Nails changes in onco-hematologic patients

What is commonly called the nail is only the end product (nail plate) of a complex system (nail unit) that includes different anatomo-functional structures.[1] When the anatomic features of the nail apparatus are known, a better comprehension of nail changes is possible. Briefly, the nail apparatus (Figure 1) is composed of 1) the nail plate, the most visible part of the nail apparatus, which results from maturation and keratinization of nail matrix cells; 2) the nail matrix, partially visible in its distal part as the lunula. The lunula is characterized by a basal cell layer, which progressively matures and produces hard keratin, and by different types of cells such as melanocytes, Langerhans' cells, and Merkel cells; 3) the nail bed, made of keratinizing epithelium, that is closely joined with the nail plate, so that they grow together; 4) the paronychium (nail fold), which is the epidermis that surrounds the nail plate laterally; 5) the proximal eponychium, the cutaneous fold that covers the matrix. The cuticle is a thin layer of epidermis that derives from the eponychium and covers a small tract of the nail.[2] Although the spectrum of nail diseases is wide and heterogeneous in onco-hematologic patients, the causes may be schematically grouped into four categories: drug-induced nail changes, graft-versus-host disease (GVHD) of nails, nail alterations due to radiotherapy, and changes secondary to hematologic diseases *per se* and immunosuppression (i.e., infectious paronychia).

Nails changes secondary to systemic drugs

The use of a vast number of different kinds of drugs in onco-hematologic patients is the commonest cause of onychopathy.[3] Sometimes it is difficult to ascertain the responsibility of a single drug, since various chemotherapeutic agents are currently combined in many protocols. A unifying view, however, is supported by the fact that different types of drugs may lead to the same nail alteration; for example, onycholysis may be due to drugs such as antimetabolic agents, but also to antibiotic or

Table 1. Nail changes related to specific classes of onco-hematologic drugs.

Diseases	*Agent*
Hyperpigmentation	bleomycin, busulfan, cyclophosphamide, dacarbazine, daunorubicin, docetaxel, doxorubicin, etoposide, fluorouracil, hydroxyurea, melphalan, methotrexate, nitrogen mustard, nitrosourea, paclitaxel
Leukonychia	cyclosporine, fluorouracil, leukovorin, levamisole, methotrexate, vincristine
Onycholysis	bleomycin, docetaxel, doxorubicin, fluorouracil, mitoxantrone, paclitaxel, retinoids, hydroxyurea
Photonycholysis	8-methoxypsoralen, retinoids
Nail shedding	doxorubicin, bleomycin, fluorouracil, mercaptopurine, mitoxantrone, retinoids
Beau's lines	bleomycin, cisplatin, docetaxel, doxorubicin, melphalan, vincristine
Splinter hemorrhages	docetaxel
Paronychia	docetaxel, methotrexate
Dystrophy	bleomycin, hydroxyurea

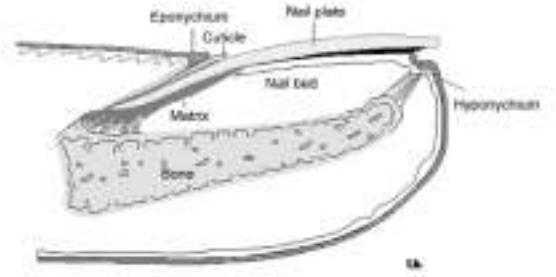

Figure 1. Anatomy of the nail apparatus.

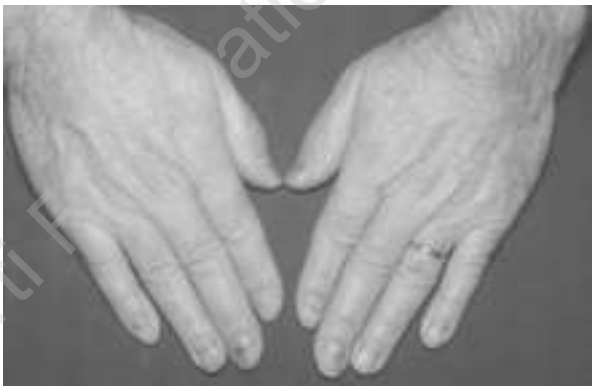

Figure 2. Diffuse and longitudinal brown-grey hyperpigmentation involving all nails.

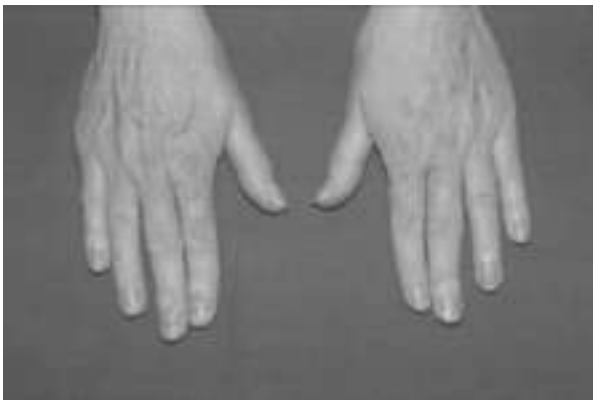

Figure 3. Distal separation of nail plate from nail bed (onycholysis) shortly after chemotherapy.

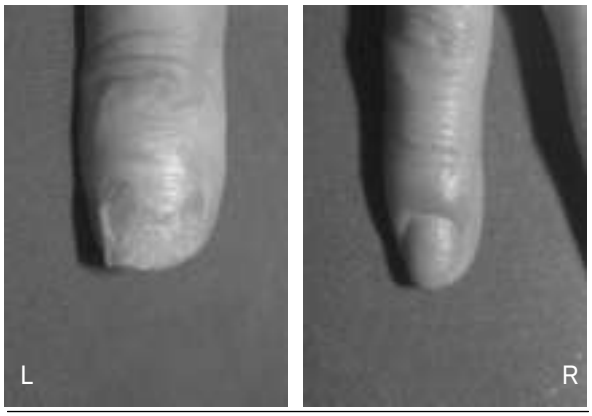

Figure 4 (L). Nail thinning and onychomadesis in a patient treated with different antineoplastic drugs.

Figure 8 (R). Chronic paronychia characterized by erythema and swelling of the eponychium due to *Candida albicans* causes dystrophic nail growth in a patient affected by chronic myeloid leukemia.

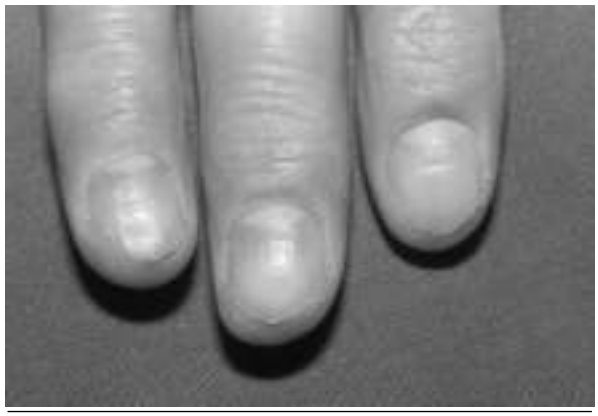

Figure 5. Slight transverse incisures (Beau's line) which are multiple on one fingernail of the right hand.

Figure 6. Splinter hemorrhages have been described in association with different conditions, including neoplastic diseases, drug reactions and after ionizing radiation.

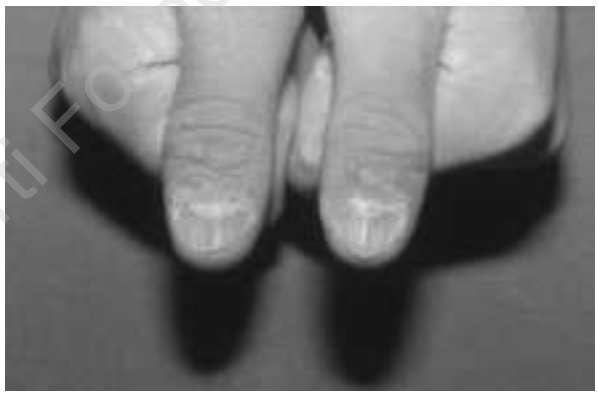

Figure 7. Chronic graft-versus-host-disease of the nails, characterized by thinning, roughness, longitudinal ridging, and early pterygium and by multiple warts on the eponychium and paronychium of the right thumb.

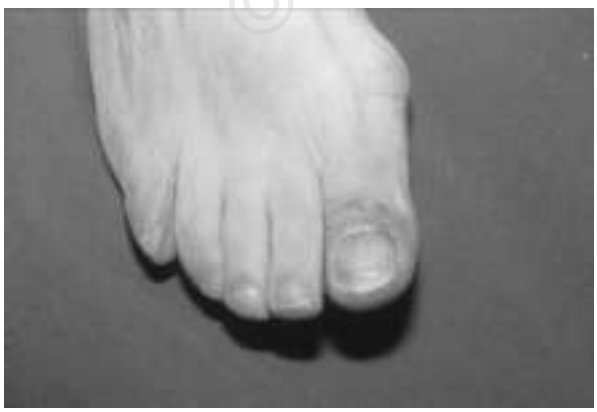

Figure 9. A bacterial infection of the first toenail caused by *Staphylococcus aureus* presents as acute paronychia characterized by swelling and erythema.

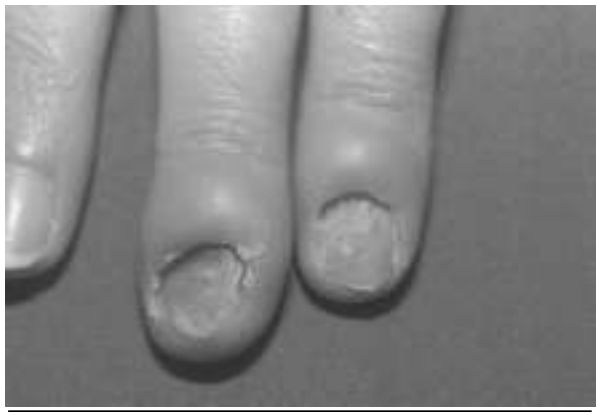

Figure 10. Severe swelling and redness of nail folds with a bulbous aspect and severely affected nail plate are present in this infection caused by both *Candida albicans* and *Pseudomonas aeruginosa*.

antifungal agents. Therefore, a simple, but useful way to approach this subject is to consider each single nail alteration and which drugs may induce it (Table 1). Nail pigmentation is one of the commonest side effects of drugs on nails and may present as longitudinal (Figure 2) or transverse brown or grey bands or as a diffuse hyperpigmentation, usually involving all the nails.[4] The term *leukonychia* means different forms of white discoloration of nails, that usually present as transverse white streaks. *Onycholysis* (Figure 3) consists of detachment of the nail plate from the nail bed, usually involving the free margin, but sometimes extending and progressively involving the whole nail until shedding (*onychomadesis*) (Figure 4). Photochemotherapy for cutaneous T-cell lymphomas (8-methoxypsoralen plus UV-A 365nm) may cause onycholysis (*photo-onycholysis*) with findings indistinguishable from those observed in photo-onycholysis induced by systemic tetracycline treatment and sun exposure.[3] Another common presentation of nail involvement in onco-hematologic patients is *Beau's line* (Figure 5), a transverse depression appearing as a consequence of severe systemic illness, and also during treatment with chemotherapy. *Splinter hemorrhages (*Figure 6) have been described in association with different conditions, including neoplastic diseases and drug reactions.[2] Acute *paronychia*, namely inflammation of paronychium, has been reported after high-dose methotrexate regimens, but also after other drugs such as docetaxel.

Nail changes induced by graft-versus-host disease

It is often difficult to determine whether nails abnormalities are due to drug toxicity or to graft-versus-host disease, especially in an early stage. In fact, in acute GVHD, onycholysis, thickening of nail plate, fluting, fragility, roughness, longitudinal ridging, cuticular telangiectases, periungual swelling and erythema may be observed both after chemotherapy and after bone marrow transplantation.[5] In chronic GVHD, however, nail changes are far more easily identifiable: dystrophy, atrophy and often ulceration of the lunula are all consequences of the lichen-planus-like lymphocytic infiltration of the matrix typical of chronic GVHD (Figure 7).

Nail alterations due to radiotherapy

The effect on nails of total body irradiation, a common procedure to induce myeloablation in bone marrow transplantation, deserves further controlled clinical investigation. It is, however, known that splinter hemorrhages in the distal nail bed and melanonychia may be seen after ionizing radiation.[6]

Nail changes secondary to hematologic conditions

Beau's lines and leukonychia have been described in patients affected by different hematologic conditions, such as Hodgkin's lymphoma. Albeit rarely, lymphomatous nail involvement in Sézary syndrome, as well as in chronic lymphocytic leukemia and non-Hodgkin's lymphoma, has been described. It should also be emphasized that primary or secondary immunosuppression may favor nail infections (Figures 8-10), caused by bacteria (e.g. *Pseudomonas aeruginosa*), yeasts (e.g. *Candida albicans*), dermatophytes (e.g. *Trichophyton rubrum*), or viruses (e.g. warts).[5]

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