Review

An overview of management of drug-induced hair and nail disorders

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Practice Points

- Educating the patient is central for managing drug-induced hair and nails disorders as they should have realistic expectations for their individual circumstance and that recovery could take months to years.
- Scalp cooling is the only effective intervention to potentially prevent chemotherapy-induced alopecia; however, it is ineffective for taxotere, adriamycin and cyclophosphamide regimens.
- In most cases of alopecia, hair regrows completely. Topical minoxidil accelerates hair regrowth in drug-induced anagen effluvium and is more rarely used in such cases of telogen effluvium.
- Permanent alopecia after chemotherapy can occur with busulphan, cyclophosphamide, thiotepa, carboplatin, cisplatin, etoposide, docetaxel and paclitaxel. This type of alopecia can be more prominent on the androgen-dependent scalp region. It is possibly caused by acute miniaturization due to stem cell damage. It can be clinically and pathologically misdiagnosed as androgenic alopecia.
- When addressing nail disorders it important to remember that most cases will not need any treatment and the defect will grow out or be reversed once the drug is discontinued.
- Certain drugs, including chemotherapeutics, EGFR inhibitors and multi-target signaling inhibitors, cause both hair and nail disorders.

The diagnosis and management of drug-induced hair and nail disorders in the clinic presents a unique challenge for the physician. Not only must the physician recognize the trigger and manage the symptoms but also consider the influence these disorders have on the patient's quality of life. This article describes the various types of drug-induced hair and nails disorders, and discusses the clinical recognition, pathophysiology and possible management options.

Keywords: anagen effluvium • EGFR inhibitors • hemorrhagic onycholysis • leukonychia • multi-target drugs • nail pigmentation • onychomadesis • permanent alopecia • pyogenic granulomas • taxanes • telogen effluvium

Physiology of hair growth

The human body is covered by two different types of hair, vellus hair and terminal hair, depending on the area of skin [1]. Every follicle is capable of developing vellus or terminal hair according to environmental stimuli. This is seen in the axillary and pubic area follicles, which initially grow fine vellus hair and change to thick terminal hair when signaled by sex hormones during puberty [1]. Vellus hairs are short, colorless, soft, and can be found on face of children and adult women. Terminal hairs are longer, pigmented, coarse, and can be found on eyelashes, eyebrows and in the scalp [2].

Each hair follicle cycles through three different phases: anagen, catagen and telogen [3]. During anagen, which is the longest phase

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lasting between months to years, the follicle produces hair continuously. Duration of anagen influences the length of the hair, however, this differs between individuals and location of hair such as scalp versus axilla [1]. The next transient phase, catagen, involves the hair follicles regressing and in part undergoing apoptosis to prepare for the next phase [2]. Telogen is the resting phase and lasts for about 3 to 4 months. Thereafter, the telogen hair is shed and the cycle is re-entered [1].

In a normal scalp, approximately 80–90% of hairs are in anagen. The mitotic activity in anagen follicles is comparable to one of the fastest tissue turnover rates in the body, such as mucous membranes. Due to the increased mitotic activity, anagen follicles are most vulnerable to toxic insults, while catagen and telogen follicles are not as jeopardized by toxic insults as their mitotic activity is significantly decreased. Thus, regions with the most proportion of anagen follicles, such as the scalp, are more traumatized by noxious events compared with regions with the least proportion of anagen follicles, such as the eyelashes [1].

Pathophysiology of drug-induced hair loss

Numerous medications may interfere with the normal hair growth cycle and induce hair loss [1,4–5]. Diagnosis of drug-induced alopecia can be challenging and can only be proven by observing improvement after withdrawing the suspected drug [4]. Fortunately, drug-induced hair loss is often reversible after discontinuation of the implicated treatment. The main types of hair loss are telogen effluvium and anagen effluvium [1]. Rarely permanent hair loss can occur after complete destruction of the hair follicle due to specific therapies. The extent of alopecia depends on the type of hair loss, the drug, its dosage, and the individual's susceptibility [5].

Drug-induced hair loss

Telogen effluvium

Telogen effluvium leads to excessive shedding of telogen hair and is the most common cause of drug-induced hair loss. Drug-induced telogen effluvium should be distinguished from other known telogen effluvium causes such as febrile illness, thyroid disorders, psychoemotional stress, and iron and Vitamin D deficiency [6]. Drug-induced telogen effluvium is most commonly caused by premature interruption of anagen due to the toxic effect of the drug (Box 1). More rarely, it may be caused by premature detachment of the club hair from the follicle, or may occur after discontinuation of a drug that prolongs the anagen phase [5]. Hair loss occurs 2–4 months after initiating treatment and the hair loss is variable, ranging from 100 to more than 300 hairs shed daily. The scalp hair is often the main target and the hair density may be normal or reduced, depending on the percent of follicles involved [1,2]. Telogen effluvium most commonly resolves spontaneously and no treatment is necessary [1].

Telogen effluvium can trigger or worsen androgenetic alopecia in susceptible patients. In this case withdrawing the causative drug may not improve hair thinning and more definitive treatment with topical minoxidil and finasteride may be required [5].

Anagen effluvium

Anagen effluvium is an acute and extreme form of hair loss that is most commonly associated with antineoplastic agents (Figure 1). The hair loss begins within 7–10 days of drug administration and becomes more apparent with time [2]. The mechanism is due to abrupt impairment of mitotic activity of the rapidly dividing hair matrix cell of the anagen follicle [1]. Some inflammatory and systemic diseases, such as alopecia areata, systemic lupus erythematous and secondary syphilis, can also diminish the metabolic activity of hair follicles and lead to anagen arrest [7]. Anagen effluvium is more common and severe with combination chemotherapy than with treatment with a single agent [2]. Anagen effluvium can occur together with telogen effluvium [1]. The temporary alopecia involves nearly all of the scalp hair, eyebrows and eyelashes [5]. Full regrowth is expected in majority of cases, but the patient should be educated that the recovery will take several months [1]. In some cases diffuse, permanent alopecia has been reported [2].

Anagen effluvium is almost exclusively observed after treatment with chemotherapy medications, especially taxane-based regimens [2]. Chemotherapy-induced alopecia can have negative psychosocial effects on the individual's quality of life. Scalp hypothermia and topical minoxidil are options to potentially avoid or improve this adverse side effect [5].

Currently, scalp hypothermia is the only effective option to partially prevent chemotherapy-induced alopecia. The scalp cooling is usually applied continuously starting 30 minutes before until 90 minutes after chemotherapy infusion. A subcutaneous scalp temperature of -18°C is required for hair preservation. Cooling can be obtained with an ice cold cap or with special cooling systems consisting of a small compact mobile refrigeration system connected to lightweight silicone caps attached to the chemotherapy chairs (Paxman®; Paxman Coolers Ltd, Huddersfield, UK). A recent literature review indicates that this technology allows for 63.5% of patients to have a good preservation of their hair [8]. The best outcomes are experienced in patients on regimens involving single agents such as anthracyclines or taxanes, rather than combination regimens [8]. The theory behind scalp cooling is twofold, the first

part involves vasoconstriction and the second includes reduction of biochemical activity. Vasoconstriction decreases the blood flow to the hair follicles during the maximal concentrations of the antineoplastic agents, which should decrease the uptake of these toxic chemicals. The reduction of biochemical activity makes the hair follicles less vulnerable to injury by the antineoplastic agents [9,10]. The largest prospective multicenter study involving 1411 scalp-cooled patients found that 50% did not wear a head cover during their last chemotherapy that normally would have caused severe chemotherapy-induced alopecia. They also showed that scalp hypothermia is effective for most agents except for the taxotere, adriamycin and cyclophosphamide regimen in which scalp cooling is not useful [9].

Topical minoxidil cannot prevent hair loss due to chemotherapy but it can accelerate hair regrowth afterwards [11]. One trial showed a trend of reducing the period of baldness by more than 1 month in patients using minoxidil [11]. The exact mechanism by which topical minoxidil helps hair regrowth is not completely understood; however, it is thought to trigger follicles in the latent part of telogen to progress onto the anagen growth phase and to prolong the anagen phase [12]. In cases with chemotherapy-induced alopecia once the chemotherapeutic agent has been cleared by the body, topical minoxidil facilitates hair regrowth by promoting follicles to the phase that will allow for hair growth and remaining in that phase for a longer period of time.

Permanent alopecia

Chemotherapy is known to cause reversible alopecia; however, there are cases of dose-dependent chemotherapy-induced permanent alopecia [13,14]. The drugs implicated for permanent alopecia include busulphan, cyclophosphamide, thiotepa, carboplatin, cisplatin, etoposide, docetaxel, and paclitaxel [13–19]. These chemotherapies were shown to reduce hair density, alter texture, leading to short and thin hair, and in some cases caused hair loss in an androgenic alopecia pattern [14,19]. Busulphan and cyclophosphamide conditioning is used prior to bone marrow transplants and permanent alopecia is a frequent complication occurring in 30–42% of adult and children patients [13,15–17]. The pathology in permanent alopecia postchemotherapy exhibits an absence of fibrosis, a preserved number of follicular units, terminal:vellus ratio close to 1:1, and is suggestive for acute miniaturization [14]. As hair loss is sometime more severe in the androgen-dependent scalp region and pathology shows a presence of miniaturized hairs, it is important for dermatologists not to confuse permanent alopecia postchemotherapy with androgenic alopecia [14]. The pathogenesis is not fully understood but is thought to be due to hair follicle stem cell depletion or perhaps acute damage to keratinocytes in the lower segment of some follicles [13].

Box 1. Drugs that cause telogen effluvium.

- Anticoagulants
- Antidepressants
- Antineoplastic agents
- Antiretroviral drugs
- Antithyroid drugs
- Anxiolytics
- Aromatase inhibitors (formestane and letrozole)
- Bromocriptine
- Esterified estrogens-methyltestosterone replacement therapy
- Fluoroscopy
- Gonatotropin-releasing hormone agonist
- Immunosuppressive drugs
- Interferons
- Mercury poisoning
- Minoxidil
- Mood stabilizers (lithium and valproic acid)
- Oral contraceptives
- Progestin-releasing implants
- Psychotropic drugs (amphetamines, levodopa and methyldopa)
- Retinoids
- Thallium poisoning

Cicatricial alopecia is the end result of irreversible insult to the follicular stem cells, disabling repair and regeneration of the follicle [2]. Cicatricial or scarring alopecia is permanent hair loss associated with radiation therapy and lichen planopilaris secondary to angiotensin-converting enzyme inhibitors and β-receptor blocking agents [5].

Currently, topical radioprotectors, growth factors and other agents that could minimize damage are being investigated [2]. A study looking at the protective effects of vitamin D3 in rats found that pretreatment before radiation helped preserve significantly more hair follicles than the control group [20]. This suggests that administration of vitamin D3 may protect hair follicles from the toxicity of radiation; however, further investigation is necessary to elucidate this mechanism. In a Phase I study, topical tempol, a nitroxide radioprotector shown to protect against radiation-induced alopecia in a murine model, was well tolerated on the scalps of patients receiving whole-brain radiation [21]. With the promising results of three of the five patients having had full scalp hair retention, a Phase II study using a different formulation to increase exposure of tempol to the scalp is underway.

Drug-induced hair growth

Excessive hair growth, specifically hirsutism and hypertrichosis, can be an adverse reaction precipitated

Figure 1. Microscopic examination of dystrophic broken roots in anagen hair loss due to chemotherapy-induced alopecia. 10× magnification.

by medications. Hirsutism is an abnormal type of hair growth pattern with masculine features seen in women [1]. The growth is due to androgenic stimulation of hormone sensitive follicles and involves the face, trunk and extremities [4]. Drug-induced hirsutism is often associated with other features of hyperandrogenism, including acne, seborrhea and androgenic alopecia [1]. Anabolic steroids, testosterone, corticotrophin and oral contraceptives of the nonsteroid progesterone class are the most common cause of drug-induced hirsutism [4].

Hypertrichosis is characterized by growth of hair in areas of the body where the hair is typically short, such as on the forehead and temporal aspects of the face. It is dependent on drug dosage, reversible after discontinuing the drug, and independent of hormone stimulation. The drugs associated with hypertrichosis are glucocorticosteroids, cyclosporine, phenytoin, diazoxide, minoxidil, tretinoin, prostaglandin analogs and acetazolamide [1].

Most of the drugs associated with unwarranted hair growth cannot be discontinued. Thus, patients can manage the symptoms with cosmetic options to remove the excess hair. Patients can utilize shaving, plucking, electrolysis, lasers or broad-based light devices to groom the area affected by drug-induced hirsutism [22]. Similarly, patients with hypertrichosis can enhance their appearance with waxing or bleaching the unwanted hair [1].

Change in hair color

Drug-induced changes in hair color are an occasional finding due to medications that alter enzymes responsible for melanin production; however, a few agents may affect hair color through unknown mechanisms [2,4]. Hypopigmentation of hair color has been reported with sunitinib, chloroquine, IFN-α, cyclosporine A and etretinate [5,23–24]. By contrast, hair darkening has been reported with imatinib, estrogens, prostaglandin analogs and tamoxifen [24,25]. Hair can seem to be darker with chemotherapeutic agents like methotrexate and sunitinib, which can cause alternating bands of color known as the flag sign [26].

Change in hair structure

Drug-induced structural hair changes can also occur [4]. Chemotherapeutic agents, lithium, valproic acid, retinoids, and indinavir may cause curling or straightening of hair [24]. Chemotherapy agents including docetaxel, doxorubin, cyclophosphamide and 5-flurouracil cause a reduction in the mean diameter of hair. They also increase the maximal diameter to minimum diameter ratio in regrowing hair. Together, these two findings suggest that chemotherapy-induced damage to the hair follicle leads to thinner hair, which causes altered shape [27]. Anecdotes of IFN-α plus ribavirin have caused both hair curling and straightening [28]. Further research is warranted to find preventative measures against chemotherapy-induced alopecia and the secondary associated hair changes or to determine how to restore hair to prechemotherapy condition.

Diagnosis & patient education of drug-induced hair disorders

Diagnosis

Confirming the suspected agent can be a challenging process. A good history of all medications taken 4 months prior to the beginning of the hair loss will provide a likely culprit for drug-induced hair loss. A pull test with examination of the hair under a microscope may help to ascertain the type of alopecia. A pull test is performed by pulling hairs between thumb and finger over 6–8 locations on the scalp of recently washed hair. If there is more than the normal 2 to 6 hairs pulled out, this represents excessive shedding or a positive pull test. Common hair disorders associated with a positive pull test include acute telogen effluvium, anagen effluvium, alopecia areata and androgenetic alopecia in the affected area. Thereafter, certain microscopic findings help distinguish the differential diagnosis of the common hair disorders. Telogen hairs, which have a club shape and small bulb of keratin on the ends, are seen in telogen effluvium and androgenetic alopecia. Broken dystrophic hairs where the fiber is broken at the keratogenous zone are found in patients with anagen effluvium and alopecia areata [29]. For cases of drug-induced hair loss, hair regrowth can take 2–3 months after withdrawing the agent [5].

Patient education

Educating the patient is a crucial part of managing drug-induced alopecia. The physician should explain

the hair growth cycle and the temporal link between the implicated agent and the hair loss [30]. Patients undergoing antineoplastic treatment that can induce hair loss should be prepared for the acute hair loss before starting their chemotherapy regimen [1]. Realistic expectations should be discussed in terms of the time expected to achieve normalization of hair regrowth. For example, once the trigger is determined and discontinued, hair shedding should slow down but can take up to 6 months [31]. Regrowth can be perceived 3–6 months after withdrawing the drug; however, noticeable regrowth may take 12–18 months [31,32]. In most cases the hair loss is reversible and after stopping the implicated drug no further treatment is necessary [5].

Physiology of nail growth

The constituents of the nail apparatus include the nail bed, nail matrix, hyponychium, nail plate, and the lateral and proximal nail folds (Figure 2) [2]. The germinal epithelium of the nail matrix, located under the proximal nail fold, produces the nail plate [33]. The nail plate growth begins proximally and extends distally while tightly residing on the nail bed [34]. The nail plate adheres to the nail bed until the level of the hyponychium, where the nail plate naturally detaches from the underlying tissue. The lateral and proximal nail folds have a cuticle that hugs the nail plate sealing it off from external insults [2].

The keratinization process is essential to produce the hard and transparent nail plate that is made up of matured cells that have lost their nuclei [33]. The maturation and differentiation of the cells occurs in an upward and distal manner [34]. Thus, the proximal matrix forms the dorsal nail plate and the nail bed forms the ventral nail plate [33]. The lunula is the distal portion of the nail matrix, which appears as the white distally convex crescent-shaped base of the nail. The average nail growth rate of a fingernail is 3 mm per month and a toenail is 1 mm per month. The growth rate can be affected by age, systemic diseases and drugs [34].

Drug-induced nail disorder

Drug-induced nail disorders are an infrequent adverse reaction. Nail abnormalities caused by drugs are usually due to acute damage to the nail unit and the symptoms correspond to the nail structure that is

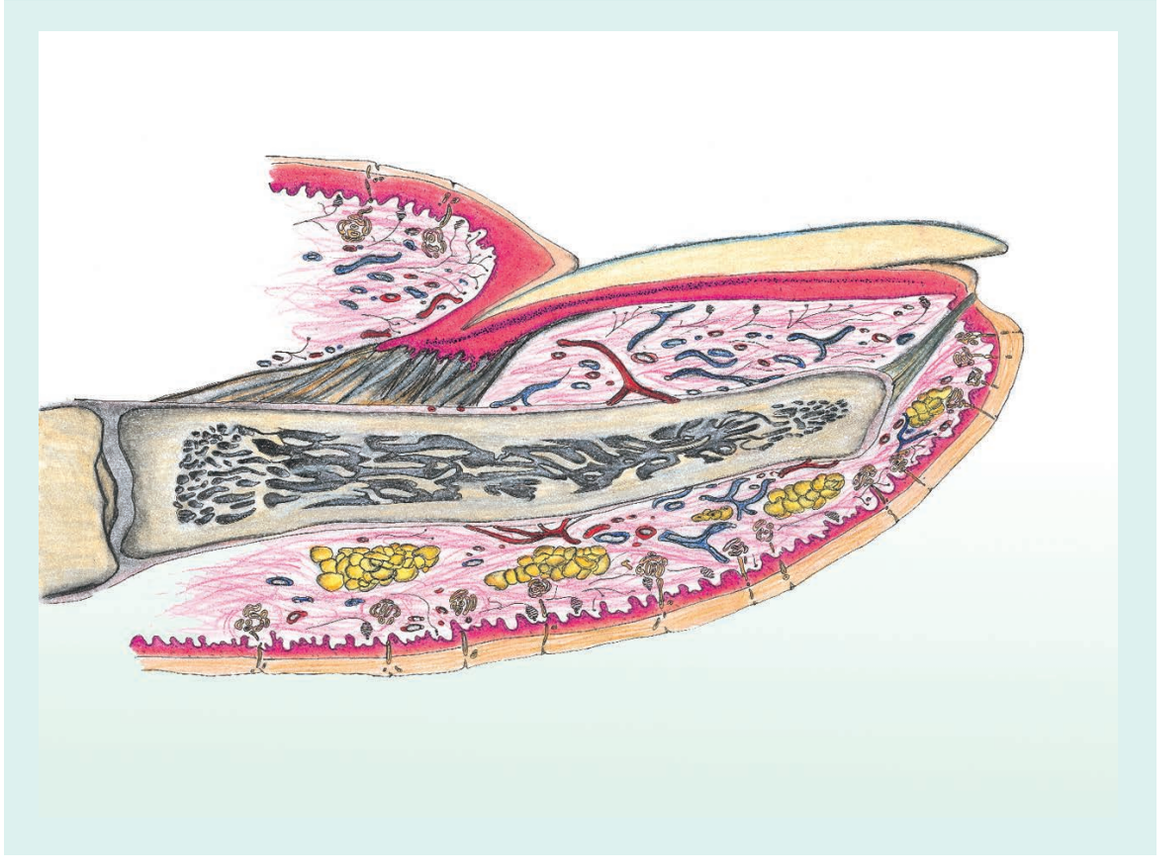

Figure 2. Longitudinal section of a normal nail.
Drawing courtesy of Luca Lionello.

involved [35]. The nail changes can range from a painless cosmetic issue to substantial impairment due to excruciating pain that may involve a few or all of the nails. The abnormalities may occur weeks after the drug administration because of the slow nail growth rate, which can make associating the symptom and the drug quite challenging. Complicating the diagnosis further is the fact that the nail symptoms often recover without discontinuation of the drug. Interestingly, rechallenge is frequently negative and the pathogenesis of the nail trauma is not entirely understood [33,35–36]. Drug-induced nail abnormalities are usually temporary and are reversed once the agent is withdrawn but in some cases they may be permanent [35].

Drug-induced nail changes due to nail matrix damage

Many drugs may disrupt the normal keratinization of nail matrix keratinocytes. A critical assault can cause an acute reduction or arrest of the mitotic activity of the nail matrix keratinocytes, which would surface as a Beau's line or an onychomadesis, while a milder assault will appear as nail plate thinning or diminished nail growth rate. Also seen with temporary injury of the nail matrix is true transverse leukonychia [34].

Beau's lines & onychomadesis

A transient pause in nail growth leads to a plate known as Beau's lines. Clinically, Beau's lines present as transverse depressions concurrently appearing on every nail plate (Figure 3) [2]. The depth of the depression correlates with the extent of matrix keratinocyte toxicity, while the longitudinal width correlates with the duration of the toxicity [35]. Onychomadesis is a severe form of Beau's lines caused by complete matrix injury leading to nail plate shedding [2,33]. Onychomadesis appears as a whole thickness sulcus that separates the nail into two parts [33,36]. Patients may complain about pain in the area of clefting because this is where the nail bed is not covered by the nail plate and is susceptible to trauma [34].

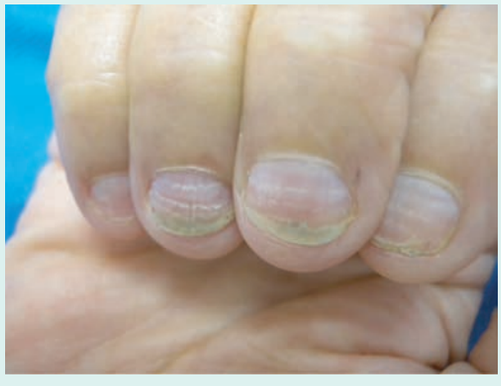

Figure 3. Beau's lines and true transverse leukonychia affecting all the nails at the same level.

Always consider a drug when the symptoms affect every nail at matching regions (Box 2). Any medication taken in the past 2–3 weeks before the onset of the nail symptoms should be suspected because fingernails take about 40 days to grow from the proximal nail fold [36]. Drugs most often associated with these symptoms include chemotherapy agents (taxanes), retinoids and radiation therapy [35,37]. These symptoms have also been reported with the use of tetracyclines, sulfonamides, dapsone, carbamazepine, cefaloridine, cloxacillin, fluorine, itraconazole, lithium, metoprolol, phenophtaleine and psoralens [38,39]. Hydantoin, trimethadione and valproic acid can be responsible for onychomadesis [35]. Other causes for Beau's lines and onychomadesis involving all nails include high fever and infection, particularly viral [40,41].

There is no prevention nor treatment necessary as they will move distally as the nail grows out [36]. Drug-induced Beau's lines and onychomadesis are reproducible with recurring series of drug administration [33].

True transverse leukonychia

True transverse leukonychia occurs when the distal nail matrix keratinocytes are temporarily impaired and retain their nuclei (parakeratosis) in the nail plate [2,36]. This appears as one or several white, transverse band across the nail plate of all the nails at the same level (Figure 3) [36]. These opaque bands are typically 1–2 mm in width [33]. This sign has been associated with chemotherapy agents, especially doxorubicin, cyclophosphamide, adriamycin and vincristine [42,43]. Other drugs reported to cause this symptom are retinoids, corticosteroids, cyclosporine A, fluorine, penicillamine, pilocarpine and sulfonamides [36]. Individuals after lead intoxication, arsenic poisoning and thallium poisoning develop Mees' lines, which are bands of transverse leukonychia affecting the entire width of the nail plate on most or all fingernails [35,36].

The bands of transverse leukonychia will extend distally with the nail plate and eventually grow out [34].

Nail thinning/nail fragility/nail brittleness

Nail thinning is a consequence of diffuse damage to the proximal nail matrix and involves the entire nail length [36]. Nail fragility is caused by mild damage to fully keratinized nail plate or damage to the nail matrix that changes the nail plate production [33]. Antineoplastic drugs can cause nail fragility due to altered nail plate production [35]. Damage to the distal matrix will likely affect the shape of the nail plate-free

edge and not the superficial nail plate [33]. There are two types of nail fragility – lamellar onychoschizia and onychorrhexis. Lamellar onychoschizia may involve the whole nail plate and appears to have a lamellar exfoliation of the superficial layer of the nail plate. Antiretrovirals and retinoids are associated with lamellar onychoschizia. Onychorrhexis is a single split at the free edge of the nail plate that may extend toward the proximal end [36]. Other causes of nail brittleness include repeated trauma, excessive contact with chemicals, nutritional deficiencies (anemia), diseases involving the nail matrix (psoriasis), and metabolic and endocrine disorders (thyroid disorders) [44].

Managing brittle nails includes avoidance of repeated immersion of hands in soap and water. Avoiding repeated use of nail polish removers will help sidestep the dehydration that can occur. Keeping nails short, cuticles untouched, and wearing rubber gloves over cotton gloves during housework are a few rules to help prevent nail plate dehydration. Nail moisturizers containing occlusives, humectants and proteins may be helpful [45]. Oral biotin supplements (5 mg/daily) may help strengthen nails [46].

Nail growth rate alteration

Certain drugs are shown to speed up or slow down the nail growth rate. The mechanism of how drugs speed up nail growth is still unknown. The decrease in nail growth is understood as a reduction of mitotic activity of the nail matrix keratinocytes [36]. Fluconazole, itraconazole, levodopa, and oral contraceptives are associated with an increased nail growth [47,48]. Whereas azidothymidine, zidovudine, cyclosporin A, heparin, lithium, and methotrexate are known to decrease nail growth [33,35–36]. Retinoids are unique because they have been observed to increase and decreased nail growth [36].

Nail growth rate normalizes once the drug causing the alteration is discontinued [34].

Drug-induced nail changes due to nail bed damage

Onycholysis

Onycholysis is a consequence of severe toxicity to the nail bed characterized by the loss of adhesion between the nail plate and nail bed [35]. The nail plate is separated from the nail bed and this appears to be white [33]. It is possible for a painful hemorrhagic bulla to be present under the nail plate [34]. Treatments that can cause onycholysis include taxanes, tetracyclines, fluoroquinolones, psoralens, NSAIDs, captopril, retinoids, phenothiazines, clofazimine and sodium valproate [4,35].

Onycholysis is reversible, in some cases without even discontinuing therapy. Patients can prevent microbial colonization by soaking affected fingers in antiseptic solution, particularly those with subungual bulla [36]. Other recommendations include clipping away the detached nail plate every 2 weeks until the nail plate grows adhered to the nail bed and gently drying the exposed nail after each hand washing [45].

Box 2. Drugs that cause Beau's lines and onychomadesis.

Drugs that cause Beau's lines
- Arsenic
- Chemotherapy agents
- Dapsone
- Fluorine
- Metoprolol
- Penicillamine
- Psoralens
- Retinoids
- Sulfonamides
- Tetracyclines

Drugs that cause onychomadesis
- Anticonvulsants
- Arsenic
- Cefalosporine
- Chemotherapy agents
- Cloxacillin
- Gold
- Lithium
- Mepacrine
- Oral contraceptives
- Retinoids
- Sulfonamides
- Tetracyclines

Photo-onycholysis

Photo-onycholysis is the detachment of the nail plate from the nail bed caused by a photo-mediated allergic or toxic effect of the drug. The thumbs are usually spared and photo-onycholysis is almost exclusively affiliated to patients on psoralen UVA therapy. Photo-onycholysis is also caused by captopril, chlorpromazine, doxycycline, thiazide diuretics, oral contraceptives and fluoroquinolones [36].

Similar to onycholysis, photo-onycholysis is reversible, in some cases without even discontinuing therapy [36]. Patients should be advised to avoid excessive sun exposure during treatment with associated drugs and to apply topical colored nail polish that can protect the nail bed [34].

Apparent leukonychia

Apparent leukonychia appears as white, parallel bands (Muehrcke's lines) results from nail bed damage and is a common side effect of antineoplastic agents [35,36]. It is easily distinguished from true leukonychia because

Figure 4. Hemorrhagic onycholysis caused by paclitaxel. The detachment of the nail plate from the nail bed is accompanied by pain.

it is blanchable and does not migrate with the nail growth [2,35]. The pathogenesis of these asymptomatic bands is unknown [2].

Apparent leukonychia does not require any treatment and will resolve after discontinuation of the drug [2].

Drug-induced nail changes due to proximal nail fold damage

Acute paronychia

Drug-induced acute paronychia is the inflammation of the nail folds affecting one or several nails [2]. The nail folds become extremely tender and erythematous within 1 to 3 months after treatment initiation. The exact pathogenesis is unknown, but a noxious effect on the nail epithelia or an infection may be the trigger [36]. Paronychia is associated in patients on methotrexate, antiretroviral and retinoid therapy [49–52].

Nail abnormalities regress with dose reduction or discontinuation of the drug [35]. Topical corticosteroids can alleviate some inflammation [53].

Periungual pyogenic granulomas

Pyogenic granulomas involve the proximal and lateral nail folds and are secondary to retinoid or cyclosporine therapy [35,36]. They appear on one or several nails as raw throbbing nodules with granulation tissue [35]. The pathogenesis is also unknown [36]. Paronychia along with pyogenic granulomas has been described with epidermal growth factor inhibitors such as cetuximab and with antiretroviral drugs such as indinavir [54,55].

Discontinuing the agent will improve this painful abnormality [33]. Topical corticosteroids and mupirocin may relieve the nail symptoms [36]. Topical alitretinoin (9-*cis*-retinoic acid) has been recommended as a treatment of pyogenic granuloma as well [56]. Cauterization of the granuloma with 8% phenol solution is also useful. Surgically excising the lesions is futile as they will recur [36].

Drug-induced nail changes due to alteration of nail blood flow

Ischemic changes

Ischemic changes or worse necrosis occur when medications disrupt distal digit perfusion. Raynaud's phenomenon is the initial harbinger of digital ischemia that begins with the digit becoming cold and potentially developing gangrene if the blood flow is not returned. This is associated with systemic nonselective β-blockers and with systemic or intralesional bleomycin therapy [36].

Unfortunately, the symptoms may not revert even after discontinuing the medication and digit amputation could occur [34,36].

Subungual hemorrhage

Medications that disrupt the nail bed blood vessels can damage the nail unit with splinter hemorrhages and subungual hematoma. Splinter hemorrhages are almost exclusive to fingernails and look like several, short longitudinal lines that are purple to brown in hue. Hematomas consist of trapped reddish to brown blood between the nail plate and the nail bed. With time the subungual hematoma grows out with the nail plate [36]. Both are caused by antithrombolytics, anticoagulants, taxanes and tetracyclines [57,58].

Hemorrhages depend on the dose and slowly regress after discontinuation of the drug [35]. They are commonly observed in patients treated with sunitinib.

Drug-induced nail atrophy

Digital atrophy can occur after extended use of high potency topical corticosteroids. The atrophy can be associated with bone resorption as well. The involved digit appears tapered along with erythematous scaling of the periungual skin [59].

Drug-induced nail pigmentation

Melanonychia

Melanonychia is the production of melanin pigment on the nail plate due to activation of melanocytes [2]. This appears as numerous light brown to black longitudinal or transverse stripes generally involving one to several nails [60]. The pathogenesis is not fully understood and is separate from ultraviolet light, melanocyte-stimulating hormone and corticotrophin activity [36]. Medications associated with melanonychia include psoralens and zidovudine [36,61]. Chemotherapeutic agents reported to cause melanonychia include hydroxyurea, methotrexate, bleomycin, cyclophosphamide, daunorubicin and 5-fluorouracil [2,62]. Electron beam therapy of an area distant from the digit can also cause melanonychia [63].

An isolated longitudinal stripe due to drug-induced melanonychia must be differentiated from a stripe of

longitudinal melanonychia resulting from a melanocytic neoplasm involving the nail matrix. If uncertain, a nail matrix biopsy must be obtained. Drug-induced melanonychia begins 3–8 weeks after the drug is administered. The discoloration is often reversible after discontinuation of the medication, but can take between 6 weeks to months [36].

Nonmelanic pigmentation

Drug-induced nail pigmentation can occur when a drug is emitted from the nail unit and collects within the nail plate. The pigmentation travels forward as the nail grows [36]. Gold salts and tetracyclines tint the nail plate yellow in color [64,65]. Clofazimine creates a dark-brown pigmentation to the nail plate [66].

Topical medications, like anthralin and tar, can accumulate within the superficial level of the nail plate, resulting in an exogenous brown-black pigmentation [36]. This exogenous pigmentation moves as the nail grows.

Other types of nail pigmentation can include the pigment settling in the dermis or periungual tissue. In these cases, the pigmentation will not move as the nail grows. This pattern is seldom seen with antimalarials that turn the nail bed a brownish-blue color and minocycline, which causes blue/gray pigmentation [67,68]. Even after withdrawing the medication, the pigmentation can take months to disappear and in some cases does not fully resolve [36]. For women affected by this type of pigmentation, they can apply colored nail polish for a better aesthetic outcome [34].

Drug-induced nail malformations in newborns

Certain medications taken by mothers during pregnancy may disrupt fetal nail development [36]. This could result in a wide spectrum of issues ranging from mild hypoplasia to absence of the entire nail. Nail teratogenic medications include hydantoin, trimethadione, valproic acid, carbamazepine, and warfarin [69,70]. Partial improvement of nail hypoplasia may be experienced in the first months of life [36].

Newer medications responsible for both drug-induced hair and nail changes

Taxanes

Taxanes can trigger chemotherapy-induced permanent alopecia as mentioned above. Paclitaxel and more so docetaxel for breast cancer therapy can cause moderate to severe permanent alopecia that also involves eyebrows, eyelashes, pubic and axillary hair. Educating and trying to prevent this outcome is important because the potential of this class of drugs to cause permanent alopecia may play a role in the patient's decision about this regimen [18].

Nail changes due to taxanes include multiple Beau's lines and hemorrhagic onycholysis with subungual abscesses, which can involve several or all nails (Figure 4) [37]. Nail changes typically arise after a few cycles of taxanes and usually resolve over a few weeks regardless of continuation of treatment. Hemorrhagic onycholysis with subungual abscesses is almost exclusive to taxanes and begin as painful hematomas that develop into onycholysis and possibly become infected with purulent discharge [71]. The pathogenesis may be due to direct nail bed toxicity or disruption of nail bed angiogenesis. The pain is related to the pressure that is relieved after drainage. This complication can increase the risk of sepsis and could impair quality of life, so it is crucial to prevent and heal. Elasto-Gel (Akromed, Saignon, France) frozen gloves and socks can help prevent unwanted side effects [72,73]. Treatment includes antiseptic soaks, which can be supplemented with systemic antibiotics as these patients need to be monitored closely due to their immunosuppressive state. Another treatment option is using cyclooxygenase-2 inhibitors, which have been shown to prevent noxious effects, including nail changes, and potentially enhance the therapeutic efficacy of taxoids [74].

EGFR inhibitors

EGFR inhibitors that are associated with hair disorders include vemurafenib and gefitinib. Vemurafenib is a selective BRAF kinase inhibitor to treat metastatic melanoma from which 30% of patients experience severe alopecia. Gefitinib is associated with both inflammatory and scarring alopecia [75,76]. After treatment with EGFR inhibitors, scalp hair can become curlier, brittle and fine [76]. Trichomegaly, elongated lashes, has been reported with EGF inhibitors, including gefitinib, erlotinib, cetuximab and panitumumab (Figure 5) [77,78]. In some cases, the long, misdirected

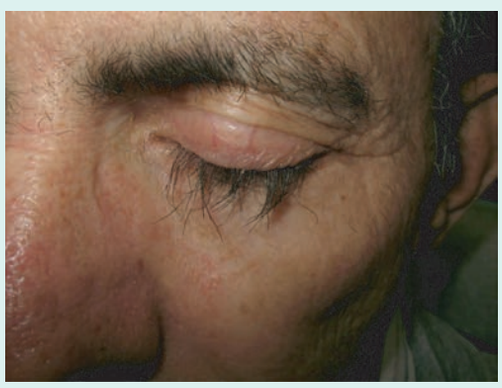

Figure 5. Eyelash trichomegaly caused by EGFR inhibitors. There is significant lengthening and some curling of the eyelashes.

and extremely curly lashes require trimming or removal by an ophthalmologist [77].

Nail disorders associated with EGFR inhibitors, such as cetuximab, are paronychia, which can worsen into pyogenic granulomas with fissures, pain, and impaired function. Symptoms involving one to two nails can occur in 10–15% of patients, beginning a month after treatment initiation [79]. The pathogenesis is related to the fragility and penetration of nail fragments into the periungual tissues. Proper nail cutting, wearing wide shoes and antiseptic baths can help prevent this condition. Treatment includes potent topical steroids, tetracycline antibiotics, adapalene application, surgical removal or withdrawal of causative agents [80,81].

Multi-target drugs (VEGF/VEGFR) signaling inhibitors

Multi-target drugs can cause hair loss, hypopigmented hair, and changes in hair shape. Combination of sorafenib, a multikinase inhibitor, and PEGylated IFN-α-2b has been reported with 36.5% of patients experiencing alopecia [82]. Another multikinase inhibitor, sunitinib, has been reported to cause hypopigmentation involving scalp hair, beard and skin in approximately 7–10% of patients due to the effects on c-KIT receptor kinase, which is related to melanocytic activity. Interestingly, sunitinib can cause the flag sign or intermittent hair discoloration, which can be appreciated on a single strand of hair [83].

Patients taking sorafenib, sunitinib, and imatinib can experience Muehrcke's lines, pigmentary changes and subungual splinter hemorrhages [84]. The asymptomatic subungual splinter hemorrhages occur in 30–70% of patients and appear after 2–4 weeks of beginning the oral therapy. This is thought to be a result of selective VEGF blocking [85].

Conclusion & future perspective

The constant introduction of new drugs will definitely produce new hair and nail side effects. It is important for dermatologists to recognize and report hair and nail disorders that may be related to drug intake as these may have been overlooked in clinical trials, which are more focused on systemic drug toxicity. Postmarket experience, for instance, recognized scalp and nail psoriasis induced by TNF-α inhibitors or permanent alopecia occurring after taxane chemotherapy [86]. A better understanding of the molecular mechanisms involved in chemotherapy alopecia will hopefully produce more effective ways of preventing these side effects. The recent observation that concomitant sustained treatment with EGFR inhibitors may prevent cyclophosphamide-induced alopecia in mice may indicate a novel type of approach [87].

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