Dermoscopic and Reflectance Confocal Microscopic Features of Exogenous Ochronosis

Inmaculada Gil, MD; Sonia Segura, MD; Estela Martínez-Escala, MD; Josep Lloreta, MD; Susana Puig, MD; Mariano Vélez, MD; Ramón M. Pujol, MD; Josep E. Herrero-González, MD

Background: Exogenous ochronosis presents as an acquired asymptomatic hyperpigmentation on photoexposed areas, predominantly over bony prominences, and is caused by the topical application of several skin-lightening agents.

Observations: We describe a 63-year-old Hispanic woman who developed exogenous ochronosis lesions on her face after using topical bleaching creams containing hydroquinone, 2% to 3%, and oxybenzone, 2%, for several years. Dermoscopy revealed irregular brown-gray globular, annular, and arciform structures that corresponded to focal deposition of ochronotic pigment on the dermis. These deposits correlated with multiple banana-shaped nonrefractile structures seen using reflectance confocal microscopy. Histopathologic sections revealed the deposition of a banana-shaped, yellow to brown material in the papillary and middle dermis. Ultrastructural examination revealed an amorphous electron-dense material mostly located in the core of elastic fibers and also in smaller amounts in the interstitium with prominent degenerative changes in the elastic fibers. A good correlation was observed between the results of both noninvasive techniques and the diagnostic histologic features of this condition.

Conclusions: We characterized by means of dermoscopy, reflectance confocal microscopy, and electronic microscopy a case of exogenous ochronosis. To our knowledge, this is the first description of reflectance confocal microscopic findings in this condition. Dermoscopy and reflectance confocal microscopy are proved to be useful noninvasive techniques for the diagnosis of this pigmented disorder.

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EXOGENOUS OCHRONOSIS IS AN uncommon disorder characterized by the deposition of microscopic, ochre-colored pigment in the dermis, giving rise to a blue-black hue in the skin. It is usually manifested by asymptomatic blue-black macules on photoexposed areas, predominantly on bony prominences (malar areas, temples, lower cheeks, and neck), and it is often associated with the prolonged application of various topical chemical substances, such as hydroquinone, phenol, resorcinol, mercurials, and picric acid, as well as quinine injections and oral antimalarial agents. Hyperpigmentation occurs strictly on the topically treated areas.

Exogenous ochronosis can be clinically mistaken for other disorders manifested by acquired localized hyperpigmented facial macules and, specifically, for melasma. In some patients, histopathologic study is required to reach a definite diagnosis. Dermoscopy and in vivo skin reflectance confocal microscopy (RCM) are noninvasive in vivo diagnostic tools that may permit us to define morphologic patterns of skin disorders and to avoid the practice of unnecessary skin biopsies. We herein describe a patient with hydroquinone-induced exogenous ochronosis with some peculiar dermoscopic features. The morphologic features of deposition of ochronotic pigment using in vivo skin RCM were also defined. A correlation of RCM findings with dermoscopic and histopathologic findings was performed.

REPORT OF A CASE

A 63-year-old Hispanic woman with phototype V skin, a history of hypertension treated with enalapril maleate and hydrochlorothiazide, and primary hypothyroidism presented with a history of long-term localized symmetrical facial hyperpigmented macules on both cheeks, the supraciliary arches, and the nasal dorsum (Figure 1A). She denied having any joint, genitourinary, or cardiac symptoms.
Figure 1. A, Clinical examination. Ill-defined gray macules on the cheeks. B, Dermoscopy. Irregular brown-gray globular-like structures throughout the lesion. C, Arciform to annular structures around the follicular openings. D, Punch biopsy specimen. Exogenous yellow to brown material (banana-shaped bodies) in the papillary and middle dermis (hematoxylin-eosin, original magnification ×400). E, Reflectance confocal microscopy 1×1-mm block image at the upper dermis. Multiple dark round to oval spaces located next to the follicles. F, Reflectance confocal microscopy 0.5x0.5-mm image at the upper dermis. Banana-shaped amorphous dark structures in the papillary dermis correlate with the histologic findings.
Her family history was noncontributory. The patient stated that she had been treated for melasma in her country of origin, Colombia, with bleaching creams and lotions containing hydroquinone, 2% to 3%, and oxybenzone, 2%, for several years. She noted worsening of the hyperpigmentation in the involved areas despite good adherence to those topical products. On physical examination, there were bilateral ill-defined speckled gray macules over both malar areas. A light brown regular oval macule 1 cm in diameter clinically consistent with solar lentigo was also noted above her left eyebrow. The remainder of the skin examination findings were unremarkable. Dermoscopic examination of the malar areas revealed irregular brown-gray globular, annular, and arciform structures and granules distributed throughout the lesion (Figure 1B). In some areas, these striking short arciform and annular structures were located around the follicular openings (Figure 1C).

A 4-mm punch biopsy sample was collected from the malar area. Deposition of a banana-shaped yellow to brown material was found in the papillary and middle dermis (Figure 1D). A sparse lymphocytic infiltrate was present, and a focal foreign body reaction surrounding this material was also detected. No remarkable epidermal changes were found. An additional biopsy performed on the left eyebrow macule showed characteristic histopathologic features of solar lentigo along with focal deposition of the same banana-shaped material in the dermis.

Ultrastructural examination of the skin dermal tissue revealed an amorphous electron-dense material mostly located in the core of elastic fibers and also in smaller amounts in the interstitium. In addition, elastic fibers showed several degenerative changes, including elastolysis (clearing), elastorrhexis (fragmentation into minute fiber fragments), and motheaten defects in the external outline (Figure 2). An RCM examination of the malar area (VivaScope 1500; Lucid Inc, Rochester, New York) was also performed. These instruments use a diode laser at 830 nm with a power of less than 16 mW at tissue level and ×30 water-immersion lenses, allowing a horizontal optical resolution of 2 µm and a vertical resolution of 5 µm. Each given image corresponds to a horizontal 500 × 500-µm section of the skin at a selected depth from the epidermal surface to the upper dermis at a maximum depth of 250 to 350 µm.\(^1\) Using confocal examination, the epidermis exhibited a normal honeycombed pattern. At the dermoepidermal junction, we noted typical refractile basal cells corresponding to physiologic hyperpigmentation of the basal layer. At the dermal level, we observed widespread hyporefractile oval to banana-shaped spaces that corresponded to the banana-shaped bodies observed on histologic sections. These structures were located next to the inferior portion of hair follicles (Figure 1E and F). Complete blood and urinary biochemical surveys and chest radiographs disclosed no abnormalities. The diagnosis of exogenous ochronosis was established.

The patient underwent intense pulsed light (IPL) treatment (645 nm, 6 milliseconds, 20-22 J/cm\(^2\)) (Vasculight; Lumenis Ltd, Yokneam, Israel). Sunscreen and nonhydroquinone depigmenting cream containing kojic acid, 4%, and salicylic acid, 0.2%, were also prescribed. After 2 months of treatment and 6 IPL sessions, the patient exhibited mild clearing of the lesions (malar and supraciliary). Using dermoscopy, we observed a slight blanching of the brown background of the involved areas coexisting with a deep brown stellate network corresponding to transepidermal melanin loss. The brown-gray globules and arciform to annular structures persisted after treatment and were even more evident using dermoscopy. An RCM examination before and after IPL treatment did not show any significant differences, suggesting that the exogenous material persisted after IPL treatment.

**COMMENT**

Exogenous ochronosis presents as acquired asymptomatic hyperpigmented macules on photoexposed areas. Clinically it is manifested by asymptomatic bilateral symmetrical speckled blue-black macules and several gray-brown macules, previously described as “caviarlike” bodies, typically affecting the malar areas, temples, lower cheeks, and...
neck. Some researchers have defined 3 different stages in exogenous ochronosis: initial erythema and mild pigmen-
tary changes; followed by hyperpigmentation, black col-
loid milia, and atrophy; and, finally, papulonodules. Ex-
ogenous ochronosis most commonly results from the use
topical hydroquinones (usually used as bleaching
creams) but has also been associated with the use of phe-
nol, quinine injection, resorcinol, and oral antimalarials.

Initially, only the continual use of a high concentration
of hydroquinone (6%-8%) for at least 6 months was thought
to result in exogenous ochronosis, but at least 1 study has
demonstrated development of the disorder with the topi-
cal application of hydroquinone, 2%, for as long as 3 months.

Clinically, the differential diagnosis of exogenous ocho-
ronosis should be established with a heterogeneous group
of disorders causing facial hyperpigmented macules, such
as melasma, bilateral nevus of Ota, drug-induced hyper-
pigmentation (amiodarone, minocycline, and methotrex-
ate), postinflammatory hyperpigmentation, and derma-
tosis papulosa nigra. Melasma is, after postinflammatory
hyperpigmentation, the most common cause of acquired
facial hyperpigmentation. It is characterized by brown, gray,
or even blue macules that coalesce in patches with irregu-
lar outlines. Darkly pigmented races are prone to this dis-
order, which is exacerbated by UV exposure. Considering
that some patients with hydroquinone-induced exogenous ochronosis may have melasma, a combina-
tion of clinical, histopathologic, and dermoscopic fea-
tures of both entities is often present.

Histologic examination of exogenous ochronosis re-
veals short, curvilinear, yellow to brown banana-shaped
fibers of varying thickness in the upper dermis. Homog-
enization, swelling, and degeneration of collagen bundles
are variable. Some researchers have noted, as can a moderate inflammatory infiltrate
that may be rich in histiocytes and plasma cells. Sarco-
ideal granulomas and multinucleated giant cells with phago-
cytized ochronotic fibers have also been described. Tran-
sfollicular elimination of the abnormal fibers can also be
found. Pigment incontinence and solar elastosis are of-
ten present. Ultrastructural findings have been reported
in exogenous ochronosis and are described as homog-

genous electron-dense irregular structures nested in an amor-
phous granular material that permeates the collagen
bundles. Dermoscopic features of exogenous ochrono-
sis have received little attention in the literature. The color
of the ochronotic pigment observed clinically and using
dermoscopy is blue-gray because of the depth at which the
pigment is located. Some researchers initially pointed out
the observation of blue-gray, granular, and annular struc-
tures around the follicles. Chariot et al reported the der-
moscopic features of 2 patients with hydroquinone-
induced exogenous ochronosis with associated melasma.

They observed blue-gray amorphous areas obliterating (but
not surrounding) some follicular openings and character-
istic dermoscopic features of melasma (accentuation of the
normal pseudo-rete of the facial skin). Berman et al studied
5 patients with exogenous ochronosis secondary to the
long-term application of hydroquinone cream and 3 pa-
tients with melasma with no history of hydroquinone use.
In patients with exogenous ochronosis, dark brown glob-
ules and globular-like structures on a diffuse brown back-
ground were observed. In contrast, in patients with me-
lasma, a fine brown reticular pattern on a background of a
faint light brown, structureless area was noted. The au-
thors stressed the usefulness of dermoscopy in differenti-
tiating these 2 entities.

In the present patient, in addition to the previously
reported brown-gray globules, short, thin arciform and
annular structures were often distributed around the fol-
licular openings. To our knowledge, these peculiar der-
moscopic features have not been previously reported in
exogenous ochronosis.

Dermoscopic differential diagnosis in the present pa-
tient includes several lesions with perifollicular hyper-
pigmentation, such as melasma and Ota nevus. How-
ever, these lesions show a homogeneous pigmentation that
spares follicular openings, and brown-gray globules and
arciform to annular structures are not observed. The pre-

cence of brown-gray granules also raises the differential
diagnosis of a benign lichenoid keratosis. In such les-
ions, granules are more blue-gray than brown-gray and
correspond to the aggregates of melanophages in the
dermis. Moreover, these structures are regular and smaller
than those seen in exogenous ochronosis. In addition,

lchenoid keratoses are clinically localized and do not pre-

cent as symmetrical bilateral patches. Other tumors that
show blue-gray dots and globules are basal cell carcino-

oma and lentigo maligna, but they usually exhibit other
additional dermoscopic features that allow us to estab-
lish the diagnosis. The striking dermoscopic features ob-

served in the present patient are not previously de-
scribed, to our knowledge; are characteristic of exogenous
ochronosis; and may be considered a hallmark for the
diagnosis of this entity. The RCM features of exogenous
ochronosis are not previously described, to our
knowledge. The presence of dark, well-defined, round-
to-oval and banana-shaped structures raised the suspi-
cion of an exogenous material deposition because they
do not correspond to any previously described struc-
ture of the normal skin or cutaneous disease. Pig-
mented lesions with lichenoid changes that exhibit blue-
gray granules on dermoscopy may be distinguished using
RCM by the presence of bright, plump cells throughout
the upper dermis corresponding to melanophages in the
absence of the newly described dermal banana-shaped
dark spaces. Confocal features of other lesions, such as
melasma or Ota nevus, have not been previously re-
ported. Nevertheless, it is difficult to conclude that these
findings are specific to exogenous ochronosis. Other con-
ditions in which foreign materials are deposited in the
skin, such as argyria and chrysiasis, may have similar der-
moscopic and confocal features and, thus, need to be fur-
ther characterized.

Treatment of exogenous ochronosis is still challeng-
ing for the physician. There is agreement regarding the
convenience of stopping the use of the causative agent.
Cryotherapy and trichloroacetic acid have been proved to
be ineffective, whereas retinoic acid can be beneficial
in some patients. Topical corticosteroids and sun-
screens have variable efficacy. There have been reports
of successful treatments with dermabrasion combined
or not with carbon dioxide laser. Bellaw and Alster de-
scribed 2 patients with exogenous ochronosis suc-

cessfully treated with Q-switched alexandrite laser. To
our knowledge, IPL, commonly used in the treatment of vascular stains, photoaging, pigmented lesions, and photoepilation, has not been previously reported as a treatment for exogenous ochronosis. In the present patient, only a mild improvement and scarce lightening were achieved, especially on the background of the lesion, after 6 courses of treatment. Clear-cut involution of granular and arciform structures was not achieved. Further studies are needed to define the exact therapeutic role of IPL in the treatment of exogenous ochronosis. In conclusion, we stress the usefulness of noninvasive techniques in the diagnosis of pigmented lesions on the face. The striking dermoscopic findings should arouse the clinical suspicion of exogenous ochronosis and enable the physician to avoid unnecessary skin biopsies. In this particular setting, RCM might be of interest for confirming the existence of an exogenous material. Future RCM characterization in larger series of patients with deposit skin diseases, including exogenous ochronosis, is needed.

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Correspondence: Inmaculada Gil, MD, Department of Dermatology, Hospital del Mar-Universitat Autònoma de Barcelona, Passeig Marítim 25-29, Postal Code 08003, Barcelona, Spain (igil@imas.imim.es).

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