REVIEW ARTICLE

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Drug-Induced Nail Disorders

Incidence, Management and Prognosis

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Contents

Abstract

A large number of drugs of different classes, ranging from antibacterials to chemotherapeutic agents to psoralens, can be responsible for the development of nail changes. Drug-induced nail changes usually involve several or all 20 nails and appear in temporal correlation with drug intake. Some nail changes are asymptomatic and only cause cosmetic problems, while others cause pain and discomfort and impair manual activities or deambulation. Drug-induced nail abnormalities are usually transitory and disappear with drug withdrawal, but sometimes persist in time.

The pathogenesis of the nail changes is usually a toxic effect of the drug on the different nail constituents, but other mechanisms can be involved.

Drugs that are well known to produce nail abnormalities include cancer chemotherapeutic agents, psoralens, retinoids, tetracyclines, antimalarials and zidovudine. Arsenic poisoning is also always associated with nail changes that have medico-legal importance.

Some drugs taken during pregnancy may impair nail development of the fetus, and nail hypoplasia or other nail dystrophies will be evident in the newborn.

1. Anatomy and Physiology of the Nail

The nail apparatus is composed of 4 epithelia: nail folds, nail matrix, nail bed and hyponychium, and a horny product, the nail plate.[1] The nail plate is produced by the nail matrix, which lies under the proximal nail fold. As it grows, the nail plate emerges from under the proximal nail fold and progresses distally, lying on the nail bed, to which it closely adheres.

At the tip of the digit the nail plate detaches from the underlying tissues at the hyponychium. Proximally and laterally, the nail plate is surrounded by the nail folds. The proximal nail fold consists of 2 layers of epithelium, a dorsal layer, which is the distal continuation of the skin of the dorsum of the digit, and a ventral layer, which continues with the nail matrix.

The nail matrix, which is responsible for the production of the nail plate, consists of an epithelium that keratinises without the formation of a granular layer. This characteristic and unique pattern of keratinisation allows the production of the horny, hard, and transparent nail plate made up of completely keratinised, flattened and strictly adhesive cells that have completely lost their nuclei. Nail matrix keratinisation follows an oblique axis, since during the process of maturation and differentiation cells move upward and distally. For this reason, the proximal portion of the nail matrix produces the upper portion of the nail plate, while the distal matrix is responsible for the production of the dorsal nail plate. The distal portion of the nail matrix is visible through the transparent nail plate as a white distally-convex half moon, the lunula.

The matrix contains melanocytes that usually do not produce melanin. Nail matrix melanocytes may, however, become activated and synthesise pigment that is transferred to the surrounding keratinocytes. Distal migration of melanin-containing keratinocytes will give rise to a pigmented nail plate.

Nail plate production occurs continuously, starting from the fifteenth week of embryonic life until death. Nail growth rate can be influenced by several factors, including age, systemic diseases and drug intake. Under normal conditions, mean growth rate of a finger is 3mm per month and that of a toe is 1mm per month.

2. Drug-Induced Nail Disorders

Drug-induced nail changes include adverse effects that are well known and considered a common sequela of treatment, such as nail abnormalities induced by cancer chemotherapeutic agents, and less common nail changes that have been reported in only a few cases.[2,3] Table I provides a comprehensive list of drug-induced nail changes which has been compiled from the references cited in this review.

Drug-induced nail abnormalities usually involve several or all 20 nails and appear in temporal correlation with drug intake. The nail changes are usually transitory and disappear with drug withdrawal, but sometimes persist in time. They can be asymptomatic or be associated with pain and impaired digital function.

The pathogenesis of drug-induced nail abnormalities is not always understood; however, the following points can be made.

- In most cases the nail alterations are due to the toxic effect of the drug on the nail epithelia. Nail changes will vary depending on the nail constituent that has been damaged (table II). The same drug may cause the contemporaneous presence of different nail symptoms, indicating that the drug has affected more than 1 nail component.
- Drug-induced nail changes may be a conse-

quence of excretion and storage of the drug within the nail plate, with the appearance of a nail pigmentation.
- Nail pigmentation may also be a consequence of dermal deposition of the drug; in these cases nail discolouration is usually associated with pigmentation of the skin and/or mucosae.
- Other drugs may only indirectly affect the nail by impairing the distal digital perfusion, causing necrosis of the nail apparatus or damaging the nail bed blood vessels, with the appearance of splinter haemorrhages or subungual haematoma.

2.1 Drug-Induced Nail Abnormalities Due to Damage to the Nail Matrix Keratinocytes

A large number of drugs may interfere with the normal kinetics and keratinisation of nail matrix keratinocytes.

A severe insult will produce an acute decrease or arrest of the mitotic activity of nail matrix keratinocytes, which will become evident as a Beau's line or as an onychomadesis, whereas a lighter insult to nail matrix keratinocytes will manifest as nail plate thinning, brittleness and/or decreased nail growth rate. Another symptom of a transient impairment of nail matrix keratinisation is true transverse leuconychia.

2.1.1 Beau's Lines

Beau's lines appear as transverse depressions of the surface of the nail plate.[4] They are caused by a transient decrease of the mitotic activity of the nail matrix keratinocytes. The depth of the depression indicates the degree of nail matrix damage and its width indicates the duration of the insult. Drug-induced Beau's lines typically involve all 20 nails and appear a few weeks after the beginning of treatment.

Beau's lines are one of the most common adverse effects of cancer chemotherapeutic agents and reflect their toxicity on actively dividing tissues, such as the nail matrix, hair matrix and mucosae.[5]

Multiple Beau's lines in the same nail indicate repetitive cycles of drug intake and their width corresponds to the duration of chemotherapeutic drug administration. All chemotherapeutic agents may cause Beau's lines, which are more common after short and intensive chemotherapy, especially combined chemotherapy.

Other frequent causes of Beau's lines are radiation therapy and retinoids (etretinate).[6]

Beau's lines do not require any treatment, since they only reflect previous damage to the nail matrix. They will move distally as the nails grow and eventually disappear.

2.1.2 Onychomadesis

Onychomadesis describes the presence of a transverse whole-thickness sulcus that divides the nail into 2 parts (fig. 1). Onychomadesis represents the extreme degree of Beau's lines and shares the same pathogenesis, i.e. a temporary arrest of nail matrix mitotic activity.

All drugs responsible for the development of Beau's lines may cause the appearance of onychomadesis, depending on the dosage of the drug and possibly on the patients' conditions. Onychomadesis is especially frequent in patients receiving high dosages of cancer chemotherapeutic agents, but has also been reported in patients undergoing radiation therapy, or after treatment with carbamazepine, lithium, high dosages of cefaloridine and cloxacillin.[7] In toxic epidermal necrolysis, onychomadesis can be followed by permanent loss of the nail due to matrix destruction. Onychomadesis and Beau's lines, together with other nail abnormalities, may be observed in patients who develop a photosensitivity reaction to sulfonamides during treatment with these drugs.[8]

As with Beau's lines, there is no treatment for onychomadesis, which will gradually progress distally with the nail growth. Patients may complain of pain in the area of the fissuration, where the nail bed is not covered by nail plate and therefore exposed to traumas.

2.1.3 True Leuconychia

Damage to the distal nail matrix keratinocytes may impair normal keratinisation with the persistence of cell nuclei within the nail plate. This portion of nail plate will not be transparent but white

Table I. Drug-induced nail changes reported in the medical literature[a]

Drug	Nail symptoms									
	Beau's lines/ onychomadesis	true leuconychia	nail growth rate alterations	nail thinning/ brittleness	pigmentation	onycholysis/ photo-onycholysis	apparent leuconychia	paronychia	vascular alterations	others
Miscellaneous agents										
Arsenic	BL, OM	Transverse			NM				Gangrene	Keratosis
Biotin			<							
Carotenoids					NM					
Chromium salts					NM					
Cystine			<							
Cyclosporin			>						Raynaud's phenomenon	
Dimercaptosuccinic acid (DMSA)										Longitudinal ridging
Fluorine	BL	Punctate, transverse		Brittleness	NM, M					Pitting
Peloprenoic acid derivatives				Brittleness						
Psoralens	BL				M	OL, PHO			Splinter haemorrhages Subungual haematoma	
Retinoids	BL, OM	Transverse	> or <	Thinning, brittleness, elkonyxis		OL		+		Pyogenic granulomas, ingrowing nails, curly nails
Retinol (vitamin A)				Brittleness						Nail dystrophy
Salbutamol								+		
Hormones										
Androgens							Half-and-half nails			
Corticotropin, melanocyte-stimulating hormone					M					
Cortisone		Transverse		M						

Oral contraceptives	OM	<	Decreased brittleness		PHO				
Parathyroid extracts	OM								
Anti-inflammatory and analgesic agents									
Acetanilide								Cyanosis/purple discolouration	
Aspirin (acetylsalicylic acid)								Purpura	
Benoxaprofen		<			OL, PHO				Koilonychia
Gold	OM	>	Thinning, brittleness	NM, M	OL				
Ibuprofen				M					
Penicillamine	BL		Brittleness, elkonyxis	M		Leuconychia		Subungual haemorrhages	Longitudinal ridging, YNS
Phenazopyridine				NM					
Antimalarials									
Amodiaquine				NM					
Camoquine				NM					
Chloroquine				NM					See note[b]
Hydroxychloroquine									See note[b]
Mepacrine (quinacrine)	OM			NM					Pitting, ridging
Quinine					OL, PHO				
Antimicrobials									
Acriflavine			Brittleness		PHO				
Cefaloridine	OM				PHO				
Cefalosporin	OM						+		
Chloramphenicol					OL, PHO			Subungual haemorrhages	
Clofazimine				NM, M	OL				Hyperkeratosis
Cloxacillin	OM				PHO				
Dapsone	BL								
Emetine						White nails			
Fluconazole		<							
Indinavir							+		Pyogenic granulomas

Continued on next page

Table I. Contd

Drug	Nail symptoms									
	Beau's lines/ onychomadesis	true leuconychia	nail growth rate alterations	nail thinning/ brittleness	pigmentation	onycholysis/ photo-onycholysis	apparent leuconychia	paronychia	vascular alterations	others
Itraconazole			<							Longitudinal ridging
Ketoconazole					M				Splinter haemorrhages	
Lamivudine								+		Pyogenic granulomas
Quinolones						PHO			Subungual haemorrhages	
Sulfonamides	BL, OM	Transverse	>		M	OL		+		
Tetracyclines	BL, OM				NM, M	PHO			Subungual haemorrhages, Raynaud's phenomenon	
Trypaflavine						PHO				
Zidovudine			>		M					
Drugs acting on the nervous system										
Buspirone				Thinning						
Carbamazepine	OM				M					
Chlorpromazine				Brittleness	NM	PHO				
Clorazepate dipotassium						PHO			Subungual haemorrhages	
Cocaine								+		
Levodopa			<	Nail hardness	M					
Lithium	OM		>		NM	OL				Psoriasiform changes
Phenytoin					NM, M					Lichen planus-like changes
Pilocarpine		Transverse								
Trazodone		Leuconychia								
Chemotherapeutic agents	BL, OM	Transverse	>	Brittleness	M, NM	OL, PHO	Half-and-half nails/Muehrcke's lines	+	Splinter haemorrhages, subungual haemorrhages, Raynaud's phenomenon, gangrene	

Drugs acting on the cardiovascular system							
Amrinone			NM				
Atenolol[c]						Splinter haemorrhages	Periungual telangiectasia
Calcium antagonists							Nail dystrophy
Captopril				OL, PHO			Lichen planus-like changes
Clonidine						Raynaud's phenomenon	
Dinitrophenol			NM				
Enalapril				PHO			
Heparin		>				Purple discolouration	
Metoprolol[c]	BL						
Phenylephrine						Purpura	
Phenindione			NM				
Practolol[c]				PHO			See note[d]
Propranolol[c]							
Quinidine			NM				
Timolol[c]			M				
Warfarin						Haematoma, subungual haemorrhages	Purple toe syndrome
Diuretics							
Thiazides				OL, PHO			
							Clubbing
Cathartics							
Phenolphthalein	BL		NM		+		

a Compiled from the references cited in this article.

b Chloroquine and hydroxychloroquine may induce or worsen psoriasis.

c All β-blockers may be responsible for the development of psoriasiform nail changes, Raynaud's phenomenon, pterygium inversum unguis, digital gangrene.

d Practolol administration has also been associated with the development of psoriasiform nail changes, pincer nail deformity, periungual pustules.

BL = Beau's lines; **M** = nail pigmentation due to deposition of melanin; **NM** = nail pigmentation due to deposition of nonmelanic pigment; **OL** = onycholysis; **OM** = onychomadesis; **PHO** = photo-onycholysis; **YNS** = yellow nail syndrome; + = paronychia has been reported; **<** indicates increased nail growth rate; **>** indicates decreased nail growth rate.

Table II. Drug-induced nail abnormalities vary depending on the nail constituent that has been damaged

Nail constituent	Symptom
Nail matrix keratinocytes	Beau's lines
	Onychomadesis
	True transverse leuconychia
	Nail growth rate alteration
	Nail thinning
	Nail fragility
Nail matrix melanocytes	Diffuse pigmentation
	Transverse melanonychia
	Longitudinal melanonychia
Nail bed	Onycholysis
	Photo-onycholysis
	Apparent leuconychia
Nail folds	Paronychia

and opaque, due to light reflection. Whitish discolouration of the nail plate due to nail matrix damage is termed 'true' leuconychia, as opposed to the 'apparent' leuconychia due to nail bed abnormalities. Drug-induced transverse leuconychia appears as 1 or several transverse bands, 1 or 2mm wide, usually located on the same site of each nail, indicating contemporaneous damage to all nail matrices.

Transverse leuconychia is usually caused by chemotherapeutic agents.[9] There is no specific cancer chemotherapeutic drug, combination of drugs or drug class that causes transverse leuconychia, but cyclophosphamide, doxorubicin and vincristine are the therapeutic agents most frequently involved. Transverse leuconychia has also been reported after overdose or poisoning with sulfonamide, pilocarpine and arsenic. In both acute and chronic arsenic poisoning, the nails typically show 1 or multiple tiny bands of transverse leuconychia, called Mees' lines, which involve the whole width of the nail plate.[10]

Bands of transverse leuconychia move distally with nail growth and eventually disappear.

2.1.4 Nail Growth Rate Alteration

Several drugs have been associated with an increased or a decreased nail growth rate. In some cases this finding is only anecdotal or has been reported in a single patient, while in other cases the association of the drug with nail growth rate alteration is well documented.

While a decreased nail growth rate can be explained by decreased mitotic activity of nail matrix keratinocytes, the mechanism by which a drug may cause an accelerated nail growth rate is still unknown. Drugs that have been associated with a decreased nail growth rate are lithium, methotrexate, zidovudine, cyclosporin and heparin. Retinoids have been reported to induce either an increased or a decreased nail growth rate.[8]

An increased nail growth has been reported in patients taking oral contraceptives, levodopa[11] and in patients treated with pulse itraconazole (400 mg/day for 1 week per month) for onychomycosis; in the latter case the nails also showed increased longitudinal striations (nail beading).[12] Accelerated nail growth has also been reported in patients treated with fluconazole.[13]

The nail growth rate returns to normal with treatment withdrawal.

2.1.5 Nail Thinning and Nail Brittleness

Mild damage to nail matrix keratinocytes can result in the production of a nail plate that is thinner and more brittle than normal.

Drug-induced nail brittleness can manifest as lamellar onychoschizia, where the superficial layers of the nail plate detach due to horizontal cleavages, or as elkonyxis, where nail fragility involves the

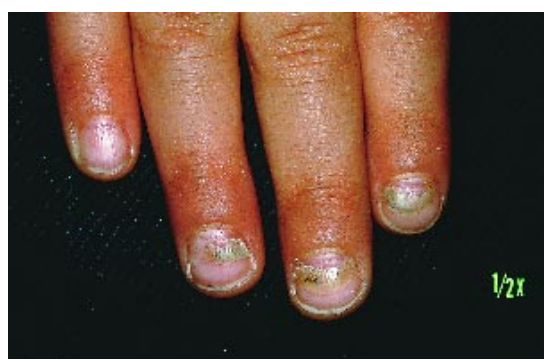

Fig. 1. Drug-induced onychomadesis. The nails show a transverse whole thickness sulcus that reflects a transitory arrest of nail matrix mitotic activity.

Fig. 2. Elkonyxis in a patient treated with chemotherapeutic agents. The superficial layers of the nail are brittle and easily shed.

proximal portion of the superficial nail plate (fig. 2).

Treatment with cancer chemotherapeutic drugs is often associated with an increased nail brittleness. This adverse effect is also frequently seen in patients treated with retinoids,[6] where the increased nail fragility may be responsible for the incidence of ingrowing nails and multiple pyogenic granulomas, due to breakage of the distolateral portion of the nail plate and its penetration into the lateral nail fold. This, together with the retinoid-induced increased formation of granulation tissue, leads to the development of pyogenic granulomas and ingrowing nails (fig. 3).[14]

A decreased nail brittleness associated with an increased nail growth rate has, on the other hand, been reported in patients taking oral contraceptives.[15]

2.2 Drug-Induced Nail Abnormalities Due to Damage to the Nail Bed

2.2.1 Onycholysis

Onycholysis describes the separation of the nail plate from the nail bed, with the formation of a new space that usually appears white. Drug-induced onycholysis can be a consequence of the damage to the nail bed epithelium with epidermolysis and loss of nail bed-nail plate adhesion or can follow a complete destruction of the epithelium with formation of a haemorrhagic bulla. In this case onycholysis is very painful, involves a large portion of the nail and may be associated with blisters of the soles.

Cancer chemotherapeutic agents, especially methotrexate, are the most common cause of drug-induced onycholysis.[16] The condition regresses spontaneously, over several months, after drug withdrawal.

Onycholysis can also be an unusual adverse effect of retinoids through a different mechanism, an accelerated desquamation of the distal nail bed horny layer, induced by these drugs.[17]

2.2.2 Photo-Onycholysis

In drug-induced photo-onycholysis, nail plate detachment from the nail bed results from a photomediated allergic or toxic effect of the drug. Photo-onycholysis usually involves several digits, and tends to spare the thumbs.[18] Baran and Juhlin[19] distinguished three clinical varieties of photo-onycholysis, depending on the shape and localisation of the detachment. In type I and type II photo-onycholysis, nail plate/nail bed separation involves the central portion of the nail free margin, sparing the lateral edges, and shows a half-moon shape with a more or less regular proximal convexity. Several nails are involved in type I, whereas only 1 digit is affected in type II (fig. 4). In type III photo-onycholysis the detachment involves the central portion of the nail bed. All 3 varieties are often associated with subungual haemorrhages.

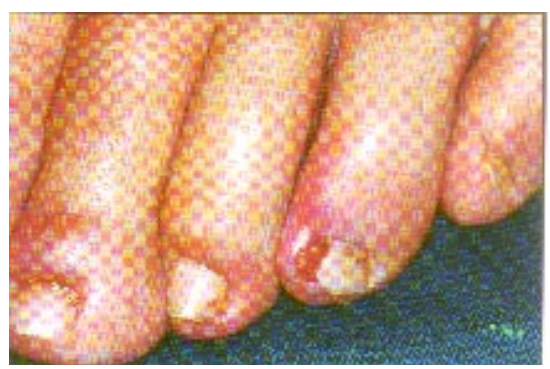

Fig. 3. Retinoid-induced multiple pyogenic granulomas of the toenails.

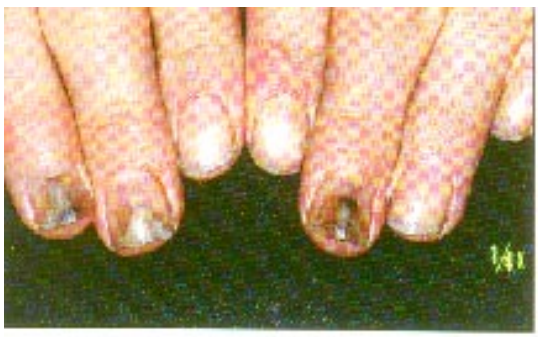

Fig. 4. Drug-induced type II photo-onycholysis. Nail plate/nail bed separation involves the central portion of the distal nail of several fingers. Subungual haemorrhages are present.

Photo-onycholysis can occur at any time during treatment and sometimes even after discontinuation of drug intake, indicating persistence of the drug in the skin. It may be painful, and pain may even precede the development of the nail changes. A photosensitivity reaction of the skin is often associated.

Photo-onycholysis usually regresses spontaneously after drug withdrawal; psoralen-induced photo-onycholysis may regress spontaneously even if treatment is not interrupted. Readministration of the drug does not always induce a recurrence.

The drugs that most commonly produce onycholysis are tetracycline (especially demeclocycline and doxycycline)[20] and psoralens,[21-22] both with natural sunlight and with artificial sources [psoralen plus ultraviolet A (PUVA)]. Other drugs that can occasionally cause photo-onycholysis include thiazide diuretics, oral contraceptives, quinolones,[23] captopril, enalapril and practolol.

Photo-onycholysis is rare in dark skinned individuals and can be prevented with the topical application of coloured nail varnishes on the nail plate, in order to protect the nail bed from exposure to light. Patients should be instructed to avoid prolonged sun exposure during treatment with drugs known to produce this adverse effect.

2.2.3 Apparent Leuconychia

Apparent leuconychia describes a white pigmentation of the nail that results from an alteration of the nail bed. In a normal nail the nail bed is visible through the transparent nail plate and appears pink due to the rich vascularisation. Abnormalities of the nail bed blood flow result in modification of its colour.

Drug-related apparent leuconychia may show two clinical features: half-and-half nails and Muehrcke's lines. In half-and-half nails, the proximal portion of the nail shows an abnormal white colour, which obscures the lunula, while the distal half of the nail is pink, reddish or brown in colour. Half-and-half nails are usually an adverse effect of chemotherapy.[24]

Chemotherapeutic agents are also a common cause of Muehrcke's lines. These appear as multiple transverse whitish opaque bands, parallel to the lunula, separated from each other by a strip of normally pink nail bed (fig. 5).

Muehrcke's lines were first described in patients with hypoalbuminaemia.[25] Each band was related to an episode of hypoalbuminaemia and a consequent oedema of the nail bed papillary dermis. After the initial description, several other systemic diseases and drugs have been associated with the development of Muehrcke's lines, especially cytotoxic drugs.[26] The exact mechanism by which chemotherapeutic agents may induce Muehrcke's lines is still unknown.

Both drug-induced half-and-half nails and Muehrcke's lines are asymptomatic, do not require

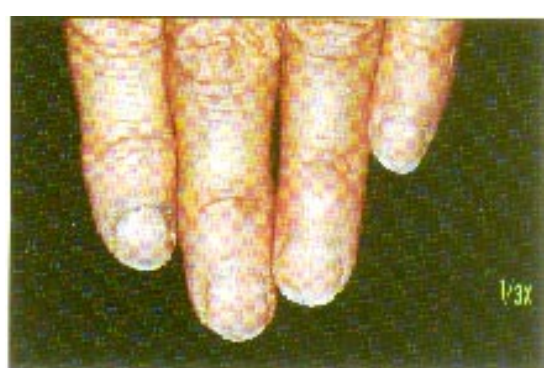

Fig. 5. Chemotherapy-induced Muehrcke's lines.

any treatment and disappear after withdrawal of the drug.

2.3 Paronychia

In acute paronychia the nail folds appear intensely red, erythematous and extremely tender. Drug-induced paronychia may involve 1 or several nails and usually develops soon after drug administration.

Paronychia frequently develops during methotrexate treatment (fig. 6).[27] The pathogenesis is still unclear: either a toxic effect of the drug on the nail matrix and nail fold epithelia or an acute pyogenic infection in an immunocompromised patient may be implicated. Paronychia gradually resolves after treatment interruption and is frequently followed by the development of onychomadesis.

Acute paronychia is a common adverse effect of oral retinoids, both etretinate and isotretinoin, where it seems to be due to retention of scales under the proximal nail fold and consequent foreign body inflammatory response.[28]

Paronychia and pseudopyogenic granulomas of several nails have been recently reported in HIV-infected patients receiving multiple-drug therapy including the nucleoside analogue lamivudine[29] and/or the protease inhibitor indinavir.[30-31]

The antibacterial cefalexin has been reported to induce a fixed drug eruption resembling acute paronychia.[32]

2.4 Drug-Induced Alteration of the Nail Blood Flow

Drug-induced vascular abnormalities involving the nail include both haemorrhagic and ischaemic changes.

2.4.1 Haemorrhages

Drug-induced haemorrhages range from splinter haemorrhages, which indicate involvement of the nail bed capillaries, to purpura or haematoma of the nail bed, which result from subungual haemorrhage. These signs usually appear in the toenails, which are more exposed to traumas. Blood extravasation is a frequent finding in drug-induced photo-

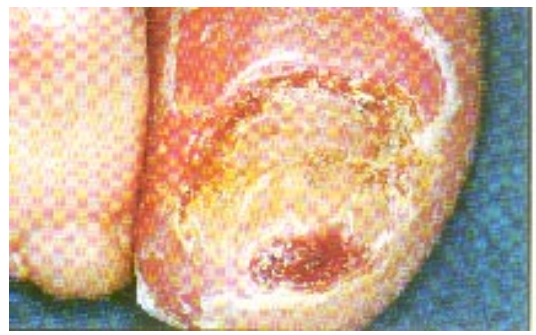

Fig. 6. Paronychia in a patient treated with methotrexate. Acute inflammation of the periungual folds associated with loss of the nail plate.

onycholysis, especially due to quinolones.[23] Cancer chemotherapeutic agents may be responsible for the development of splinter haemorrhages and subungual haematoma due to thrombocytopenia. Docetaxel has been very commonly associated with this adverse effect.[33] The anti-inflammatory agents aspirin (acetylsalicylic acid), acetalinide and penicillamine are a common cause of subungual haemorrhages, which result from their antithrombotic effect.[34] Warfarin and other anticoagulants may also cause nail bed haemorrhages.[35]

2.4.2 Ischaemic Changes

Drug-induced impaired nail vascularisation ranges from Raynaud's phenomenon to digital gangrene.

Raynaud's phenomenon is a common adverse effect of both systemic and intralesional bleomycin administration, occurring in up to 37% of patients.[36] Bleomycin can also be responsible for fingertip gangrene. Both bleomycin-induced Raynaud's phenomenon and digital gangrene are possibly related to the sclerodermatous changes that follow alterations of the dermal matrix (increased synthesis of collagen and glucosaminoglycans) induced by the drug.[37]

Digital gangrene can be a serious adverse effect of β-blocker administration.[38] This is usually seen in patients who already have peripheral vascular diseases and is due to the decreased cardiac output (caused by the β_1 adrenoceptor blockade

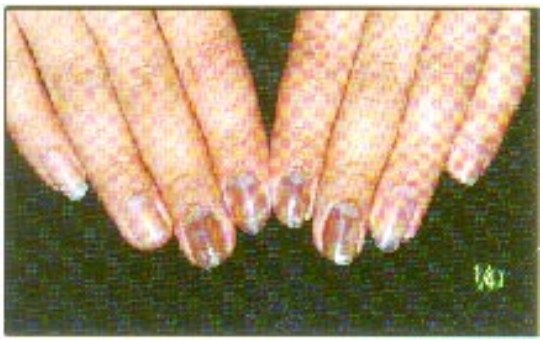

Fig. 7. Drug-induced melanonychia. Diffuse or banded black pigmentation of several nails.

exerted by these drugs) that can not be balanced by peripheral vasodilation (due to the β_2 adrenoreceptor blockade of these drugs, i.e. particularly β-blockers which are not cardioselective). Impaired distal perfusion leads to peripheral gangrene. Drug withdrawal is not always associated with regression of the symptoms and digit or limb amputation is often the final outcome.

2.5 Drug-Induced Nail Pigmentation

2.5.1 Melanic Pigmentation

A toxic effect of drugs on nail matrix melanocytes may induce their activation with production of melanin.[39] This is more frequent in dark skinned than in fair skinned individuals. Activation of a cluster of melanocytes will produce a single longitudinal pigmented band, known as longitudinal melanonychia, while diffuse activation of melanocytes will give rise to a pigmentation of the whole nail plate. The nail may therefore show 1 or multiple longitudinal bands brown to black in colour, or may be diffusely pigmented (fig. 7). More rarely, melanocyte activation produces transverse pigmented bands parallel to the lunula, alternating with bands of normal colour, indicating an intermittent production of melanin. Transverse melanonychia is an adverse effect of cancer chemotherapeutic agents and each band corresponds to a course of chemotherapy.

Nail pigmentation due to nail matrix melanocyte activation is a common adverse effect of cancer chemotherapeutic agents.[40] Of these, the most commonly responsible for melanic nail pigmentation are cyclophosphamide, doxorubicin, fluorouracil, bleomycin and hydroxycarbamide (hydroxyurea). Combination of these drugs increases the possibility of melanocyte activation. Other drugs that frequently induce longitudinal melanonychia or diffuse nail pigmentation are zidovudine,[41] psoralens and radiation therapy.[42]

Drug-induced nail pigmentation typically involves several nails and is usually reversible. Interruption of melanin-production by nail matrix melanocytes may, however, take years after drug withdrawal.

Differential diagnosis with nonmelanocytic pigmentation can be made with microscopic observation of nail clipping stained with Masson-Fontana stain, which indicates melanin granules.

2.5.2 Nonmelanic Pigmentation

Although drug-induced nail pigmentation is most commonly due to melanin production by nail matrix melanocytes or may result from subungual haemorrhages, some drugs may be responsible for nail discolouration of other origin.[43]

This occurs when drugs are excreted via the nail matrix and stored within the nail plate, being eventually eliminated with nail growth. A yellow discolouration of the nails which is fluorescent under Wood's light has been reported in patients treated with tetracycline, and is due to drug incorporation within the nail plate.[44] Deposition of the drug within the nail plate is also the cause of the dark-brown nail pigmentation observable in patients treated with the antileprosy drug clofazimine.[45] A pink-brown discolouration of sun-exposed areas of the skin is commonly associated. Gold particles stored within the nail plates may produce a characteristic yellow nail discolouration in patients treated with gold salts for rheumatoid arthritis.[46]

In other cases nail discolouration involves the subungual area, due to deposition of pigment (drug, haemosiderin, or melanin) in the dermis. Typically, the pigmentation does not move as the nail grows and is often associated with pigmentation of the skin and mucosae.

Minocycline can rarely be responsible for a blue-grey pigmentation of the nail that spares the lunula region and is associated with pigmentation of skin, sclerae and mucous membranes.[47] Minocycline-induced nail pigmentation is possibly due to dermal deposition of an iron chelate of the drug. Other tetracycline derivatives can be responsible for cutaneous and nail pigmentation.

Skin, nail and eye pigmentation can also be observed in patients treated with antimalarials. The nails show a blue, brown or grey pigmentation that does not move distally with nail growth.[48] Drug discontinuation leads to a decrease in intensity of the pigmentation that does not usually resolve completely.

3. Drug-Induced Nail Malformations in Newborns

Some drugs taken by mothers during pregnancy may induce nail malformations in their children. Nail hypoplasia, usually associated with distal digit malformation, has been reported in newborns of mothers treated with trimethadione, carbamazepine, warfarin and phenytoin.[2] In some cases nail hypoplasia may spontaneously regress during the first months of life. Alcohol abuse during pregnancy may also produce similar malformations.

Administration of valproic acid (sodium valproate) during pregnancy has been associated with long thin digits with hyperconvex nails in the newborns.[49]

4. Diagnosis

An accurate clinical history is essential to confirm the diagnosis of drug-related nail changes. Rechallenge is not useful, since most drugs induce nail abnormalities through mechanisms that are not well understood and the nail symptoms may not re-occur even in the same patient. In some cases nail changes may even disappear without interrupting treatment.

Longitudinal melanonychia due to drugs should be differentiated from longitudinal melanonychia due to nail matrix nevi or nail matrix melanoma. In doubtful cases a nail matrix biopsy can be considered.[50]

5. Treatment

There are no effective treatments for nail abnormalities due to a transient impairment or arrest of nail matrix mitotic activity. The abnormalities of the nail plate will disappear with nail growth. It is, however, important to tell patients that this will require several months.

Nail fragility can be partially improved by oral biotin administration (5 mg/day)[51] and careful avoidance of exposure to chemicals and strong detergents that can worsen the nail changes.

Management of drug-induced onycholysis includes keeping the nails short, local application of antimicrobial solutions and avoiding contact with irritants. Scarring of the nail bed with a persistent nail dystrophy may be the final outcome of severe cases.

In drug-induced paronychia and periungual inflammation we usually prescribe a topical corticosteroid to be applied in the evening and a topical antibiotic to be applied in the morning.

Nail pigmentation may persist unchanged for years after drug interruption. When the pigmentation involves fingernails of women, application of coloured nail lacquers is useful to improve the aesthetic appearance.

6. Conclusions

Drug-induced nail changes are quite common, and usually indicate a transient damage to the nail constituents.

Adequate knowledge of the possible adverse effects of a drug on the nail may be helpful to prevent their development and to avoid diagnostic problems.

Cancer chemotherapeutic agents are the most frequent cause of nail changes, which are a sign of their antimitotic activity and cytotoxic effect. Nail abnormalities, usually associated with hair loss and signs of mucosal damage, include Beau's lines, onychomadesis, nail fragility, melanocytic pig-

mentation, onycholysis, paronychia and vascular problems.

Retinoids are another frequent cause of nail abnormalities, ranging from asymptomatic nail brittleness to a painful and distressing paronychia.

Photo-onycholysis is the most frequent adverse effect of tetracyclines and this should be considered when prescribing these drugs during summer months.

Photo-onycholysis can also be a serious adverse effect of psoralens, which most commonly cause a brown to black diffuse or banded nail pigmentation due to nail matrix melanocyte activation.

The occurrence of subungual haematomas or haemorrhages involving several nails should always raise the suspicion of anticoagulant drug intake.

In addition to the abovementioned drugs, which are well known to induce nail changes, numerous other drugs have only occasionally been associated with the development of nail abnormalities.

Diagnosis of drug-induced nail changes is suggested by the involvement of several or all nails, the development of the nail changes during drug intake and their spontaneous disappearance after drug withdrawal. The diagnosis is always confirmed by recurrence of the nail abnormalities with drug readministration even though this does not necessarily occur.

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