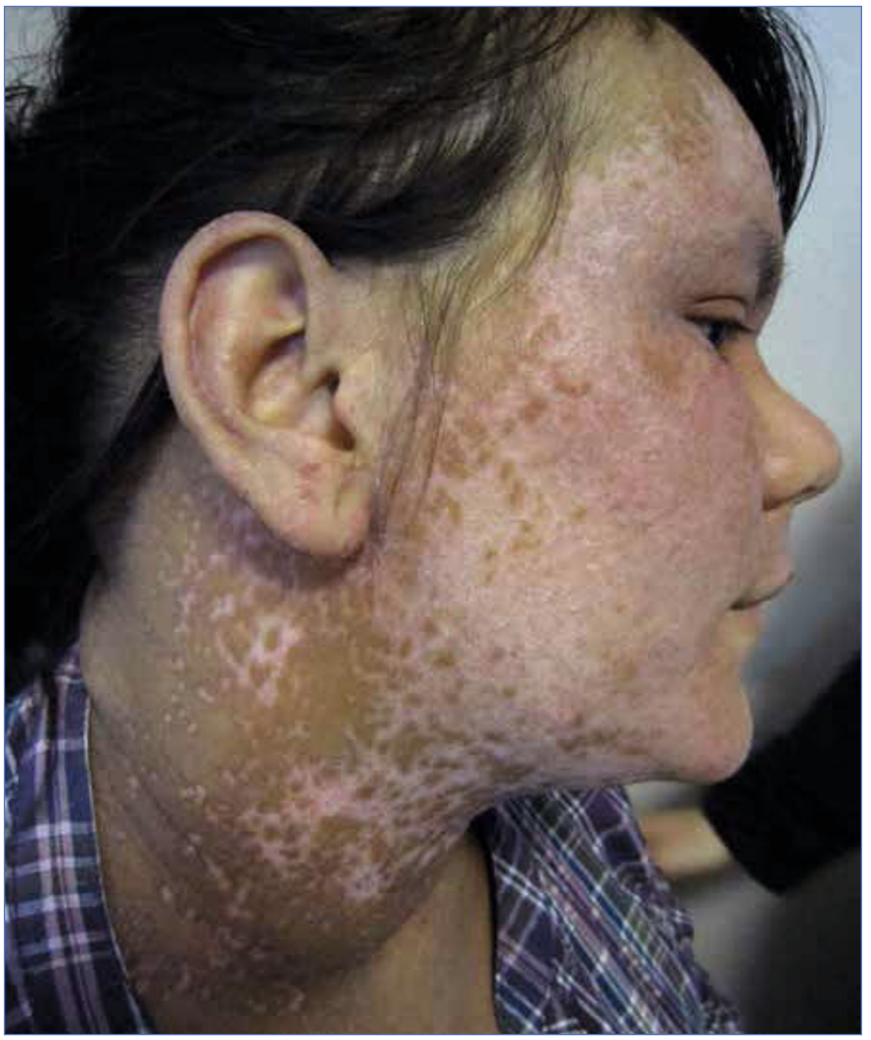
- Morand JJ, Simon F, Garnotel E, et al. Panorama des tréponématoses. Méd Trop, 2006;66:15-20.

HERPES

Arun Inamadar



Kaposi-juliusberg infection in a patient with severe atopic dermatitis.



Hypopigmented sequelae after resolution of the infection. Note that the hypopigmented lesions reproduce the distribution of the vesicles.

EPIDEMIOLOGY

Herpes simplex virus (HSV) is distributed worldwide. Humans are the only natural reservoirs, and no vectors are involved in transmission. Two types of infection exist: herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2). Endemicity is easily maintained in most human communities owing to latent infection, periodic reactivation, and asymptomatic virus shedding. Varicella-zoster virus (VZV) is distributed worldwide. It causes chickenpox and reactivation from remained dormant virus within dorsal root ganglia causes herpes zoster. More than 95% of adults have antibodies against VZV. Herpes zoster can occur at any age but it is more frequent in immunocompromised patients and the incidence increases with age.

PATHOPHYSIOLOGY

HSV is transmitted by close personal contact, and infection occurs via inoculation of virus into susceptible mucosal surfaces (eg, oropharynx, cervix, conjunctiva) or through small cracks in the skin. HSV is known to cause neurovirulence (the capacity to invade and replicate in the nervous system), and is characterized by latency (the establishment and maintenance of latent infection in nerve cell ganglia proximal to the site of infection):
In orofacial HSV infections, the trigeminal ganglia are most commonly involved, while, in genital HSV infection, the sacral nerve root ganglia (S2-S5) are involved.
There can be reactivation: The reactivation and replication of latent HSV, always in the area supplied by the ganglia, in which latency was established, can be induced by various stimuli like fever, trauma, emotional stress, sunlight, and menstruation, resulting in overt or covert recurrent infection and shedding of HSV.
Herpes zoster is due to the reactivation of VZV that has remained dormant within dorsal root ganglia.

CLINICAL DERMATOLOGICAL PRESENTATION

The clinical course of HSV infection depends on the age and immune status of the host, the anatomic site of involvement, and the antigenic virus type. Primary HSV-1 and HSV-2 infections are accompanied by systemic signs, longer duration of symptoms, and higher rate of complications. Recurrent episodes are milder and shorter. Typical presentation is with grouped vesicles over an erythematous base. Widespread vesicular eruption can be observed in immunocompromised patients and in atopic patients (Kaposi-Juliusberg infection).
Post-inflammatory hypopigmentation is quite frequent in dark skinned individuals. The grouped pattern or hypopigmentation along dermatomal distribution is highly suggestive of the diagnosis of herpes simplex and herpes zoster, respectively. Localization: HSV infection can occur in all body sites; however, gingivostomatitis, pharyngo tonsillitis, herpes labialis and genital herpes are by far the most common infections.
Herpes zoster typically follows one single dermatome. However, eruption may concern two or more dermatomes simultaneously. Any dermatome can be involved but thoracic and facial nerves are most commonly affected.

EXTRACUTANEOUS SIGNS

Herpex simplex: Aseptic meningitis, pneumonia, hepatitis
Herpes zoster: post-herpetic neuralgia (50% of cases after 60 years), conjunctivitis, keratitis, nerve palsy. Disseminated zoster, meningoencephalitis and visceral involvement can occur in immunocompromised patients. Guillain-Barré syndrome can occur after VZV infection.

HISTOPATHOLOGY

Cells infected with HSV or VZV demonstrate ballooning and reticular epidermal degeneration; epidermal acantholysis and intra-epidermal vesicles are common. Intranuclear inclusion bodies, steel-gray nuclei, multinucleate giant keratinocytes, and multilocular vesicles may also be present.

DIFFERENTIAL DIAGNOSIS

- Candidiasis.
- Atopic dermatitis.
- Chancroid.
- Coxsackie virus infection.
- Insect bites.
- Syphilis.

TREATMENT

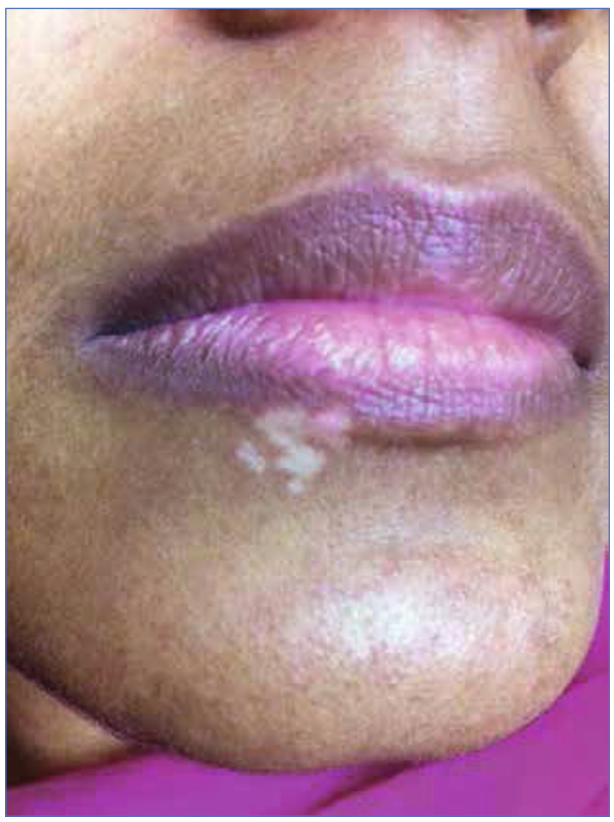
Medical treatment of HSV infection is only required in severe cases. Acyclovir, penciclovir valacyclovir, and famciclovir are the drugs used.
Antiviral treatment of herpes zoster has to be given for ophthalmic forms and in immunocompromised patients. Early treatment (in the first 72 hours) is also recommended for patients older than 50 years of age to prevent post-herpetic neuralgia.
Hypopigmentation usually regresses with time and sun exposures.

KEY REFERENCES

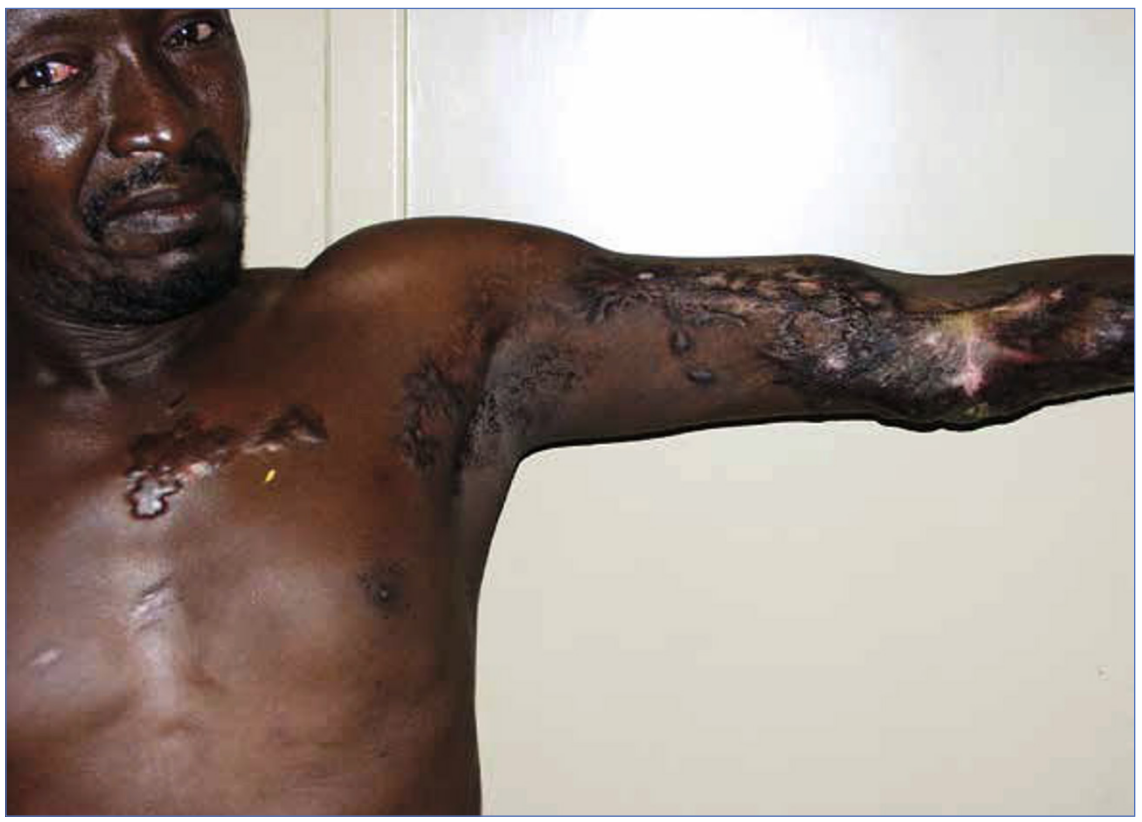
- Fleming DT, McQuillan GM, Johnson RE, et al. Herpes simplex virus type 2 in the United States, 1976 to 1994. N Engl J Med. 1997;337:1105-11.
- Rabella N, Otegui M, Labeaga R, et al. Antiviral susceptibility of Herpes simplex viruses and its clinical correlates: a single center's experience. Clin Infect Dis. 2002;34:1055-60.

HERPES

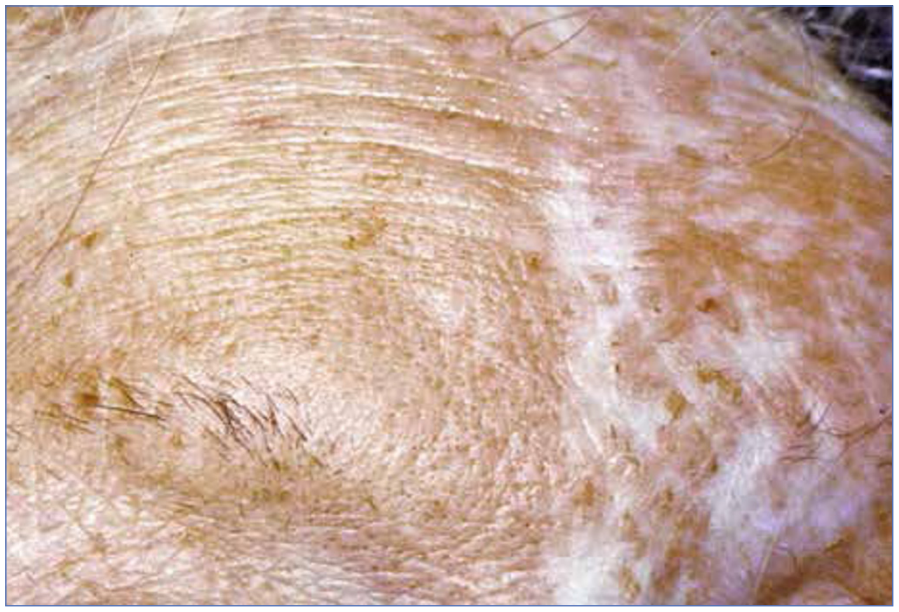
Arun Inamadar



Hypopigmentation post-herpetic infection. Note the typical localization and disposition of the hypopigmented lesions reproducing the grouped vesicles (coll. Arun Inamadar).



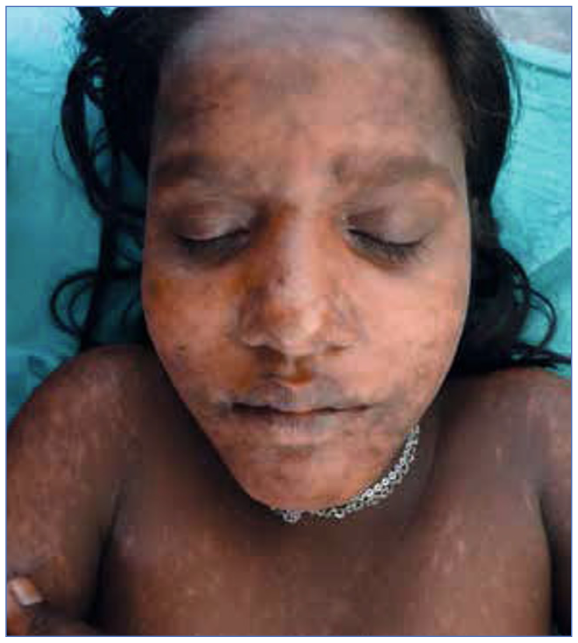
Depigmentation and keloids following herpes zoster eruption.



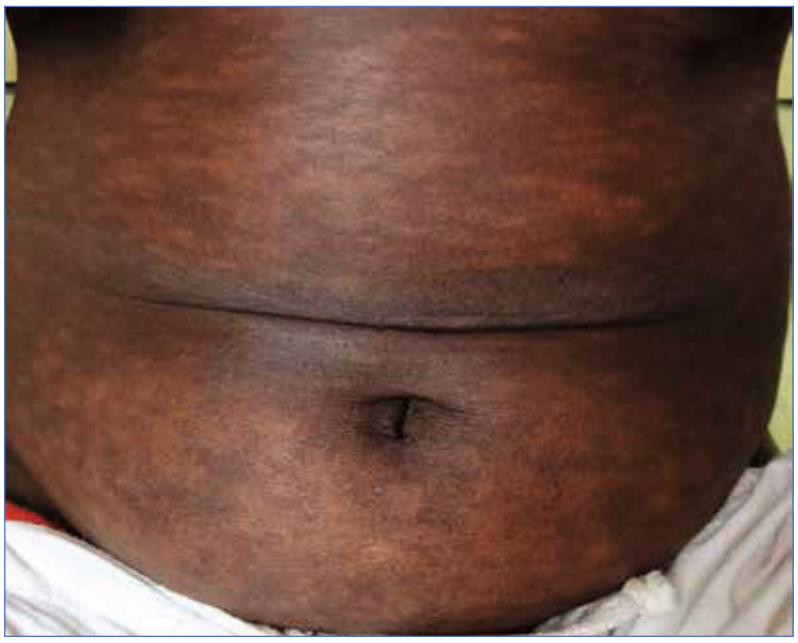
Achromic macules following herpes zoster in the area of the left V1.

KALA-AZAR

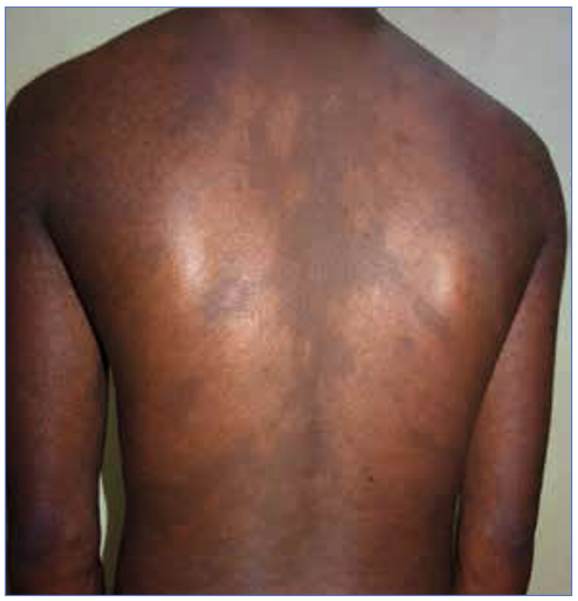
Arun Inamadar



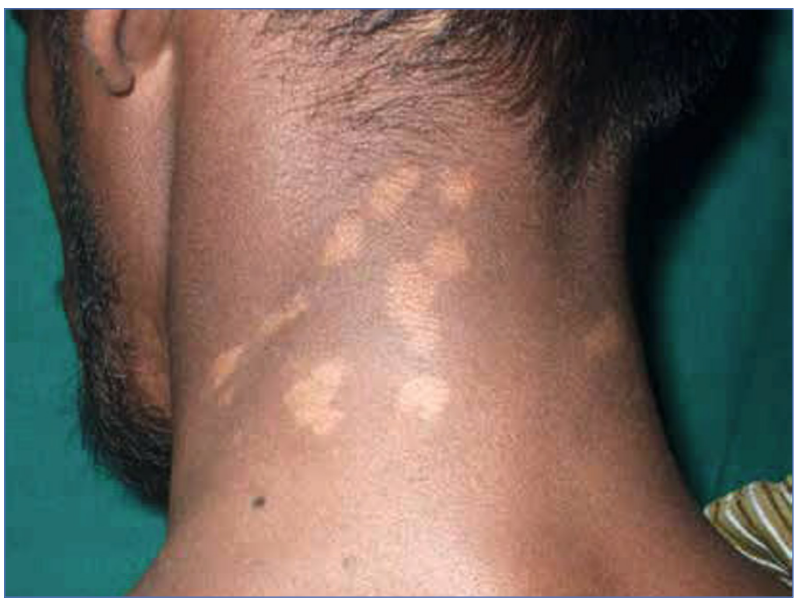
Multiple hypopigmented lesions of post kala azar dermal leishmaniasis over face (coll. Samujjala Deb).



Multiple hypopigmented lesions of post kala azar dermal leishmaniasis over abdomen (coll. Samujjala Deb).



Post kala azar dermal leishmaniasis. multiple hypopigmented lesions over back of the trunk (coll. Piyush Choudhari).



Multiple hypopigmented lesions of post kala azar dermal leishmaniasis over nape of the neck (coll. Rajesh Kumar Mandal).

SYNONYMS

Post-Kala-Azar dermal leishmaniasis (PKDL).

EPIDEMIOLOGY

Mainly seen in Sudan and India where it follows treated visceral leishmaniasis in 50% and 5 to 10% of cases, respectively. Thus, it is largely restricted to areas where *Leishmania donovani* is the causative parasite. The interval at which PKDL follows visceral leishmaniasis is 0 to 6 months in Sudan and 2 to 3 years in India. PKDL probably has an important role in interepidemic periods of visceral leishmaniasis, acting as a reservoir for parasites.

PATHOPHYSIOLOGY

The pathogenesis is largely immunologically mediated; high concentrations of interleukin 10 in the peripheral blood of visceral leishmaniasis patients predict the development of PKDL. During visceral leishmaniasis, interferon gamma is not produced by peripheral blood mononuclear cells (PBMC). After treatment of visceral leishmaniasis, PBMC start producing interferon gamma, which coincides with the appearance of PKDL lesions due to interferon-gamma-producing cells causing skin inflammation as a reaction to persisting parasites in the skin.

CLINICAL DERMATOLOGICAL PRESENTATION

Bilateral hypopigmented macules with often symmetrical distribution, in a patient who has recovered from visceral leishmaniasis and who is otherwise well.
The lesions can coalesce to large hypopigmented areas.
Macular, maculopapular, and nodular lesions can be associated.
Asymptomatic.
Localization: the lesions usually start around the mouth from where they spread to other parts of the body depending on severity.

EXTRACUTANEOUS SIGNS

None.

HISTOPATHOLOGY

Diagnosis is mainly clinical, but parasites can be seen by microscopy in smears with limited sensitivity. Polymerase chain reaction (PCR) and monoclonal antibodies may detect parasites in more than 80% of cases. Serological tests and the leishmanin skin test are of limited value.

DIFFERENTIAL DIAGNOSIS

- The differential diagnosis includes a large number of other skin conditions including post-inflammatory and post-infectious hypopigmentions. Leprosy is not uncommonly mistaken for PKDL and distinction between these two conditions may be difficult.

TREATMENT

Treatment is always needed in Indian PKDL; in Sudan most cases will self-cure but severe and chronic cases are treated. Sodium stibogluconate is given at 20 mg/kg for 2 months in Sudan and for 4 months in India. Liposomal amphotericine B seems effective; newer compounds such as miltefosine that can be administered orally or topically are of major potential interest.

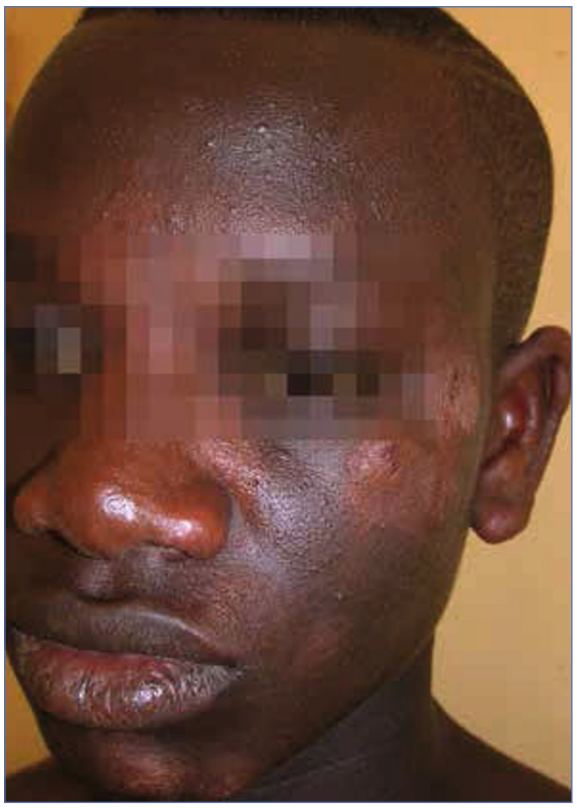
KEY REFERENCES

- Ramesh V, Mukherjee A. Post-kala-azar dermal leishmaniasis. Int J Derm. 1995;34:85-91.
- EE Zijlstra, AM Musa, EAG Khalil, IM El Hassan, AM El-Hassan. Post-kala-azar dermal leishmaniasis. The Lancet Infect Dis. 2003;3,:87-98.

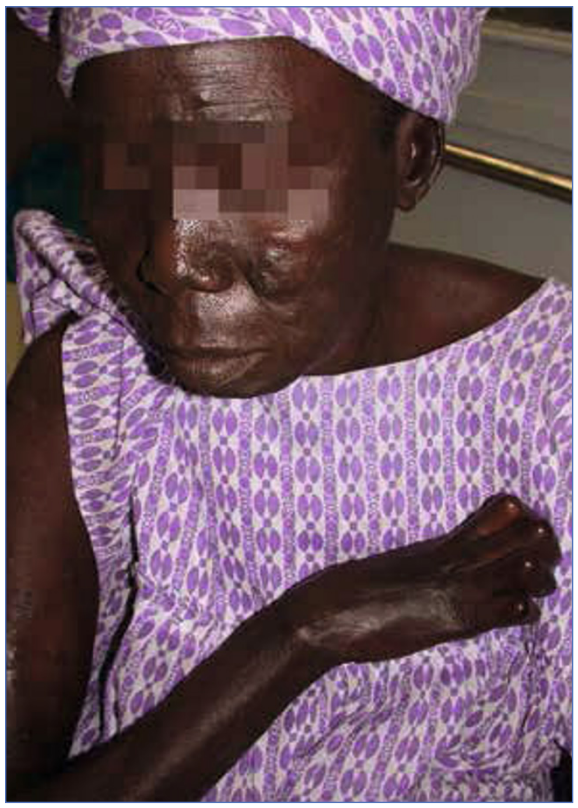
LEPROSY

Jean-Jacques Morand

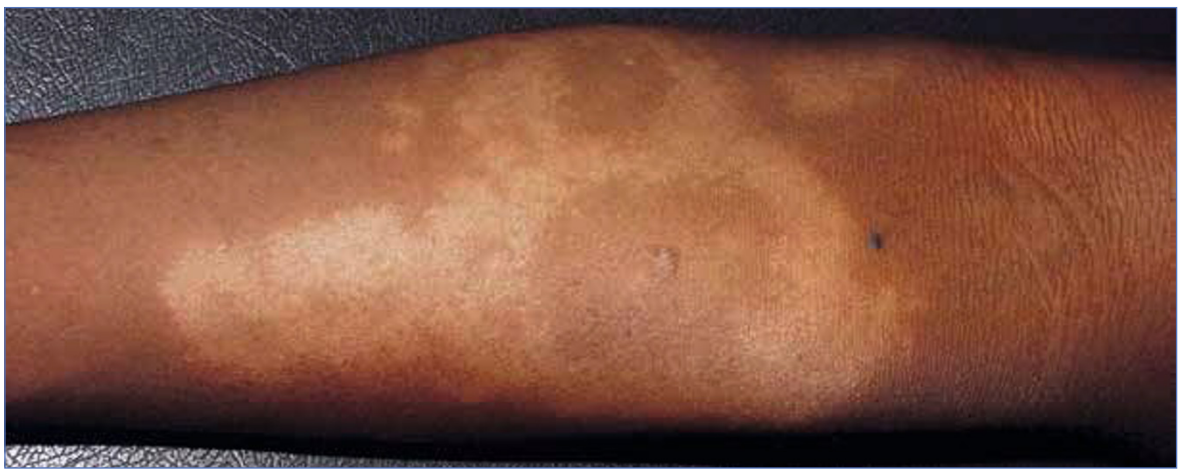
Borderline leprosy with hypopigmented macule and cubital paralysis (coll J.J. Morand).



Copper-colored depigmentation in borderline leprosy with reverse reaction (coll J.J. Morand).



Hyperpigmentation of erythema nodosum leprosum in borderline leprosy with cubital and median paralysis (coll J.J. Morand).



Borderline leprosy.

SYNONYMS

Hansen's disease.

EPIDEMIOLOGY

Mycobacterium leprae.
180,000 current cases, 220,000 new cases in the world every year, 2 million people with sequalae.
India (50% of cases), Brazil, Burma, Nepal, Africa (Madagascar, Mozambique, Tanzania), Western Pacific.

PATHOPHYSIOLOGY

Mycobacterial infection of humans' skin and peripheral nerves. Infection also reported in African chimpanzee, mangabey, macaque and American nine-banded armadillos.
Genetic susceptibility to leprosy, long incubation.
Transmission from person to person in nasal droplets or by prolonged close contact.
Immune system response causing reverse reaction or erythema nodosum leprosum.

CLINICAL DERMATOLOGICAL PRESENTATION

Ridley-Jopling classification: tuberculoid (TT), borderline (TB, BB, BL), lepromatous (LL) leprosy.
WHO system: pauci ou multibacillary leprosy.
Tuberculoid leprosy: 1 to 5 depigmented macules or papules with hypoesthesia.
Lepromatous leprosy: a lot of symetrical papules and nodules with or without depigmentation and hypoesthesia.

EXTRACUTANEOUS SIGNS

Neurologic (paralysis trophic, lagophtalmia, ulcer) and ocular involvement (retinitis).

HISTOPATHOLOGY

Skin and nasal smear: acid-fast bacteria, red with Ziehl-Neelsen stain, unculturable in laboratory except by injection into the footpads of mice.
Serology, PCR.
Lepromin test (IDR).
Histology: granulomatous dermal infiltrate/dermal inflammatory infiltrate with Virchow cell and acellular Unna band.

DIFFERENTIAL DIAGNOSIS

- Pityriasis alba.
- Atopic dermatitis.
- Vitiligo minor.
- Sarcoidosis.
- Leishmaniasis.

TREATMENT

Paucibacillary leprosy: daily dapsone and monthly rifampicin for 6 months.
Multibacillary leprosy: daily dapsone and clofazimine with monthly rifampicin for 12 months.

PREVENTION

Bacillus Calmette–Guérin (BCG) vaccine.

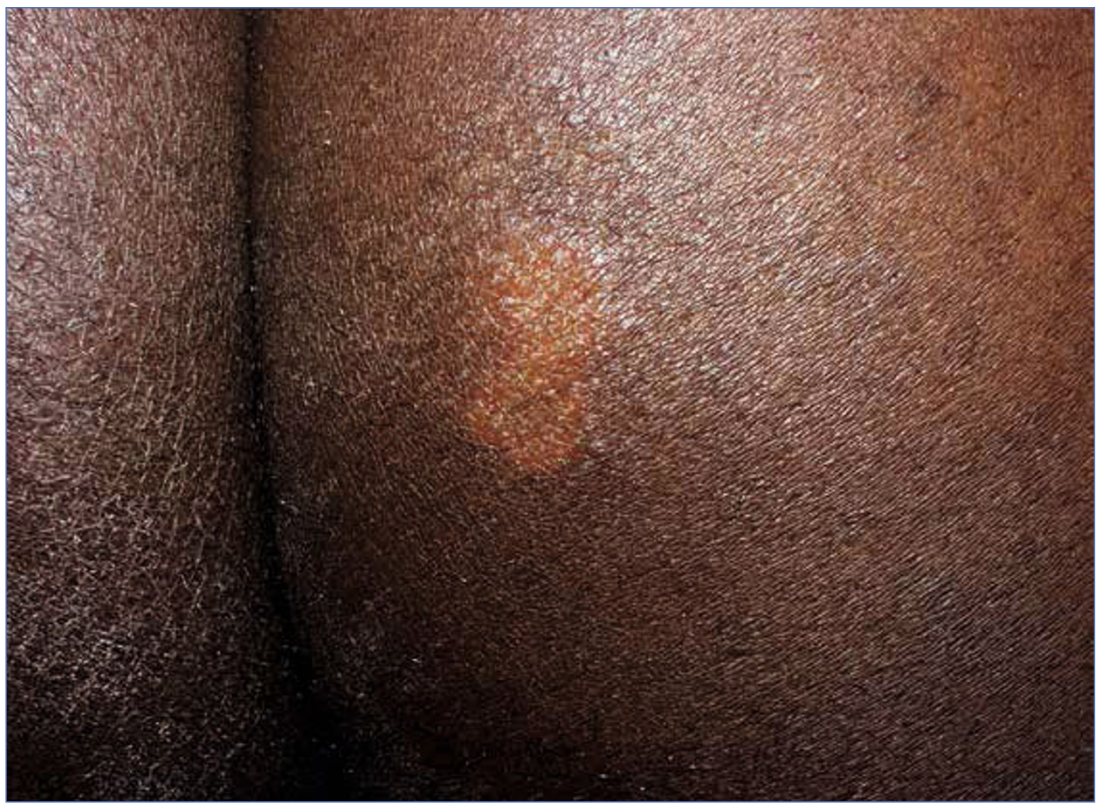
KEY REFERENCES

- Bret S, Flageul B, Girault PY, Lightburne E, Morand JJ. Epidemiological survey of leprosy conducted in metropolitan France between 2009 and 2010. Ann Dermatol Venereol. 2013;140:347-52.
- Massone C, Cavalchini A, Clapasson A, Nunzi E. Hypopigmented macules: leprosy, atopy or pityriasis versicolor? G Ital Dermatol Venereol. 2010;145:779-82.
- Murthy PK. Clinical manifestations, diagnosis and classification of leprosy. J Indian Med Assoc. 2004;102:678-9.

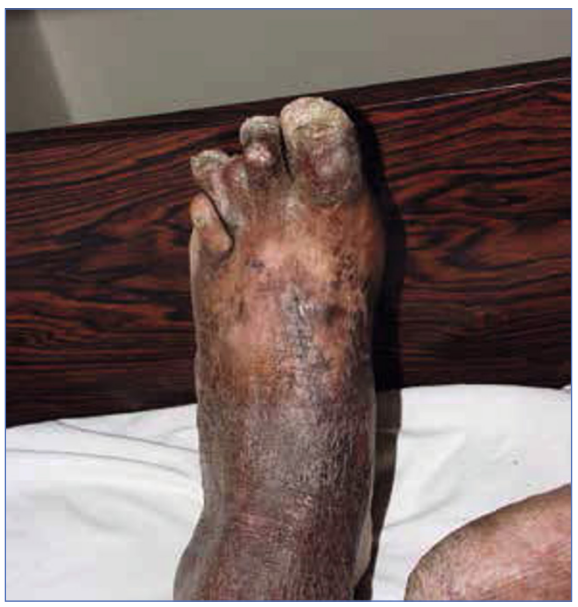
LEPROSY

Jean-Jacques Morand

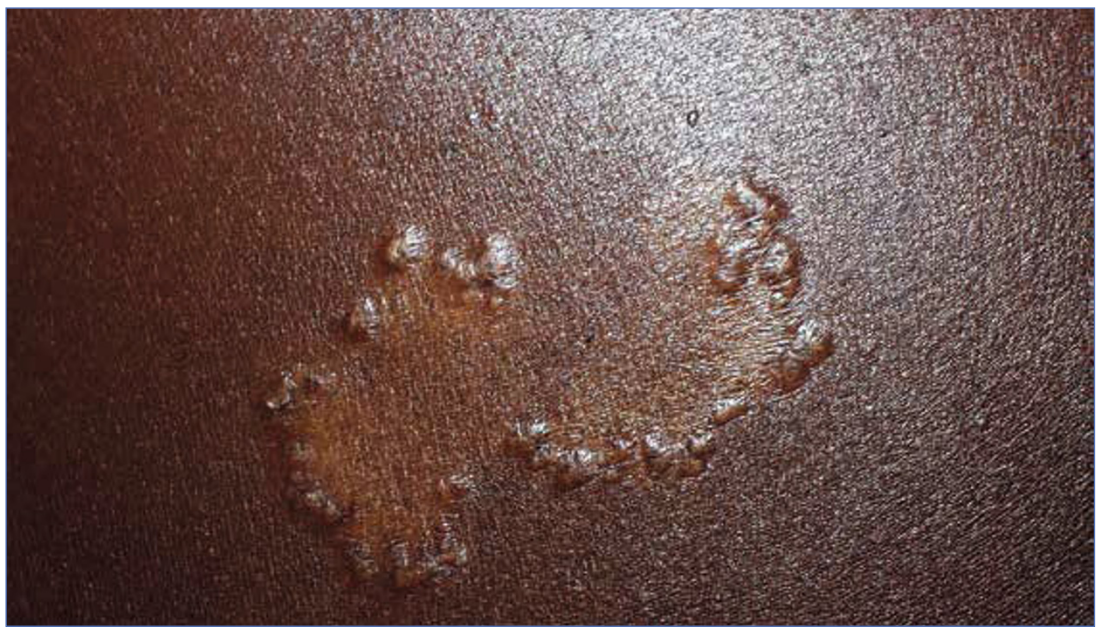
Multibacillary leprosy (ll) (coll J.J. Morand).



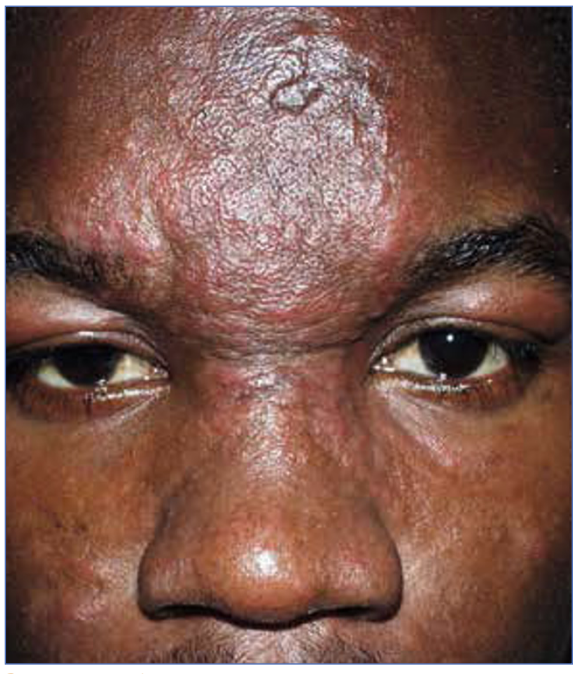
Tuberculoid leprosy.



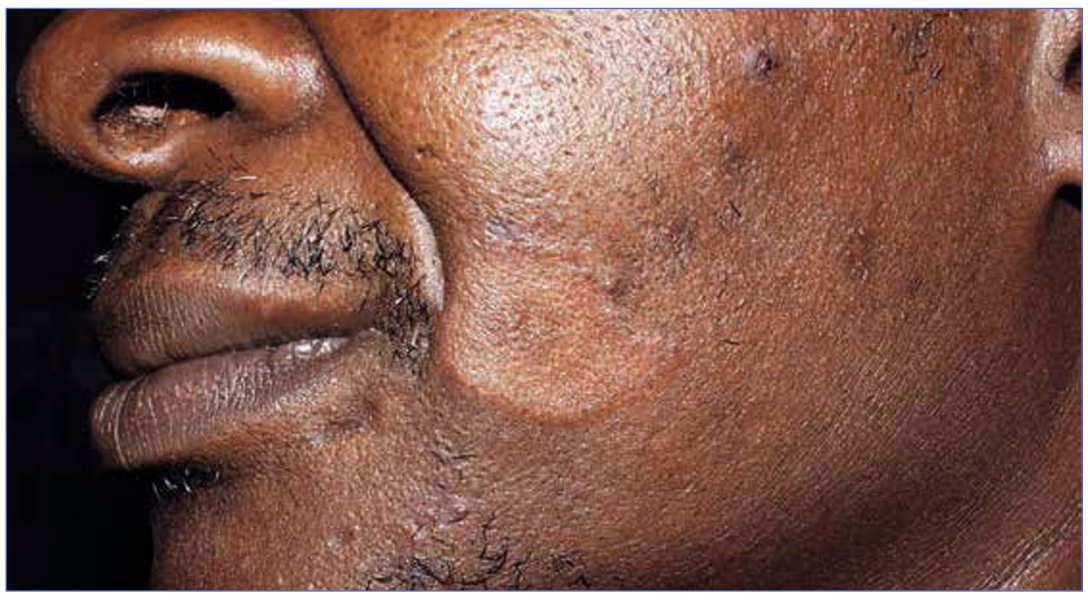
Neurologic and dyschromic sequelae of leprosis.



Tuberculoid leprosy. Note the granulomatous border and the hypopigmentation in the center of the lesion.



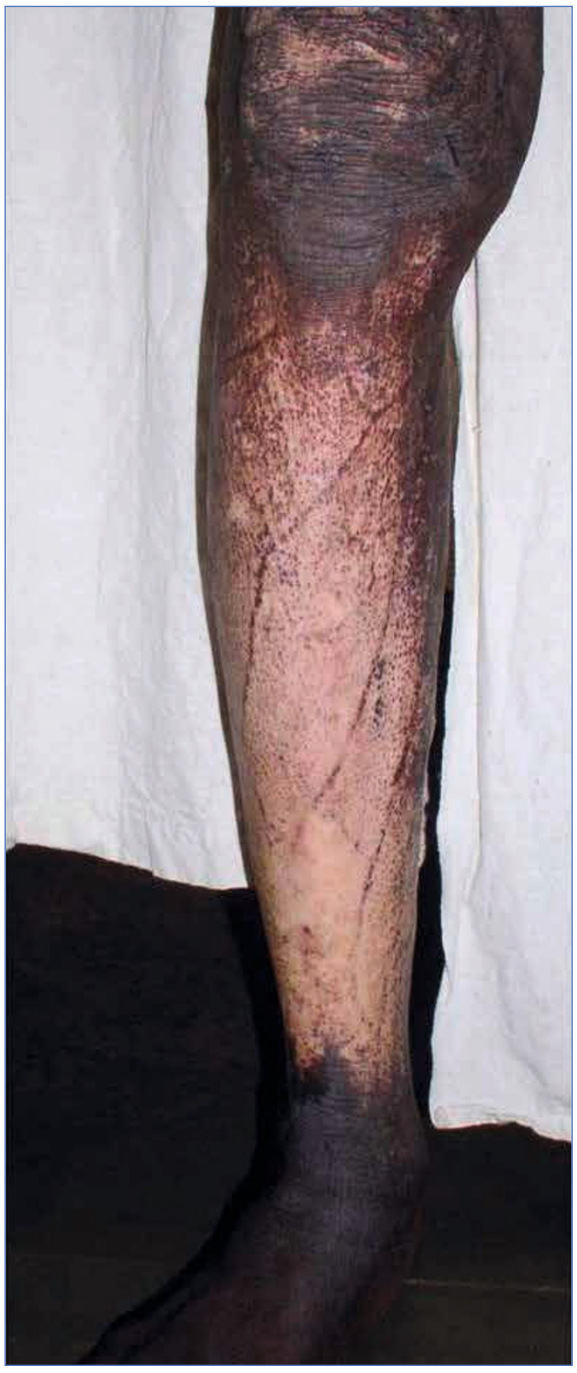
Reverse reaction.



Tuberculoid leprosy.

ONCOCERCOSIS

Jean-Jacques Morand



Hyperpigmentation with spotted depigmentation (leopard skin) (coll. Edward Lightburne).

Onchocerciasis: note lichenified hyperpigmented plaques and the dorsal nodule at an inhabitant of the ivory coast (coll. J.J. Morand).

EPIDEMIOLOGY

Central Africa (99% of cases), Central and South America
18 million infected people, 300,000 blind (second largest infectious cause in the world).
Nematode: *Onchocerca volvulus*.
Transmitted to humans through the bite of a black fly of the genus *Simulium* living near the rivers.

PATHOPHYSIOLOGY

Endosymbiotic bacteria *Wolbachia pipientis*.
Immune system response causing itch and blindness.
Severity of illness directly proportionate to the number of infected microfilariae and the release of *Wolbachia* surface protein.

CLINICAL DERMATOLOGICAL PRESENTATION

Acute scattered pruritic papules.
Subcutaneous nodules (containing the adult worms located mainly on the trunk).
Chronic lichenified hyperpigmented plaques (Mal morando).
Oedema of a limb (Cameroon swollen arm) and lymphadenopathy (elephant skin).
Hyperpigmentation with spotted depigmentation (leopard skin).
Thickened, wrinkled skin (lizard skin).
Secondary bacterial infections.

EXTRACUTANEOUS SIGNS

Ocular involvement, punctuate keratitis, sclerosing keratitis (river blindness), chorioretinitis.

BIOLOGY/HISTOPATHOLOGY

Eosinophilia, serology.
Bloodless biopsy: dermal microfilariae.
Macronodule's biopsy: adult worms.

DIFFERENTIAL DIAGNOSIS

- Eczema.
- Prurigo.
- Scabies.

TREATMENT

Ivermectin (two doses 6 months apart) + doxycycline (daily for at least 4 to 6 weeks) or rifampicin.
Diethylcarbamazine: Mazzotti reactions (fever, urticaria, arthralgia, hypotension).

PREVENTION

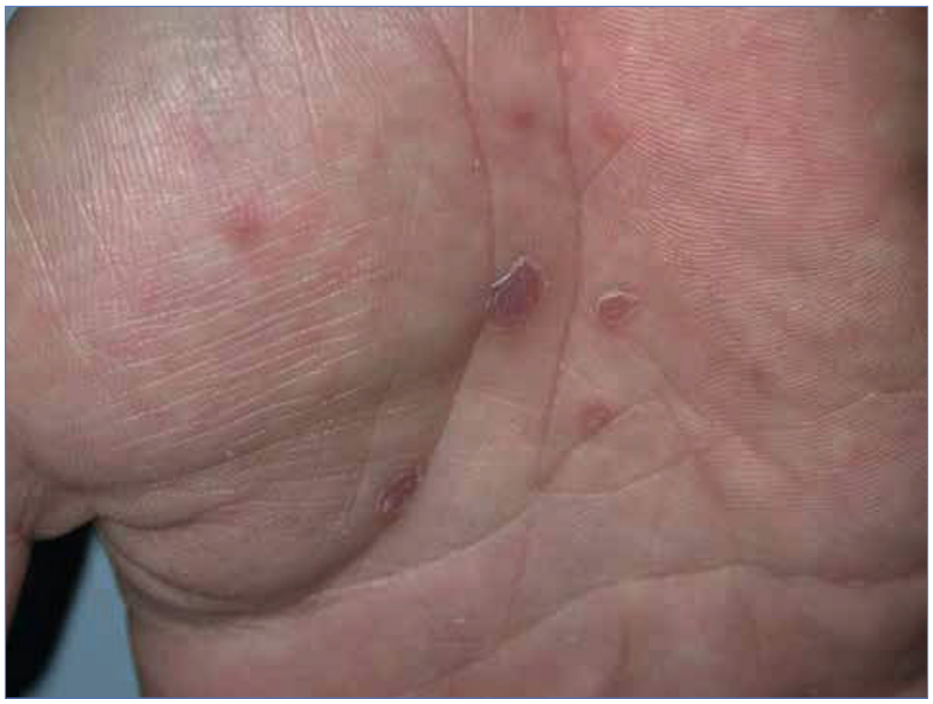
Mass drug administration (Onchocerciasis Control Programme).
Vectorial fight: larvicide spraying of fast-flowing rivers to control black fly populations.

KEY REFERENCES

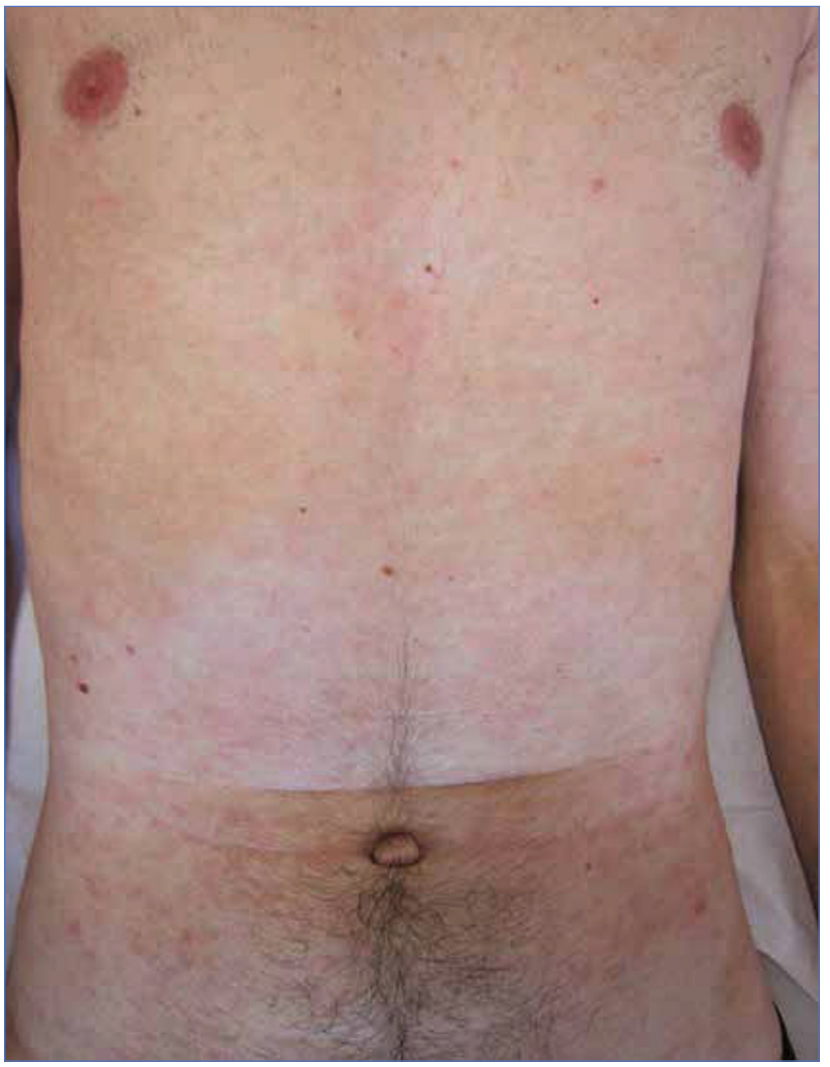
- Katabarwa M, Eyamba A, Habomugisha P, et al. After a decade of annual dose mass ivermectin treatment in Cameroon and Uganda, onchocerciasis transmission continues. Trop Med Int Health. 2008;13:1196-203.
- Hoerauf A, Specht S, Marfo-Debrekyei Y, et al. Efficacy of 5-week doxycycline treatment on adult Onchocerca volvulus. Parasitol Res. 2009;104:437-47.

SYPHILIS

Arun Inamadar



Typical palmar involvement of secondary stage of syphilis.



Macular exenthema of the secondary stage of syphilis.

EPIDEMIOLOGY

United States Centers for Disease Control and Prevention (CDC) estimate that, annually, 55,400 people in the US get new syphilis infections. Of new cases of syphilis, 15,667 cases were of primary and secondary (PS & SS) syphilis, the earliest and most infectious stages of syphilis. Internationally, the prevalence of syphilis varies by region. Syphilis remains prevalent in many developing countries and in some areas of North America, Asia, and Europe, especially Eastern Europe. The highest rates are in South and Southeast Asia, followed closely by sub-Saharan Africa. The third highest rates are in the regions of Latin America and the Caribbean.

PATHOPHYSIOLOGY

Syphilis is transmitted from person to person by direct contact with syphilis sores. Syphilis can be transmitted during vaginal, anal, or oral sexual contact. In acquired syphilis, *Treponema pallidum* rapidly penetrates intact mucous membranes or microscopic dermal abrasions and, within a few hours, enters the lymphatics and blood to produce systemic infection. Incubation time from exposure to development of primary lesions, which occur at the primary site of inoculation can range from 9 to 90 days.

CLINICAL DERMATOLOGICAL PRESENTATION

Primary chancre sore is usually firm, round, and painless. Because the primary chancre sore is painless, it can easily go unnoticed. The ulcer lasts 3 to 6 weeks and heals regardless of whether or not a person is treated.
Secondary syphilis: bilaterally symmetrical exanthem consisting of macules, papules or mixed lesions with scaling. The non-pruritic lesions are of coppery hue and there is special predilection for palms and soles. Moth eaten alopecia, pustular and plaque lesions on moist, intertriginous areas calles as 'condyloma lata' are characteristic.
Tertiary syphilis: gummas.
Dyschromia is only an occasional sign of secondary syphilis.
Leukoderma syphiliticum can be observed on the lateral face of the neck and low neckline. Hypopigmented macules can be obvious but in most cases only careful examination with Wood's lamp allow them to be noticed. Slightly hypopigmented 1-2 cm round macules on grayish or brownish background, called leukomelanoderma, can be also observed.

EXTRACUTANEOUS SIGNS

Primary syphilis: none.
Secondary syphilis: acute glomerulonephritis, gastritis, or gastric ulceration, optic neuritis and polyarthritis can be observed
Tertiary syphilis: neurosyphilis including headache, meningitis, dizziness, dementia, cranial nerve palsies, tabes dorsalis, incontinence, and weakness. Cardiovascular involvement with aortic dilatation and valvular insufficiency.

HISTOPATHOLOGY

The chancre is characterized by mononuclear leukocytic infiltration, macrophages, and lymphocytes. The inflammatory reaction causes an obliterative endarteritis.
The inflammatory reaction of secondary syphilis is histologically similar to that of the primary chancre but is less intense.
The infiltrate will be dense, diffuse, and, in some instances, nearly completely plasmocytic. Coat sleeve like plasma cell infiltration is characteristic finding.

DIFFERENTIAL DIAGNOSIS

- Candidiasis.
- Chancroid.
- Condyloma acuminata.
- Drug eruptions.
- Genital warts.
- Granuloma inguinale (Donovanosis).
- Herpes simplex.
- Lymphogranuloma venereum (LGV).
- Yaws.

TREATMENT

The drug of choice is penicillin G. Intramuscular (IM) benzathine penicillin is recommended. Alternatively doxycycline/tetracycline can be prescribed for penicillin-sensitive patient.
The following regimens are recommended for penicillin treatment:

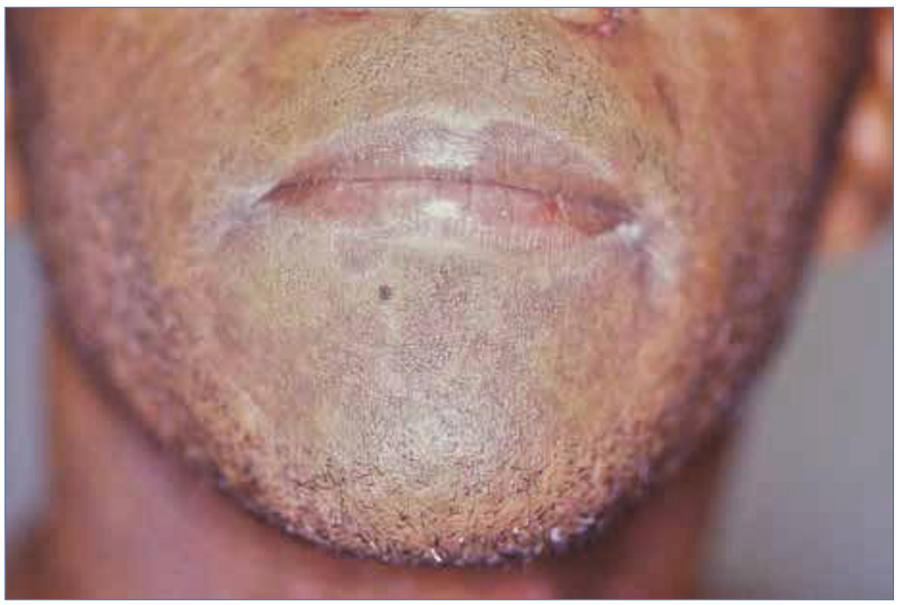
- Primary or secondary syphilis: benzathine penicillin G 2.4 million units IM in a single dose.
- Early latent syphilis: benzathine penicillin G 2.4 million units IM in a single dose.
- Late latent syphilis or latent syphilis of unknown duration: benzathine penicillin G 7.2 million units total, administered as three doses of 2.4 million units IM each at 1-week intervals .
- Pregnancy: treatment appropriate to the stage of syphilis is recommended.

KEY REFERENCES

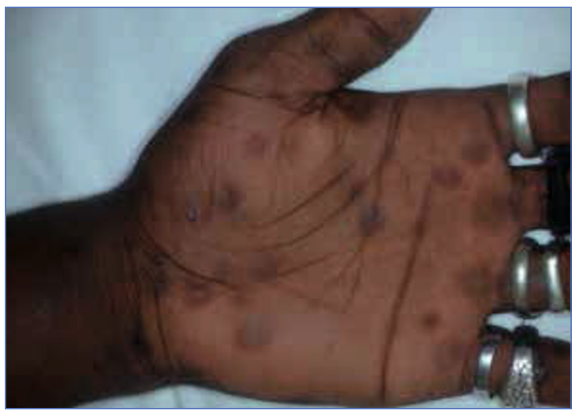
- Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance, 2007. 33 2008; Atlanta, Georgia.
- Harrison LW. The Oslo study of untreated syphilis, review and commentary. Br J Vener Dis. 1956;32:70-8.

SYPHILIS

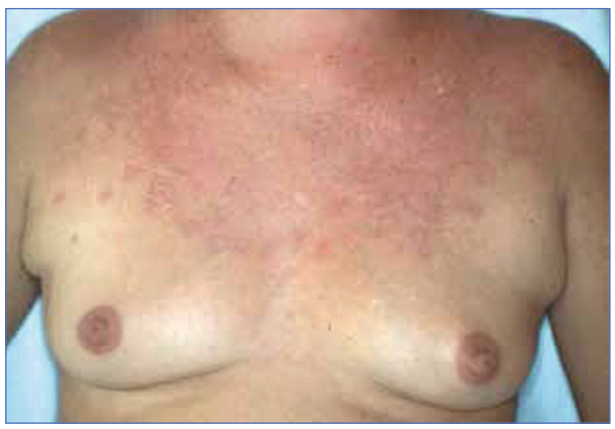
Arun Inamadar



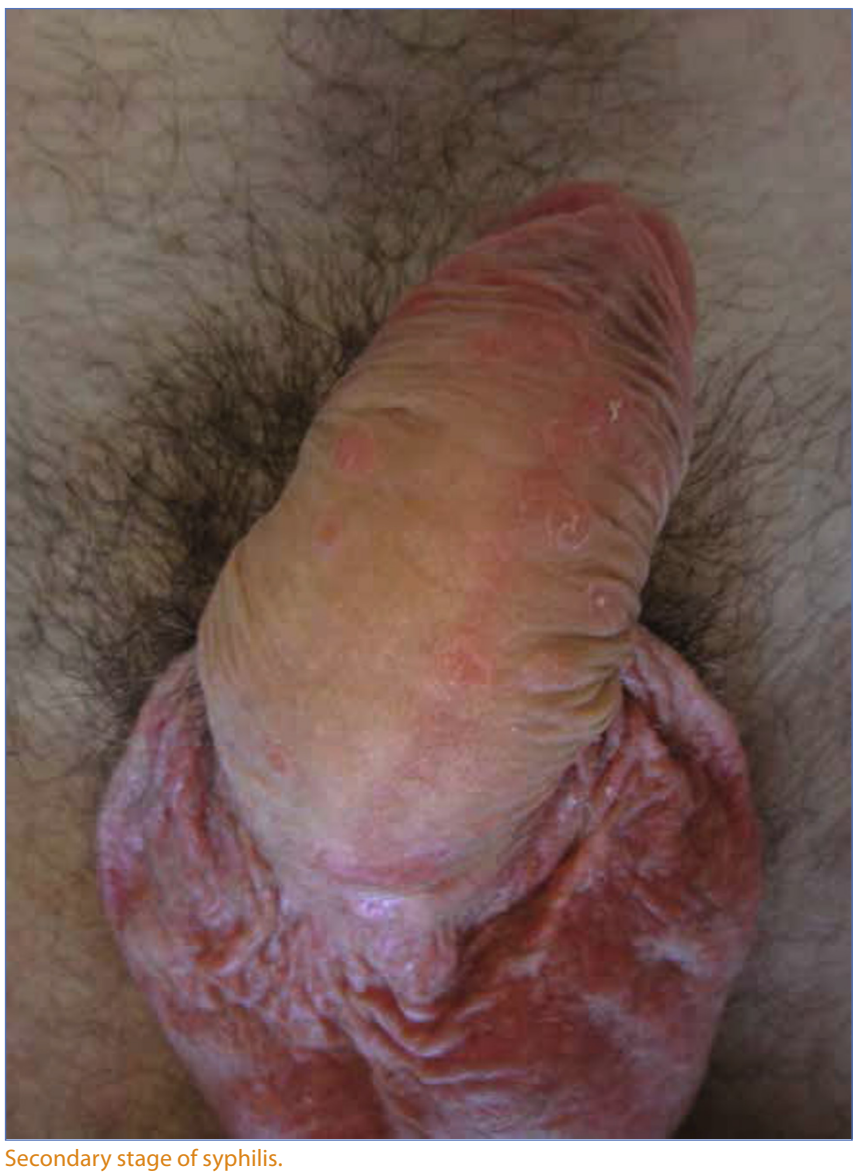
Leukomelanoderma in secondary stage of syphilis (coll. Pascal del Giudice).



Palmar involvement of secondary stage of syphilis (coll. Pascal del Giudice).



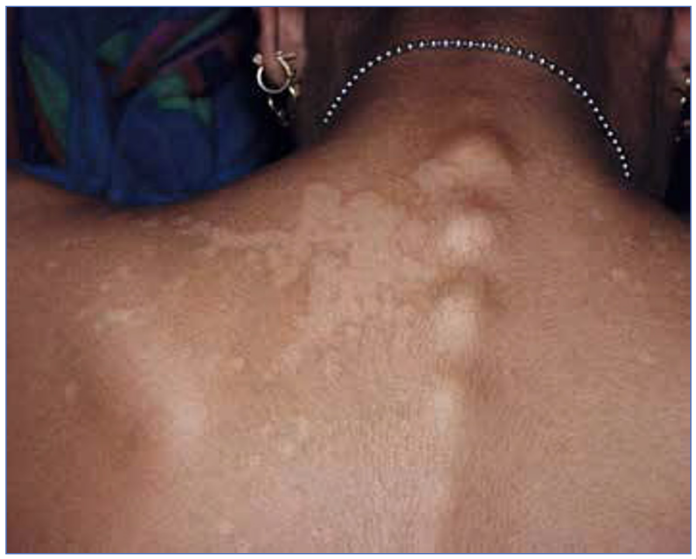
Necklace of venus. note the slight hypopigmentation associated with erythematous macules (coll. Pascal del Giudice).



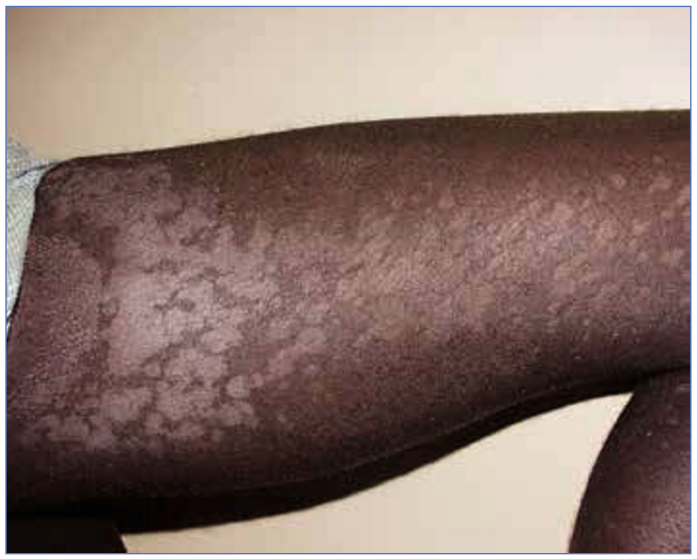
Secondary stage of syphilis.

TINEA VERSICOLOR

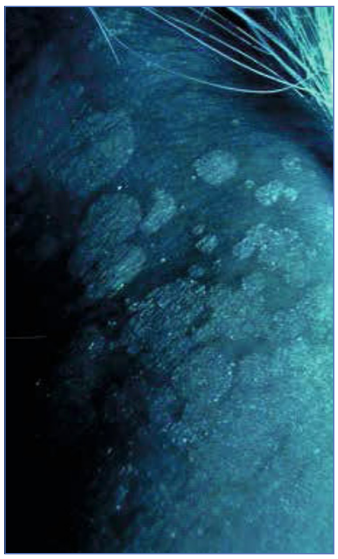
Arun Inamadar



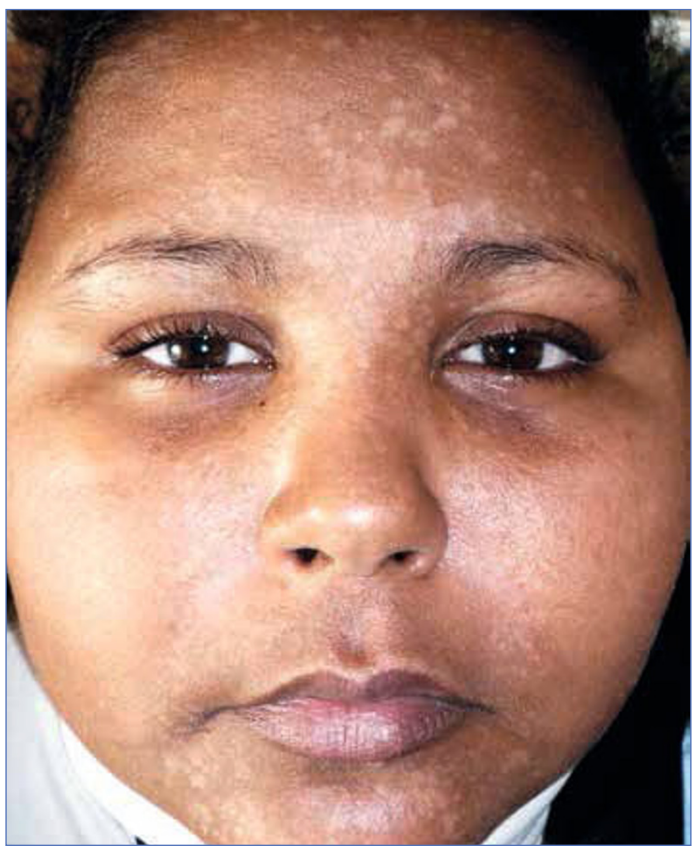
Tinea versicolor. Note the slightly erythematous borders of some hypopigmented macules.



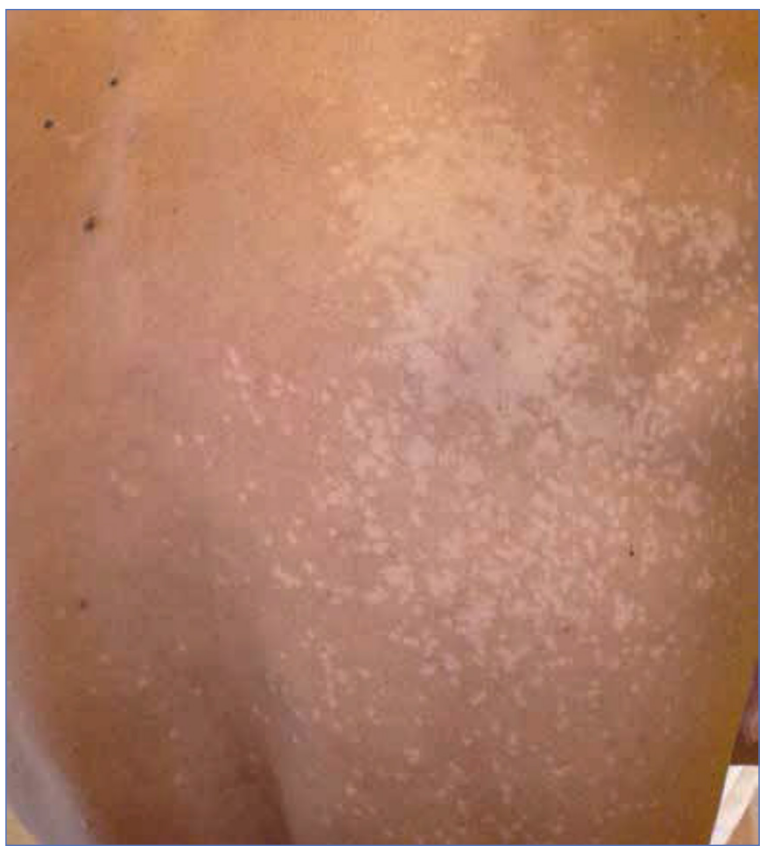
Widespread tinea versicolor in an immunocompromised hiv patient. Note the associated tinea cruris.



Wood's lamp examination of tinea versicolor. Note the yellowish coloration of the lesions.



Tinea versicolor of the face.



Widespread tinea versicolor of the back.

EPIDEMIOLOGY

Occurs more frequently in areas with higher temperatures and higher relative humidities.

PATHOPHYSIOLOGY

Tinea versicolor is caused by the dimorphic, lipophilic organisms in the genus *Malassezia*, formerly known as *Pityrosporum*. Human peptide cathelicidin LL-37 plays a role in skin defense against this organism. Factors that lead to the conversion of the saprophytic yeast to the parasitic, mycelial morphologic form include a genetic predisposition; warm, humid environments; immunosuppression; malnutrition; and Cushing disease.

CLINICAL DERMATOLOGICAL PRESENTATION

Most individuals with tinea versicolor report abnormal pigmentation. The color of each lesion varies from almost white to reddish brown or fawn colored.
A fine, dustlike scale covers the lesions. Wood's lamp examination reveals a yellowish fluorescence.

Localization: the commonly involved skin regions are the trunk, the upper back, the abdomen, and the proximal extremities.

EXTRACUTANEOUS SIGNS

None.

HISTOPATHOLOGY

The epidermis reveals mild hyperkeratosis and acanthosis, and a mild perivascular infiltrate is present in the dermis. An acanthosis nigricans-like epidermal change is noted in the papular variety, with dilated blood vessels observed in erythematous lesions.
Periodic acid-Schiff (PAS) stain will help to detect the organism.

DIFFERENTIAL DIAGNOSIS

- Progressive macular hypomelanosis.
- Erythrasma.
- Pityriasis alba.
- Psoriasis guttate.
- Seborrheic dermatitis.
- Tinea corporis.
- Vitiligo.

TREATMENT

Effective topical agents include selenium sulfide, ciclopiroxolamine, as well as azole and allylamine antifungals. Various regimens can be used. Topical azole antifungals can be applied every night for 2 weeks. Oral therapy can also be used in consort with topical regimens. Ketoconazole, fluconazole, and itraconazole are the preferred oral agents.

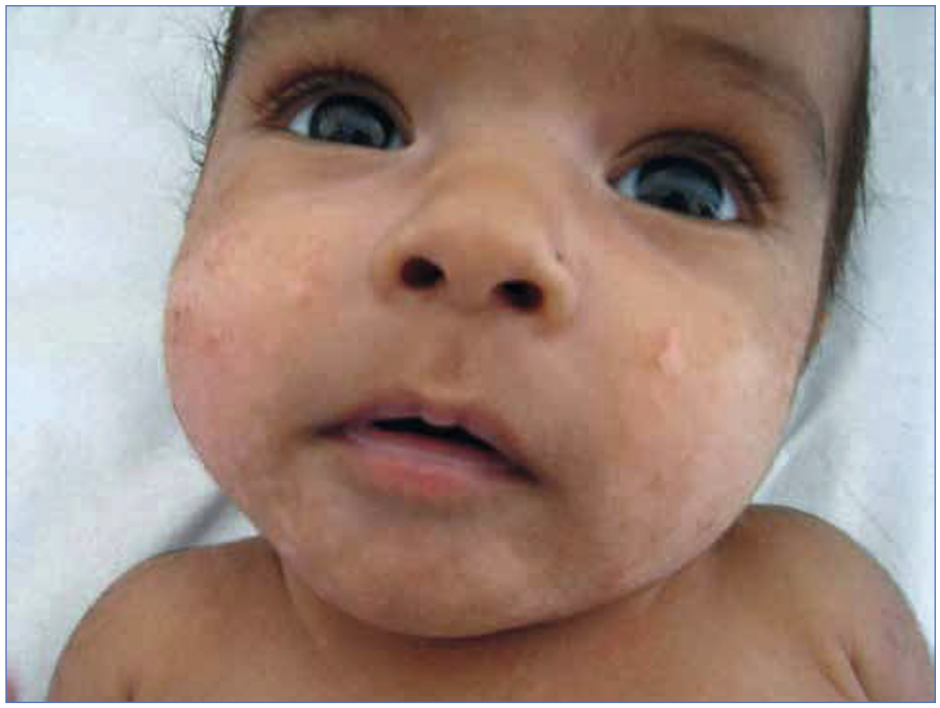
KEY REFERENCES

- Crespo-Erchiga V, Florencio VD. Malassezia yeasts and pityriasis versicolor. Curr Opin Infect Dis. 2006;19:139-47.
- Inamadar AC, Palit A. The genus Malassezia and human disease. Indian J Dermatol Venereol Leprol. 2003;69:265-70.

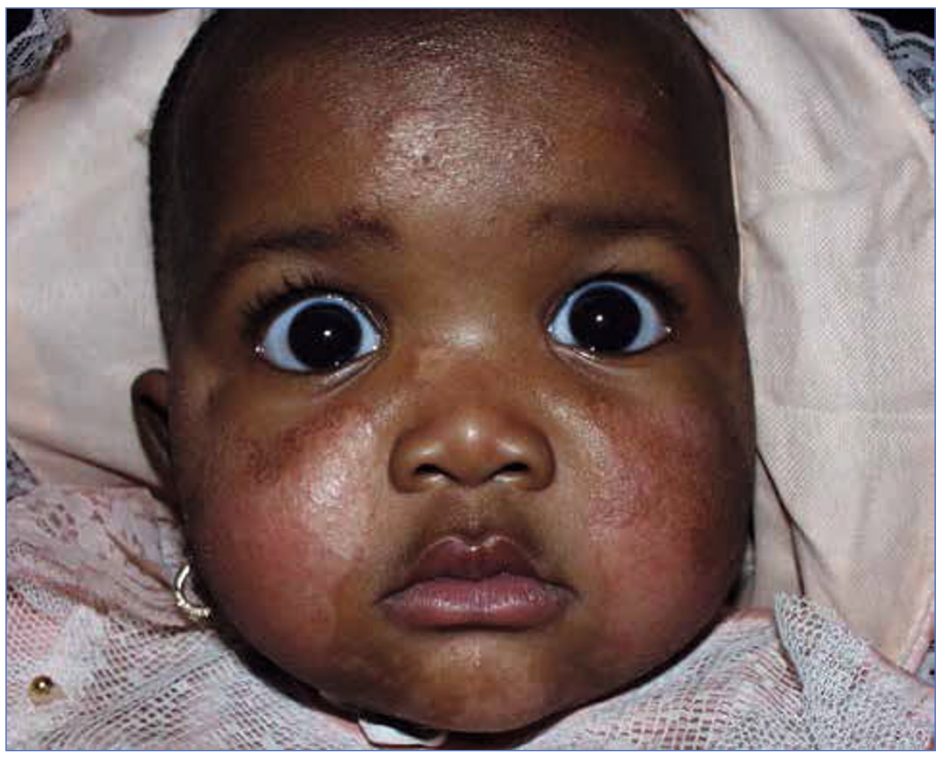
ACQUIRED HYPOMELANOSIS

Inflammatory hypomelanosis

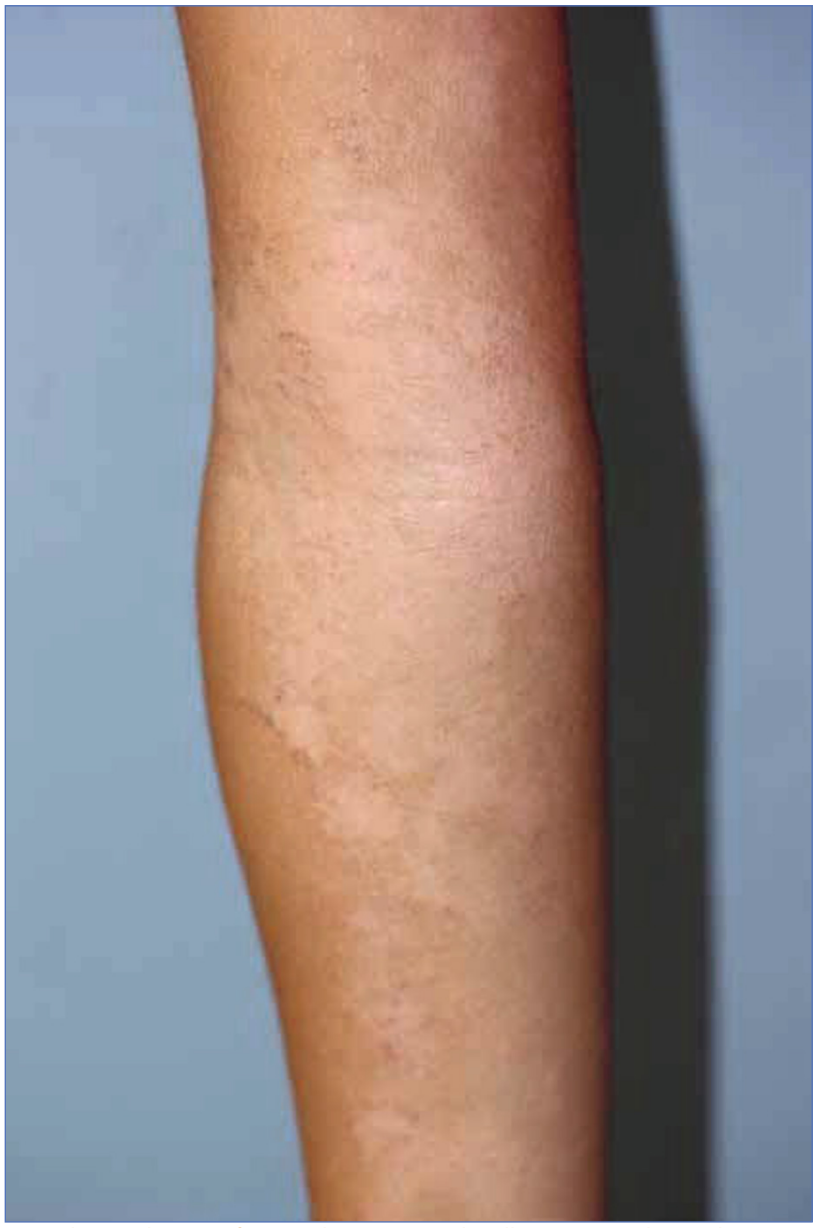
ATOPIC DERMATITIS



Hypochromic lesions of atopic dermatitis of the face. Note the slight erythema and crusting on the plaques.



Hypochromic lesions of atopic dermatitis in a young girl. Note the irregular and hyperpigmented borders.



Hypochromic lesions of atopic dermatitis on the elbow crease. The erythema and scales are almost absent but the localization, and the irregular and ill-defined hyperpigmented borders are highly suggestive of the diagnosis.

EPIDEMIOLOGY

Hypopigmentation is quite common in patients with atopic dermatitis.
All skin types can be affected, but it is more pronounced in dark skinned individuals.

PATHOPHYSIOLOGY

The hypopigmentation is post-inflammatory. Spongiosis, parakeratosis and lichenification also affect the melanogenesis. The chronic use of topical steroids may play a role in some patients but it is not the main causative factor of the hypopigmentation.

CLINICAL DERMATOLOGICAL PRESENTATION

Hypopigmented lesions from one to several centimeters in diameter. The borders are irregular and ill-defined and sometimes are hyperpigmented.
Erythema, exudation or scales are observed in active lesions but hypopigmented macules in suggestive localizations may be the only clinical sign.
Slight to severe pruritus.
Localization: predilection for flexural areas. The face is the main site in young children.

EXTRACUTANEOUS SIGNS

None.

HISTOPATHOLOGY

Reduced melanin contained in the basal layers of the epidermis. Some authors have reported a decrease in melanocyte number.
Histological signs of atopic dermatitis in active lesions.

DIFFERENTIAL DIAGNOSIS

- Other post-inflammatory hypopigmentations such as mycosis fungoides, psoriasis, sarcoidosis, leprosy, pityriasis lichenoides chronica.
- Vitiligo (Wood's lamp examination shows that lesions are not totally amelanotic – contrary to vitiligo).

TREATMENT

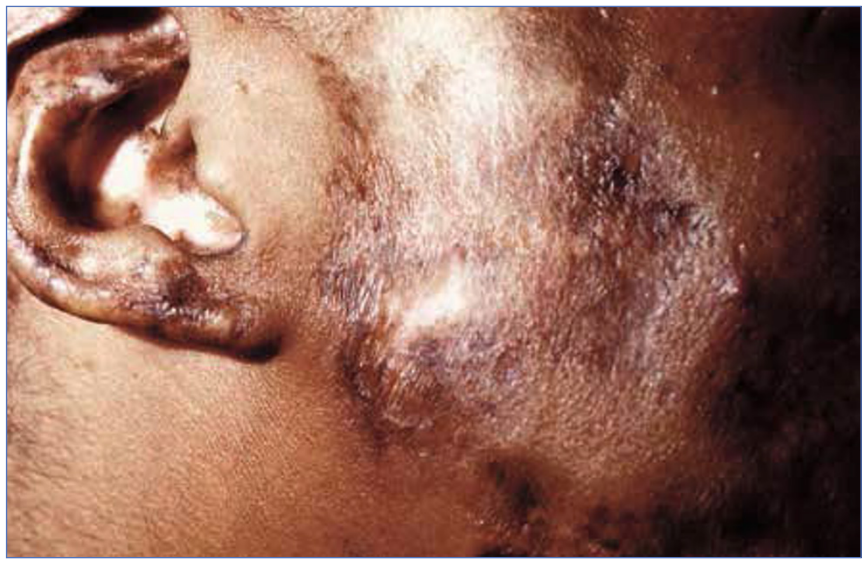
Emollients, topical steroids or topical calcineurin inhibitors in active lesions, phototherapy.

KEY REFERENCES

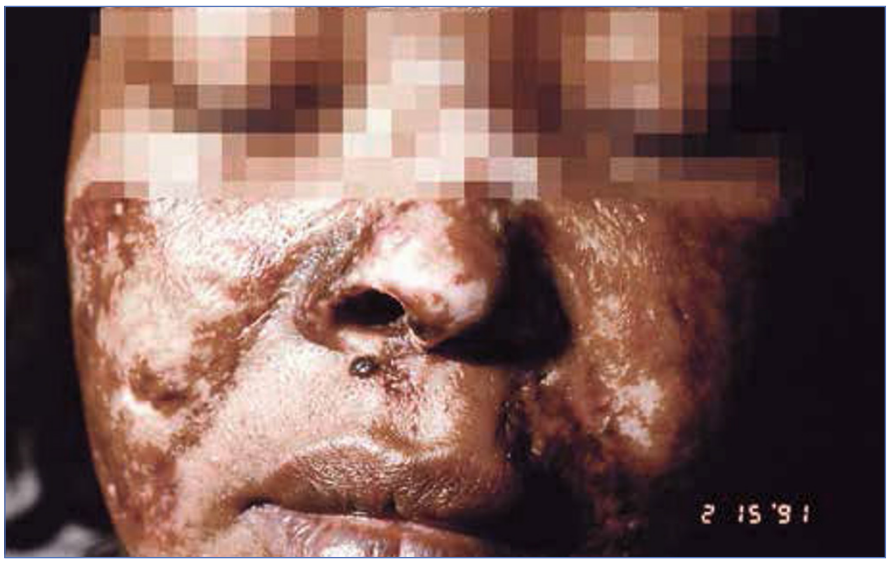
- Larrègue M, Martin J, Bressieux JM, Canuel C, De Giacomoni P, Ramdenée P, Babin P. Vitiligoid achromias and severe atopic dermatitis. A propos of 4 cases. Ann Dermatol Venereol. 1985;112:589-600.
- Eichenfield LF, Tom WL, Chamlin SL, Feldman SR, Hanifin JM, Simpson EL, et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. J Am Acad Dermatol. 2014;70:338-51.

DISCOID LUPUS

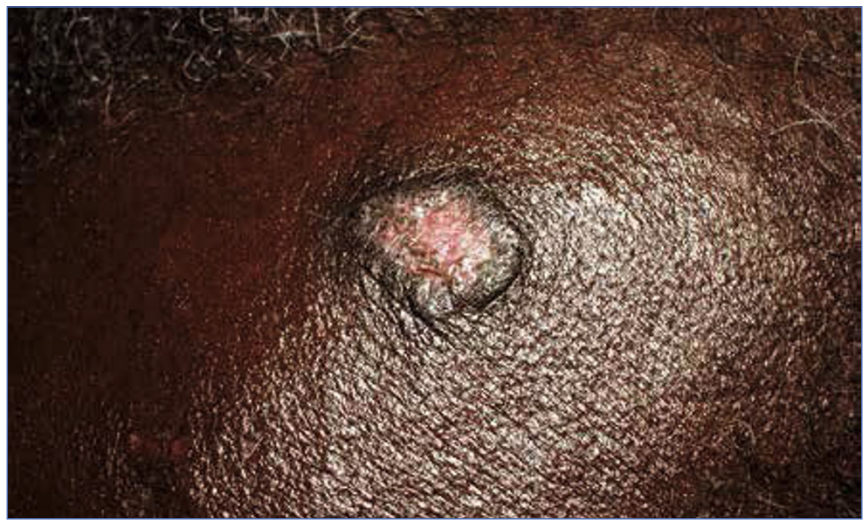
Amit G. Pandya and M. Rodrigues



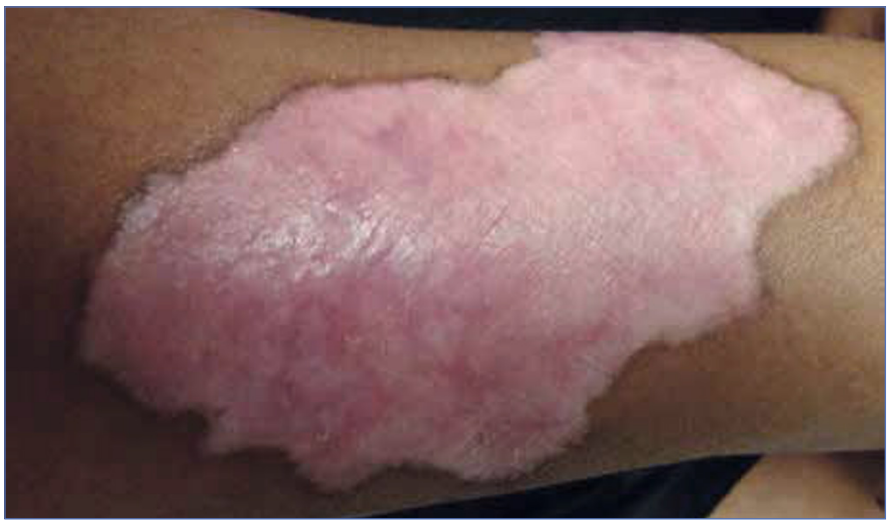
Discoid lupus erythematosus involving of the cheek and the conchal bowl of the ear (coll. Amit G. Pandya and M. Rodrigues).



Scarred, atrophic and dyspigmented plaques with alopecia (coll. Amit G. Pandya and M. Rodrigues).



Close-up of a lesion of discoid lupus erythematosus. Note the hyperpigmented border and the hypochromic and atrophic center.



Hypochromic lesions with hyperpigmented borders in discoid lupus erythematosus (coll. Amit G. Pandya and M. Rodrigues).

EPIDEMIOLOGY

Discoid lupus erythematosus (DLE) is one of the three main subtypes of chronic cutaneous lupus (CCL) and accounts for approximately 75% of cases seen. The prevalence of CCL is said to be similar to systemic lupus erythematosus (SLE) which is reported to be as high as 48 cases per 100,000 people. Most authorities suggest DLE is more frequent in women and in African Americans compared with Caucasians or Asians. While the age of onset is usually 20–50 years, African American patients seem to develop DLE at a younger age compared with their Caucasian counterparts.

PATHOPHYSIOLOGY

While the exact etiology of DLE is not completely understood, an increasing body of evidence suggests ultraviolet irradiation, autoantibody generation and T cell dysfunction as well as dendritic and other immune cells may be involved.

CLINICAL DERMATOLOGICAL PRESENTATION

Erythematous to violaceous scaly papules and plaques with follicular plugging are often seen.
Over time, lesions cause disfiguring, scarred, atrophic and dyspigmented plaques with alopecia.
In patients with colored skin, marked hypopigmentation and/or hyperpigmentation is usually seen. Anecdotal experience from dermatologists who specialize in colored skin indicate discoid lesions (either isolated or as part of SLE) are more severe in people with colored skin.
Localization: face, scalp, lips and sun exposed areas.
Involvement of the conchal bowl of the ear is characteristic but not always present.
These lesions may cause burning or pain but are more often asymptomatic.

EXTRACUTANEOUS SIGNS

Approximately 16% of patients with DLE may develop systemic involvement within 3 years of initial diagnosis. DLE confers a better prognosis than SLE with a lower frequency of nephritis and end stage renal disease. Arthritis and terminal renal failure are positively associated with African-Americans but negatively associated with Hispanic populations.

HISTOPATHOLOGY

Features on biopsy will vary depending on the location and stage of lesion examined. Histopathological features include hyperkeratosis, follicular plugging, epidermal atrophy, basal layer vacuolation, apoptotic keratinocytes and a dense perivascular and peri-appendageal infiltrate. Thickening of the basement membrane, pigment incontinence and abundant mucin may also be seen.

DIFFERENTIAL DIAGNOSIS

Depending on morphology and location of the lesion(s), the differential diagnosis may be wide.

- Other forms of lupus.
- Sarcoidosis, cutaneous lymphomas, lichen planus, inflammatory vitiligo and granuloma faciale.

TREATMENT

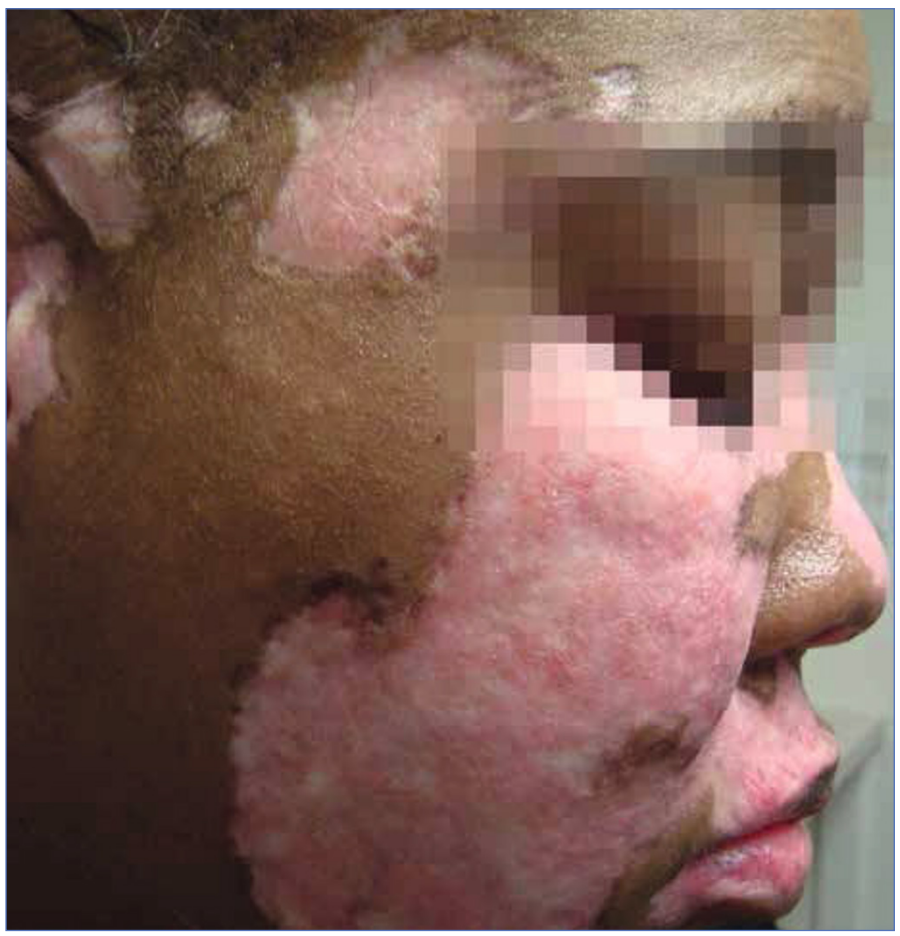
While mortality is low in those with DLE, morbidity may be high. For this reason, early recognition and treatment of DLE lesions is essential to prevent long-term sequelae. Triggers including medication, smoking and UV exposure must be avoided. Cosmetic camouflage may be helpful for some patients. Topical and intralesional steroids and hydroquinone are first-line agents but other topical agents (calcineurin inhibitors, pimecrolimus, tacroliumus) may also be useful. Topical retinoids, calcipotriol and imiquimod have been useful in a few cases. In severe, recalcitrant cases, systemic steroids may be required. Other reported systemic therapies include retinoids, dapsone, methotrexate, cyclosporin and mycophenolate mofetil. Rare reports of intravenous immunoglobulin and rituximab have been published in the literature.
Consultation with other medical specialists in a multi-disciplinary team approach may be necessary for patients with systemic disease.

KEY REFERENCES

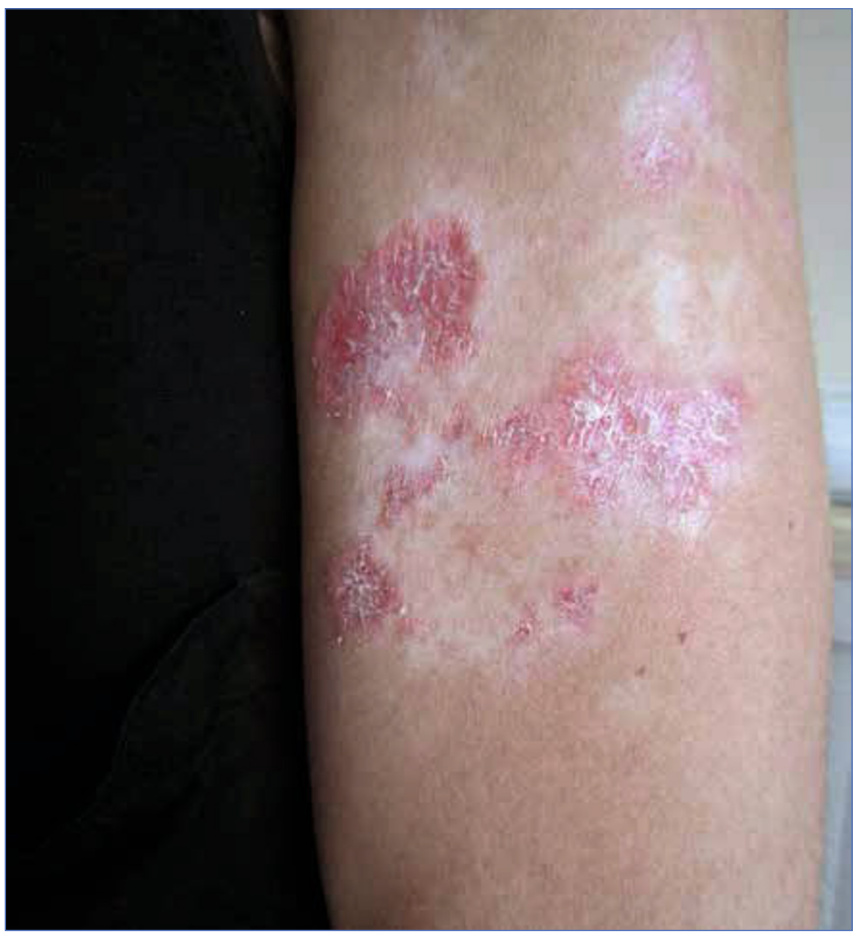
- Deligny C, Marie DS, Clyti E et al. Pure cutaneous lupus erythematosus in a population of African descent in French Guiana: a retrospective population-based description. Lupus. 2012;21:1467-71.
- Petit A, Dadzie O.E. Multisystemic diseases and ethnicity: a focus on lupus erythematosus, systemic sclerosis, sarcoidosis and Behçet disease. BJD. Special Issue: Ethnic Skin: a New Era for Studying Human Cutaneous Diversity. 2013;169 (Suppl s3):1-10.
- Merola JF, Prystowsky SD, Iversen C et al. Association of discoid lupus erythematosus with other clinical manifestations among patients with systemic lupus erythematosus. J Am Acad Dermatol. 2013;69:19-24.

DISCOID LUPUS

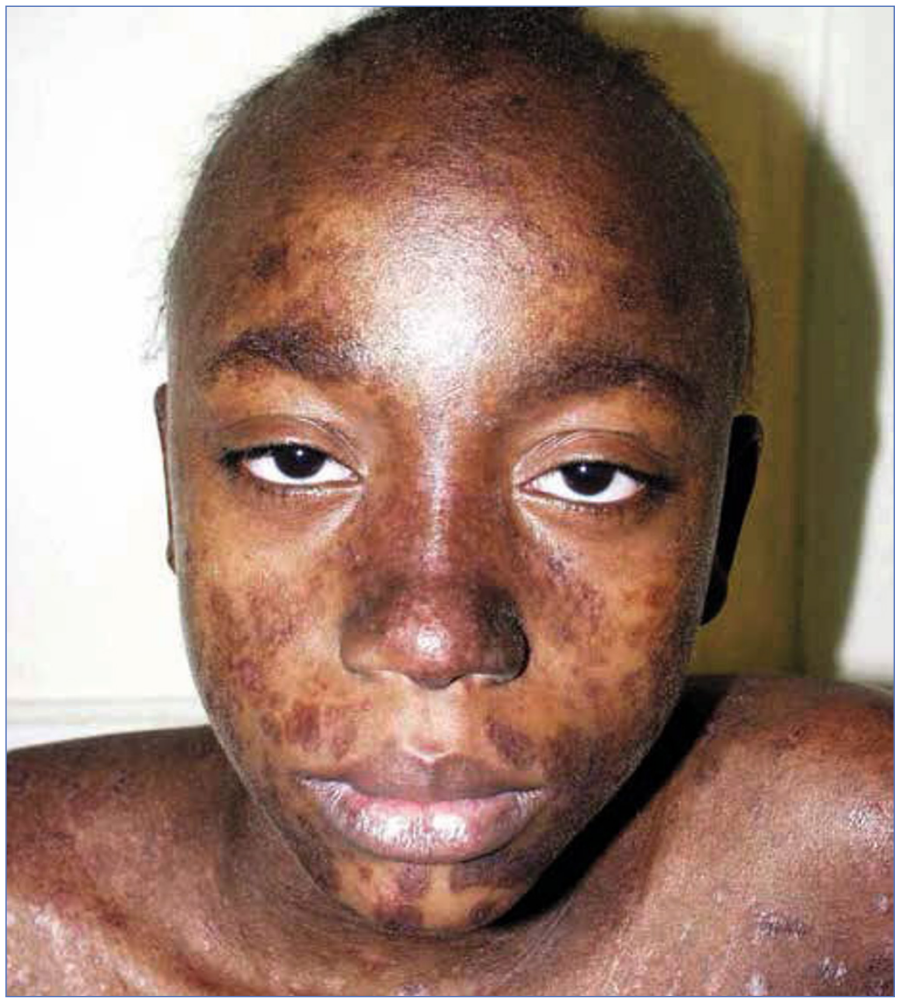
Amit G. Pandya and M. Rodrigues



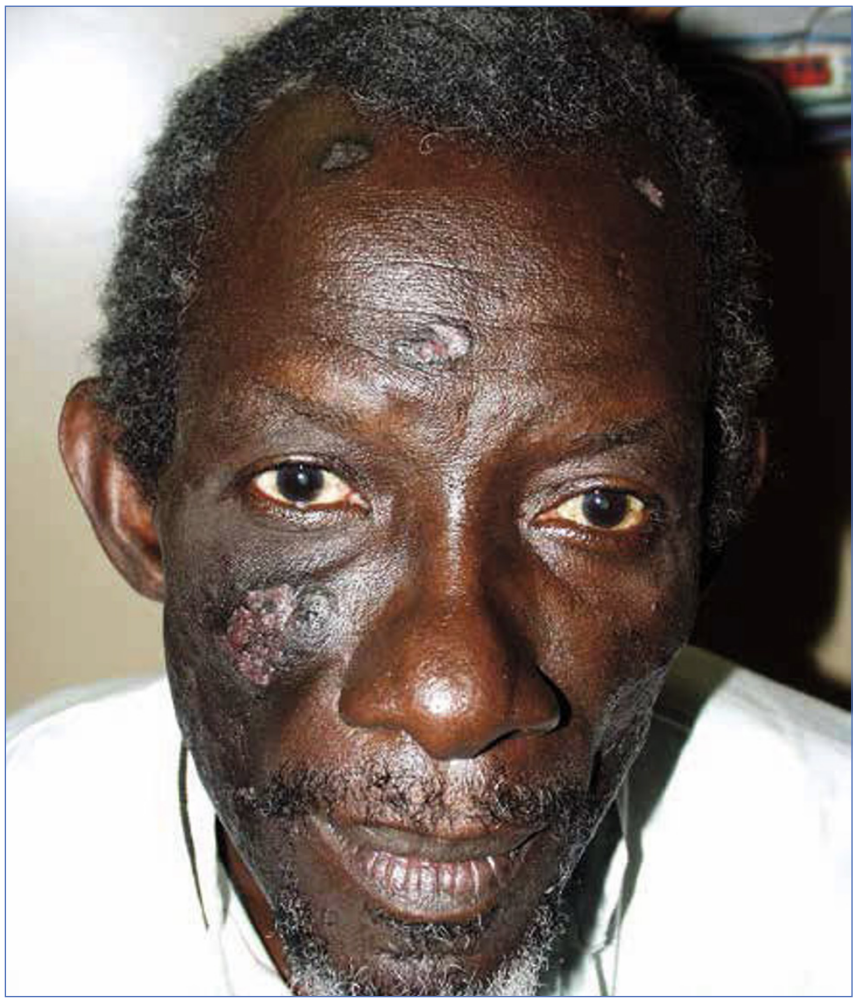
Hypochromic lesions of the face in discoid lupus erythematosus. Note the hyperpigmented borders (coll. Amit G. Pandya and M. Rodrigues).



Inflammatory and hypochromic lesions in subacute form of lupus.

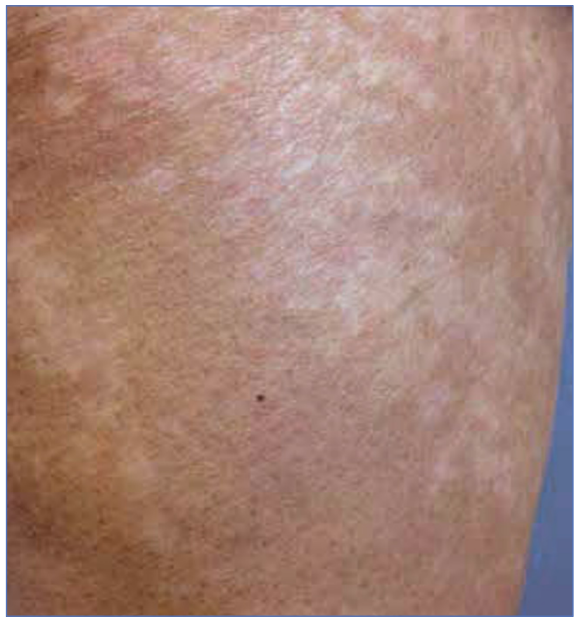


Dyschromia in severe systemic lupus erythematosus.

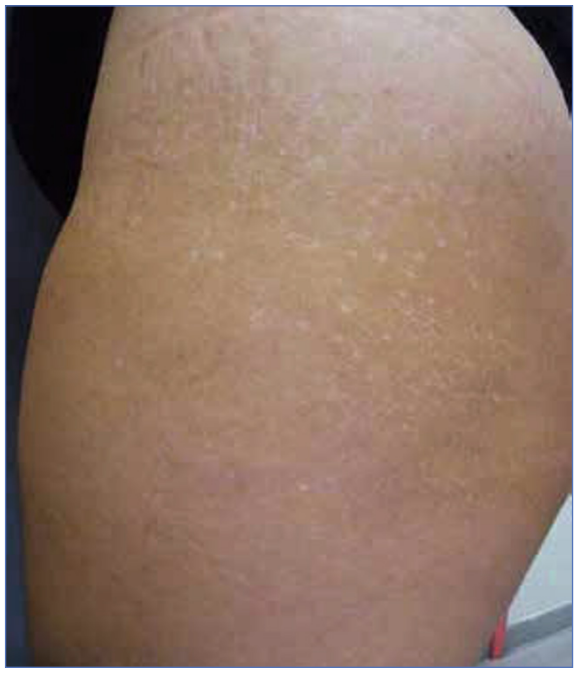


Discoid lupus erythematosus.

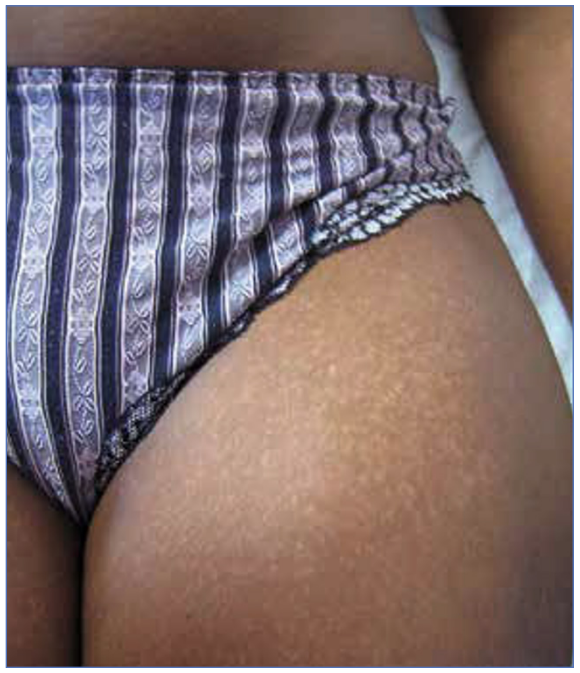
LICHEN SCLEROSUS ATROPHICUS



Extra genital lichen sclerosus et atrophicus with coalescence of the lesions into plaques.

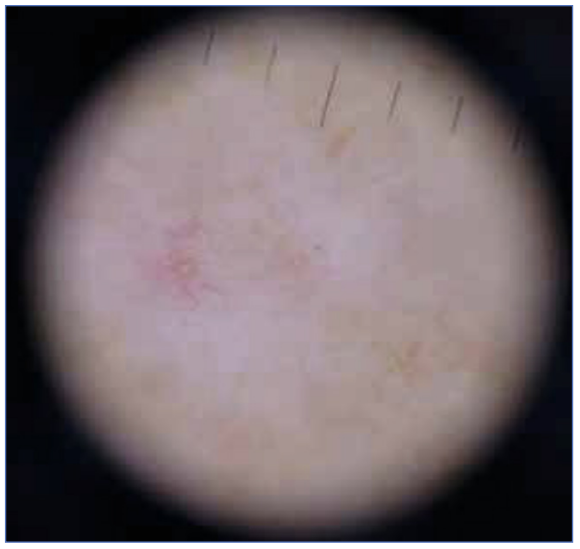


Early form of lichen sclerosus and atrophicus of the thigh.



Extra genital lichen sclerosus and atrophicus on the thigh. Note the polygonal hypopigmented papules coalescing into plaques.

Vulvar lichen sclerosus and atrophicus on a young girl.



Dermoscopy of a porcelain-white spot. Note the telangiectasia and the follicular plugs.

EPIDEMIOLOGY

The prevalence is unknown but estimates range from 1:60 to 1:1000. Genetic predisposition is reported with some familial cases.
Female predominance (6 females:1 male) without racial predilection.
Genital (mainly vulvar) lichen sclerosus et atrophicus (LSA) is frequently observed in children while extra genital LSA mostly affects adults.

PATHOPHYSIOLOGY

The pathogenesis of LSA is unknown. The development of hypopigmented LSA lesions may be related to decreased melanin production, reduced transfer of the melanin to the surrounding keratinocytes and partial melanocyte loss.

CLINICAL DERMATOLOGICAL PRESENTATION

Polygonal hypopigmented papules that coalesce into plaques with irregular but quite distinct borders. With time, lesions are take on a characteristic pattern of smooth, porcelain-white spots.
Telangiectasias and follicular plugs are often present and can be easily observed using dermoscopy. Blisters can be observed.
Gradual synechias and stenosis are observed in genital LSA.
Asymptomatic or mild pruritus in extragenital LSA. Pruritus is common in genital areas and can lead to lichenification.
Transformation in squamous cell carcinoma is rare but required careful follow-up of the chronic forms.
Localization: any area of the skin can be affected by extra-genital LSA. Vulvar LSA mostly affects the labia majora but the lesions can be more widespread. In males, the penis glans and the prepuce or foreskin remnants are the most involved.

EXTRACUTANEOUS SIGNS

Dyspareunia, dysuria.

HISTOPATHOLOGY

Compact hyperkeratosis with thin epidermis. Lichenoid mononuclear infiltrate in the dermal-epidermal junction. Edema in the papillary dermis in early lesions, replaced by sclerosis and hyalinization.
Reduced number of active melanocytes with a decrease or total disappearance of melanin.

DIFFERENTIAL DIAGNOSIS

- Extra-genital LSA: vitiligo punctate, other post-inflammatory hypopigmentations such as sarcoidosis, leprosy, lichen planus, lupus, pityriasis lichenoides chronica, tinea versicolor. Atrophoderma of Pierini and Pasini. Idiopathic guttate hypomelanosis.
- Genital LSA: warts, balanitis xerotica obliterans, Bowen's disease, genital vitiligo.

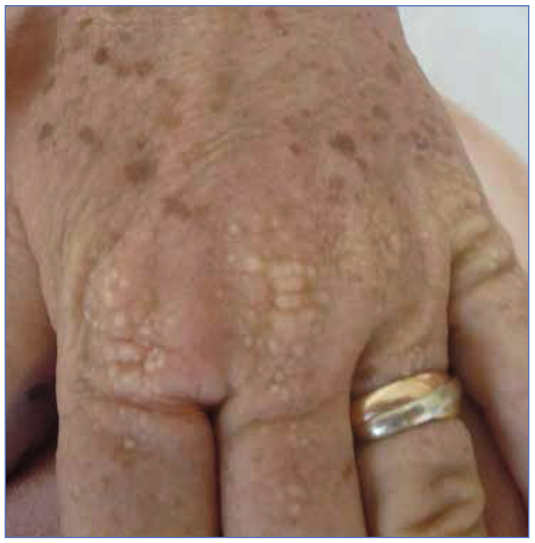
TREATMENT

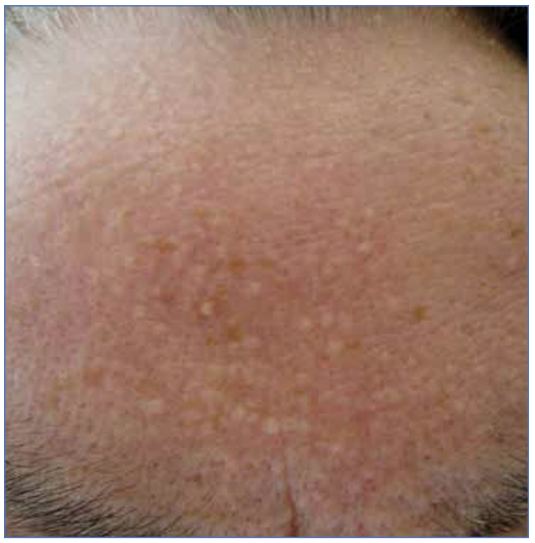
High potent topical steroids and topical calcineurin inhibitors for genital LSA.
Circumcision may be of benefit in male genital LSA.
Phototherapy can be proposed for extra-genital forms of LSA.

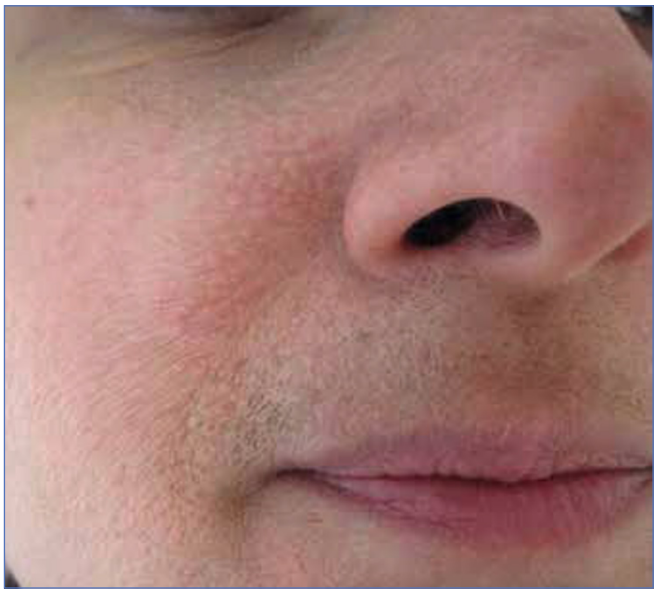
KEY REFERENCES

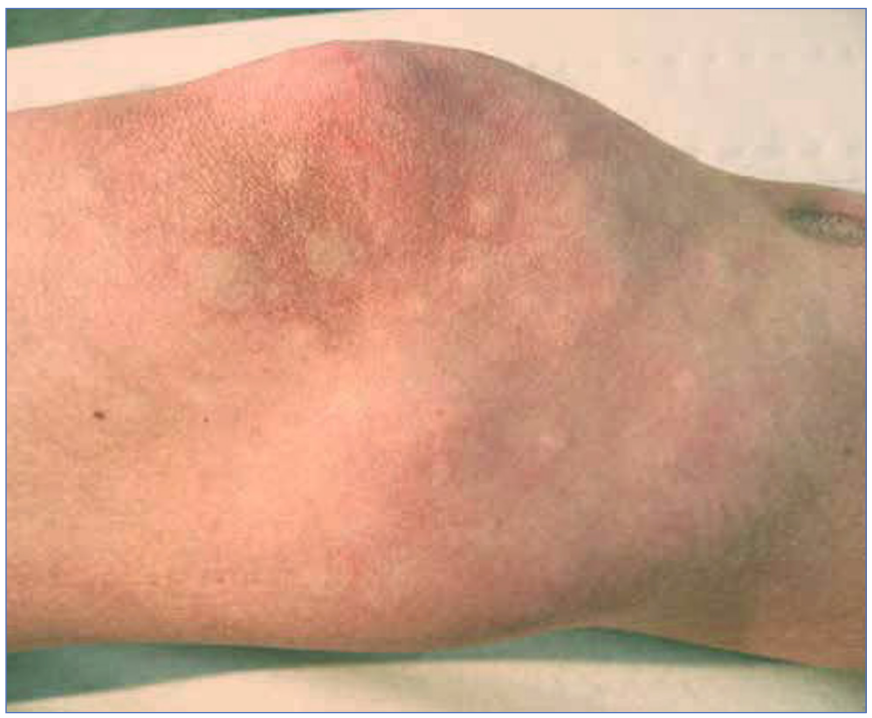
- Carlson JA, Grabowski R, Mu XC, Del Rosario A, Malfetano J, Slominski A. Possible mechanisms of hypopigmentation in lichen sclerosus. Am J Dermatopathol. 2002;24:97-107.
- Sherman V, McPherson T, Baldo M, Salim A, Gao XH, Wojnarowska F. The high rate of familial lichen sclerosus suggests a genetic contribution: an observational cohort study. J Eur Acad Dermatol Venereol. 2010;24:1031-4.
- Chi CC, Kirtschig G, Baldo M, Lewis F, Wang SH, Wojnarowska F. Systematic review and meta-analysis of randomized controlled trials on topical interventions for genital lichen sclerosus. J Am Acad Dermatol. 2012;67:305-12.

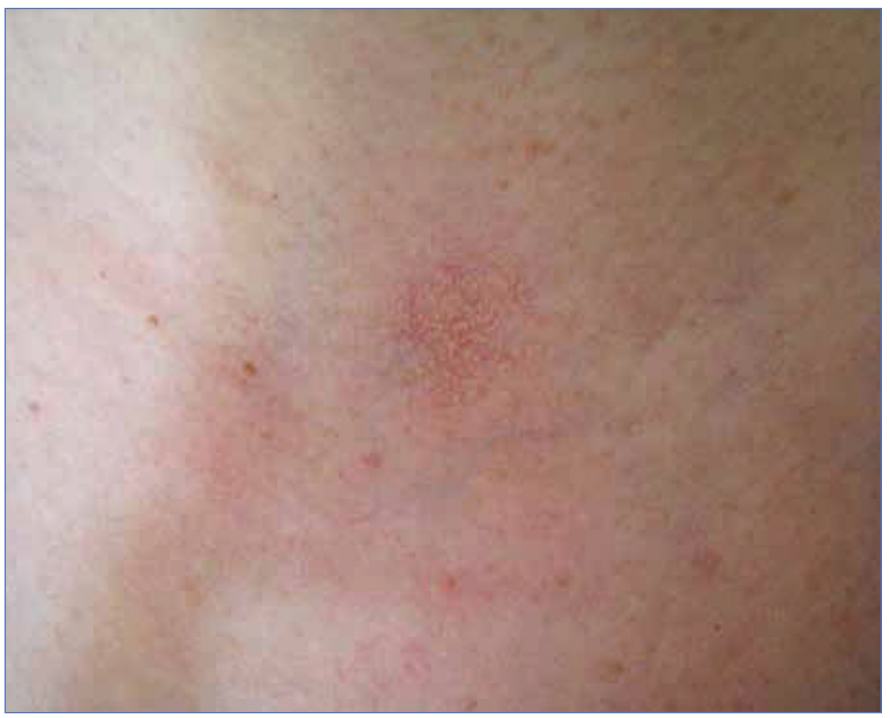
MUCINOSIS


Papular mucinosis on the dorsum of the hands.


Papular mucinosis on the face of the same patient.


Follicular mucinosis of the face secondary to lupus.


Discrete papular mucinosis in a patient with HIV.


Primary localized follicular mucinosis.

Mucinoses are due to the accumulation of acid glycosaminoglycans (mucin). This deposit can be in the outer root sheath of hair follicle (follicular mucinosis), or within the dermis (papular mucinosis).

SYNONYMS

Alopecia mucinosa (for follicular mucinosis).
Lichen myxedematosus (for papular mucinosis).

EPIDEMIOLOGY

Both follicular and papular mucinoses are rare.
They have been reported in all races.
Both sexes are equally affected by papular mucinosis while a male predominance is reported for follicular mucinosis.
Primary localized follicular mucinosis occurs generally before the age of 40 years, while primary generalized follicular mucinosis, secondary follicular mucinosis and papular mucinosis usually affect older individuals.

PATHOPHYSIOLOGY

The hypopigmentation is due to the mucin deposit.

CLINICAL DERMATOLOGICAL PRESENTATION.

Follicular mucinosis

- Pink to yellow-white papules and plaques with follicular accentuation that spontaneously resolve in less than 2 years. Chronic generalized form may persist for years.
- Hair loss in hair-bearing areas.
- Follicular mucinosis can be also secondary to other conditions such as cutaneous lymphoma (mycosis fungoides), lupus, HIV.
- None to mild pruritus.
- Localization: face, scalp, neck and shoulder are the most frequent sites.

Papular mucinosis

- Pink to yellow-white papules that can coalesce into plaques.
- None to mild pruritus.
- Myeloma and HIV can be associated with papular mucinosis
- Localization: face, dorsal hands, extensor surfaces of the arms and legs.

EXTRACUTANEOUS SIGNS

None in follicular mucinosis.
A monoclonal paraprotein band is frequently found in papular mucinosis.

HISTOPATHOLOGY

Accumulation of mucin in the outer root sheath of hair follicle (follicular mucinosis), or within the dermis (papular mucinosis). An inflammatory cell infiltrate is often associated.

DIFFERENTIAL DIAGNOSIS

- **Follicular mucinosis:** alopecia areata, keratosis pilaris, pityriasis rubra pilaris, seborrheic dermatitis. In daily practice, the main problem is to differentiate primary follicular mucinosis to follicular mucinosis associated to mycosis fungoides.
- **Papular mucinosis:** amyloidosis, xanthoma, sarcoidosis, leprosis, granuloma annulare.

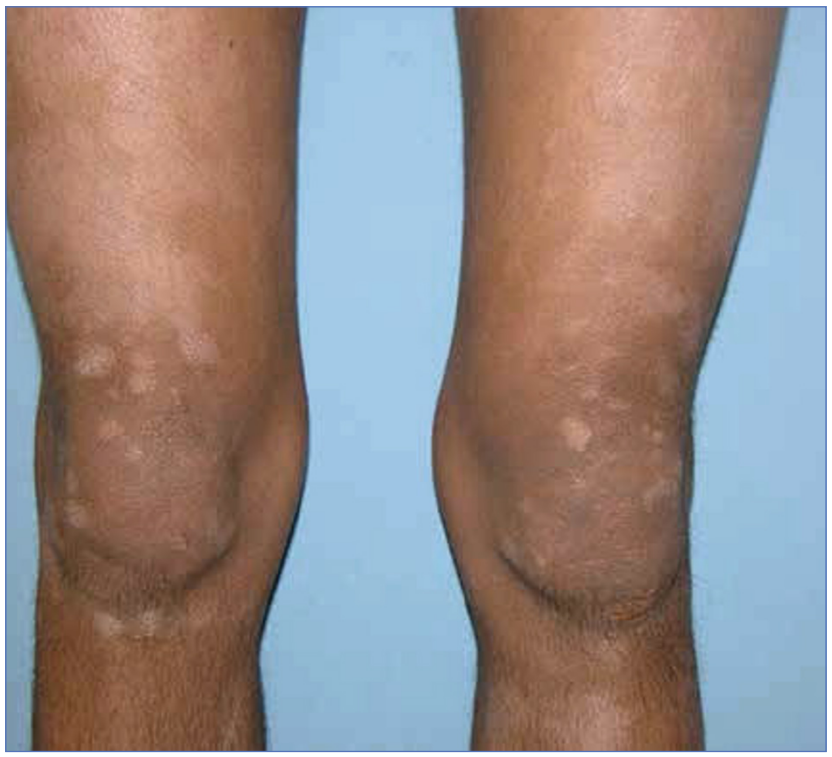
TREATMENT

Follicular mucinosis: treatment is not always required, especially in localized forms that spontaneously resolve after several months. PUVA, steroids (topical or systemic), interferon, dapsone can be proposed. Treatment of the underlying disorder in a secondary follicular mucinosis.
Papular mucinosis: systemic steroids, immunoglobulins, PUVA, thalidomide, anti-tumor necrosis factor-alpha antibodies.

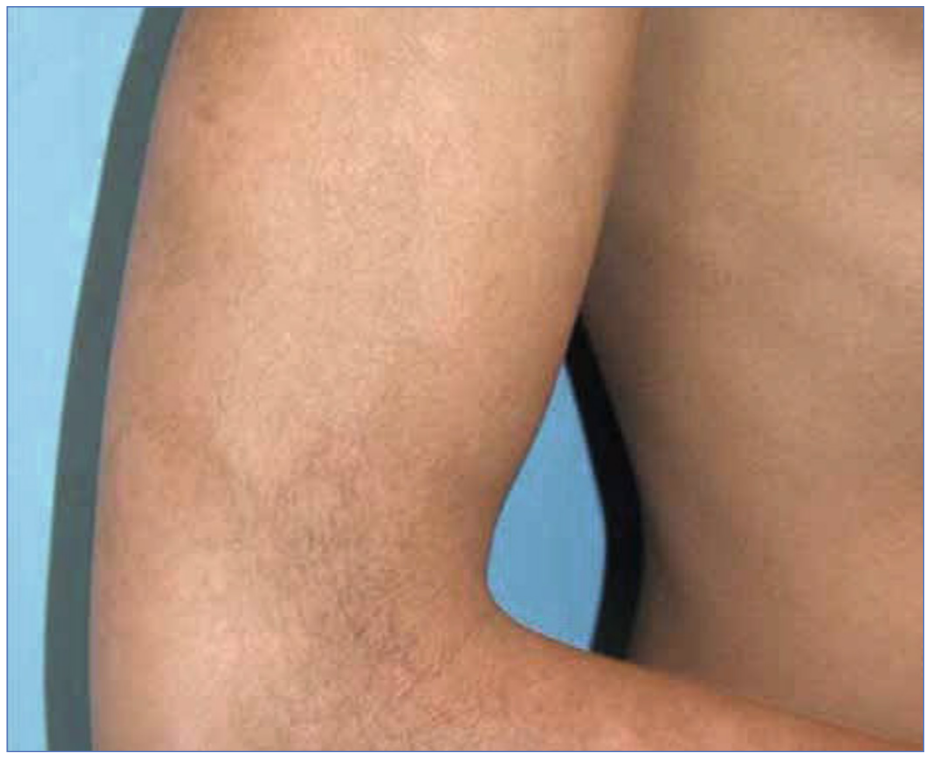
KEY REFERENCES

- Rongioletti F, Ghigliotti G, De Marchi R, Rebora A. Cutaneous mucinoses and HIV infection. Br J Dermatol. 1998;139:1077-80.
- Jackson EM, English JC 3rd. Diffuse cutaneous mucinoses. Dermatol Clin. 2002;20:493-501.

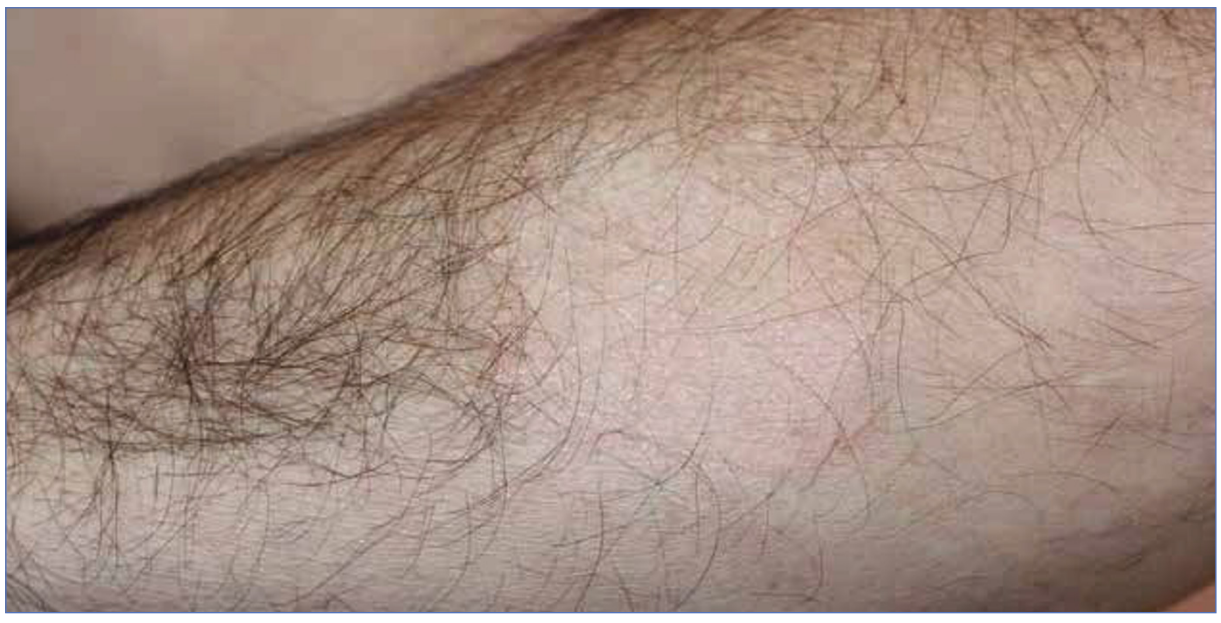
MYCOSIS FUNGOIDES



Multiple hypopigmented patches of the leg in mycosis fungoides.



Multiple hypopigmented patches of the arm. Note the slight decrease of hair density in affected areas.



Large patch of mycosis fungoides. Along with the hypopigmentation, a slight erythema with discrete scales can be observed here. The marked alopecia is highly suggestive of the diagnosis of mycosis fungoides.

EPIDEMIOLOGY

Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma and most of dyschromia observed with cutaneous lymphoma are due to MF. The incidence of MF has been reported to be as high as 0.9 per 100,000.
Hypochromic forms of cutaneous lymphoma is more frequently observed in children (about 25% of MF in children are hypochromic).

PATHOPHYSIOLOGY

The development of hypopigmented MF lesions may be related to melanocytes degeneration and abnormal melanogenesis cause by a nonspecific response to cell injury associated with inflammation.

CLINICAL DERMATOLOGICAL PRESENTATION

Hypopigmented macules with irregular but quite distinct borders. Some lesions can be circular or oval.
Keratosis pilaris-like papules and alopecia can be observed and are highly suggestive of a folliculotropic form.
Slight or no pruritus.
Hyperpigmented macules are rarer in MF but they can be observed in heavily pigmented individuals.

Poikiloderma with a mixed pattern of hypo- and hyperpigmentation can be observed, especially after treatment.
Many other clinical variants of MF without dyschromic changes are also described.
Localization: any area of the skin can be affected. In early stages lesions are often distributed asymmetrically in sun-protected areas.

EXTRACUTANEOUS SIGNS

In latter stages, a lymph node or visceral involvement can be observed.

HISTOPATHOLOGY

Atypical lymphocytic cells with cerebriform nuclei mostly confined to the epidermis (epidermotropism) are characteristic of MF. Pautrier abscesses are also suggestive of MF.
At early stages the histopathology can be nonspecific and shows similar aspects of other inflammatory disorders, especially eczema. Immunohistochemistry and search for clonal T-cell receptor gene rearrangements can be helpful. However, careful clinical follow-up and repeating biopsies can be necessary to confirm the diagnosis.
Melanin may be reduced or absent and mild to marked pigmentary incontinence may be seen.

DIFFERENTIAL DIAGNOSIS

- Pityriasis alba (diagnosis can be very difficult at early stages, even at histology. The persistence or the recurrence of the lesions at the same place, even after topical steroids, and a partial alopecia in the affected zone are suggestive of MF).
- Other post-inflammatory hypopigmentations such as sarcoidosis, leprosy, pityriasis lichenoides chronica.
- Vitiligo (especially vitiligo minor in dark skin types).

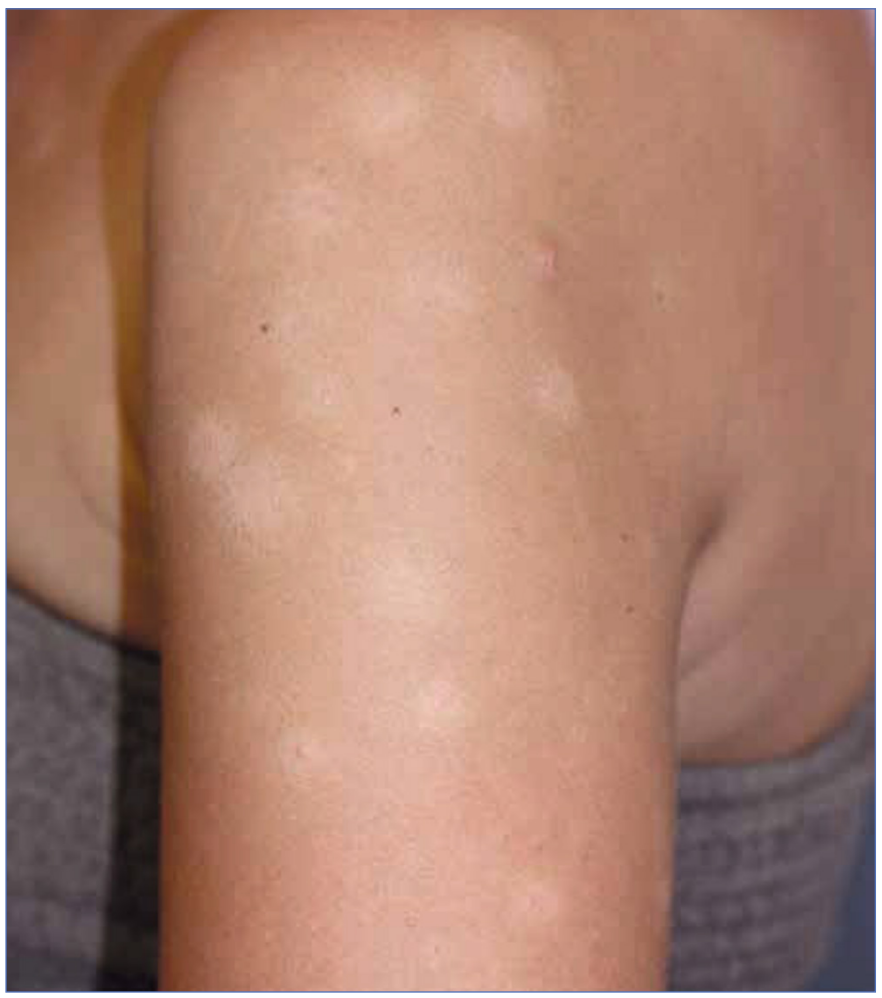
TREATMENT

High potent topical steroids.
Phototherapy.
Irradiation, oral retinoids, photodynamic therapy, topical or systemic chemotherapies.

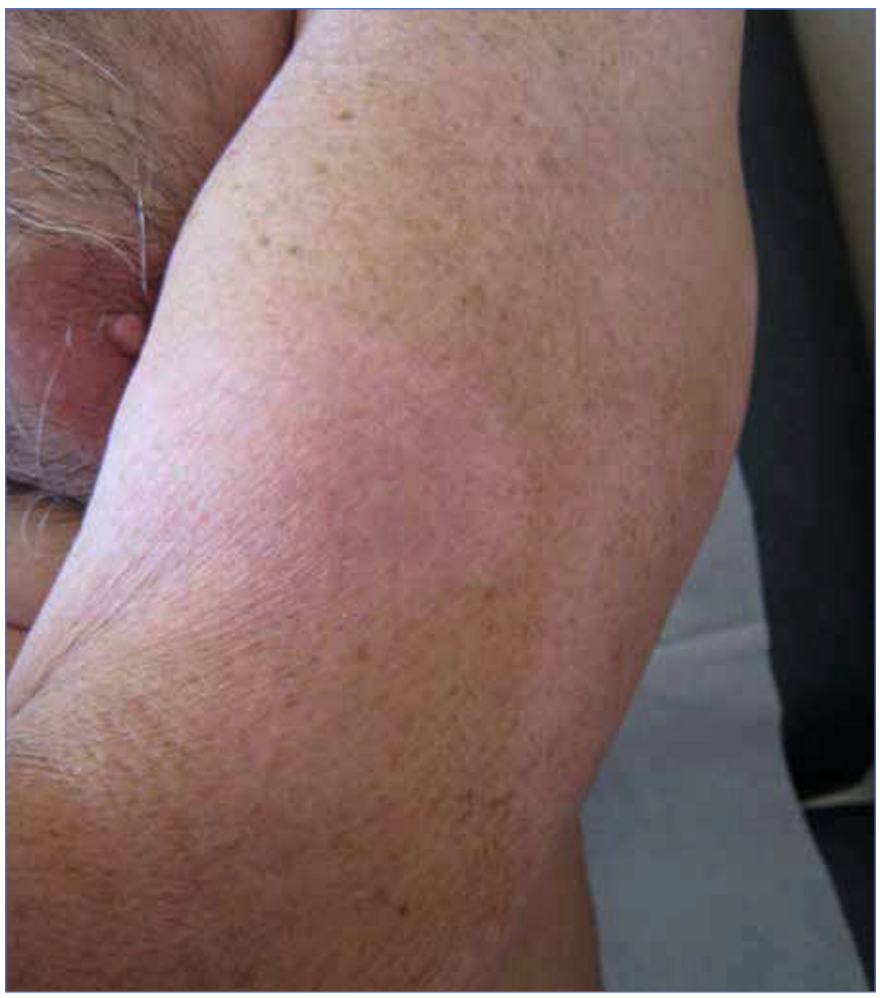
KEY REFERENCES

- Lombroza E, Cohen SR, Phelps R, Lebwohl M, Braverman IM, DiConstanzo D. Hypopigmented variant of mycosis fungoides: dermogrpahy, histopathology and treatment. JAAD 1995;32:987-93.
- Weberschock T, Strametz R, Lorenz M, Röllig C, Bunch C, Bauer A, Schmitt J. Interventions for mycosis fungoides. Cochrane Database Syst Rev. 2012;9.

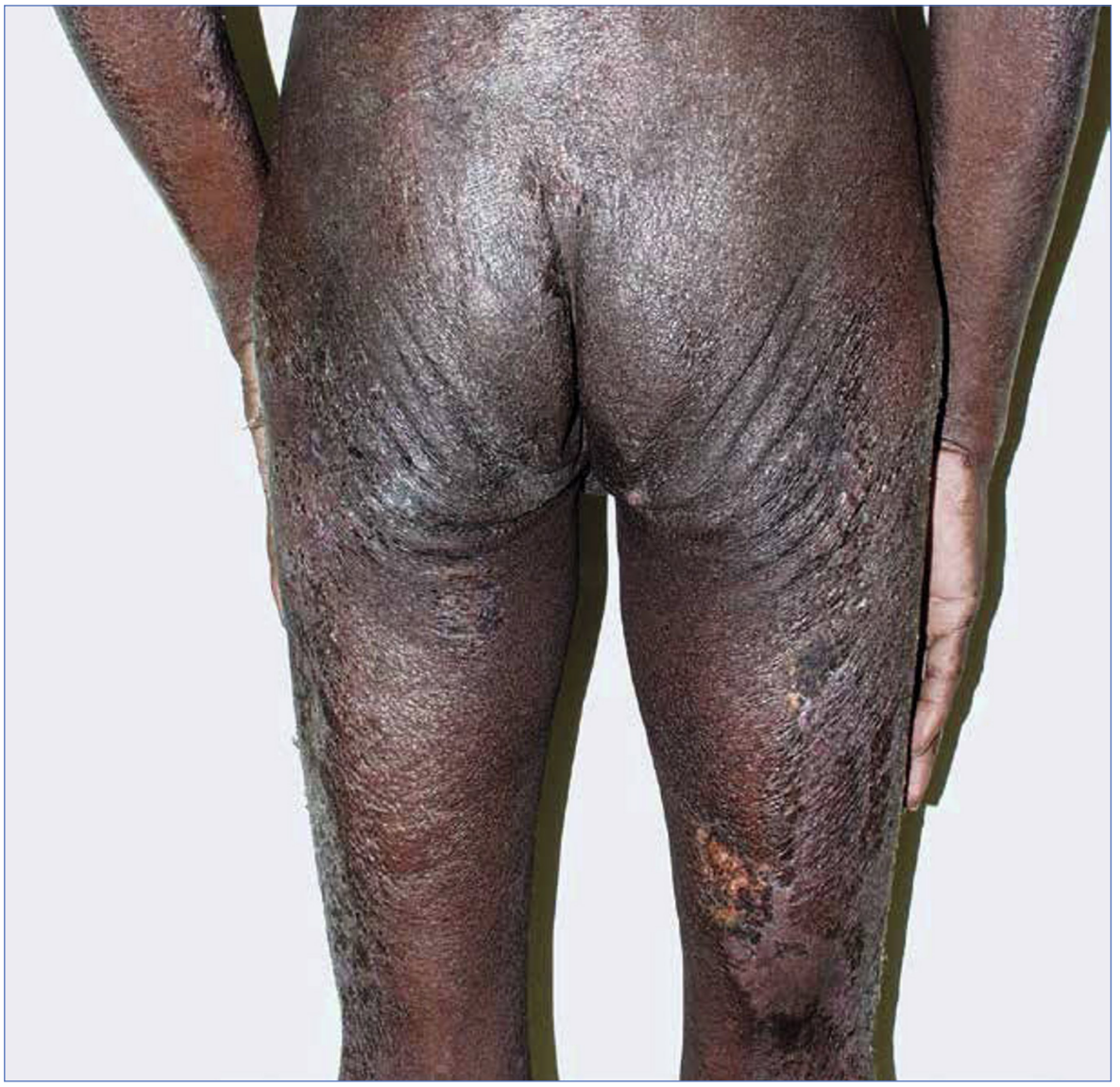
MYCOSIS FUNGOIDES



Early form of hypopigmented mycosis fungoides. the differential diagnosis with eczema is very difficult at this stage.

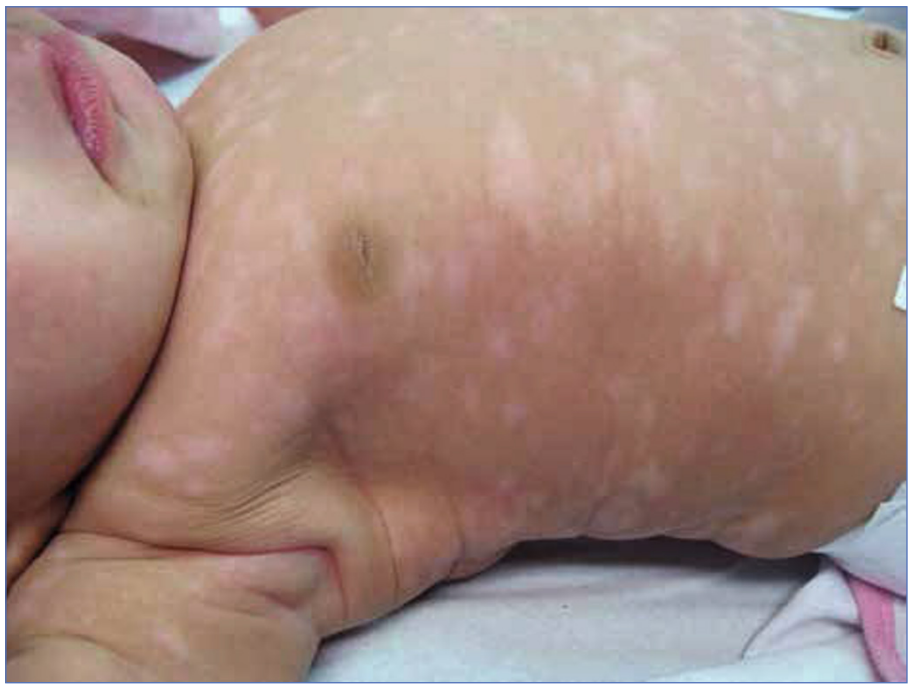


Mycosis fungoides with large hypopigmented slightly inflammatory patches.

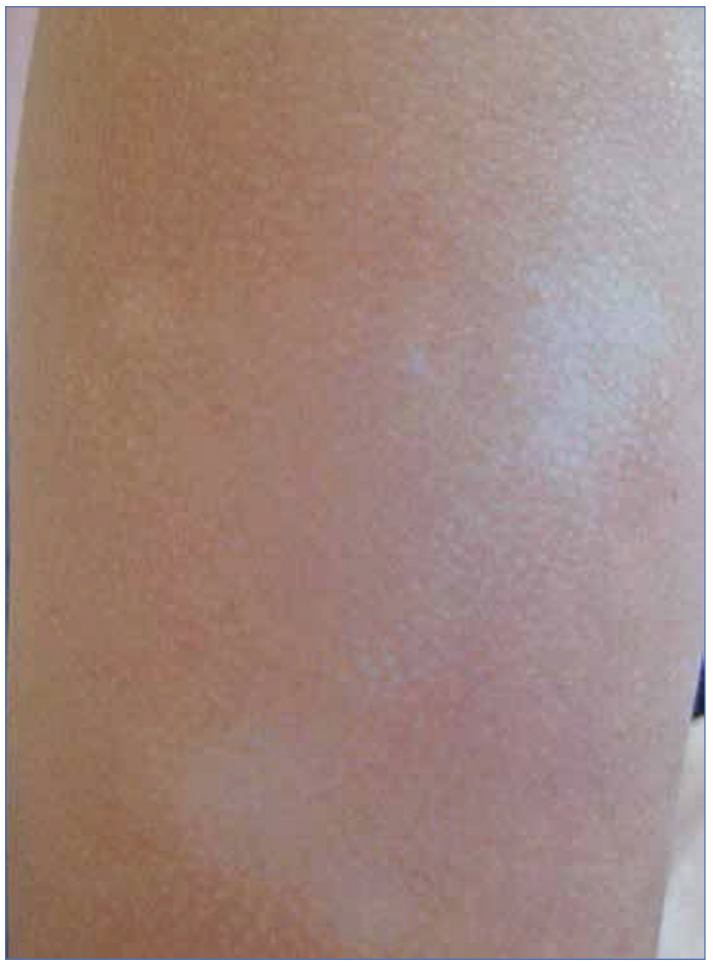


Mixed pattern of hypo- and hyperpigmentations in a patient with sezary syndrome. Erythroderma with crusts and lichenification due to the chronic pruritus are suggestive of the diagnosis.

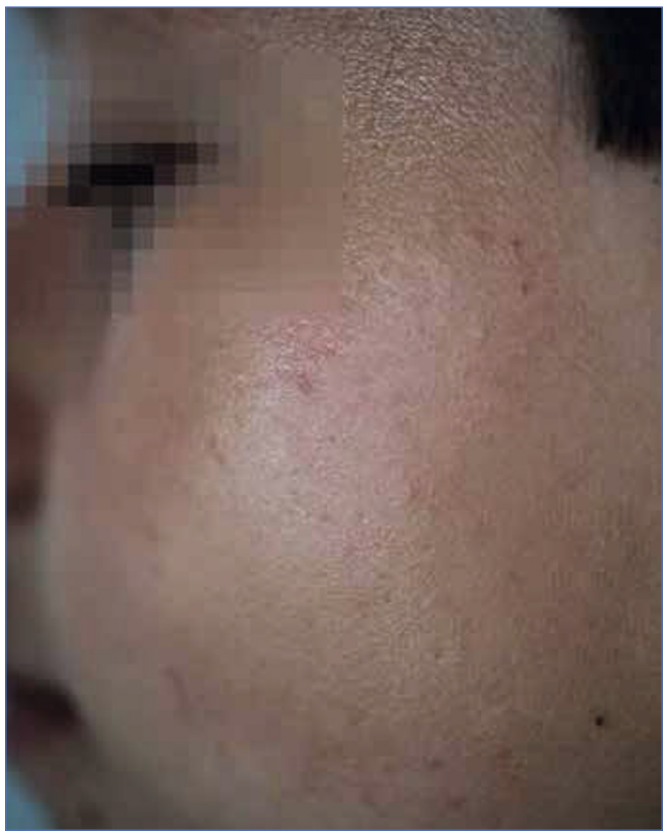
PITYRIASIS ALBA



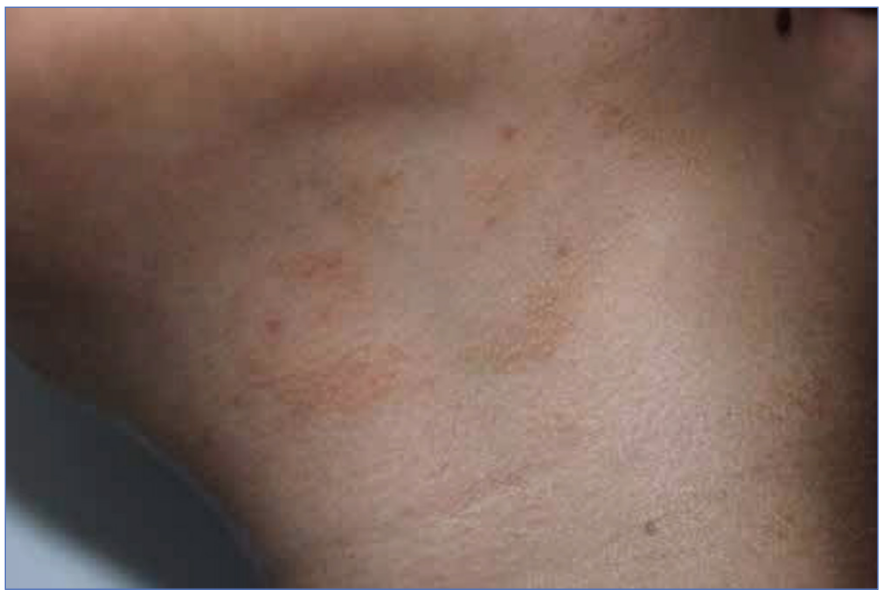
Generalized lesions of pityriasis alba in a young child.



Pityriasis alba of the arm. Note the ill-defined borders.



Large pityriasis alba of the cheek.



Early stage of pityriasis alba.

EPIDEMIOLOGY

Very common (6% of children in a recent Egyptian study).
Mostly observed in children and young adults.
All skin types can be affected, but it is more pronounced in dark skinned individuals.
More apparent in summer and fades during winter.

PATHOPHYSIOLOGY

Unknown. The role of dryness seems to be important.
For some authors, pityriasis alba is a variant of atopic dermatitis. The hypopigmentation is post-inflammatory.

CLINICAL DERMATOLOGICAL PRESENTATION

Hypopigmented macules from 5 to 30 mm in diameter with ill-defined and sometimes slightly raised borders.
The shape is round, oval, or irregular.
Early lesions are slightly erythematous and progressively become dry, scaly and hypopigmented.
Slight or no pruritus.
Hyperpigmented pityriasis alba has been reported but appears to be rare.
Localization: any area of the skin can be affected, but the face is the most frequent site. Generalized lesions occur in less than 10% of cases.

EXTRACUTANEOUS SIGNS

None.

HISTOPATHOLOGY

Reduced melanin contained in the basal layers of the epidermis.
Hyperkeratosis with some parakeratosis. Follicular spongiosis and follicular plugging. Slight perivascular lymphocytic infiltrate with edema of the upper dermis.

DIFFERENTIAL DIAGNOSIS

- Vitiligo (Wood's lamp examination shows that pityriasis alba is not totally amelanotic at the contrary of vitiligo).
- Other post-inflammatory hypopigmentations such as mycosis fungoides, psoriasis, sarcoidosis, leprosy, pityriasis lichenoides chronica.

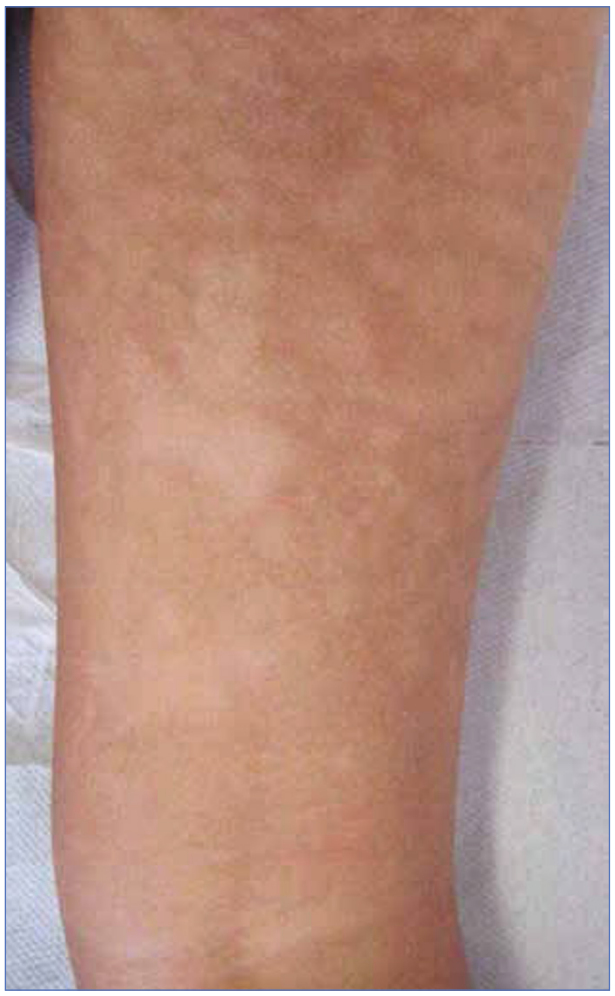
TREATMENT

Emollients.
Phototherapy or sun exposure.
Topical steroids in early stages.

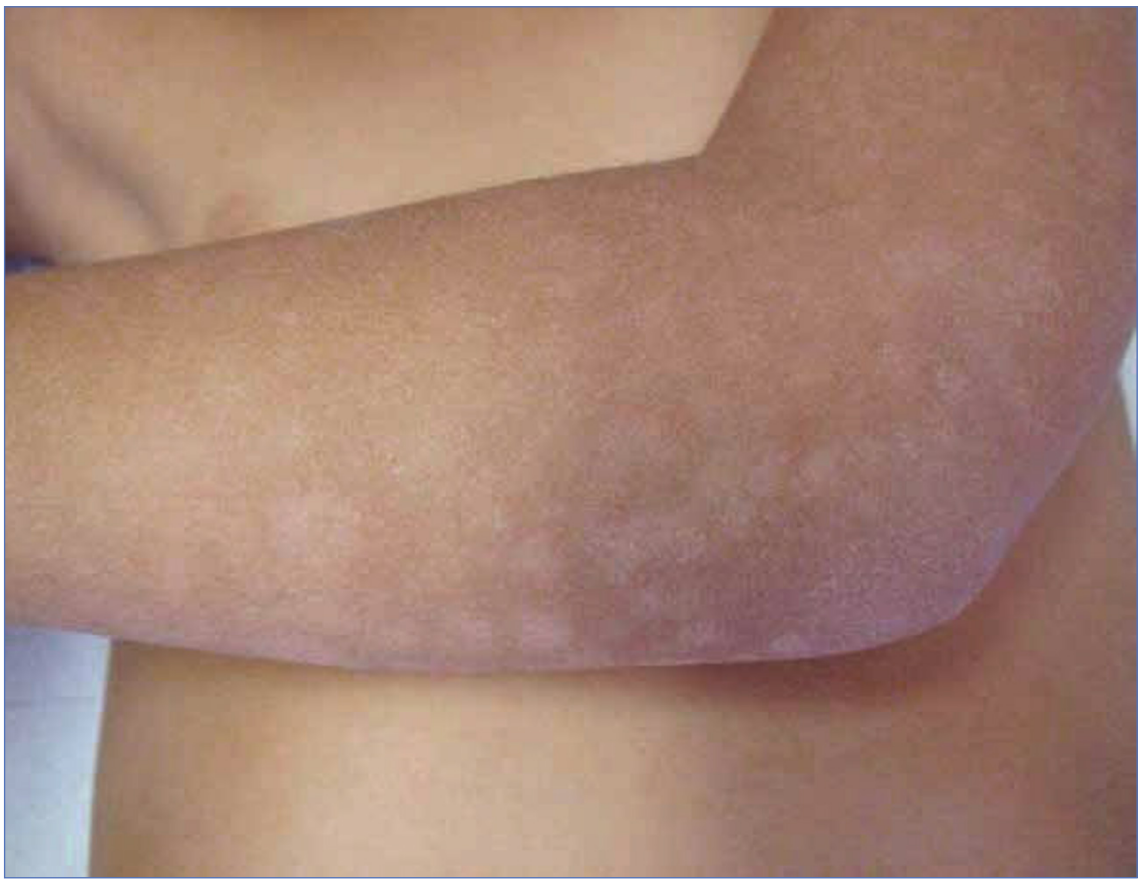
KEY REFERENCES

- Lin RL, Janniger CK. Pityriasis alba. Cutis. 2005;76:21-4.
- El-Khateeb EA, Lotfi RA, Abdel-Aziz KM, El-Shiekh SE. Prevalences of skin diseases among primary schoolchildren in Damietta, Egypt. Int J Dermatol. 2014;53:609-16.

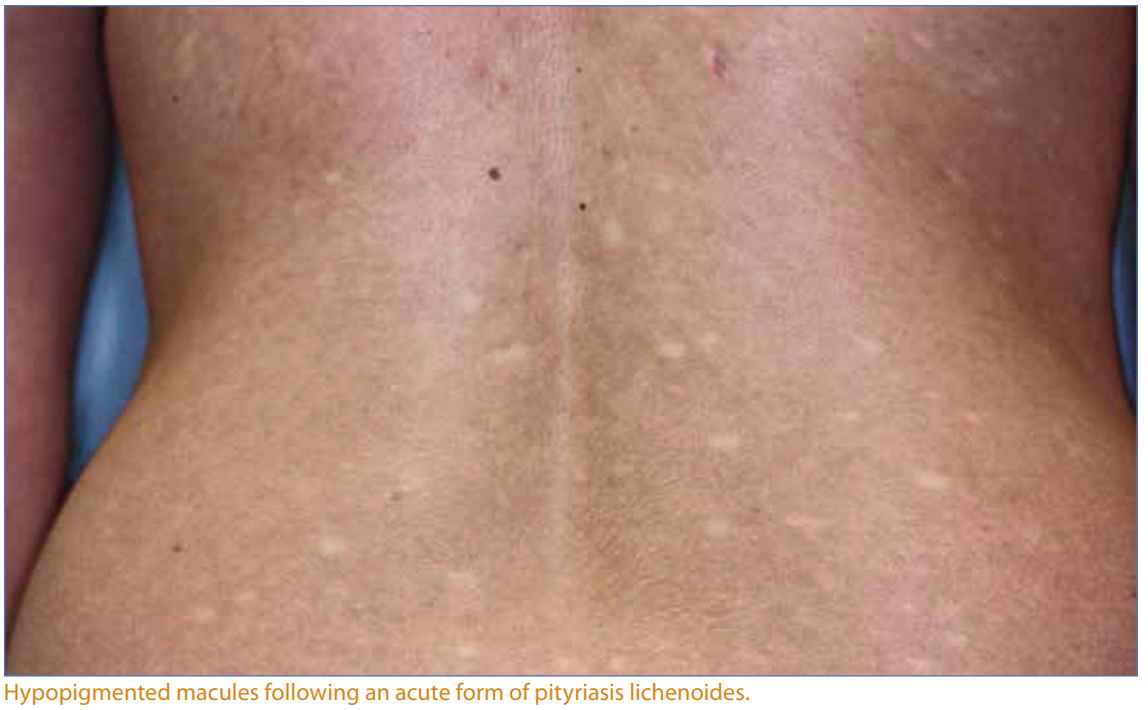
PITYRIASIS LICHENOIDES



Hypopigmented macules of the thigh following pityriasis lichenoides chronica.



Hypopigmented macules in pityriasis lichenoides chronica. Some lesions remains slightly active with faint erythema and scales.



Hypopigmented macules following an acute form of pityriasis lichenoides.

EPIDEMIOLOGY

Hypopigmentation following pityriasis lichenoides is quite uncommon.
Both acute and chronic pityriasis lichenoides can evolve into hypopigmented lesions.
All skin types can be affected, but it is more pronounced in dark skinned individuals.

PATHOPHYSIOLOGY

The hypopigmentation is post-inflammatory.

CLINICAL DERMATOLOGICAL PRESENTATION

Hypopigmented macules from 0.5 to 2 cm in diameter.
Typical lesions of pityriasis lichenoides acute or chronica may be observed concomitantly to the hypopigmented macules but the hypopigmentation remains the only clinical sign when the eruption resolves.
None to moderate pruritus.
Localization: symmetrically or asymmetrically distributed on the trunk, buttocks, thigh, upper arm and axillary folds.

EXTRACUTANEOUS SIGNS

None.
Fever, myalgias and malaise can be observed in pityriasis lichenoides et varioliformis acuta.

HISTOPATHOLOGY

Reduced melanin contain in the basal layers of the epidermis.
Epidermal spongiosis, parakeratosis and lymphocytic infiltrate in active lesions.

DIFFERENTIAL DIAGNOSIS

- Other post-inflammatory hypopigmentations such as pityriasis alba, mycosis fungoides, psoriasis, sarcoidosis, leprosy, atopic dermatitis.
- Vitiligo (Wood's lamp examination shows that lesions are not totally amelanotic at the contrary of vitiligo).

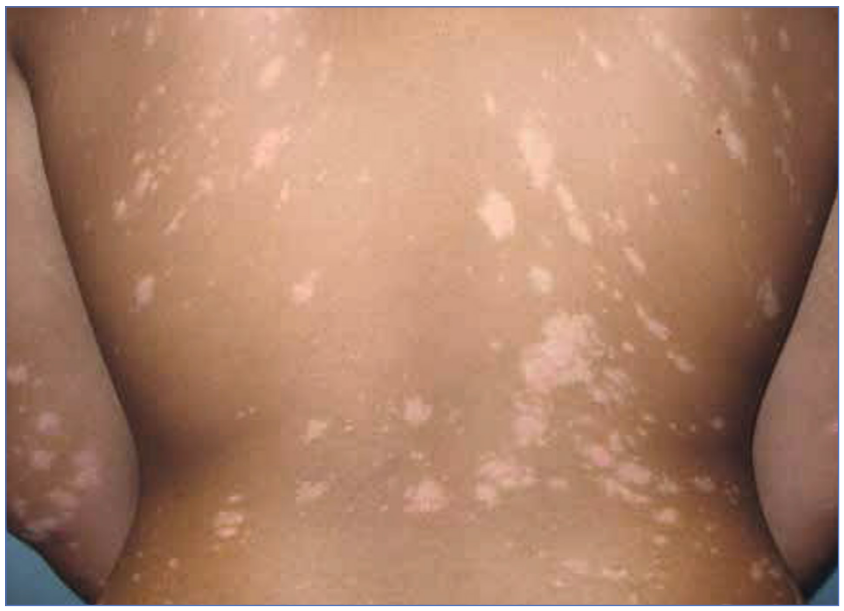
TREATMENT

Phototherapy.
Erythromycin and topical steroids can be discussed in the active phase.

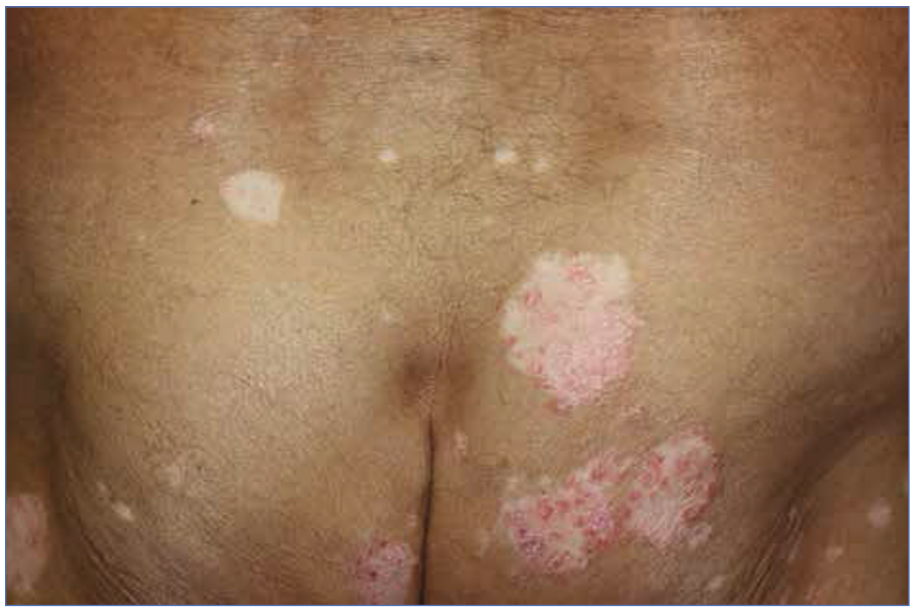
KEY REFERENCES

- Clayton R, Warin A. Pityriasis lichenoides chronica presenting as hypopigmentation. Br J Dermatol. 1979;100:297-302.
- Bowers S, Warshaw EM. Pityriasis lichenoides and its subtypes. J Am Acad Dermatol. 2006;55:557-72.

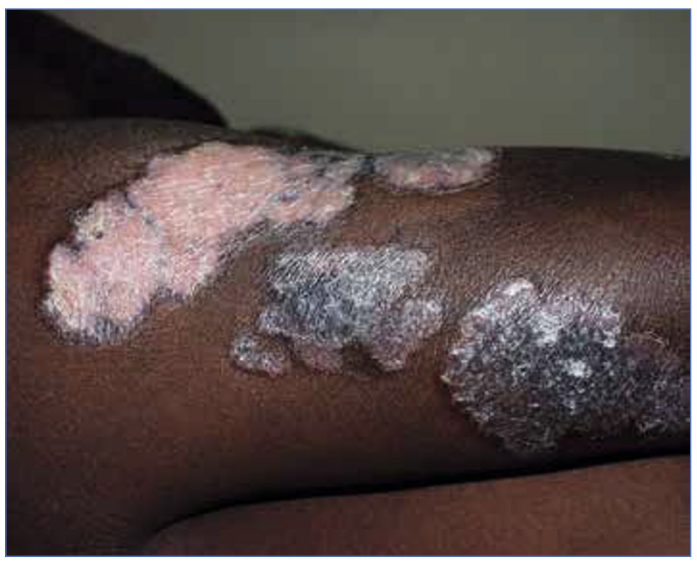
PSORIASIS



Hypopigmentation in small plaques of psoriasis. Some lesions still have a slight erythema.

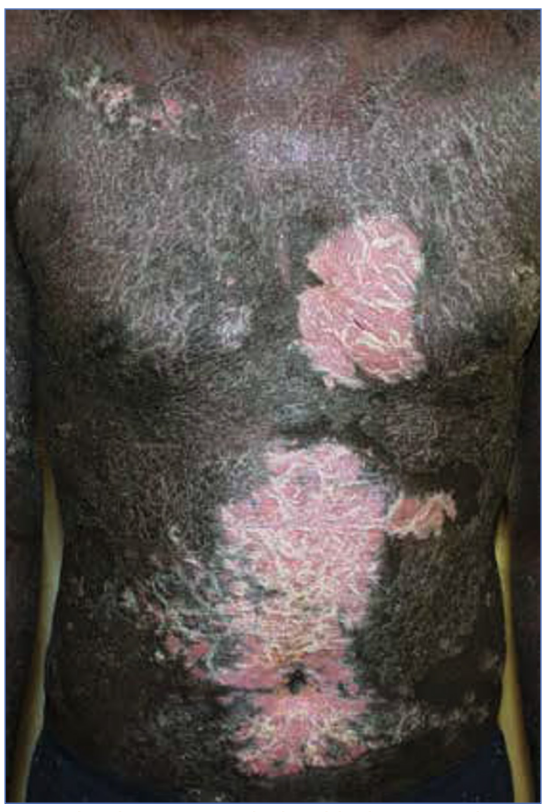


Psoriasis on vitiligo lesions. The achromy is highly suggestive of vitiligo and is against post-inflammatory hypopigmentation.



Hypopigmentation in plaque psoriasis. The lesions have well-defined borders. Note that the erythema is more visible in the hypochromic lesion.

Hypopigmentation in plaque psoriasis. The lesions are very active here and the diagnosis is obvious.



Generalized psoriasis. Only the older lesions are hypopigmented.

EPIDEMIOLOGY

Hypopigmentation is frequently observed in psoriasis occurring in dark skinned individuals.

PATHOPHYSIOLOGY

The hypopigmentation is in part post-inflammatory. However, it is also related to the increased keratinocyte turn-over, thus interfering with the melanosome transfer and increasing the elimination of the melanin contained in keratinocytes.

CLINICAL DERMATOLOGICAL PRESENTATION

Hypopigmented plaques with well-defined borders, following or associated with the typical erythematous and squamous lesions of psoriasis.
Vitiligo and psoriasis can be confined to the same areas. In this case the lesions are totally achromic.
The increased prevalence of psoriasis in vitiligo patients is still under debate. A recent review of reported cases does not support an increased prevalence.
None to mild pruritus.
Localization: knees, elbows, umbilicus and lumbar area are the localizations of predilection.

EXTRACUTANEOUS SIGNS

None.
Inflammatory arthralgias when rheumatoid psoriasis is associated.

HISTOPATHOLOGY

Reduced melanin contained in the basal layers of the epidermis.
Acanthosis, parakeratosis, proliferation of subepidermal vasculature and polymorphonuclear leukocytes and lymphocytes infiltrate in active lesions.

DIFFERENTIAL DIAGNOSIS

- Other post-inflammatory hypopigmentations such as pityriasis alba, mycosis fungoides, pityriasis lichenoides, sarcoidosis, leprosy, atopic dermatitis.

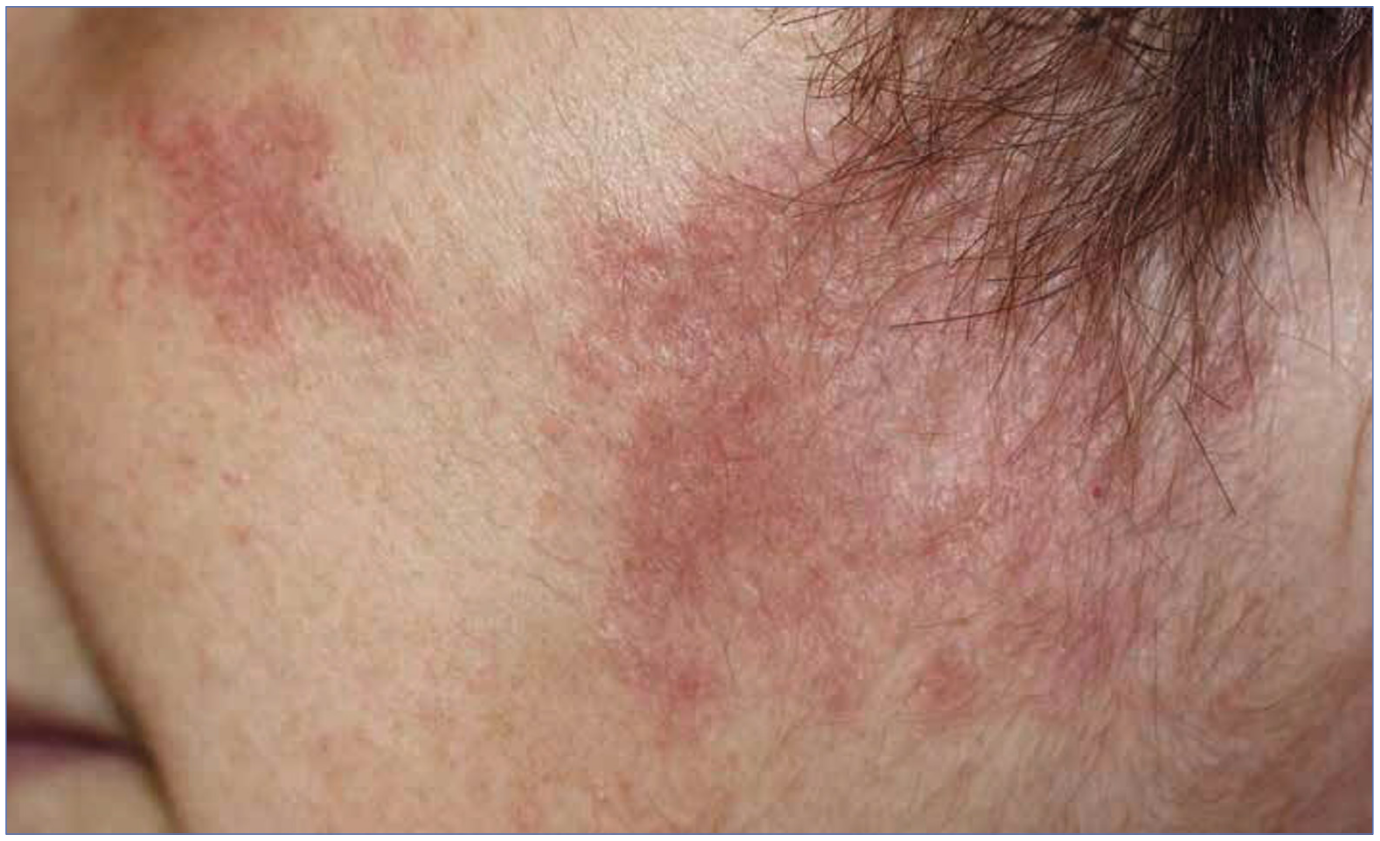
TREATMENT

Phototherapy is a treatment of choice when hypopigmentation is associated with psoriasis.
Topical steroids, topical vitamin D, acitretin, methotrexate, ciclosporin, and anti-tumor necrosis factor-alpha or anti-IL12/IL23 antibodies.

KEY REFERENCES

- Berger TG, Kiesewetter F, Maczek C, Bauer N, Lueftl M, Schuler G, Simon M Jr. Psoriasis confined strictly to vitiligo areas – a Koebner-like phenomenon? J Eur Acad Dermatol Venereol. 2006;20:178-83.
- Sawchuk M, Spano F, Loo WJ, Guenther L. The coexistence of psoriasis and vitiligo: a review. J Cutan Med Surg. 2012;16:300-5.

SARCOIDOSIS



Erythematous plaques of sarcoidosis with ill-defined borders. Note the slight hypopigmentation in the center of the larger lesion.

Small indurated hypopigmented papules of cutaneous sarcoidosis.

EPIDEMIOLOGY

Sarcoidosis affects mostly women in the third or fourth decade of life.
Hypopigmentation is a rare manifestation of cutaneous sarcoidosis and has been mostly reported in dark skinned patients.

PATHOPHYSIOLOGY

The pathogenesis of hypopigmentation in sarcoidosis is unknown. The melanocytes are not directly affected. Disturbance in the dermal epidermal interaction and in the vascularization both may play a role in this hypopigmentation.

CLINICAL DERMATOLOGICAL PRESENTATION

Hypopigmented macules, papules, plaques or nodules with circumscribed or ill-defined borders.
Erythema may be associated. Hyperpigmented borders have been described.
The size of the lesion can vary from 0.5 to several centimeters in diameter and the lesions can be indurated or not.
The lesions are asymptomatic.
Localization: arms and legs seem to be the most frequently affected but face and trunk can be involved.

EXTRACUTANEOUS SIGNS

Systemic sign of sarcoidosis such as fever, anorexia, arthralgias, dyspnea on exertion, cough, chest pain and cardiac or neurological manifestations can be associated.

HISTOPATHOLOGY

Decreased melanin contained in the epidermis and sarcoid granulomas.
The number of melanocytes is normal.

DIFFERENTIAL DIAGNOSIS

- Leprosy, lupus and mycosis fungoides are the main differential diagnoses.
- Other post-inflammatory hypopigmentations can be discussed.

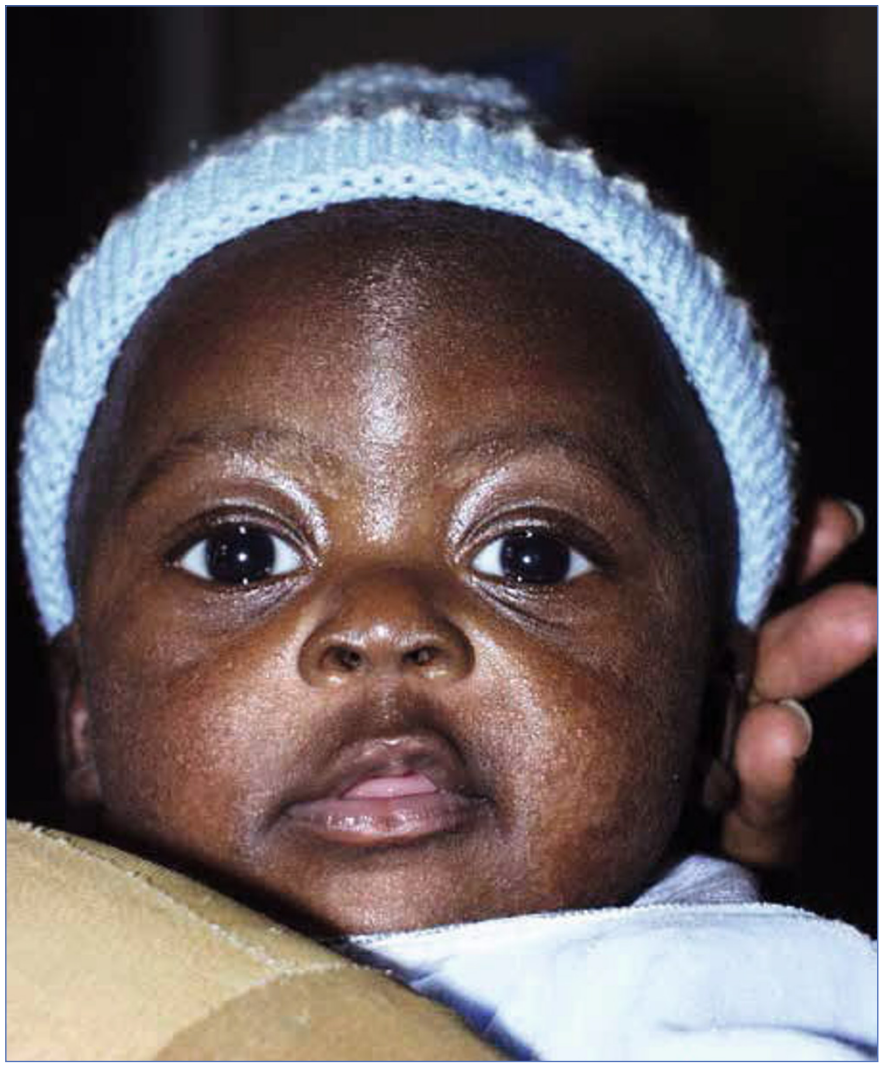
TREATMENT

The lesions poorly respond to topical steroids.
Anecdotal success has been reported with psoralen + UVA (PUVA) and minocycline.

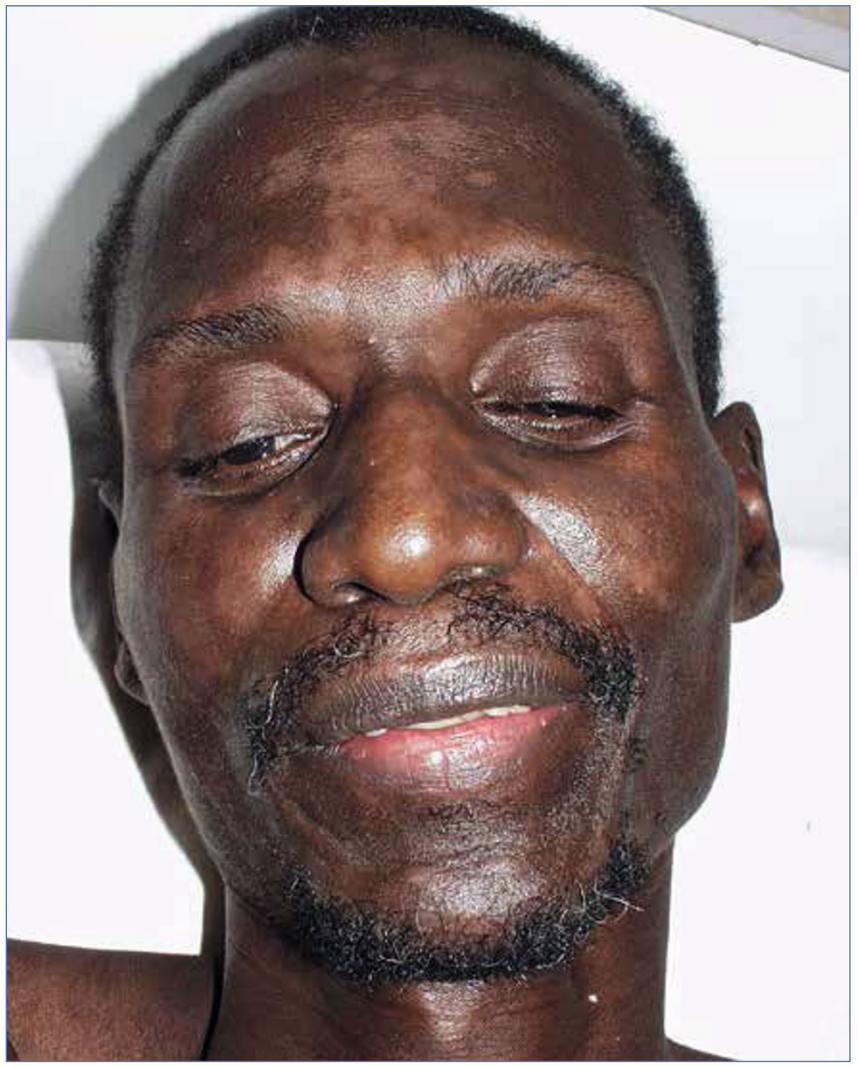
KEY REFERENCES

- Clayton R, Breathnach A, Martin B, Feiwel M. Hypopigmented sarcoidosis in the negro. Report of eight cases with ultrastructural observations. Br J Dermatol. 1977;96:119-25.
- Ortonne JP, Mosher D, Fitzpatrick T. Topics in dermatology: vitiligo and other hypomelanosis of hair and skin. New York: Plenum Medical Book Company. 1983:613-72.
- Schmitt CE, Fabi SG, Kukreja T, Feinberg JS. Hypopigmented cutaneous sarcoidosis responsive to minocycline. J Drugs Dermatol. 2012;11:385-9.

SEBORRHEIC DERMATITIS



Hypopigmented seborrheic dermatitis of the newborn.



Widespread hypopigmented seborrheic dermatitis in a patient with HIV.

EPIDEMIOLOGY

Very common (1 to 3% of general population).
Men are more affected than women.
Peaks of frequency in infants within the first 3 months of age and in young adults. The incidence increases again after the age of 50 years. Seborrheic dermatitis of the newborn and infant usually begins at 2 weeks of age.
Worsened by emotional stress and improves during summer.
All skin types can be affected, but hypopigmented lesions are more pronounced in dark skinned individuals.

PATHOPHYSIOLOGY

The localization on seborrheic areas and the increased frequency in period of life when sebaceous glands are most active suggest that the skin surface lipid composition should play a key role in the pathogenesis. Malassezia yeasts have been suspected but they are probably not the causative agent. Some authors suggested that Malassezia is incidental to a primary inflammatory dermatosis.
The hypopigmentation may be post-inflammatory, however, the toxic effects on pigment synthesis by fungal metabolites seems to play the most important role.

CLINICAL DERMATOLOGICAL PRESENTATION

Maculous, partly pityriasiform, scaly hypopigmented lesions.
The shape is usually geographic but annular or petaloid lesions can be observed.
Active lesions are branny or greasy scales over erythematous, inflamed skin.
Burning and itching is frequent in active phase.
Localization: highly suggestive of the diagnosis with lesions usually restricted on seborrheic areas (forehead, eyebrows, lash line, nasolabial folds, beard, postauricular skin and scalp. Presternal or interscapular involvement can be observed). Widespread lesions are observed in immunocompromised patients.

EXTRACUTANEOUS SIGNS

None.

HISTOPATHOLOGY

Reduced melanin contained in the basal layers of the epidermis.
Hyperkeratosis with parakeratosis, acanthosis, accentuated rete ridges, and focal spongiosis in active phase.

DIFFERENTIAL DIAGNOSIS

- Seborrheic psoriasis.
- Hypochromic vitiligo (vitiligo minor).
- Atopic dermatitis.

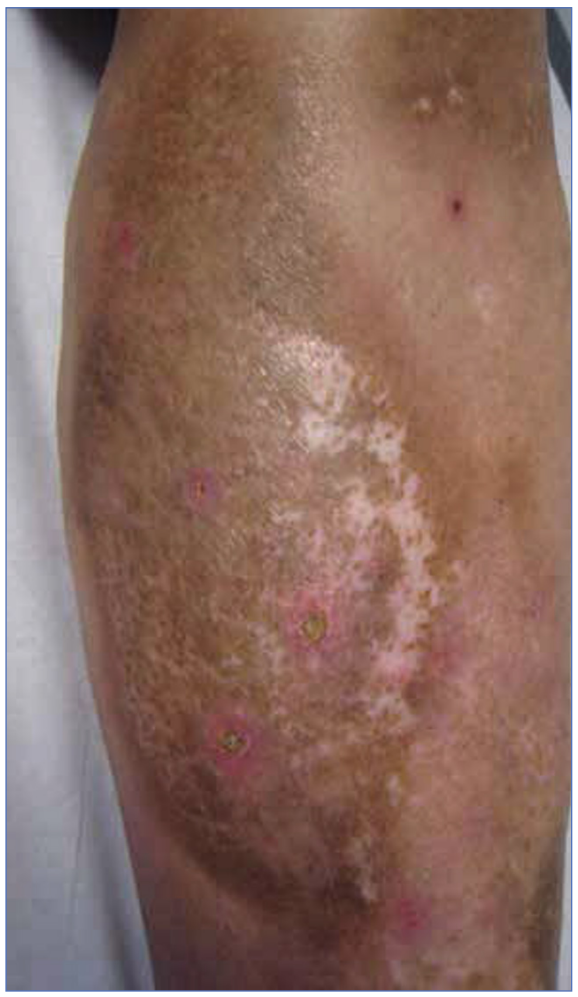
TREATMENT

Topical antifungals are the gold standard treatment of active phase. Topical lithium gel can be proposed.
Topical steroids should be used only for short-term use.
Topical calcineurin inhibitors can be useful.
Phototherapy or sun exposure for enhancing repigmentation when the active phase has been treated.

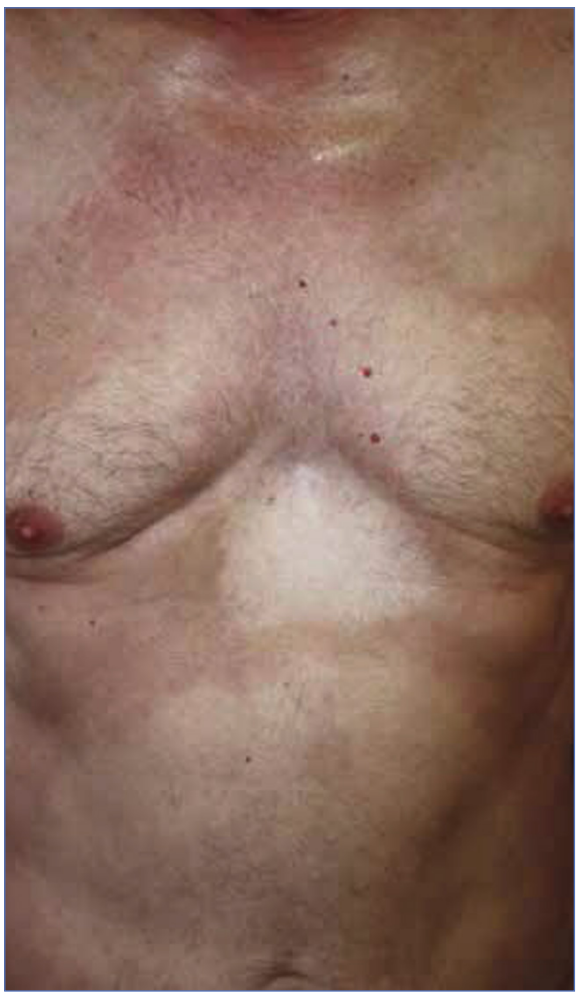
KEY REFERENCES

- Tajima M, Sugita T, Nishikawa A, Tsuboi R. Molecular analysis of Malassezia microflora in seborrheic dermatitis patients: comparison with other diseases and healthy subjects. J Invest Dermatol. 2008;128:345-51.
- Pedrosa AF, Lisboa C, Rodrigues AG. Malassezia infections: A medical conundrum. J Am Acad Dermatol. 2014;71:170-6.

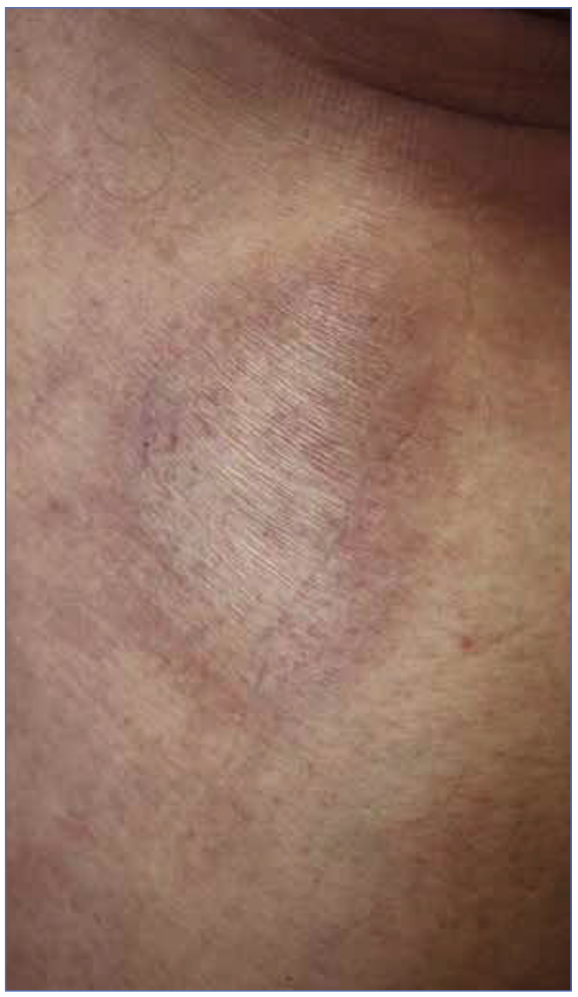
SYSTEMIC SCLERODERMA



Deep morphea of the leg with the association of hyper- and hypopigmentation.



Plaques of ivory color in late stage of diffuse superficial morphea.



Superficial morphea with active lilac ring. Note the hypopigmentation in the center of the lesion.

EPIDEMIOLOGY

Hypopigmentation occurs much less frequently than hyperpigmentation in morphea.
Leukoderma is quite common in areas of chronic sclerosis in dark skin patients.

PATHOPHYSIOLOGY

The pathogenesis of hypopigmentation in scleroderma is not well understood. The loss of melanocytes found in old lesion probably play a key role.

CLINICAL DERMATOLOGICAL PRESENTATION

After the initial erythematous-to-violaceous indurated plaques with violaceous border (lilac ring), superficial morphea can take on an ivory color over time.
Hypopigmentation can develop on areas of chronic sclerosis. Salt-and-pepper appearance is characterized by the presence of vitiligo-like depigmentation with perifollicular pigmentary retention. It is highly suggestive of systemic scleroderma and can be an early sign preceding the sclerosis.
The lesions are usually asymptomatic.

Localization: morphea can be observed in all part of the body. Anterior chest, legs, forearms and distally part of the fingers are more frequently concerned by the hypopigmentation observed in systemic scleroderma.

EXTRACUTANEOUS SIGNS

In morphea: systemic involvement is usually mild or absent. Restricted mobility can be observed in linear or deep morphea. Peripheral nerve involvement. Morphea en coup de sabre can affect the eyes and the oral cavity.
In systemic scleroderma: fatigue, weight loss, pulmonary hypertension, dyspnea, arthralgias, myalgias, joint contracture, restricted mobility, hypertension, renal crisis, chronic renal insufficiency.

HISTOPATHOLOGY

Decreased melanin contained within this epidermis and the number of monocytes is associated with a perifollicular pigment retention.

DIFFERENTIAL DIAGNOSIS

- Lichen sclerosus and atrophicus.
- Graft versus host disease.
- Vitiligo.
- Leprosy.
- Lupus.
- Mycosis fungoides.
- Other post-inflammatory hypopigmentations can be discussed.

TREATMENT

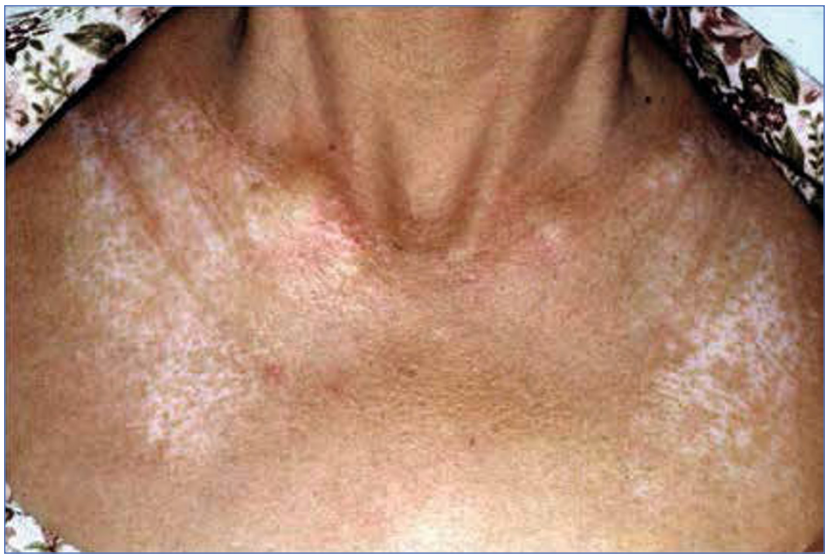
High potent topical steroid or tarcolimus for active and limited lesions.
Phototherapy (mainly PUVA or UVA1).
Methotrexate.
Systemic steroids.

KEY REFERENCES

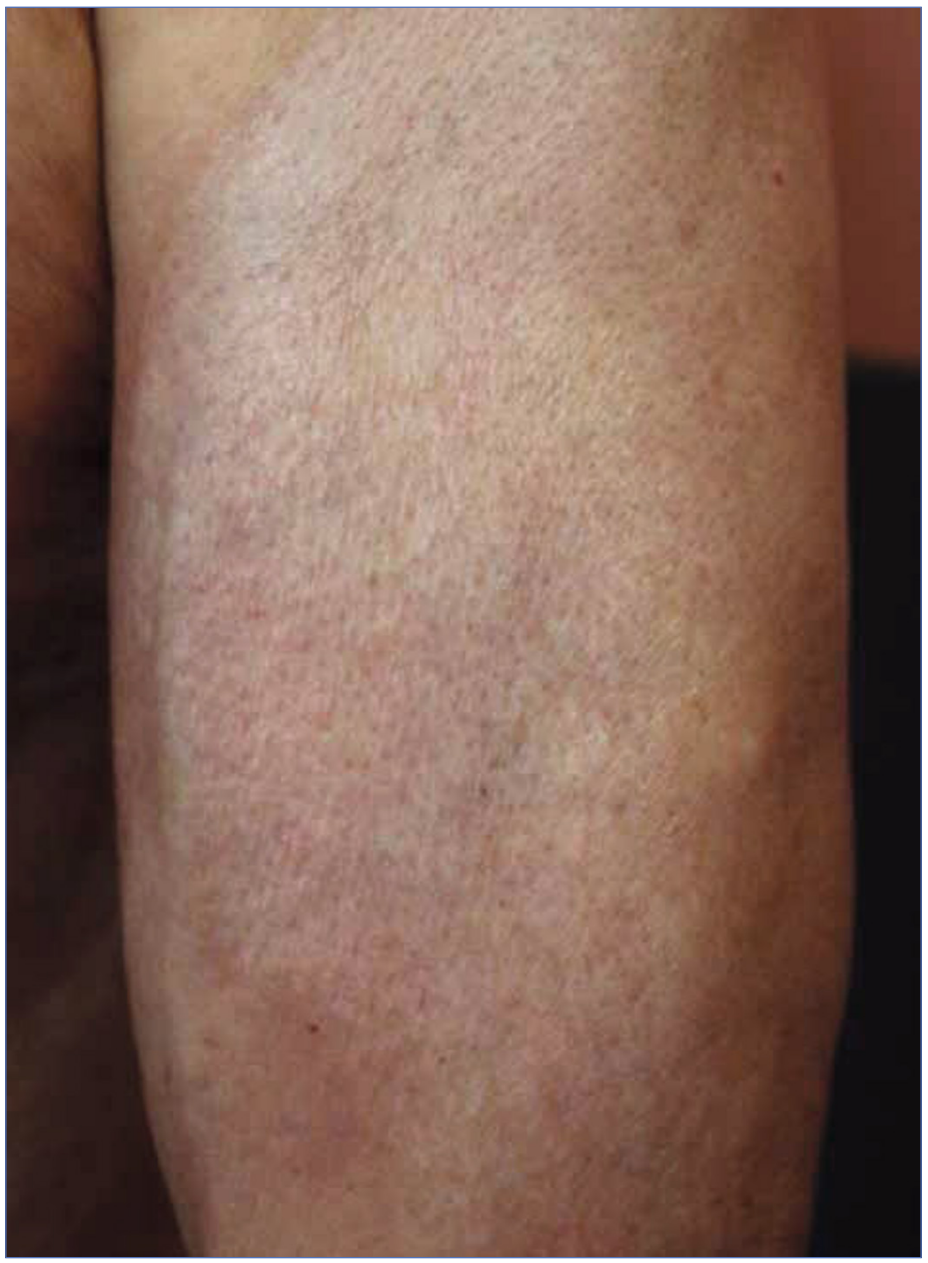
- Rai VM, Balachandran C. Pseudovitiligo in Systemic Sclerosis. Dermatol Online J. 2005;11:41.
- Ashish Singh, S Ambujam, Asha Varghese, S P Vishranth, Neenu Sadanandan Indian J Dermatol. 2012;57:412-413.

SYSTEMIC SCLERODERMA

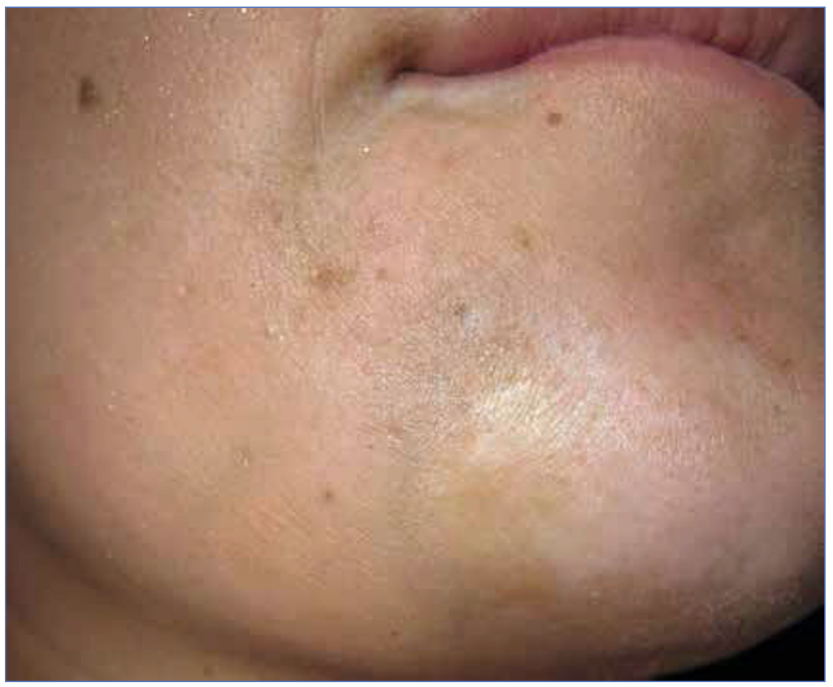
Hypopigmentation and sclerodactyly in systemic sclerosis.



Salt and pepper presentation in systemic scleroderma (coll. Goh Chee Leok).



In a fair-skinned patient, the salt and pepper aspect can be observed with a slight pigmentation around the hair follicles.

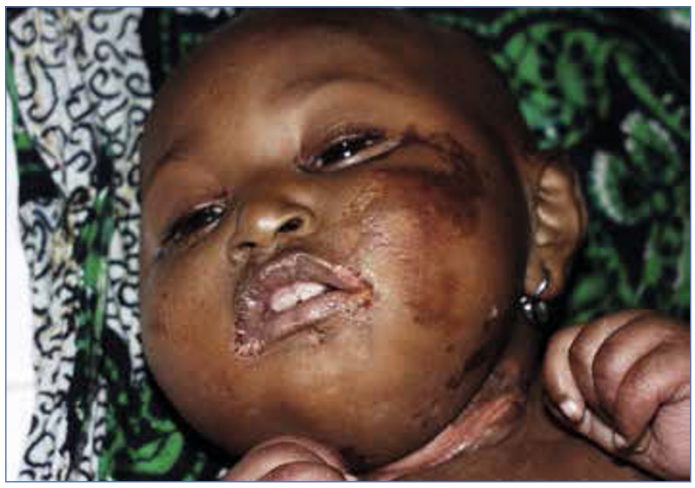


Vitiligoid depigmentation in morphea en coup de sabre. the presence of sclerosis is highly suggestive of the diagnosis.

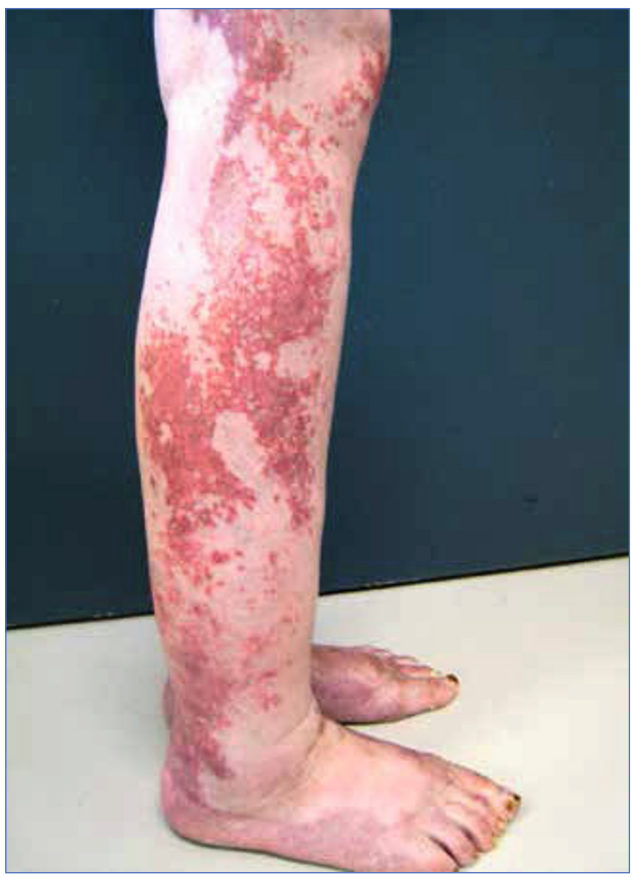
ACQUIRED HYPOMELANOSIS

Metabolic, nutritional and endocrine hypopigmentations

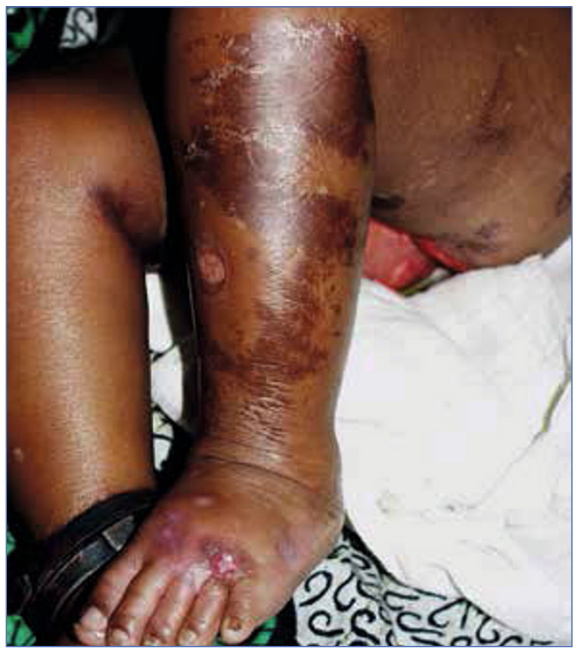
KWASHIORKOR



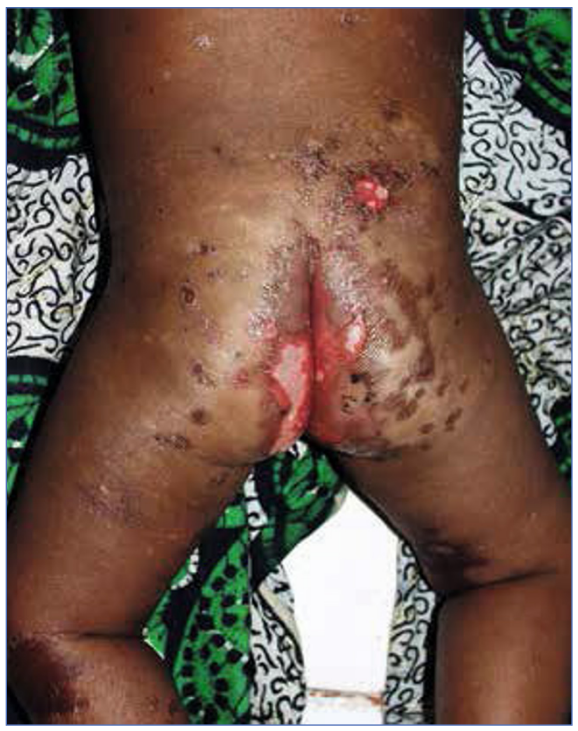
'Flaky paint' hyperpigmented patches of the cheeks associated with small hypopigmented macules. Note the superficial erosions on the neck fold, the angular cheilitis, and the edema of the face giving a 'moon face' appearance.



Erythematous and scaly patches of the leg with 'eczematous-like' presentation in a woman presenting kwashiorkor after a bypass surgery. Note the associated edema.



Hyperpigmented patches with 'flaky paint'appearance in an infant with kwashiorkor.



Hyperpigmented and scaly patches of kwashiorkor. Note the erosions on friction areas.

SYNONYMS

Protein-energy malnutrition.

EPIDEMIOLOGY

Kwashiorkor mainly affects children aged 6 months to 5 years of age. Adult cases can be reported, mainly after abdominal surgery.
Cutaneous manifestations are observed in more than 80% of patients with kwashiorkor. Dyschromic lesions are very common in kwashiorkor.

PATHOPHYSIOLOGY

The hypopigmentation could be due to a tyrosine deficiency. Altered oxidative properties appear to play a role in the hair hypopigmentation.

CLINICAL DERMATOLOGICAL PRESENTATION

Erythematous to red-brown hyperpigmented patches with marked desquamation giving an 'flaky paint' or 'crazy paving' aspect.
Superficial erosions predominantly on friction areas. Hyperpigmented post-inflammatory lesions are frequent when lesions heal.
Hypopigmented patches can be observed and usually begin on the face.
None to mild pruritus.
Localization: face, legs and areas of friction or pressure (the groin, behind the knees, on the buttocks, and at the elbows) are the most common localizations.
Angular cheilitis.
Dry and lusterless hairs that may become light red-brown in color.
Thinning and softening of nails.

EXTRACUTANEOUS SIGNS

Edema.
Retardation of growth.
Diarrhea.
Conjunctivitis and xerophtalmia.
Mental changes with irritability or apathy.
Muscle wasting.

HISTOPATHOLOGY

Reduced melanin contained in the basal layers of the epidermis in hypopigmented lesions, but increased in hyperpigmented patches. The number of melanocytes is normal.
Hyperkeratosis with atrophy of both the stratum granulosum and the prickle cell layers. Reduced collagen and elastic fibers in the dermis.

DIFFERENTIAL DIAGNOSIS

- Zinc deficiency syndrome.
- Atopic dermatitis.

TREATMENT

Protein supplementation.

KEY REFERENCES

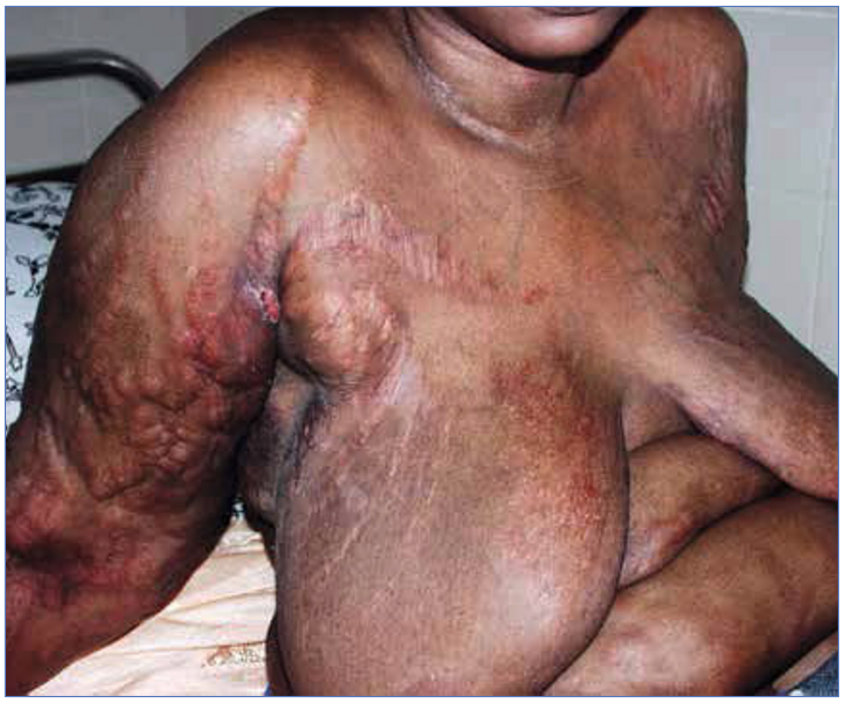
- Latham MC. The dermatosis of kwashiorkor in young children. Semin Dermatol. 1991;10:270-2.
- Ghorbel HH, Broussard JF, Lacour JP, Passeron T. Iatrogenic kwashiorkor developing after bypass surgery. Clin Exp Dermatol. 2014;39:113-4.
- Heilskov S, Rytter MJ, Vestergaard C, Briend A, Babirekere E, Deleuran MS. Dermatosis in children with oedematous malnutrition (Kwashiorkor): a review of the literature. J Eur Acad Dermatol Venereol. 2014;28:995-1001.

ACQUIRED HYPOMELANOSIS

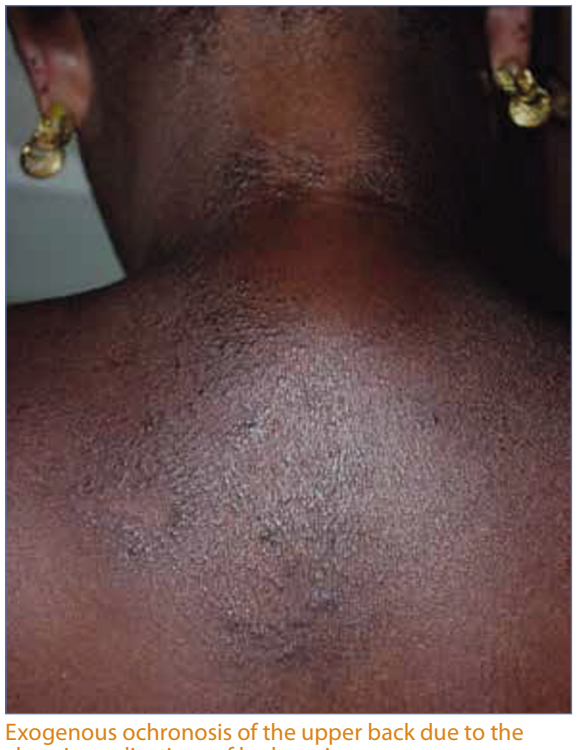
Iatrogenic hypopigmentations

COSMETIC USE OF SKIN BLEACHING PRODUCTS

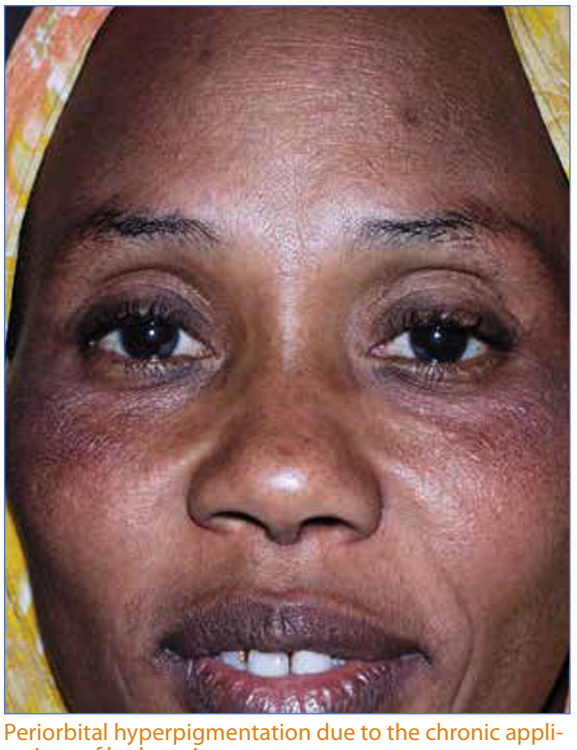
Cosmetic use of bleaching product on the face with contact dermatitis and exogenous ochronosis.



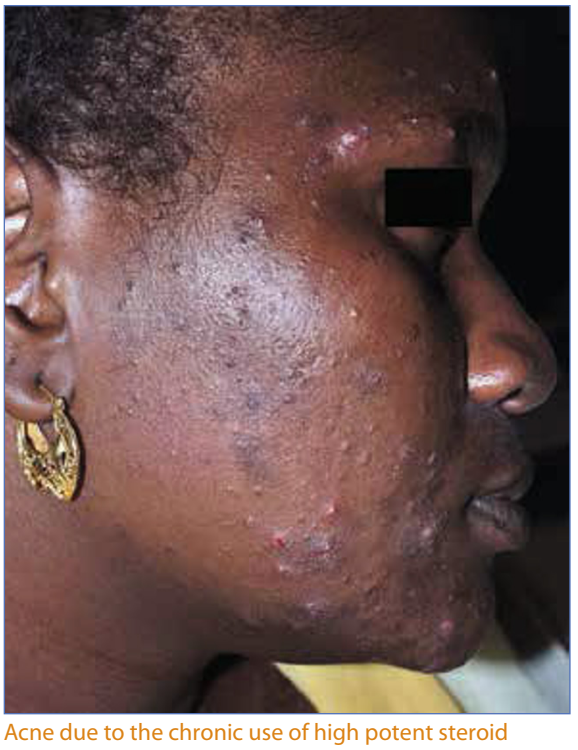
Chronic use of bleaching products on the entire body for more than 20 years. Note the android obesity associated with severe atrophy and striae.



Exogenous ochronosis of the upper back due to the chronic applications of hydroquinone.



Periorbital hyperpigmentation due to the chronic applications of hydroquinone.



Acne due to the chronic use of high potent steroid creams.

SYNONYMS

Cosmetic use of blanching products, Khessal.

EPIDEMIOLOGY

Common practice in dark-skinned women from sub-Saharan Africa. More than 52% of adult women admit to use of bleaching creams regularly in a study performed in Senegal.

PATHOPHYSIOLOGY

Daily or twice-daily applications of bleaching products on the face or larger surfaces.
Most of the time combination of several agents: hydroquinone, topical steroids, mercury, salts and caustic agents such as liquid soaps, hydrogen peroxide and salicylic preparations.

CLINICAL DERMATOLOGICAL PRESENTATION

Overall depigmentation with persistence of normal pigmentation in joints.
Others symptoms can be observed depending on product used:

- Caustics: skin irritation, contact dermatitis
- Steroids: acne, striae, telangiectasias, skin atrophy, extensive tinea corporis
- Hydroquinone: contact dermatitis, peri-orbital pigmentation, nails pigmentation, exogeneous ochronosis

EXTRACUTANEOUS SIGNS

Systemic symptoms of steroid use: android obesity, buffalo neck, high blood pressure, others signs of Cushing's syndrome.
Mercury intoxication: glomerular nephropathy, neurologic symptoms.

DIFFERENTIAL DIAGNOSIS

- Patients often consult for hyperpigmentation as they want to depigment the remaining pigmented areas. Careful examination is warranted to prevent unnecessary investigations.
- Cushing syndrome.

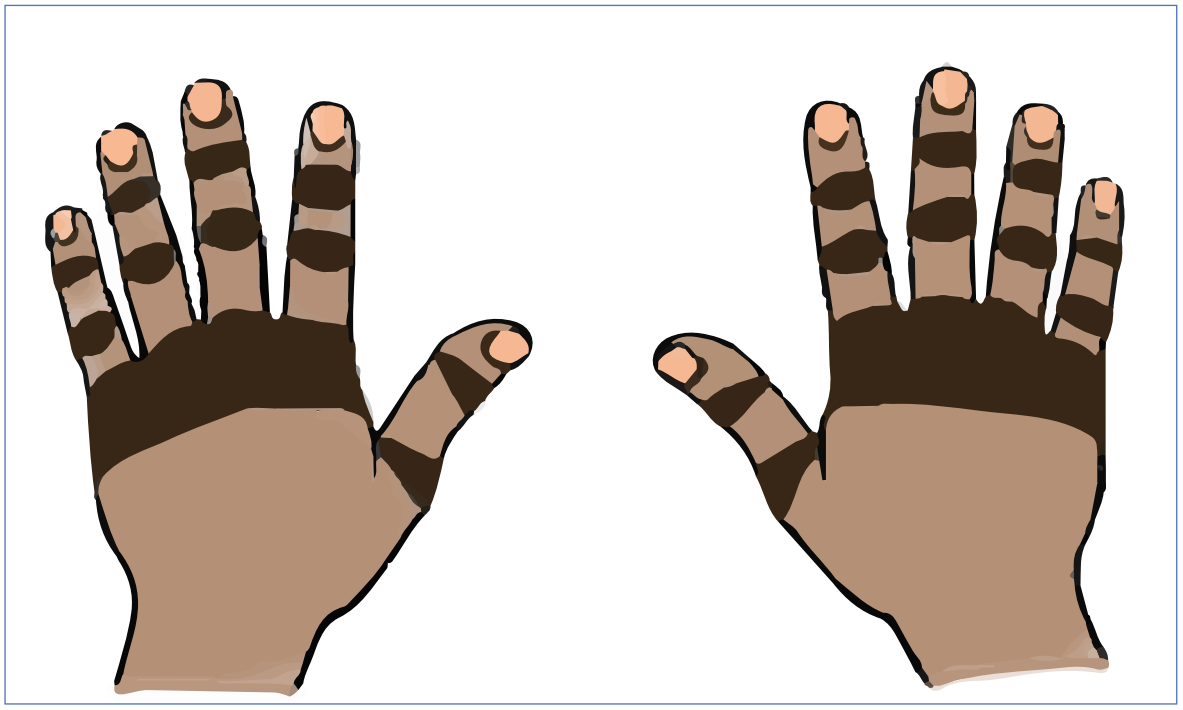
TREATMENT

Discontinuation of the bleaching agents.
Psychological support.
Prevention of adrenal insufficiency.

KEY REFERENCES

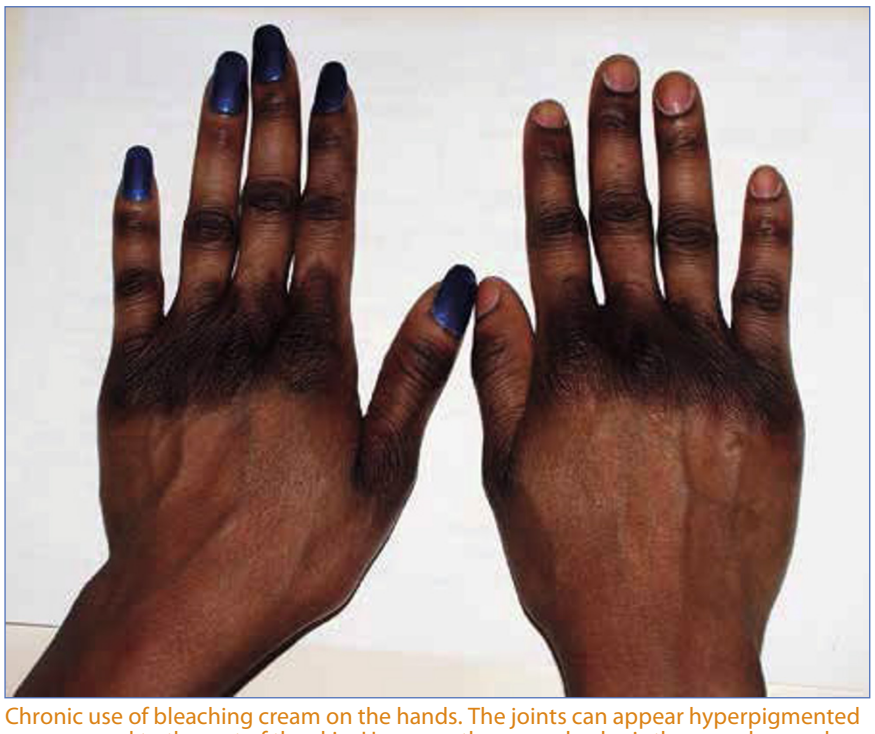
- Mahé A, Ly F, Aymard G, Dangou JM. Skin diseases associated with the cosmetic use of bleaching products in women from Dakar, Senegal. Br J Dermatol. 2003;148:493-500.
- Mahé A, Ly F, Perret JL. Systemic complications of the cosmetic use of skin-bleaching products. Int J Dermatol. 2005;44 (Suppl 1):37-8.

COSMETIC USE OF SKIN BLEACHING PRODUCTS

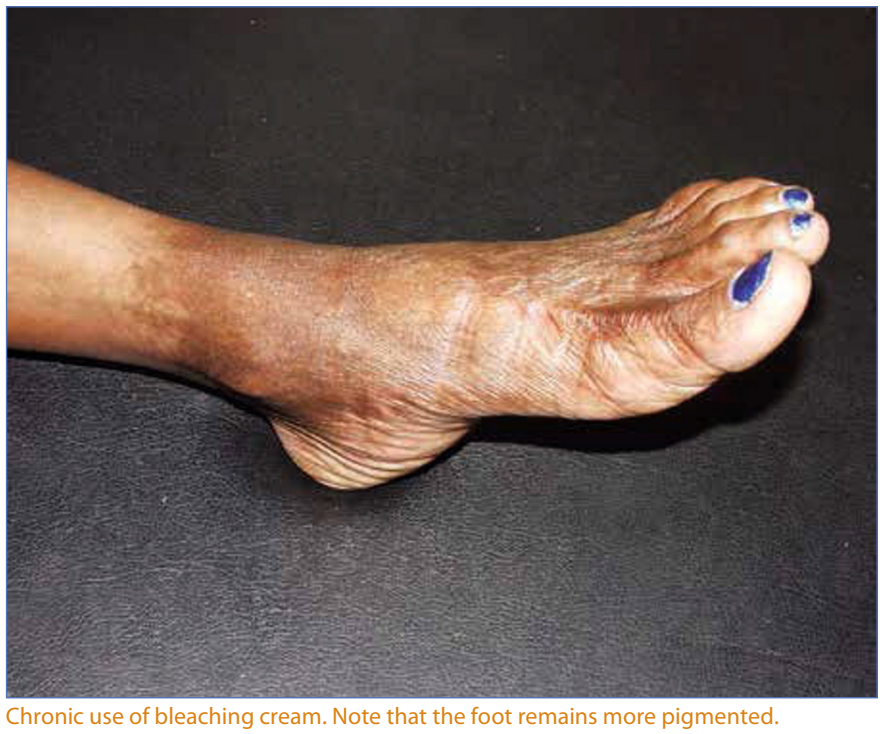


Schematic of typical aspect of use of bleaching cream on the hands.

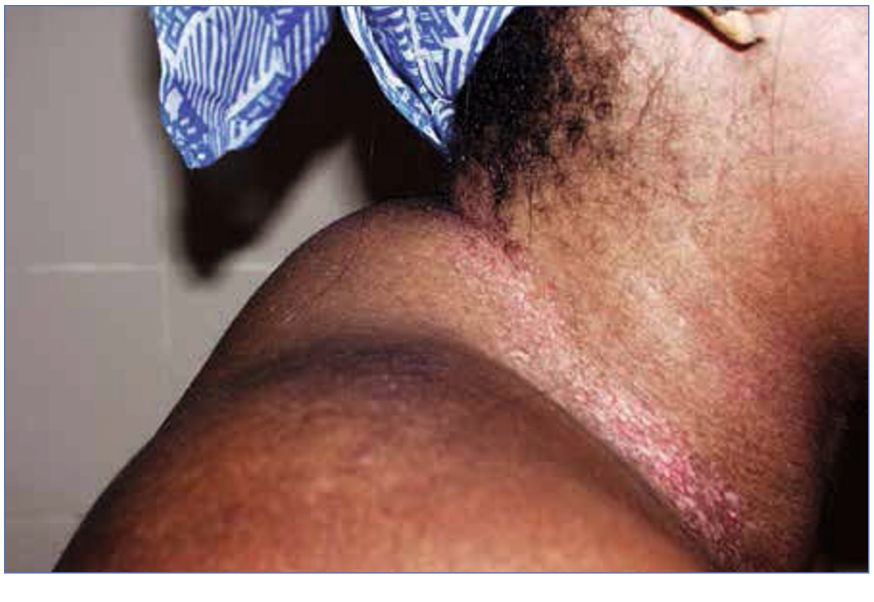
Schematic of typical aspect of use of bleaching cream on the feet.



Chronic use of bleaching cream on the hands. The joints can appear hyperpigmented as compared to the rest of the skin. However, the normal color is the one observed on the joints.



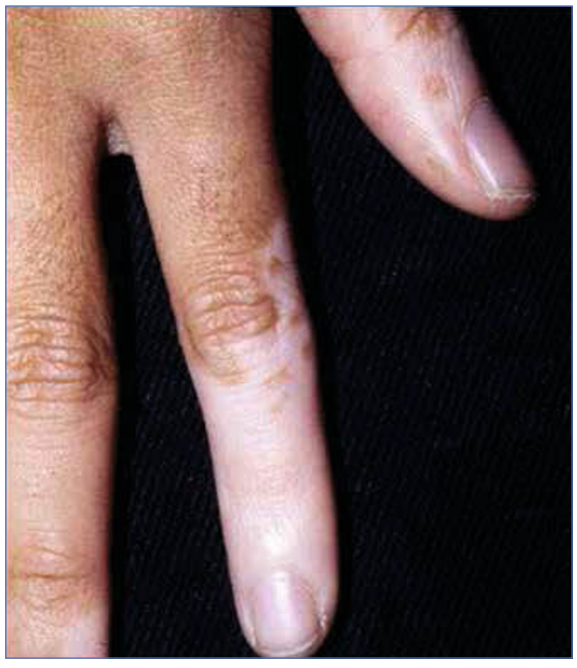
Chronic use of bleaching cream. Note that the foot remains more pigmented.



Buffalo neck due to the chronic use of high potent steroid on the entire body.

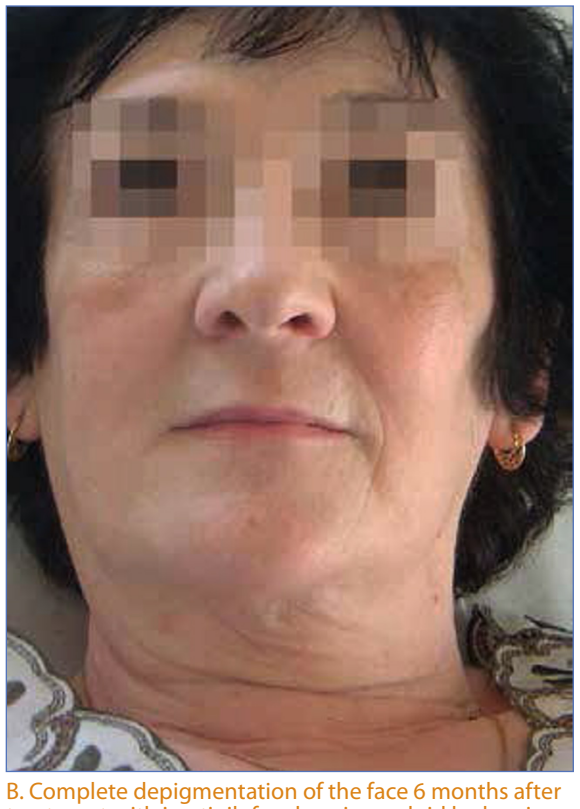
IATROGENIC HYPOPIGMENTATIONS SECONDARY TO PHARMACOLOGICAL AGENTS

Goh Chee Leok and Sai Yee Chuah



Chemical leucoderma from antioxidant in rubber gloves (coll. Goh Chee Leok).

A. Vitiligo of the face stable for years.



B. Complete depigmentation of the face 6 months after treatment with imatinib for chronic myeloid leukemia.

EPIDEMIOLOGY

Chemical leucoderma is a well-known phenomenon. Most of the topical skin whitening agents can cause leucoderma. With increasing numbers of new pharmacological agents and systemic tyrosine kinase inhibitors being used for treating medical conditions, there will probably be an increasing incidence of chemical leucoderma. Chemical leucoderma may occur at any age or with any gender. It may be seen more frequently and appears more dramatically in patients with darker skin type.

PATHOPHYSIOLOGY

A large number of chemical and pharmacological agents can cause hypomelanosis and leucoderma. The major chemical groups that cause leucoderma include:
Phenols/catechols (eg, hydroquinone and its derivatives MMEH, MBEH, para-phenylinediamines).
Sulfhydryls (eg, β-mercaptoethylamine hydrochloride [MEA]).
Miscellaneous (corticosteroids, tyrosine kinase inhibitors, imiquimod, etc).

Most chemical leucoderma have multiple pathologic mechanisms. It is postulated to occur due to a reduced number of skin melanocytes, enzymatic blockade of melanogenesis and inhibition of melanosome transfer.

Hypopigmentation or depigmentation specific to several tyrosine kinase inhibitors (imatinib, sunitinib, dasatinib and pazopanib) and antineoplastic agents including doxorubicin, imatinib, imiquimod, interferon-α, interferon-β, interleukin-2, interleukin-4, mitoxantrone, and survivin inhibitor have been reported. The proto-oncogene c-Kit mutations and blockade of the stem cell factor ligand and c-Kit signal transduction pathway of melanocytes has been postulated to be involved in the pathogenesis of the drug-induced hypopigmention or depigmentation. Imiquimod is an immune response modifier. Imiquimod is used to treat skin cancers (basal cell carcinoma, Bowen's disease and actinic keratosis) as well as genital warts (condylomata acuminata). Vitiligo-like skin depigmentation have been reported when used to treat BCC and extra mammary Paget's disease.

Topical or intralesional corticosteroids may also induce a loss of pigmentation. This loss of pigment results from the suppression of melanocytes in the production of melanin and normally is reversible over time.

CLINICAL DERMATOLOGICAL PRESENTATION

Chemical leucoderma are acquired hypopigmentation or depigmentation macules and patches that can occur as early as a few days to as long as 6 months after exposure to the associated medication/chemical. Some depigmentations appear as confetti or guttate hypopigmented macules while others may present as large confluent vitiligo-like skin depigmentation.

Intralesional corticosteroids may cause linear or stellate hypopigmentation that extends out from the original injection site as the steroid is taken up by lymphatics.

The lesions are asymptomatic.

EXTRACUTANEOUS SIGNS

None.

HISTOPATHOLOGY

Melanocytes are decreased or absent in lesional skin. A superficial perivascular lymphocytic infiltrate may be present in some instances.

DIFFERENTIAL DIAGNOSIS

- Vitiligo.
- Post-inflammatory hypopigmentation.
- Pityriasis alba.

TREATMENT

In patients who responded to the antineoplastic therapy, their drug treatment is often continued and even subsequently increased in dosage in spite of the progressive skin hypopigmentation. The hypopigmentation or depigmention appears reversible but some have persisted even after discontinuation of the associated drug.

Chemical eukoderma from skin contact with chemicals such as phenolic compounds eg, hydroquinone and paraphenylenediamine should be identified and removed from further contact. Hydroquinone induces a reversible hypopigmentation but its derivatives MMEH and MBEH often induce permanent irreversible depigmentation. Hydroquine may also induced skin darkening from ochronosis.

Vitiligo-like depigmentation from imiquimod tends to be unresponsive to treatment.

Hypopigmentation from corticosteroids may resolve over a period of months to years after discontinuation.

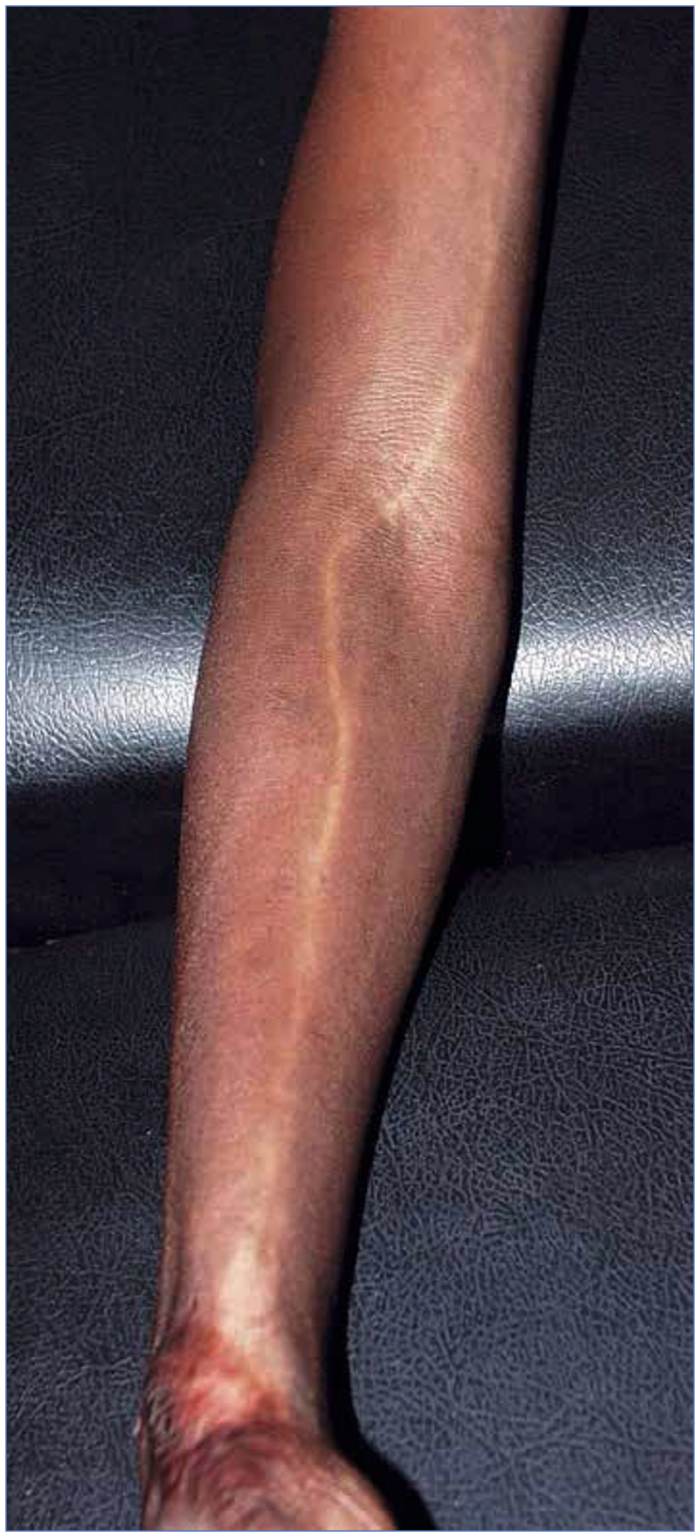
Sunlight or ultraviolet light may increase pigmentation.

KEY REFERENCES

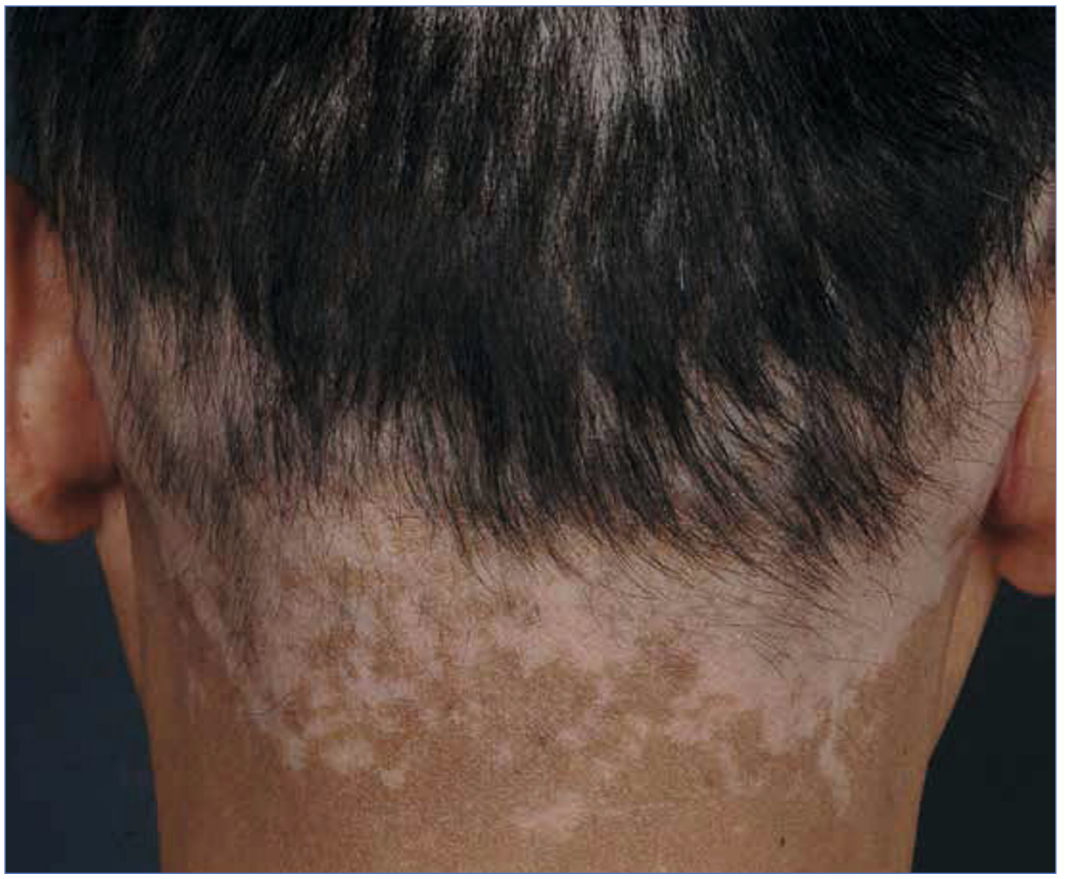
- Solano F, Briganti S, Picardo M, Ghanem G. Hypopigmenting agents: an updated review on biological, chemical and clinical aspects. Pigment Cell Res. 2006;19:550-71.
- Jalalat SZ, Cohen PR. Gefitinib-associated vitiligo: report in a man with parotid squamous cell carcinoma and review of drug-induced hypopigmentation. Dermatol Online J. 2013;19:200-20.
- Friedman SJ, Butler DF, Pittelkow MR. Perilesional linear atrophy and hypopigmentation after intralesional corticosteroid therapy. Report of two cases and review of the literature. J Am Acad Dermatol. 1988;19:537-41.
- H H Kwon, K H Cho. Induction of vitiligo-like hypopigmentation after imiquimod treatment of extramammary Paget's disease. Ann Dermatol. 2012;24:482-4.

IATROGENIC HYPOPIGMENTATIONS SECONDARY TO PHARMACOLOGICAL AGENTS

Goh Chee Leok and Sai Yee Chuah



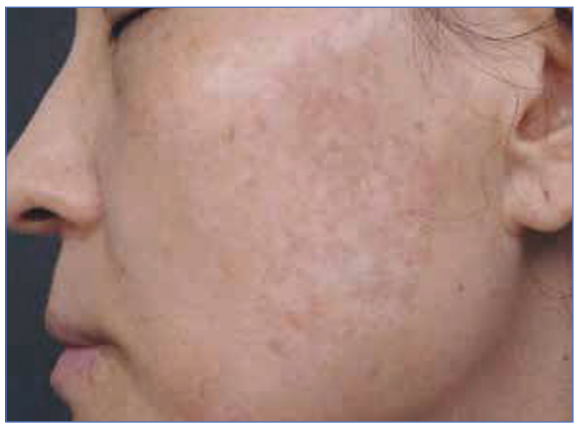
Linear hypopigmentation extending out from the original injection site of intralesional steroids (made for treating a keloid) at the wrist and following lymphatics.



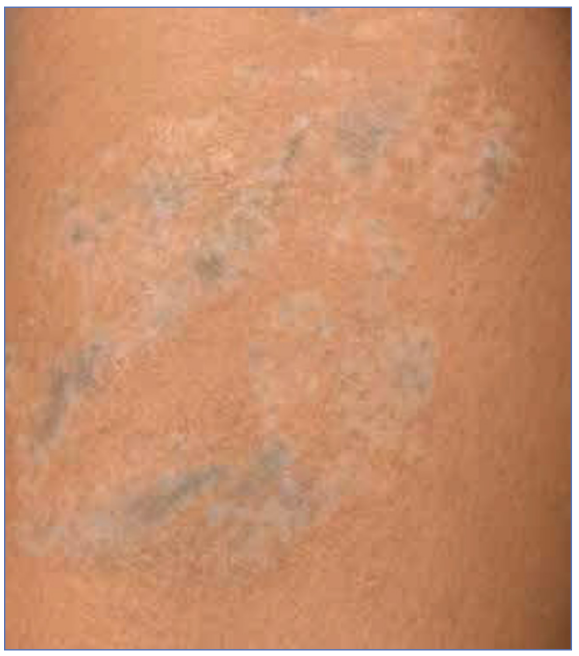
Hypopigmentation after diphenylcyclopropenone (DPCP) application for alopecia areata (coll. Yee Young Kang).

IATROGENIC HYPOPIGMENTATIONS SECONDARY TO PHYSICAL OR TOXIC AGENTS

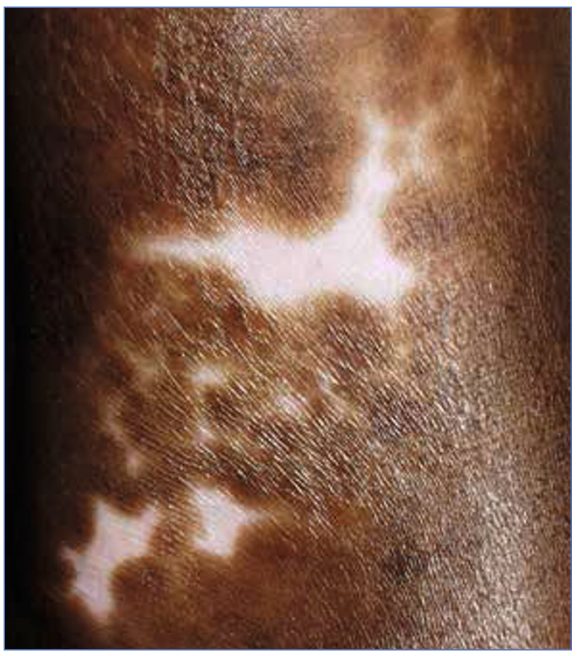
Goh Chee Leok and Sai Yee Chuah



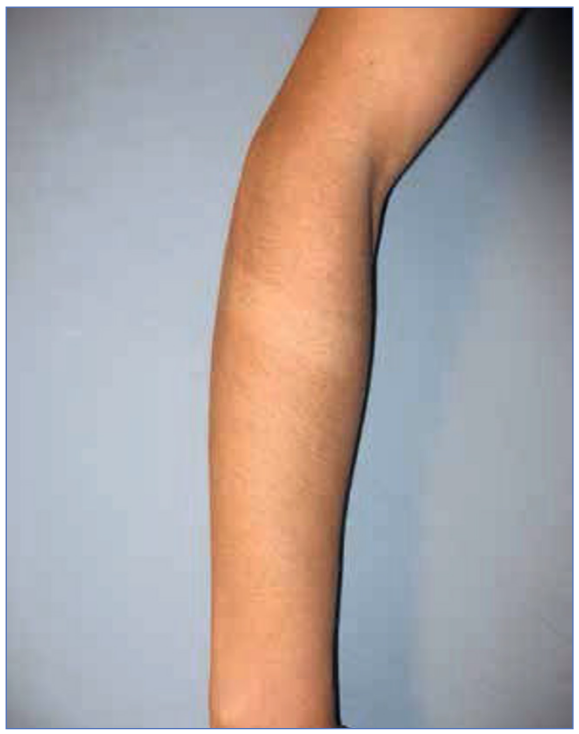
Leukoderma after laser toning for melasma (coll. Hee Young Kang).



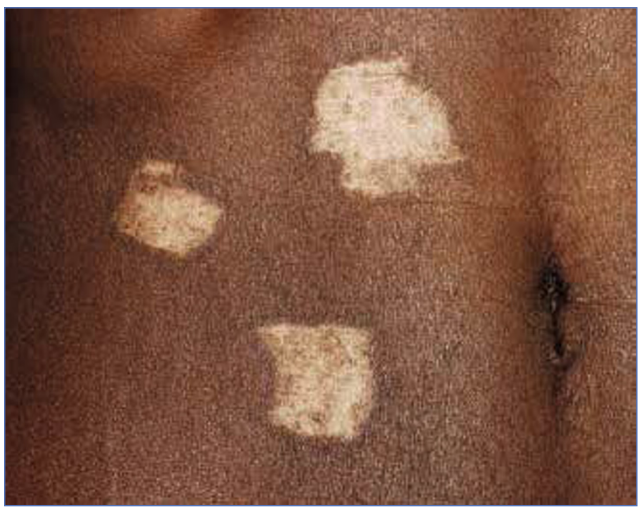
Hypopigmentation after the use of Q-switched laser for tattoo removal (coll. Hee Young Kang).



Hypopigmentation of the leg following thermal burn.



Hypopigmentation following the use of adhesive tape.



Hypopigmented lesions following application of 'points of fire' (limited thermal burns used in traditional medicine in some countries, here 'to treat' hepatitis). Note at the periphery of the lesions the hyperpigmentation due to mild thermal injury that induced hyperpigmentation while the center of the lesion that suffered the most is hypopigmented.

EPIDEMIOLOGY

Although only a few cases have been reported, the condition is quite common.
It may occur at any age or gender. It is seen more frequently and appears more dramatically in patients with darker skin types.

PATHOPHYSIOLOGY

Various types of physical injuries and toxic agents may cause cutaneous hypopigmentation or depigmentation. These include:

- Thermal burns.
- Freezing (from cryotherapy).
- Lasers (Q-switched pigment lasers).
- Ionizing radiation.
- Physical trauma from surgical procedure.
- Toxic agents (eg, amyl nitrite in inhaled recreational drug, pyrethroid insecticides).

Hypopigmentation may occur due to direct destruction of melanocytes. Repetitive exposure to these physical or toxic agents may induce melanocyte toxicity via tyrosinase-related protein-1 (Tyrp1), which catalytically converts these chemicals within melanocytes and leads to production of reactive oxygen species. It is hypothesized that the genetic inability of melanocytes to respond to Tyrp1 medicated oxidative stress by producing free radical scavenging to prevent apoptosis of melanocytes explains why only certain patients will develop hypopigmentation or depigmentation upon exposure.
Guttate leucoderma and vitiligo-like depigmentation can occur from repeated pigment lasers eg, Q-switch Nd:YAG laser treatment used for 'laser toning' for melasma. This may be seen in patients treated with the pigment laser for melasma, naevus of Ota or tattoo removal.

CLINICAL DERMATOLOGICAL PRESENTATION

Acquired hypopigmentation or depigmentation macules and patches may occur following skin injury by physical or toxic agents. The shape of the hypopigmentation and associated findings usually makes the diagnosis straightforward.
Pigment laser-induced leucoderma tends to occur following repeated treatment at short intervals usually over several months. They appear initially as guttate hypopmelanotic macules. Later the hypopigmented macules may expand to develop vitiligo-like patches. The hypopigmented macules are asymptomatic.

EXTRACUTANEOUS SIGNS

None.

HISTOPATHOLOGY

Melanocytes are decreased or absent in lesional skin. A superficial perivascular lymphocytic infiltrate may be present in some instances.

DIFFERENTIAL DIAGNOSIS

- Vitiligo.
- Post-inflammatory hypopigmentation.

TREATMENT

Avoidance of the causative agent may lead to spontaneous repigmentation.
Grafts are usually the best option.
Phototherapy, eg, sun exposure, narrowband UVB, psoralen + UVA, excimer lamp or excimer laser, and topical corticosteroid, or topical calcineurin inhibitor (eg, tacrolimus, pimecrolimus) can be proposed.

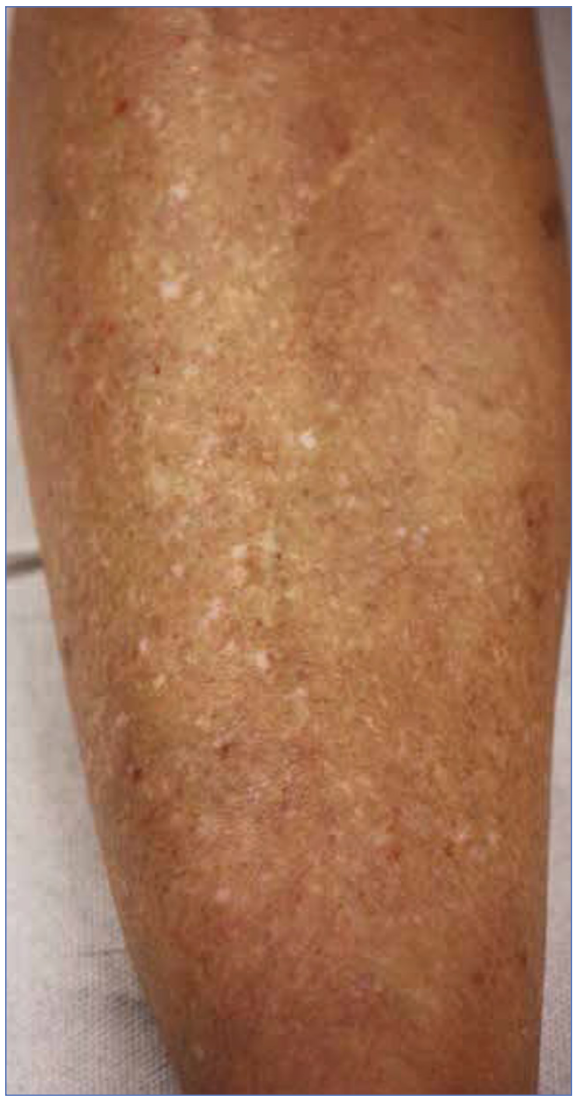
KEY REFERENCES

- Vine K, Meulener M, Shieh S, Silverberg NB. Vitiliginous lesions induced by amyl nitrite exposure. Cutis. 2013;91:129-36.
- O'Reilly KE, Patel U, Chu J et al. Chemical leukoderma. Dermatol Online J. 2011;17:29.
- Chan NP, Ho SG, Shek SY, Yeung CK, Chan HH. A case series of facial depigmentation associated with low fluence Q-switched 1,064 nm Nd:YAG laser for skin rejuvenation and melasma. Lasers Surg Med. 2010;42:712-9.

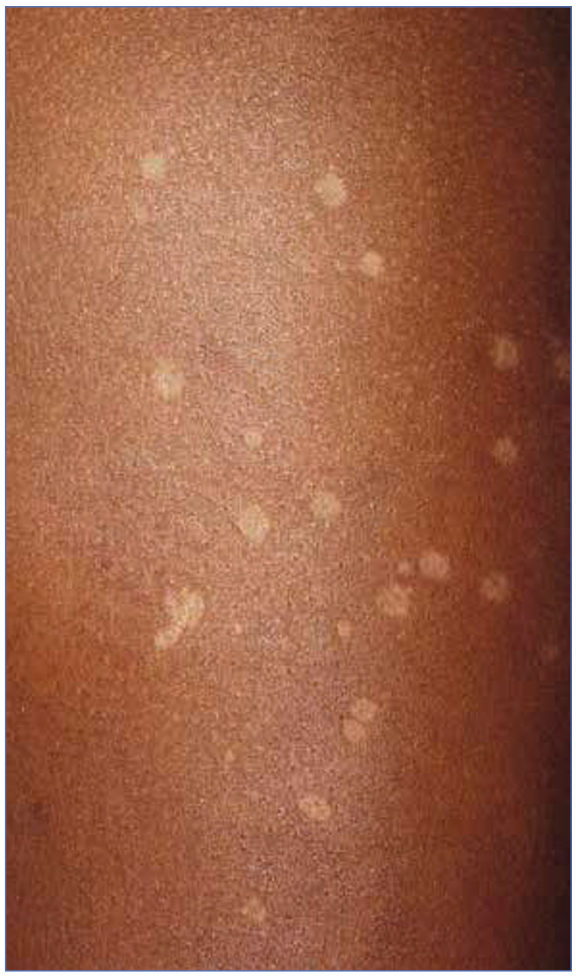
ACQUIRED HYPOMELANOSIS

Miscellaneous hypomelanosis

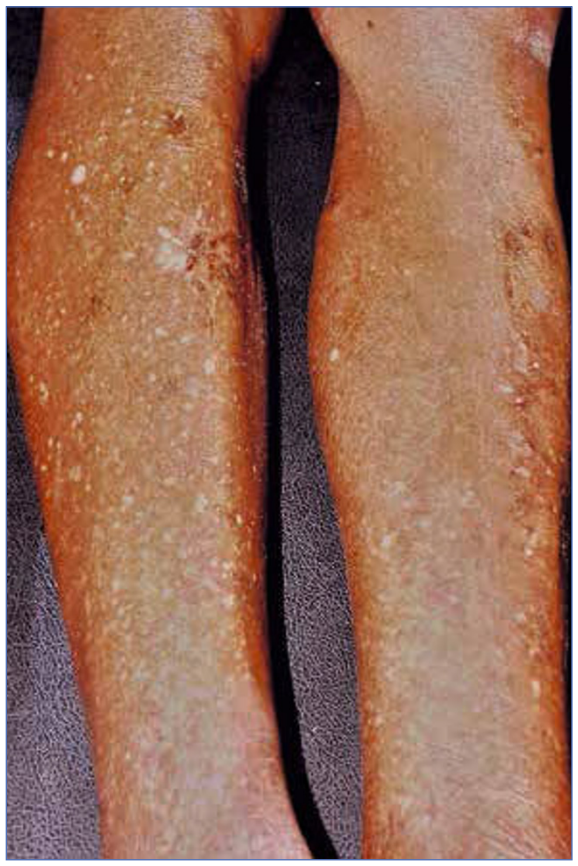
IDIOPATHIC GUTTATE HYPOMELANOSIS



Idiopathic guttate hypomelanosis of the leg.



Close-up of lesions of idiopathic guttate hypomelanosis.



Widespread lesions of idiopathic guttate hypomelanosis on the legs.

SYNONYMS

Leukopathia guttata et reticularis symetrica, leukodermia lenticularis disseminada, macular hypopigmentation of the legs in women, senile depigmented spots.

EPIDEMIOLOGY

Very common with incidence increasing with age (up to 80% in patients after 40 years of age).
While some studies report a female predilection, other found an equal prevalence between both sexes.
More frequent in fair-skinned people.

PATHOPHYSIOLOGY

Not well known. Chronic sun exposure appears to be the main causative agent. Repeated microtrauma to skin may also have an impact.

CLINICAL DERMATOLOGICAL PRESENTATION

Multiple (a dozen to more than 100) small round or angular hypopigmented or depigmented macules.
Size usually varies from 1 to 6 mm.
Larger lesions can be observed.
Localization: mostly on chronically sun-exposed areas with a predilection for the legs (anterior face) then forearms.

EXTRACUTANEOUS SIGNS

None.

HISTOPATHOLOGY

Decrease or absence of melanocytes, with a marked decrease in DOPA reaction. Ultrastructural studies showed that some melanocytes have no or only few immature melanosomes.
The epidermis can be normal or atrophic.

DIFFERENTIAL DIAGNOSIS

- Punctate vitiligo.
- Lichen sclerosus and atrophicus.
- Warts.
- Leukoderma punctata.

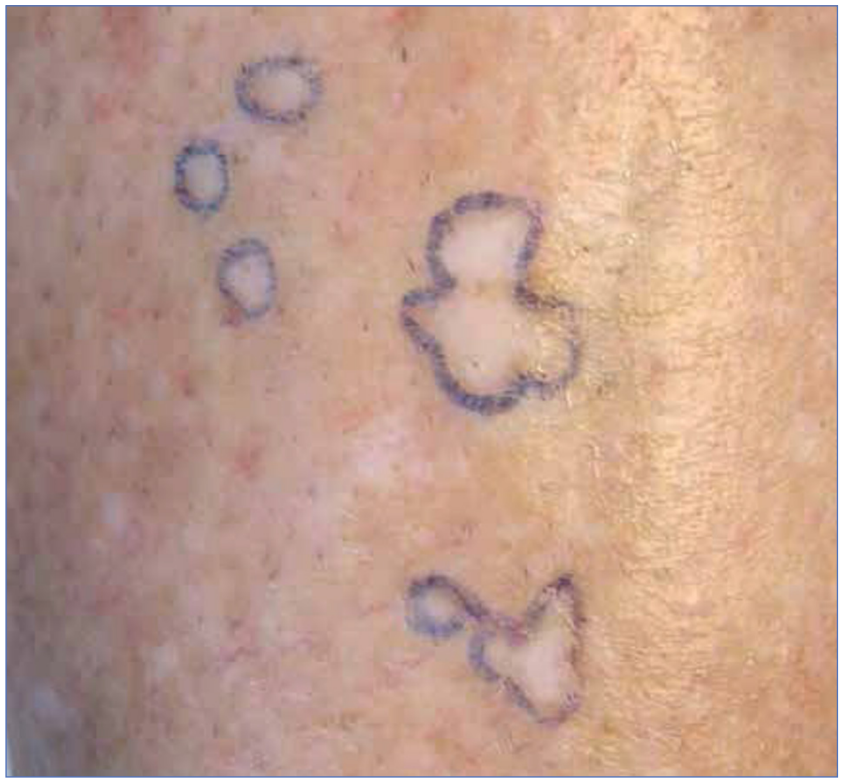
TREATMENT

The most effective treatment is the careful destruction of the lesion using trichloracetic acid, liquid nitrogen, or superficial dermabrasion. More recently, case series report the potential usefulness of fractional CO_2 lasers. Topical tretinoin, topical steroids and topical calcineurin inhibitor (tacrolimus, pimecrolimus) can be proposed.

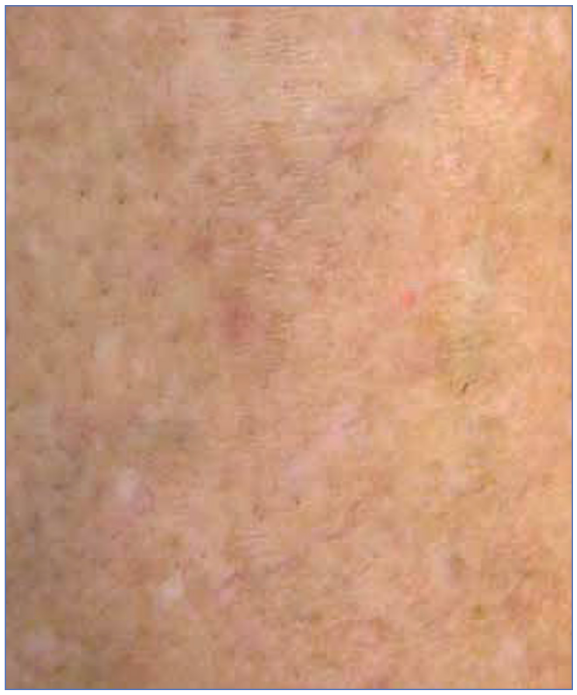
KEY REFERENCES

- Ortonne JP, Perrot H. Idiopathic guttate hypomelanosis. Ultrastructural study. Arch Dermatol. 1980;116:664-8.
- Shin MK, Jeong KH, Oh IH, Choe BK, Lee MH. Clinical features of idiopathic guttate hypomelanosis in 646 subjects and association with other aspects of photoaging. Int J Dermatol. 2011;50:798-805.
- Rerknimitr P, Disphanurat W, Achariyakul M. Topical tacrolimus significantly promotes repigmentation in idiopathic guttate hypomelanosis: a double-blind, randomized, placebo-controlled study. J Eur Acad Dermatol Venereol. 2013;27:460-4.
- Shin J, Kim M, Park SH, Oh SH. The effect of fractional carbon dioxide lasers on idiopathic guttate hypomelanosis: a preliminary study. J Eur Acad Dermatol Venereol. 2013;27:e243-6.

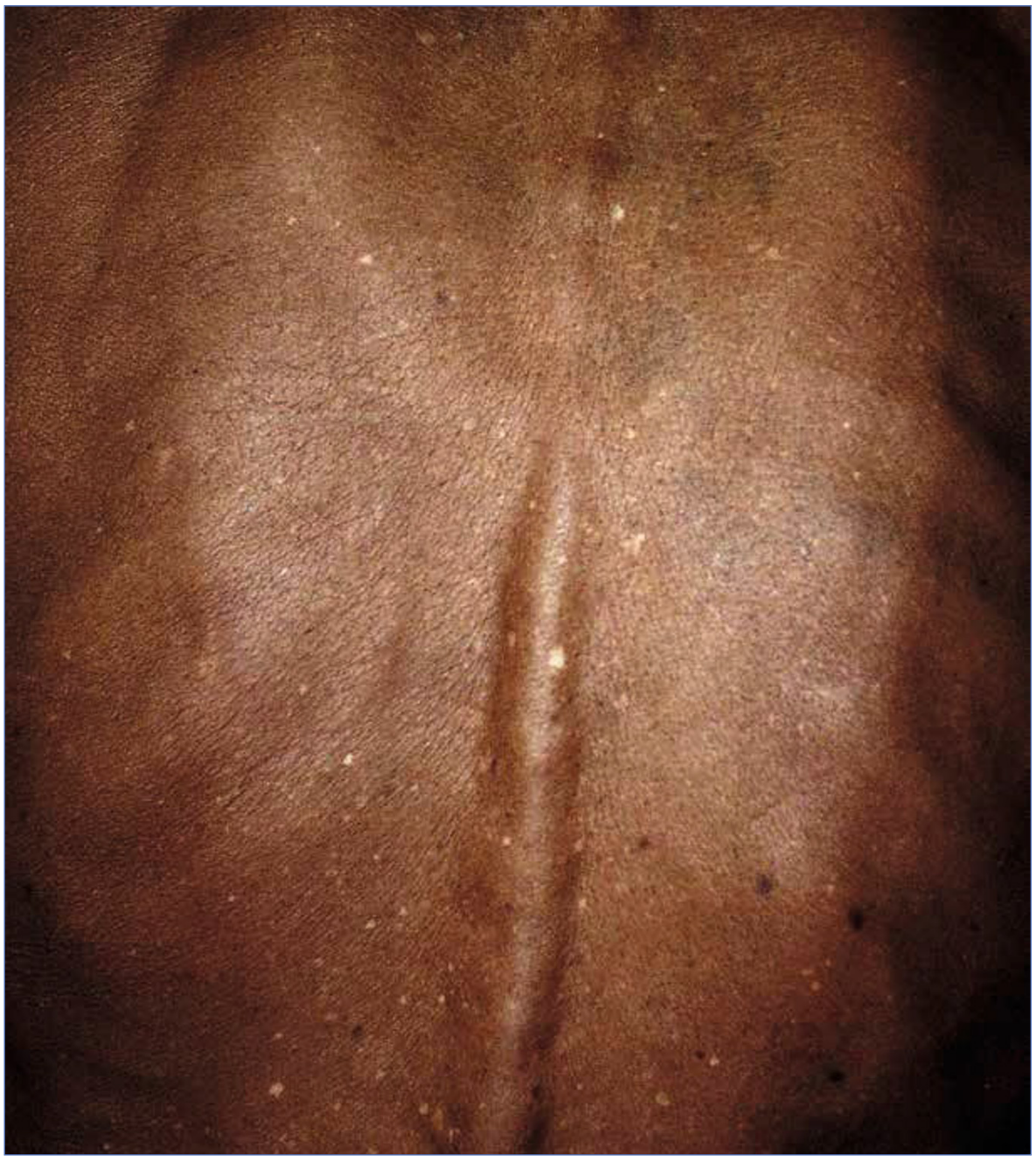
IDIOPATHIC GUTTATE HYPOMELANOSIS



A. Idiopathic guttate hypomelanosis of the leg before treatment with erbium laser-assisted dermabrasion (only the circled lesions are treated).



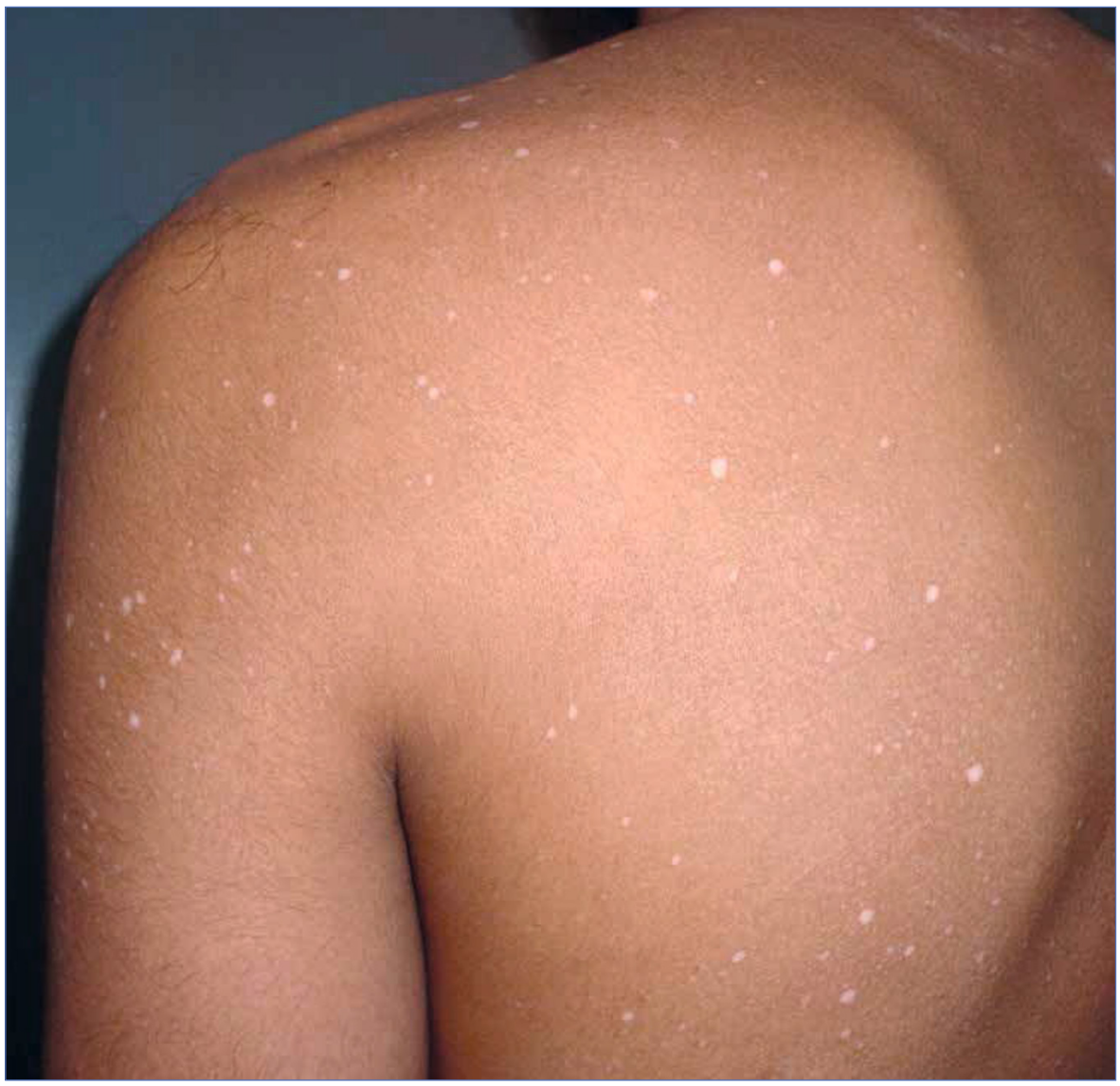
B. Clinical aspect 6 months after one session. Note the clear improvement of the treated lesions while untreated remained stable.



Idiopathic guttate hypomelanosis. Involvement of the back.

LEUKODERMA PUNCTATA

M. Sendhil Kumaran and Davinder Parsad



Multiple hypopigmented punctate macules of the back occurring after puvatherapy (coll. M. Sendhil Kumaran and Davinder Parsad).

EPIDEMIOLOGY

Leukoderma punctata was initially described by Falabella et al in 1988.
Seems more frequent in females.
Its occurrence is rare and any age can be affected.

PATHOPHYSIOLOGY

Falabella et al hypothesized that the probable etiology of leukoderma punctata was psoralen and natural phototoxicity of ultraviolet A and B (UVA-UVB).

CLINICAL DERMATOLOGICAL PRESENTATION

Multiple hypopigmented or depigmented, punctate macules.
Appear during and after PUVA-sol treatment in vitiligo.

EXTRACUTANEOUS SIGNS

None.

HISTOPATHOLOGY

DOPA and Fontana Masson staining demonstrates a reduced quantity but not absence of functional melanocytes, ultrastructural studies showed cell intracellular damage keratinocytes and melanocytes.

DIFFERENTIAL DIAGNOSIS

- Idiopathic guttate hypomelanosis is the principal differential diagnosis.

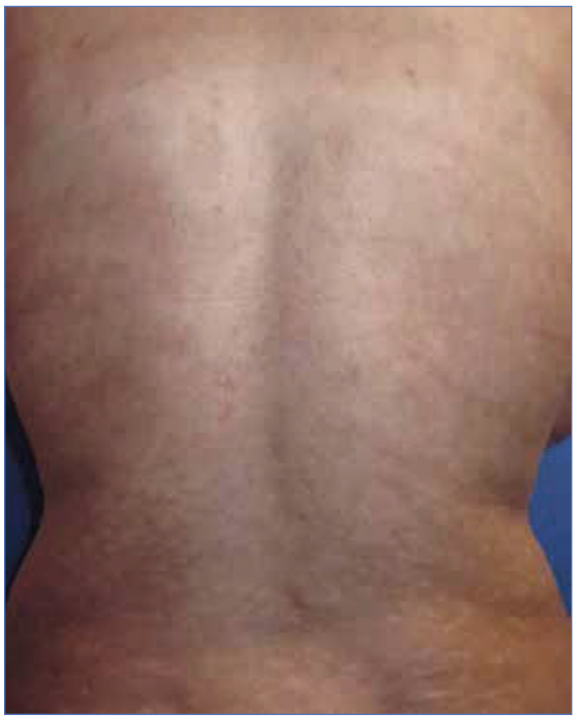
TREATMENT

No treatment has been proposed so far in the literature.

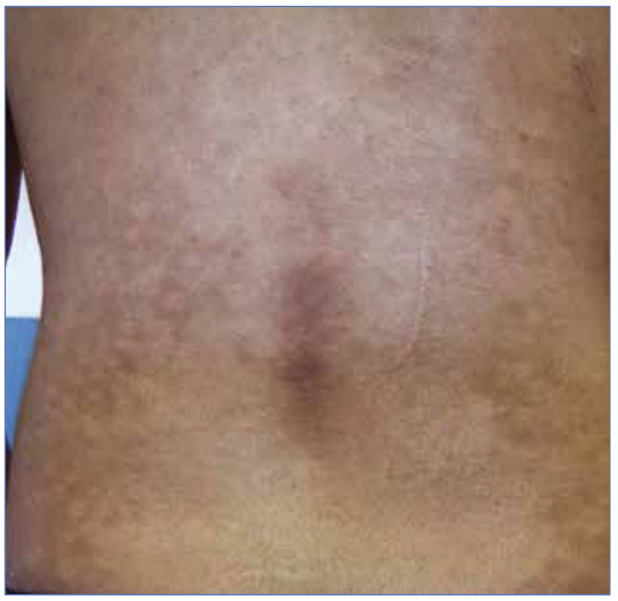
KEY REFERENCES

- Falabella R, Escobar CE, Carrascal E, Arroyave JA. Leukoderma punctata. J Am Acad Dermatol. 1998;18:485-94.
- Dogra S, Jain R, Parsad D, Handa S. Leukoderma punctatum following systemic PUVA therapy. Int J Dermatol. 2002;41:922-3.

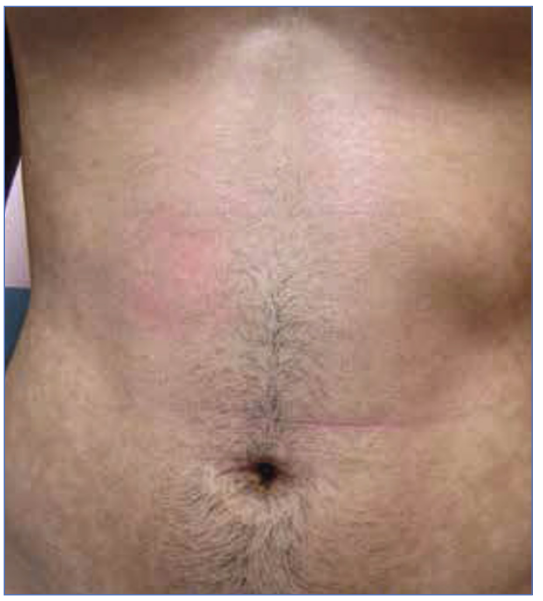
PROGRESSIVE MACULAR HYPOMELANOSIS OF THE TRUNK



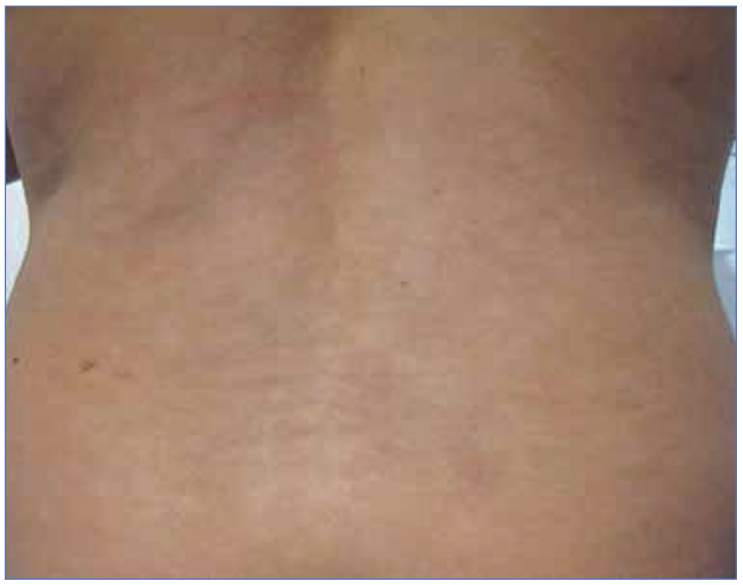
Typical pattern of progressive macular hypomelanosis.



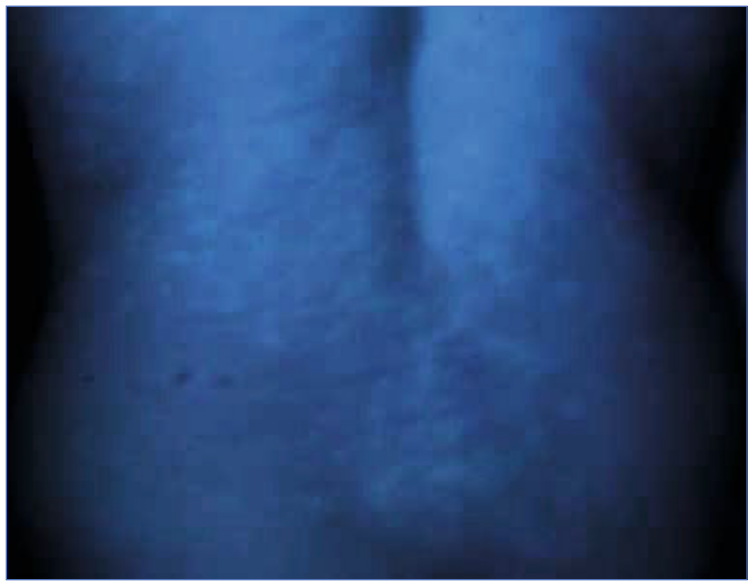
Severe progressive macular hypomelanosis. The hypopigmented macules have coalesced in the lumbar region.



Involvement of the abdomen in the same patient.



A. The hypopigmented macules mild forms of progressive macular hypomelanosis are sometimes difficult to see during winter or in fair skinned patients.



B. Same patient under Wood's lamp examination. The hypopigmented lesions become obvious.

SYNONYMS

Creole dyschromia, cutis trunci variata, nummular and confluent hypomelanosis of the trunk.

EPIDEMIOLOGY

The condition is common but often misdiagnosed.
Female predilection. Mainly observed in patients from 15 to 45 years of age.
Although first described in patients from mixed Caucasian and Negroid origin, and in South Americans, the condition can be observed in all ethnicities.

PATHOPHYSIOLOGY

Progressive macular hypomelanosis appears to be associated with the proliferation of a propionibactrium, but the bacteria is substantially different from the *Propionibacterium acnes* bacteria seen in acne.

CLINICAL DERMATOLOGICAL PRESENTATION

Nummular ill-defined hypopigmented macules from 1 to 3 cm in diameter that progressively coalesce into large plaques.
No scaling.
Asymptomatic
Localization: symmetrical disposition with general onset on the lumbar region. Progressive involvement of the rest of the trunk. Neck, face and limbs can rarely be involved.

EXTRACUTANEOUS SIGNS

None.

HISTOPATHOLOGY

The decrease in melanin content in the epidermis as compared to unaffected surrounded skin is the only histological finding.

DIFFERENTIAL DIAGNOSIS

- Mainly tinea versicolor.
- Pityriasis alba and hypochromic mycosis fungoides can sometimes be discussed.

TREATMENT

Phototherapy (PUVA and narrowband UVB) are effective.
Treatments targeting the propionibacterium proliferation (benzoyl peroxide 5% and clindamycin 1%) are also effective.
Some authors recommend to associate both approaches to decrease relapses.

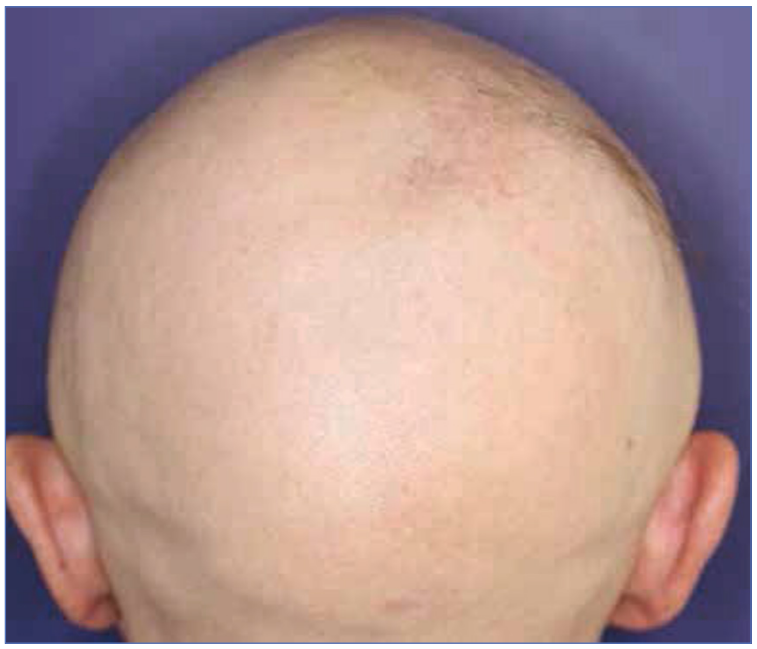
KEY REFERENCES

- Westerhof W, Relyveld GN, Kingswijk MM, de Man P, Menke HE. Propionibacterium acnes and the pathogenesis of progressive macular hypomelanosis. Arch Dermatol. 2004;140:210-4.
- Relyveld GN, Westerhof W, Woudenberg J, Kingswijk M, Langenberg M, Vandenbroucke-Grauls CM, Bos JD, Savelkoul PH. Progressive macular hypomelanosis is associated with a putative Propionibacterium species. J Invest Dermatol. 2010;130:1182-4.
- Kim MB, Kim GW, Cho HH, Park HJ, Kim HS, Kim SH, Kim BS, Ko HC. Narrowband UVB treatment of progressive macular hypomelanosis. J Am Acad Dermatol. 2012;66:598-605.
- Santos JB, Almeida OL, Silva LM, Barreto ER. Efficacy of topical combination of benzoyl peroxide 5% and clindamycin 1% for the treatment of progressive macular hypomelanosis: a randomized, doubleblind, placebo-controlled trial. An Bras Dermatol. 2011;86:50-4.

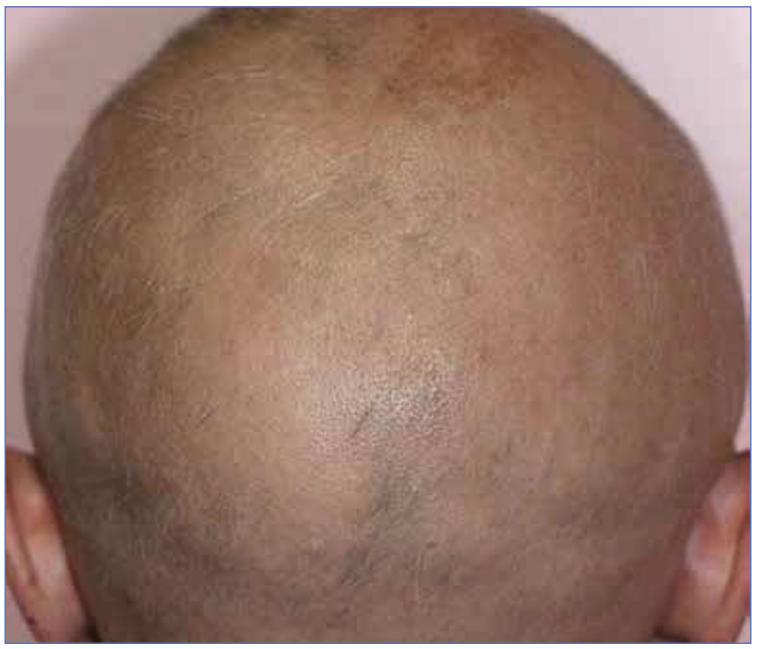
ACQUIRED HYPOMELANOSIS

Extracutaneous hypomelanosis

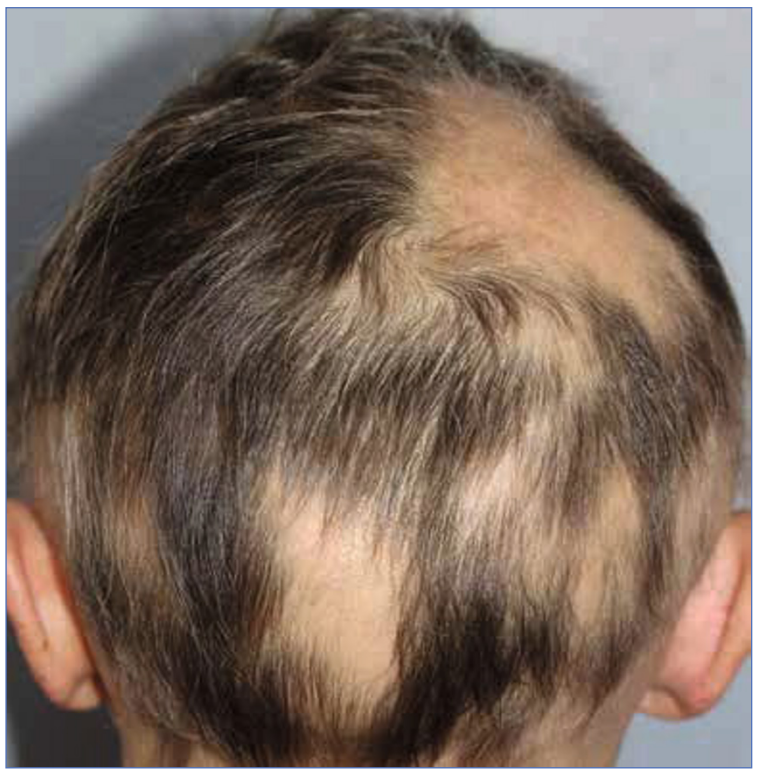
ALOPECIA AREATA



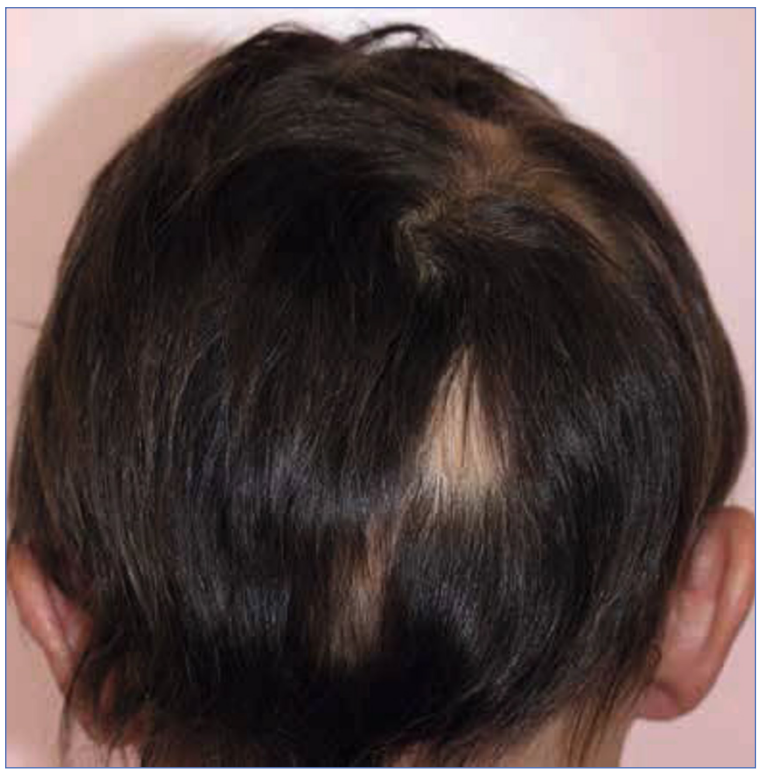
A. Severe alopecia areata.



B. Two months after treatment with low doses of interleukin 2, diffuse thin and white hairs are visible.



C. After 6 months, the regrowth is more important and the hairs become thicker and most have repigmented.



D. After one year an almost complete regrowth is observed and white hairs are no longer visible.

EPIDEMIOLOGY

Prevalence of 0.1 to 4% in the general population.
The presence of white hairs during the regrowth phase is almost constant.

PATHOPHYSIOLOGY

Unknown. Post-inflammatory hypopigmentation has been suspected such as a possible role of auto-immune T-cytotoxic lymphocytes.

CLINICAL DERMATOLOGICAL PRESENTATION

Regrowth hairs are thin and in most cases non-pigmented. Within several weeks they regain their color and thickness.
Asymptomatic in most cases but burning sensation or pruritus can be observed.
Localization: body and scalp hairs can be affected.

EXTRACUTANEOUS SIGNS

None.

HISTOPATHOLOGY

Reduced number of melanocytes and melanin contained in the hair follicle.

DIFFERENTIAL DIAGNOSIS

- Vitiligo, piebaldism, Vogt-Koyanagi-Harada.
- Achromic nevus of the scalp.
- Tuberous sclerosis.
- Senile canities.
- Iatrogenic or toxic whitening of hairs.

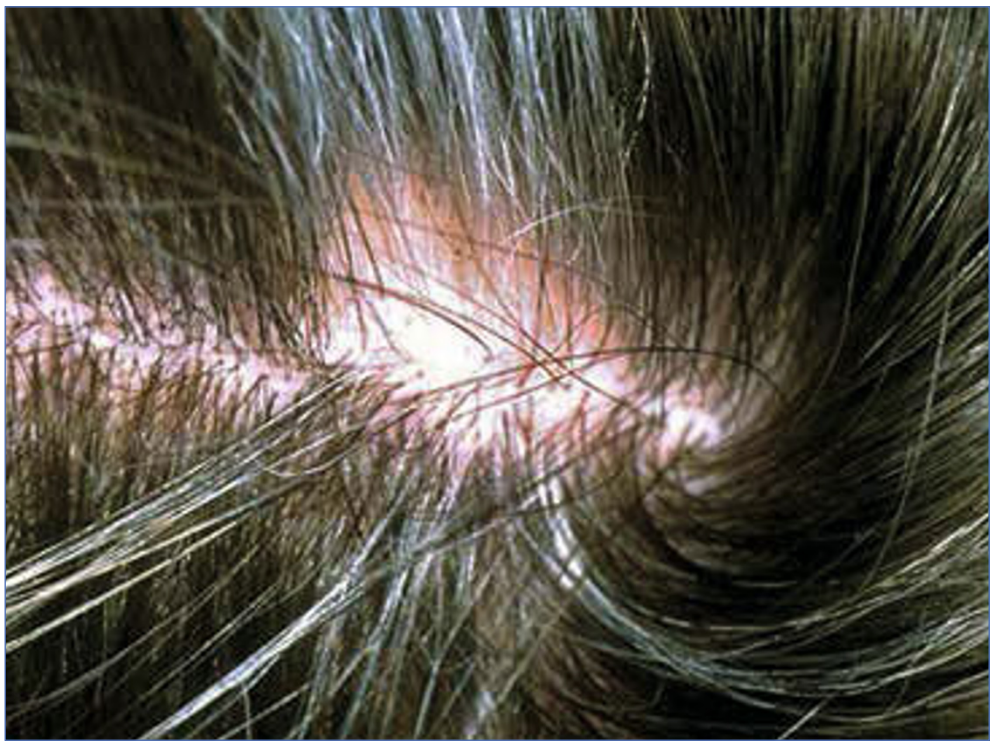
TREATMENT

No treatment has so far demonstrated a superiority against placebo.
Phototherapy.
Topical, intralesional, or systemic steroids.
Methotrexate.
Low doses of interleukin 2.

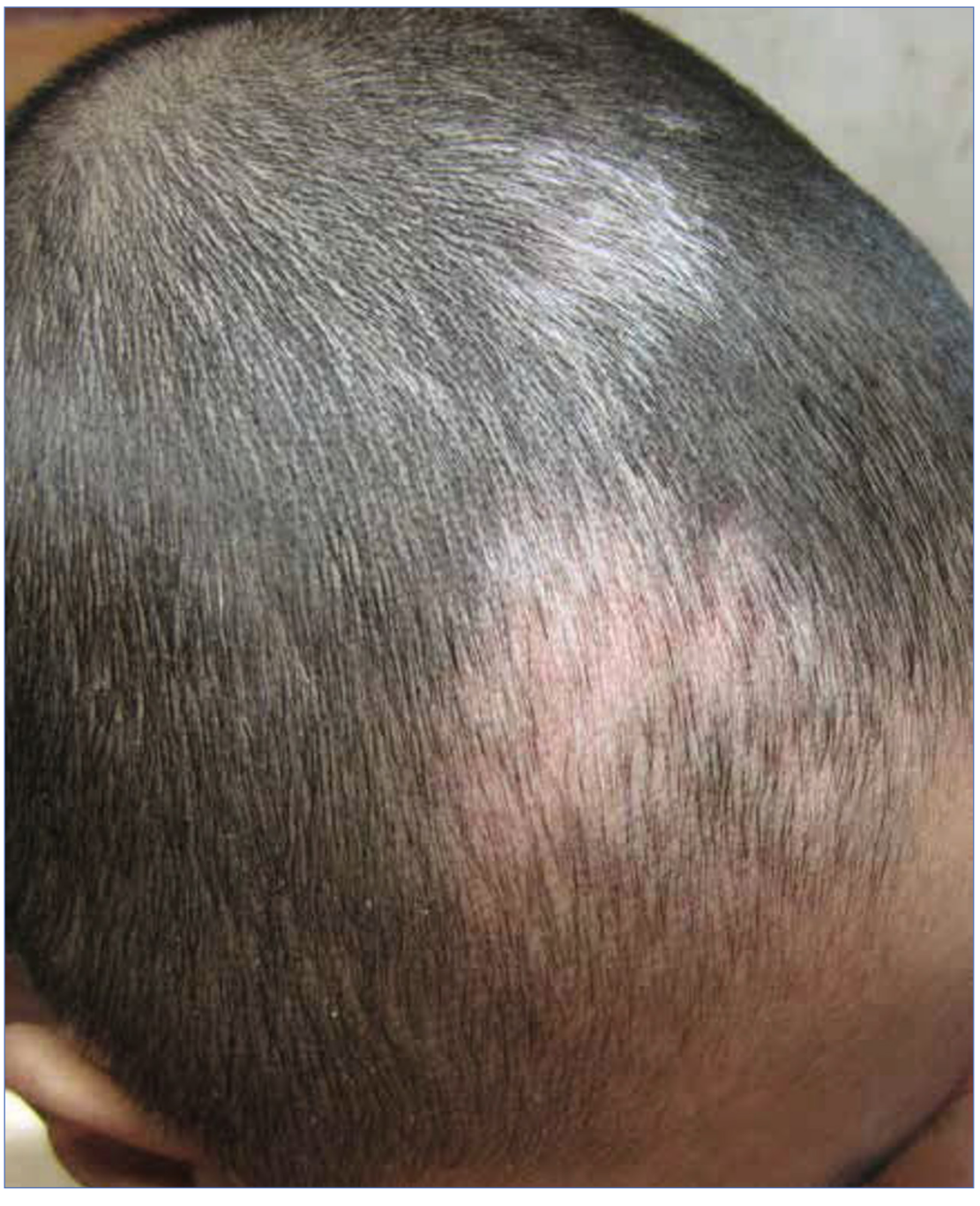
KEY REFERENCES

- Messenger AG, Bleehen SS. Alopecia areata: light and electron microscopic pathology of the regrowing white hair. Br J Dermatol. 1984;110:155-62.
- Safavi KH, Muller SA, Suman VJ, Moshell AN, Melton LJ 3rd. Incidence of alopecia areata in Olmsted County, Minnesota, 1975 through 1989. Mayo Clin Proc. 1995;70:628-33.
- Gilhar A, Etzioni A, Paus R. Alopecia areata. N Engl J Med. 2012;366:1515-25.

ALOPECIA AREATA



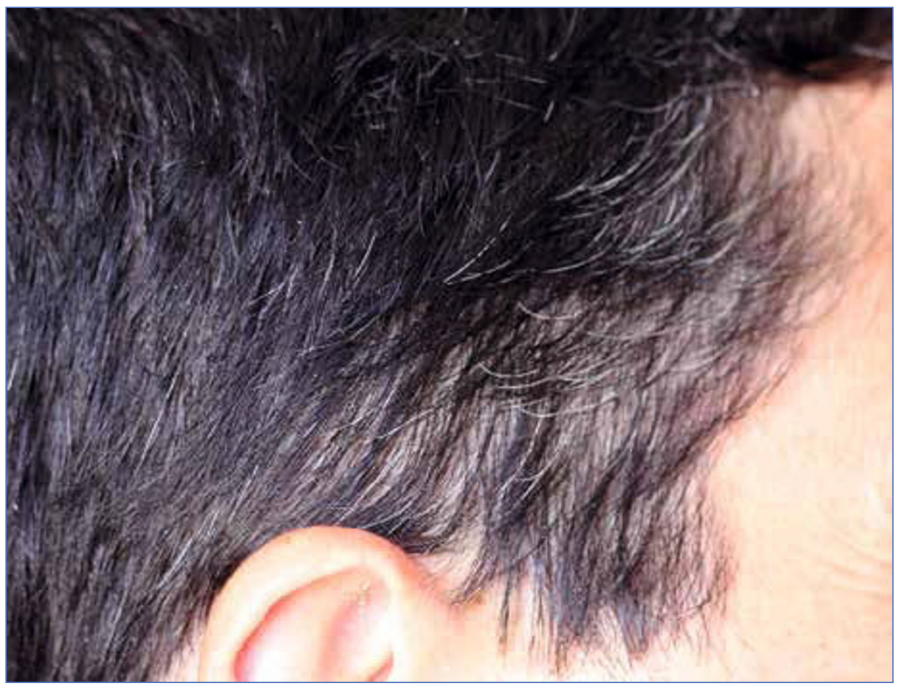
Small area of white hairs on localized alopecia areata.
The regrowth is almost completed and hairs are becoming thicker and are repigmenting.



Patches of white hairs on localized alopecia areata that has almost complete regrowth.

SENILE CANITIES

Close-up on hairs of a patient with senile canities.



Senile canities in a patient in the fourth decade of life. Note the onset on the temple.

Senile canities in a patient in the seventh decade of life.

SYNONYMS
Graying of hair.

EPIDEMIOLOGY
Physiological process that usually begins during the second or the third decade of life, but it becomes more visible in early fifties. The condition is primarily hereditary and the age of onset varies from early adulthood to the ninth decade of life.
Male and female are equally affected.
The onset is earlier in dark-haired individuals.

PATHOPHYSIOLOGY
An incomplete melanocyte stem cell maintenance in the niche and a compromised antioxidant activity in hair bulb melanocytes and their precursors are suspected.

CLINICAL DERMATOLOGICAL PRESENTATION
Progressive graying of the hair without any depigmentation of the skin.
Asymptomatic.
Localization: first on temple, then on the vertex to progressively extend to the whole scalp. Beard and body hair are usually involved later.

EXTRACUTANEOUS SIGNS
None.

HISTOPATHOLOGY
Decreased or absence of functional melanocytes (with DOPA reactivity) in hair bulbs.

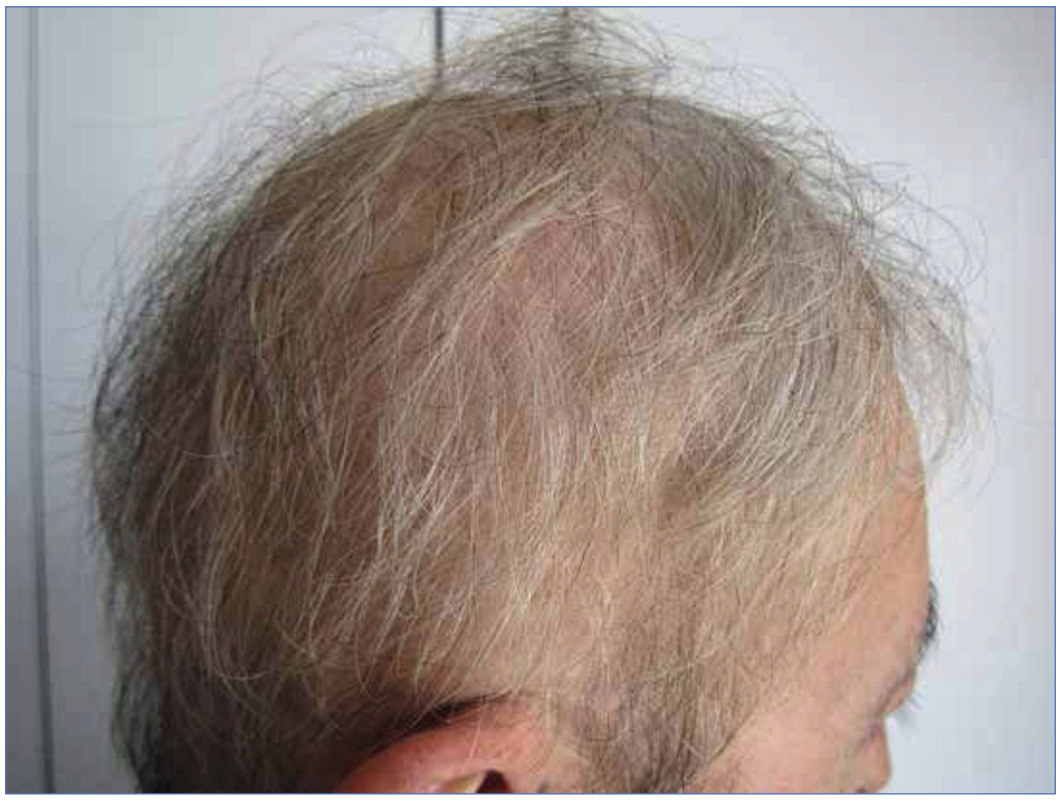
DIFFERENTIAL DIAGNOSIS
- Vitiligo.
- Alopecia areata.
- Iatrogenic or toxic whitening of hairs.
- Sudden whitening of hair.

TREATMENT
None.
Cases of repigmentation of hairs after an inflammatory process or after some systemic therapies (lenalidomide, thyroid hormone) suggest that the process of hair graying might not be irreversible.

KEY REFERENCES

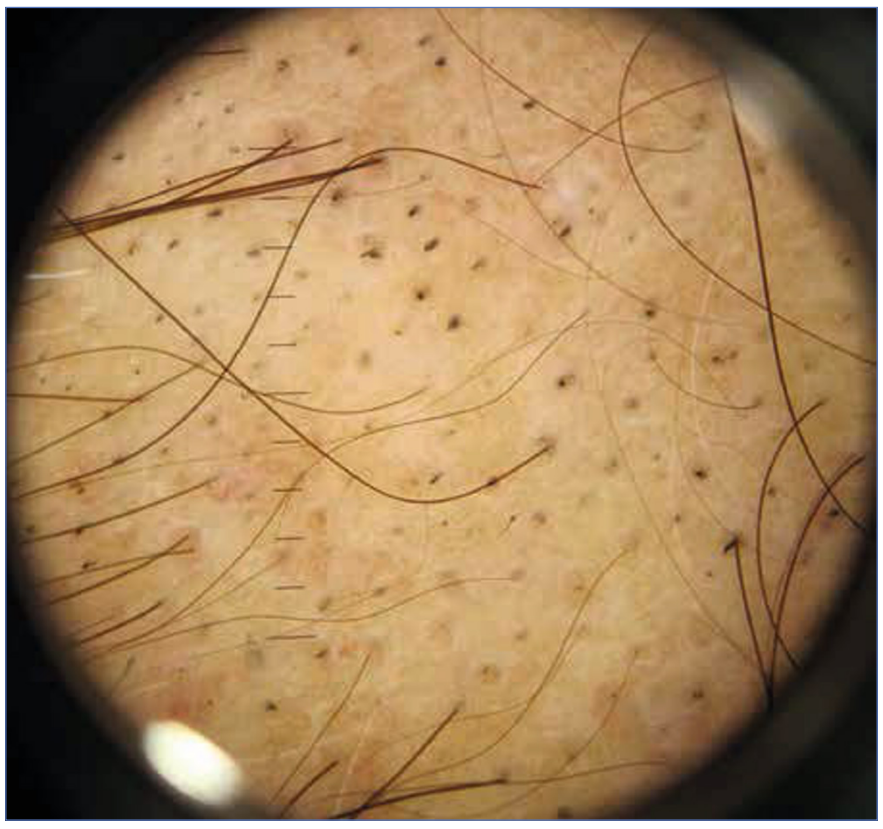
- Steingrímsson E, Copeland NG, Jenkins NA. Melanocyte stem cell maintenance and hair graying. Cell. 2005;121:9-12.
- Dasanu CA, Mitsis D, Alexandrescu DT. Hair repigmentation associated with the use of lenalidomide: graying may not be an irreversible process! J Oncol Pharm Pract. 2013;19:165-9.

SUDDEN WHITENING OF THE HAIR



Sudden whitening of the hair.

Same patient two weeks before.
Note the difference in hair density.



Dermoscopic features of alopecia areata in this patient, showing its causative role at least in this case.

SYNONYMS
Canities subita.

EPIDEMIOLOGY
The condition appears to be rare. The search in medical and non-medical literature since 1800 found 196 reported cases with 44 authenticated.
Men and women are affected.

PATHOPHYSIOLOGY
Selective loss of pigmented hairs due to alopecia areata diffusa is the most common explanation. However, alopecia was reported in only 6 out of the 44 authenticated reported cases suggesting that other factors might induce such a phenomenon.

CLINICAL DERMATOLOGICAL PRESENTATION
Rapid whitening of the hairs without any depigmentation of the skin. Occurs within a few days or weeks, and sometimes in one night.
Some hair loss can be reported by the patient.
Hair scalp is usually involved but cases with whitening of beard or body hair has been reported.
A context of emotional stress is sometimes reported.
Asymptomatic.

EXTRACUTANEOUS SIGNS
Some cases have been reported in a context of neurological and psychiatric disorders.

HISTOPATHOLOGY
Rare and conflicting reports. Alterations of the internal fine structure of hair shafts and air inclusions in the hair cortex have been described.

DIFFERENTIAL DIAGNOSIS
- Iatrogenic or toxic whitening of hairs.
- Vitiligo.
- Senile canities.

TREATMENT
None.

KEY REFERENCE

- Nahm M, Navarini AA, Kelly EW. Canities subita: a reappraisal of evidence based on 196 case reports published in the medical literature. Int J Trichology. 2013;5:63-68.