Chapter

Drug-Induced Pigmentation

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Abstract

Drug-induced pigmentation occurs in up to 20% of acquired pigmentary disorders of the skin. Association of its occurrence was reported in certain drugs, including alkylating/cytotoxic agents, analgesics, antiarrhythmics, anticoagulants, antiepileptics, antimalarials, antimicrobials, antiretrovirals, metals, prostaglandin analogs, and psychotropic agents, among others. Proposed mechanisms include (1) accumulation of melanin, (2) accumulation of drug, (3) generation of new pigment, and (4) deposition of iron. Though difficult to confirm the drug association, the history, with emphasis on currently used drugs, and clinical examination may guide practitioners to an accurate diagnosis. Treatment options include cessation of the drug, adequate sun protection, and non-ablative pigment lasers.

Keywords: drug reactions, pigmentation, drug-induced, pigment lasers, histopathology of pigmented disorders

1. Introduction

Pigmentary disorders are commonly seen in dermatologic practice that may have a negative impact on the quality of life of patients. In some of them, it may be brought by the use of certain medications leading to drug-induced pigmentation. The occurrence of drug-induced pigmentation has been estimated in 10–20% of acquired pigmentary disorders seen in the clinics [1]. Its incidence depends on the suspected medication, which varies from exceptional incidents to 25% of patients taking the medication [2]. Based on the literature, a number of reports have been attributed to be associated with developing drug-induced pigmentation. This includes alkylating/cytotoxic agents, analgesics, antiarrhythmics, anticoagulants, antiepileptics, antimalarials, antimicrobials, antiretrovirals, metals, prostaglandin analogs, and psychotropic agents, among others [1]. Despite the documented associations, the level of evidence supporting these has been variable. Most of these associations were reported in individual case reports and some case series. In addition, published systematic reviews have been limited; hence, the need for further prospective investigations regarding this disorder.

2. Pathomechanism of drug-induced pigmentation

The exact mechanism in the development of pigmentary disorders related to drug use is currently unknown. From the currently published papers, the evidence

pointing to the pathomechanism of drug-induced pigmentation have been limited. Despite its occurrence in newer drugs, the deposition of pigments in the skin and mucosal surfaces has remained to be elucidated. With the advent of more sophisticated techniques, such as electron microscopy and mass spectrometry, further progress in its pathogenesis can be seen. Currently, there are four mechanisms proposed in the development of drug-induced pigmentation.

The first mechanism involves the accumulation of free melanin pigments in the dermis, or in the macrophages surrounding the blood vessels. This may be due to Ref. [1], the direct stimulation of the melanocytes by the culprit drug to produce melanin, [2] the inflammatory response to the culprit drug, or [3] the formation of a stable drug-melanin complex incapable of macrophage clearance [1]. Another mechanism implicates the accumulation of the culprit drug saturating the macrophages, which incapacitates its function to clear the foreign materials, or the culprit drug itself freely exists within the dermis as pigment granules [1]. Next, the culprit drug may influence directly the generation of new pigments, such as lipofuscin [1]. Lastly, the culprit drug may induce vascular damage within the dermis causing red blood cell extravasation and degradation, eventually leading to the deposition of iron [1].

These proposed mechanisms may not strictly explain the pathway in the development of pigmentation in each drug reported. With the development of new medications on the horizon, this may be accompanied by future perspectives on the pathogenesis of drug-induced pigmentation.

3. Clinical manifestations

The clinical picture varies for each drug based on the available reports. However, the sites of involvement, the pattern of pigmentation, and the color of pigmentation may help the clinician to suspect the culprit drug involved. The author divided the section into the pattern of pigmentation caused by drugs which is shown in **Table 1**.

3.1 Localized and diffuse pigmentation

There are many cases documented presenting with localized and diffuse pigmentation associated with medication use. Most of them usually start with a localized pigmentation evolving into a diffused pattern in the sun-exposed areas. The drugs more commonly described to cause pigmentary changes are clofazimine, amiodarone, minocycline, antimalarials, and chemotherapeutic drugs [3].

Clofazimine, an agent used in the treatment of leprosy, causes reddish-blue discoloration evolving into a violaceous to reddish-brown pigmentation. The pigmentation may be found in the skin and conjunctiva with prolonged use [5]. On dermoscopy, it shows yellow to white globules on a black background and honeycomb patterns [6]. Clofazimine-induced pigmentation resolves after months to years upon discontinuation [7].

Amiodarone-induced pigmentation has been well documented. It manifests with slate-gray to purple skin pigmentation found in sun-exposed areas, such as face, nose, and ears. The pigmentation appears after 6 months of administration and may be dose dependent. Patients who are taking more than 400–800 mg/day have a higher risk of developing pigmentation. It also may resolve upon drug cessation but in some cases, it persisted for up to 1 year [1, 8].

Distribution of pigmentation	Reported causative drug
Localized	Antimalarials, Tetracyclines, Amiodarone, Adriamycin, Tegafur, Antiretrovirals
Diffuse	Antimalarials, Tetracyclines, Amiodarone, 5-Fluorouracil, Cyclophosphamide, Adriamycin, Gefitinib, Sorafenib, Anticoagulants, Antipsychotics, Clofazimine, Antiretrovirals
Reticulated	Diltiazem, Paclitaxel
Flagellated	Bleomycin
Nail pigmentation	Antimalarials, Tetracyclines, Amiodarone, Clofazimine, 5-Fluorouracil, Cyclophosphamide, Adriamcin, Hydroxyurea, Sunitinib, Dapsone, Antiretrovirals
Mucosal pigmentation	Antimalarials, Tetracyclines, Antipsychotics, Amiodarone, Dapsone, Rifampin

Table 1.
Some drugs reported to cause pigmentation [4].

Minocycline, another established inducer of pigmentation, develops four characteristic clinical patterns. Type I shows blue-black pigmentation in the sites of previous inflammation or acne scars. Type II shows localized diffuse pigmentation in the anterior lower legs or in the photosensitive areas. Type III produces "muddy skin" presenting with diffuse bluish-brown to slate-gray pigmentation that can be aggravated by ultraviolet rays. Lastly, a noticeable pigmentation along the vermilion border of the lower lip. In addition, pigmentation of the other mucosal surfaces, such as conjunctiva, sclera, and nails, have also been described. Minocycline-induced pigmentation has a higher risk in the following: [1] those on prolonged treatment, [2] with a cumulative dose of more than 50 g, [3] with presence of other cutaneous inflammatory disorders, and [5] with co-administration of drugs that may induce pigmentation. Minocycline pigmentation occurs as early as 1 week of therapy up to 3 years after initiation [1, 8–11].

Chloroquine, hydroxychloroquine, mefloquine, and quinacrine are antimalarial drugs associated with drug-induced pigmentation. Its incidence occurs in one in every four patients taking these drugs. Generally, the discoloration is characterized by bluish-gray to deep purple shade of macules forming patches in the anterior legs and head that may progress into diffuse pigmentation accentuated in the photo distributed areas. In quinacrine-induced pigmentation, light yellow discoloration may be appreciated in the skin and mucosal areas. The pigmentation improves 2–6 months after drug cessation [1, 4, 12, 13].

Antipsychotic medications, such as phenothiazines (chlorpromazine) and tricyclic antidepressants (imipramine/desipramine), produce slate-gray to purple-gray pigmentation in the photodistributed areas, including the face and the extremities. Other affected areas include the nail beds and the eyes. The pigmentation happens over time and was associated with high cumulative doses. It was proposed that the antipsychotic medications, together with sun exposure, stimulate the melanocytes to produce melanin that results in discoloration. In chlorpromazine-induced pigmentation, the drug binds to the melanocyte to stimulate melanin synthesis. On the other hand, in imipramine-induced pigmentation, the drug or its metabolite may activate the enzyme tyrosinase subsequently increasing melanin production [1, 4, 14].

3.2 Reticulated pigmentation

Reticulated pigmentation has been described as "net-like" and "chicken wire" pigmentation with varying shades of pigments and unclear borders [15]. Drug-induced reticulated pigmentation was considered rare and was associated with some medications [16]. Diltiazem is a calcium channel blocker used to treat cardiovascular diseases. The development of diltiazem-induced pigmentation happens between 8 to 15 months from the administration of the drug. It was described as slate-gray reticulated pigmentation found in sun-exposed areas. Interestingly, the histopathologic findings reported were similar to lichen planus pigmentosus [17, 18]. Chemotherapeutic drugs, such as paclitaxel, cyclophosphamide, 5-fluorouracil, idarubicin, ifosfamide, and cytarabine, have also been implicated to cause reticulated pigmentation [19]. However, previous reports have used multiple chemotherapeutic drugs, and implicating its association in the development of reticulated pigmentation is quite limited [20].

3.3 Flagellate pigmentation

Bleomycin is a cytotoxic agent used to treat squamous cell carcinomas, testicular cancers, and lymphomas [21]. It is known to develop flagellate pigmentation that may be appreciated upon administration for up to 9 weeks. The pigmentation starts from erythema that can be found anywhere in the face, trunk, and extremities. It usually resolves after drug cessation and in some cases, it may persist up to 1 year later. In patients with more than 100 units of cumulative doses, the incidence of developing cutaneous reactions to bleomycin is around 8–20% [22]. Other medications reported with flagellate pigmentation include docetaxel, trastuzumab, peplomycin, and bendamustine [23–26].

3.4 Nail pigmentation

Drug-induced pigmentation of the nails may be due to the melanocyte activation in the nail matrix, or the deposition of the drug or its metabolites in the nail unit. Melanonychia usually results from the activation of melanocytes in the nail matrix. This produces streaks of longitudinal or transverse bands of brown to black stripes involving several nails [27]. Several medications have been reported to cause nail pigmentation which include zidovudine, 5-fluorouracil, methotrexate, cyclophosphamide, hydroxyurea, bleomycin, and daunorubicin. Melanonychia usually starts after 3–8 weeks of drug administration and resolves upon cessation of the drug between 6 weeks to months [28–30]. In some reports, the deposition of the drug happens in the nail plate. It may present with yellow tinted color of the nail plate in gold salts and tetracyclines while dark-brown to bluish-brown discoloration is associated with clofazimine and antimalarial administration [27, 31, 32].

3.5 Mucosal pigmentation

Mucosal pigmentation has been fairly documented in the conjunctiva and oral mucosa. This is more commonly documented in females and found in the gingiva, tongue, and buccal cavity. It presents with blue to poorly defined black pigmentation, which is promptly investigated to rule out the possibility of a mucosal melanoma [9, 33]. The development of drug-induced mucosal pigmentation may happen rapidly at onset or may

take several days or years [34]. Its pathogenesis is still under investigation but may still be attributed to the proposed mechanisms mentioned [35]. Patients, who take antineoplastics, antimalarials, minocycline, and chemotherapeutic drugs, have a significantly higher risk of developing drug-induced mucosal pigmentation. Other drugs include zidovudine, golimumab, amlodipine, and clofazimine [36].

4. Diagnosis and assessment

The diagnosis of drug-induced pigmentation can directly be made on clinical grounds if the typical presentation of the pigmentation coincides with the exposure of the culprit drug especially with the known medications to cause drug-induced pigmentation. However, it may also be complicated due to insufficient evidence relating to the culprit drug, especially in the delayed onset of manifestations and the use of multiple drugs [37]. Given its complicated situation, the diagnosis for drug-induced pigmentation may be guided as follows:

1. A thorough patient history is recommended with emphasis on previous and current medications, including over-the-counter drugs and supplementation, and detailed medical history. If feasible, electronic medical records and previous pharmacy visits may aid the clinician in retrieving the drug list of the patient. It is important to take note of the common drugs that have been documented in the literature that may induce pigmentation. This includes antiarrhythmics, anticoagulants, antiepileptics, antimalarials, antimicrobials, antiretrovirals, metals, prostaglandin analogs, and psychotropic agents.

2. The onset and evolution of the lesions should be asked from the patient as keenly as possible. This should be done with a drug chart corresponding to the clinical course of the disease. It is important to note the changes in the intensity of pigmentation in correlation with the change in drugs as some drugs may be dose-dependent like amiodarone. An adverse drug reaction probability scale may help to assess the drug causality, such as the Naranjo algorithm [38].

3. Complete physical examination of the skin, nails, and mucosal surfaces is a must. The distribution pattern, morphology, and color may aid the clinician to suspect which drug may have caused the disease. Dermoscopic examination may be able to help distinguish other diseases that may present with odd pigmentation such as melanoma and hemosiderin deposition from a purpuric disorder.

4. Skin biopsy should be considered and may be correlated with the clinical picture. The location of the pigment, pattern of inflammation, and special stain patterns should be documented.

5. Differential diagnosis

Sun exposure has been the greatest contributory factor in developing pigmentary disorders and, coincidentally, a number of reports have documented the development of drug-induced pigmentation in sun-exposed areas. However, more common pigmentary disorders should have been considered first before thinking of

Melasma
Addison's disease
Hemochromatosis
Nutritional deficiencies (niacin and vitamin B12 deficiencies)
Ashy dermatosis or erythema dyschromia perstans
Pigmented contact dermatitis
Poikiloderma of civatte

Table 2.
Differential diagnosis of drug-induced pigmentation [1].

a possible drug-induced pigmentation in a patient. The list of differential diagnoses is included in **Table 2**.

Melasma is characterized by symmetrical hyperpigmented macules and patches on centrofacial and malar areas, especially in patients with skin of color. The factors contributing to its development include sun exposure, pregnancy, and hormone replacement therapy. Addison's disease presents with slate-gray pigmentation on both skin and mucosal surfaces. Pigmentation is accentuated in the flexural areas, scars, and areola. The diagnosis can be established with symptoms related to adrenal insufficiency and hormonal laboratory workup. Hemochromatosis should be considered in patients presenting with bluish-gray discoloration involving the skin and nails. This hereditary condition is usually accompanied by other diseases, such as diabetes mellitus, ophthalmologic problems, heart failure, and liver cirrhosis. Laboratory workups show abnormal levels of iron or copper and may be related to genetic mutations involving iron absorption.

Nutritional deficiencies, such as niacin and vitamin B12 deficiencies, may present with photodistributed pigmentation. Ashy dermatosis or erythema dyschromia perstans is a rare progressive disorder presenting with ash-brown discoloration predominantly seen in the trunk and proximal extremities. This condition may be hereditary and may be transmitted in an autosomal dominant way. Pigmented contact dermatitis is usually exacerbated by cosmetic products and is prevalent in middle-aged females of skin of color. It starts as erythematous pruritic patches progressing to diffuse and reticulated hyperpigmentation on face and neck. Poikiloderma of Civatte may also present with reticulated hyperpigmentation of the sides of the neck and V area of the chest. Factors contributing to the development of this condition include sun exposure, allergic reactions to fragrances/cosmetics, menopause, and genetic predilection [39]. Though histopathology may describe the deposition of some pigments in the skin, it is best to be correlated with the clinical information to arrive at the diagnosis of drug-induced pigmentation.

6. Histopathology of drug-induced pigmentation

Limited studies have correlated the histologic features with the clinical presentation of each drug class reported in the literature. This section will be discussing on the histologic findings of each drug class published. The histologic findings in each culprit drug-producing drug pigmentation mostly vary [40]. Generally, the epidermis may or may not show proliferation of melanin in the basal cell layer of the epidermis.

In the dermis, free pigment granules can be appreciated in perivascular and/or interstitial patterns. The pigment granules may show yellow-brown to black color. Some of these granules can be found inside the macrophages or adhere to the elastic fibers. The granules may have positive staining for Perls' method for iron, Masson-Fontana method for melanin, or both.

In minocycline-induced pigmentation, the histologic findings depend on its clinical variants. The type I and II variants show normal melanin pigmentation of the basal layer of the epidermis and the presence of golden brown to brown-black granules engulfed by macrophages in perivascular and periccrine patterns in the dermis. In type III variant, there is an increase in basal cell melanin pigmentation [41–43].

Amiodarone-induced pigmentation shows normal pigmentation of the epidermis with yellow-brown, lipofuscin-like granules surrounding the blood vessels in the dermis. These granules were positive for periodic acid–Schiff, Ziehl–Neelsen, Fontana, and Sudan black stains. At first, the granules were thought to be lipofuscin but recent findings support that the granules were amiodarone deposits in the dermis [44–47].

The histopathologic findings of pigmentation caused by the antimalarials, quinacrine, and hydroxychloroquine, show yellow-brown granular deposits within the macrophages scattered throughout the dermis and may be found extracellularly. However, the pigments in quinacrine-related pigmentation show a weak reaction or Perls' iron stain and negative for Masson-Fontana, while the pigments in hydroxychloroquine-related pigmentation show a positive reaction to Masson-Fontana and negative to Perls' iron stain [48, 49].

Antipsychotics, such as chlorpromazine, imipramine, and desipramine, demonstrate golden brown granules seen in the upper dermis surrounding the superficial vascular plexus. These granules are found within the macrophages. However, in imipramine and desipramine pigmentation, some granules are found floating in the dermis. The granules stain is positive for Masson-Fontana and negative for Perls' iron stain [50, 51].

In clofazimine-induced pigmentation, routine hematoxylin-eosin sections do not show any pigment deposits; however, birefringent red crystals can be appreciated in the fresh frozen sections. On fluorescence microscopy, these crystals are found surrounding large vessels in the dermis and show vivid red color. Interestingly, recent animal studies found that the crystals attributed to clofazimine pigmentation were from the separation of the free base form of clofazimine into the subcutaneous layer [52].

7. Treatment

Treatment strategies for drug-induced pigmentation have been limited. Avoidance and substitution of the culprit drug are the most reasonable option to treat drug-induced pigmentation. In some drugs, such as amiodarone, decreasing the dosage may help ameliorate the occurrence and severity of drug-induced pigmentation. In addition, sun protection, with the use of sunscreens, may avoid some drug-induced pigmentation brought by sun exposure from the use of certain drugs, such as antimalarials, antipsychotics, amiodarone, and tetracyclines [53]. Aside from sunscreens, physical barriers like umbrellas, hats, and wide-rimmed sunglasses should be advised, especially in patients at risk for intense sun exposure. Whitening topical medications, such as hydroquinone and hydroxy acids, have been found to be ineffective due to the location of pigment deposition in the dermis and/or adnexal structures [54].

Physical modalities, such as cryotherapy, have been documented in a case report of drug-induced pigmentation of the lip. A single cryotherapy session of open spray method using liquid nitrogen was applied for 30 seconds producing frost on the affected mucosal surface. Two weeks after, it produced a shallow ulceration which further improved 4 weeks after with minimal residual discoloration [55]. However, the improvement with the use of cryotherapy may be site-specific. The desired target in the dermis may outweigh the benefits of this modality, especially in the skin. Complications include scar formation, further pigmentary changes, and tissue disfigurement [56]. On a positive note, cryotherapy may be a good, cheaper alternative to lasers in drug-induced pigmentation of the mucosal surfaces.

Evidence supporting the use of lasers who may have failed or are unsatisfied with the current treatment option has been promising and may be an option for patients [54]. Conventional pigment lasers, such as quality-switched neodymium-doped yttrium aluminum garnet (Nd:YAG), alexandrite, and ruby lasers, have shown favorable results. Some studies have demonstrated good results in combining Q-switched pigment lasers with pulsed dye lasers or non-ablative 1550 nm fractional resurfacing lasers [57, 58]. These conventional pigment lasers induce photothermolysis of the pigment particles, making them less visible or promoting their clearance via recruitment and engulfment of pigments by phagocytic cells [59]. Frequency of treatment varies from a single treatment session of combination laser to multiple treatment sessions in single laser modality. This may suggest a combination of treatment strategies with the use of lasers may be more advantageous than single modality alone. Despite favorable reports of its efficacy, the optimal settings with the use of lasers have been variable. In addition, limited clinical trials have been published hence, the need for more studies such as prospective clinical trials.

Currently, picosecond lasers are cleared by the United States Food and Drug Administration in the treatment of pigmented disorders. It has been proven to be safer and more effective than nanosecond lasers in the treatment of dermal pigmentary disorders [60]. Several case reports and a case series have been published in terms of its efficacy in treating drug-induced pigmentation specifically to minocycline [61–64]. The frequency of treatment varies from a single session to five monthly sessions of picosecond lasers. All of them resulted in significant clinical improvement to complete clearance of pigmentation. Although the results were promising, further evidence is required to conclude its better efficacy than nanosecond lasers. Also, the lack of studies for other medications inducing drug pigmentation should reserve the use of picosecond lasers in the future and depend on the clinician's call.

8. Course and prognosis

Upon discontinuation of the culprit drug, pigmentation persists in most cases that may even last decades after drug cessation. This may result in an impact on the psychological and social aspects of each patient's life. Despite higher chances of persistence, drug-induced pigmentation is not associated with higher chances of mortality [65].

9. Conclusions

Drug-induced pigmentation is a rare, acquired pigmentary disorder brought on by various medications that have been used in our daily lives. Its development remains

elusive but with the enhancements in research, the pathogenesis may be explained in the future. As clinicians, we have to keep in mind to include the possibility of drug-induced pigmentation in patients who have history of medication use. Prospective studies in the treatment of this condition may help clinicians to ease the burden on the patients' quality of life.

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Conflict of interest

The author declares no conflict of interest.

Notes/thanks/other declarations

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