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Indinavir-Induced Retinoid-Like Effects

Incidence, Clinical Features and Management

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Contents

Abstract

Since 1998, many cases of antiretroviral therapy-related paronychia of the toes or fingers and ingrown toenails have been reported. Most of them were related to indinavir. Other indinavir-induced mucocutaneous disorders resembling the adverse effects of systemic retinoid therapy have also been reported. Although there is some uncertainty in the literature regarding a cause-effect relationship, results of several epidemiological and *in vitro* studies, together with cumulated clinical experience leave no doubt that indinavir causes a retinoid-like effect and nail alterations. Indeed, indinavir is the only antiretroviral drug that produces these disorders, although ritonavir may enhance indinavir-induced retinoid-like effects through pharmacokinetic interactions leading to increased plasma indinavir concentrations.

Approximately 30% of patients receiving indinavir show two or more retinoid-like manifestations and 4–9% develop paronychia. These adverse effects are not related to other epidemiological variables such as the patient's sex, age or other

risk factors or immune status. They seem to be exposure dependent and, therefore, largely dose-dependent.

Chronic paronychia is considered generally to be caused by contact irritants and candidal infection. Nevertheless, indinavir is currently the most frequent cause of chronic or recurrent paronychia in HIV-infected patients. In addition, retinoid-like manifestations such as cutaneous xerosis and cheilitis are frequent mucocutaneous adverse effects related to indinavir.

The exact mechanism of indinavir-induced retinoid-like effects is unclear. Hypotheses for pathogenesis include interference with retinoid metabolism by enhancing the retinoic acid signalling pathway, or by increasing retinoic acid synthesis, or by reducing cytochrome P450-mediated retinoic acid oxidative metabolism.

Replacement of therapy by an antiretroviral regimen not containing indinavir, while retaining other protease inhibitors and lamivudine, resolves retinoid-like manifestations without recurrences.

In April 1998, Zerboni et al.[1] reported paronychia of the toes or fingers in 12 HIV-infected patients with negative fungal and bacterial cultures. These authors interpreted the paronychia as being an adverse effect of lamivudine, as it was the only drug taken by all 12 patients in the 3 months before the onset of paronychia.

In August of the same year, Bouscarat et al.[2] reported paronychia and ingrown nails involving the great toes in 42 seropositive patients. In 28 of the 42 patients there was a severe skin dryness. In 21, one-half of the series, these alterations caused functional impairment. The authors attributed these disorders to indinavir therapy, and drew attention to their resemblance with the adverse effects of oral retinoids. In six patients indinavir was withdrawn for various reasons and this resulted in the total or partial regression of skin and nail alterations.

Subsequently there were many reports of paronychia involving fingers[3-6] and toes[3-13] or ingrown toenails,[3,4,6-8,14-17] most of which were related to indinavir,[4,5,8,10,15] or to indinavir and lamivudine,[3,11] or indinavir plus ritonavir; [17] paronychia has also been reported in patients treated with protease inhibitors other than indinavir, such as ritonavir.[7] Sibel[12] reported a series of 50 HIV-infected male patients with paronychia of the toes, 14 of whom received no lamivudine while six received no indinavir and, four received no protease inhibitors. The presence of other manifestations suggesting a retinoid-like effect was not mentioned in most of the reports on antiretroviral therapy-induced paronychia.

In addition to nail alterations, other phenomena caused by systemic retinoids that have also been described in association with antiretroviral therapy include mucocutaneous xerosis,[2,4,9,10,14,17-19] asteatotic eczema,[4,10,19] pruritus,[10,19,20] erosive or desquamative cheilitis,[4,9,18,21-23] body or scalp alopecia[14,18,24-26] and curling of previously straight hair.[27,28]

In the First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV-infected patients, held in June 1999 in San Diego, California, USA, skin dryness, cheilitis, ingrown toenails and hair alterations were included within the spectrum of HIV-associated lipodystrophy syndrome.[29,30]

There is thus some uncertainty in the literature about antiretroviral-related paronychia and retinoid-like effects. Different drugs have been incriminated but the identification of an antiretroviral agent as a cause of the mucocutaneous adverse effects has been difficult because these drugs are very rarely used as monotherapy.

1. Epidemiology

There are very few reports on the epidemiological features of antiretroviral therapy-induced paronychia. Bouscarat et al.[2] reported a frequency of 4% in their patients receiving indinavir. Two retrospective case-control studies[6,14] evaluated the association of paronychia or ingrown toenails with antiretroviral treatment and epidemiological variables. Both studies found a statistically significant association of paronychia with indinavir; there was no significant association of paronychia with lamivudine, other drugs, immune status or other epidemiological variables (age, sex, risk factors for HIV infection).

There are no published epidemiological data on antiretroviral therapy-induced retinoid-like effects. Calista and Boschini prospectively studied 84 patients treated with indinavir for dermatological manifestations.[10,19] Duration of follow-up was at least 12 months (range 12–20 months; average 16 months). Forty-eight of the 84 patients (57.1%) developed cheilitis, 34 (40.5%) experienced xerosis and pruritus, 10 (11.9%) developed asteatotic dermatitis, 9 (10.7%) had alopecia, 10 (11.9%) showed other hair alterations, and 5 patients (5.9%) developed pyogenic granuloma-like lesions on the toes. As all patients in that study received indinavir, it was not possible to assess an association of paronychia or retinoid-like effects with antiretroviral agents other than indinavir.

A prospective study evaluated dermatological manifestations in 335 consecutive HIV-infected patients, paying special attention to hair and nail disorders.[20,31] A statistical evaluation of the association of antiretroviral drugs given to these patients with clinical manifestations indicative of a possible retinoid-like effect was carried out. These clinical manifestations consisted of skin xerosis, with or without asteatotic eczema, non-infectious cheilitis, paronychia not attributed to other causes (mycotic, psoriasic, irritative), ingrown toenails, alopecia, pruritus sine materiae, and prurigo and scratching-induced excoriation. As a working definition, we considered that a patient had retinoid-like effects when there were two or more of these clinical factors (excluding pruritus and prurigo) together with a consistent temporal relationship with antiretroviral therapy. There was no significant association between alopecia, pruritus and prurigo and any of the drugs administered. All other clinical data were significantly associated with indinavir. Although cheilitis was significantly associated with indinavir and lamivudine, and retinoid-like effects with indinavir, lamivudine and stavudine, the analysis demonstrated that real associations were confined to indinavir, while lamivudine and stavudine were confounding variables. There was no significant relationship between a retinoid-like effect or any of its manifestations and other epidemiological and immune parameters (age, sex, risk factors for HIV infection, viral load, CD4+ cell count, Centers for Disease Control and Prevention [CDC] stage, associated diseases, etc.). Twenty-one patients met criteria for a retinoid-like effect. They constituted 27.63% of patients receiving indinavir. This frequency may be underestimated, as the diagnostic criteria required the presence of at least two clinical manifestations.

During the period of the study, only two cases of indinavir-induced morbilliform rash (2.63% of patients receiving indinavir) were noted. Calista and Boschini did not observe hypersensitivity or allergic reactions in their series of 84 indinavir-treated patients.[10] Therefore, it appears that a retinoid-like effect is the most frequently observed skin adverse effect related to the administration of indinavir. Overall, in the series of patients described above, there were seven cases of indinavir-induced paronychia (9.21% of patients receiving indinavir). Paronychia was not significantly associated with epidemiological variables or immune status. During the study period, four cases of psoriatic paronychia of the fingers and toes, three cases of candidal paronychia of the fingers and one case of paronychia of a great toe and caused by dermatophytes were noted. To date, it has been considered that in HIV-infected patients chronic paronychia is generally related to candidal infec-

tion.[1,17,32] Our observations suggest that indinavir is currently the most frequent cause of paronychia in HIV-infected individuals.

2. Evidence for a Cause-Effect Relationship

The association of indinavir with paronychia[6,14,20] and retinoid-like effects[20] is well established in epidemiological studies. The simultaneous occurrence of paronychia with other clinical manifestations resembling oral retinoid administration, the temporal relationship between antiretroviral drug administration and clinical manifestations, regression of the clinical signs after drug discontinuation and recurrence after drug reintroduction,[10,20] together with results from *in vitro* studies,[33,34] leave no doubt that indinavir causes a retinoid-like effect and nail alterations in this context.

In fact, indinavir is the only antiretroviral drug that causes paronychia and retinoid-like effects. The replacement of indinavir with other antiretroviral agents, including other protease inhibitors, lead to regression of retinoid-like effects, regardless of keeping lamivudine if it formed part of combination therapy.[4,11,18,20] In an *in vitro* study,[33] it was found that indinavir, but not the other protease inhibitors investigated (saquinavir, ritonavir, nelfinavir and amprenavir), enhanced retinoic acid signaling in cell cultures. Lopinavir was not available to be evaluated in that study. In another *in vitro* study,[34] indinavir was the only antiretroviral drug that induced the gene expression of retinal dehydrogenase (RALDH), a key enzyme involved in the biosynthesis of retinoic acid. Although in that study it was found that ritonavir and saquinavir significantly increased RALDH activity (but not RALDH mRNA), suggesting that these protease inhibitors might be also responsible for retinoid-like effects, cumulated clinical experience[4,8,11,18,20] suggests that indinavir is the only antiretroviral drug that produces retinoid-like effects *in vivo*.

Contrary to what has been repeatedly stated in the literature,[1,3,11,35-37] it seems improbable that lamivudine causes paronychia. It is possible that the cases of paronychia attributed to lamivudine or to antiretroviral drugs other than indinavir were actually related to the concurrent use of indinavir or to other causes.

We also consider that retinoid-like effects must be separated from lipodystrophy syndrome, since the later is related to different classes of antiretroviral agents, while the former is exclusively related to indinavir. Paronychia and other retinoid-like effect manifestations regress after discontinuation of indinavir, while manifestations of lipodystrophy persist.[10,18]

3. Drug Dosage and Toxicity

Mucocutaneous adverse effects of oral retinoids are largely dose related. Some anecdotal reports[15,17] suggest than indinavir-induced paronychia is also dose related. In a recent study on toxicity of indinavir plus ritonavir combination therapy,[38] it was found that indinavir-induced adverse effects, including retinoid-like effects, were related to plasma drug concentrations, and the frequency and severity of adverse effects decreased after dosage adjustment.

3.1 Effect of Ritonavir on Indinavir-Induced Adverse Effects

Ritonavir inhibits the cytochrome P450 (CYP) 3A4 isoenzyme and P-glycoprotein, which speed the metabolism and limit the bioavailability of other protease inhibitors, respectively. The combination of indinavir and other protease inhibitors with low-dose ritonavir is therefore increasingly used in clinical practice for treatment of patients with HIV, as it provides increased plasma concentrations of indinavir with increased antiretroviral effects, reduced frequency of dose administration, lack of food restrictions and improved patient adherence to therapy.[17]

It is probable that ritonavir enhances indinavir-induced retinoid-like effects. As mentioned in the

previous paragraph, indinavir-induced toxicity is related to its plasma concentration, which is increased by ritonavir. In the study by Solas et al., indinavir-related adverse effects occurred after the introduction of ritonavir.[38] James et al. observed three patients with ingrown toenails, secondary to indinavir/ritonavir combination therapy; these patients previously received standard-dose indinavir without developing nail complications.[17] To our knowledge, there are no studies evaluating whether the incidence of retinoid-like effects is increased when indinavir is combined with ritonavir. Our study[20] could not asses this question because only two patients in the series received indinavir plus ritonavir and none of them developed retinoid-like effects. However, we have subsequently seen patients with retinoid-like effects secondary to therapy with indinavir plus ritonavir.

4. Mechanism of Action

Molecular homologies between the catalytic region of HIV-1 protease, the target of protease inhibitors, and cytoplasmic retinoic acid-binding protein type 1 (CRABP I) have been described.[39] On the basis of this fact, it has been suggested that protease inhibitors may produce a retinoid-like effect by inhibiting endogenous proteases or by interfering retinoic acid metabolism through CRABP I.[2,18,39] The latter hypothesis was supported by results of an *in vitro* study which showed that indinavir enhanced the effect of retinoic acid in cell cultures, but not in presence of the retinoic acid receptor agonist CH55, which does not bind to CRABP I.[33] In addition to enhancement of the retinoid-mediated signalling pathway, another *in vitro* study found that protease inhibitors altered retinoic acid synthesis by increasing RALDH activity or/and gene expression (only indinavir) which could increase retinoic acid concentrations.[34]

Other authors have suggested that indinavir might decrease the oxidative metabolism of retinoic acid by inhibiting the CYP3A isoenzyme.[9]

Retinoids affect keratinocyte differentiation and their pattern of keratin expression and produce effects on the epidermis resembling those of retinol (vitamin A), with thinning of the stratum corneum of the epidermis, nail plate and hair follicular epithelium. Among their many actions, some retinoids inhibit sebaceous secretion and decrease the lipid content of the epidermal surface, which may result in the so-called 'retinoid dermatitis' that is clinically identical to asteatotic eczema.[40] They also induce excess granulation tissue production with formation of pyogenic granulomata, mainly on nail folds and acne lesions (when treated with isotretinoin).[41]

In an *in vitro* study[42] it was found that during granulation tissue formation a subpopulation of fibroblasts express cellular retinol-binding protein-I (CRBP-I) and this expression is increased by retinoic acid, suggesting that CRBP-I and retinoic acid play a role in the evolution of granulation tissue.

Retinoid-related nail alterations were explained by Baran[43] as part of the general desquamative process, leading to thinning, softening and fragility of the nail plate. The soft and brittle keratin of the nail plate would result in fine spicules which could emerge from the lateral edges and break through the lateral nail grooves acting as a foreign body stimulating an inflammatory response and formation of excess granulation tissue, occasionally leading to ingrown nail.

5. Clinical Features

5.1 Clinical Manifestations

Clinical features are similar to adverse effects of oral retinoids on skin and mucosae. They are showed in table I. Clinical features usually appear within the first 2 months after introduction of indinavir therapy.

The absolute and relative frequencies of the different manifestations in a series of 21 patients with indinavir-induced retinoid-like effects are shown in table II.[20] Cheilitis and cutaneous xerosis are the most frequent manifestations.[10,20] Although most patients with indinavir-induced retinoid-like effects had skin xerosis and many of them complained of pruritus (table II), most of the patients

Table I. Clinical features of indinavir-induced retinoid-like effects

Cutaneous xerosis	Asteatotic eczema
	Acquired ichthyosis
	Pruritus, burning sensation
Cheilitis	
Nail alterations	Paronychia
	Ingrown toenails
	Hypertrophic granulation tissue
	Nail plate dystrophy
Hair alterations	Body alopecia
	Scalp alopecia
	Curly hair
Hyperlipidaemia	

with xerosis and pruritus did not meet the criteria for a retinoid-like effect.[20] Conversely, non-infectious cheilitis, diagnosed in 16 of 20 (80%) of the patients, met the criteria for a retinoid-like effect. In our series of patients, [20] alopecia was attributed to other causes and there was no statistical association between alopecia and any of the drugs administered. However, subsequently we have seen cases of body alopecia induced by indinavir plus ritonavir therapy.

5.2 Cutaneous Xerosis

The condition manifests as diffuse scaling and roughness of the skin, frequently with pruritus, which often lead to further skin lesions as a result of scratching such as excoriation and lichenification. Asteatotic eczema is characterised by itching and sometimes tender dermatitis with fine scaling and cracks and slightly infiltrated erythematous patches located predominantly on the extensor surface of the limbs.[19] Occasionally, indinavir-related xerotic dermatitis is so intense that it constitutes an acquired ichthyosis-like syndrome.[4] The intensity of mucocutaneous dryness seems to correlate with the severity of paronychia.[4] Skin xerosis, pruritus and acquired ichthyosis are non-specific findings that often occur in HIV-infected patients without any relationship to antiretroviral therapy.

5.3 Cheilitis

Cheilitis presents as diffuse desquamation and erythema of the lips, occasionally with erosions, crusts, fissures and oedema[21,22] (figure 1a). It sometimes causes a troublesome burning sensation or pain, but in many cases it is mild and may be overlooked if it is not purposely looked for. Cheilitis is a frequent (see table II) and rather specific manifestation and its presence supports the diagnosis of a retinoid-like effect in patients with paronychia, alopecia or other less specific clinical findings.

5.4 Nail Alterations

5.4.1 Paronychia

This condition is characterised by a painful inflammation of the tissues surrounding the nail plate. It may be mild or severe, with erythema, swelling, exudation, crusting and hypertrophic granulation tissue (figures 1b and 2). The large toes are involved more frequently than other digits. Indinavir-induced paronychia has no specific morphological features, and diagnosis must be made by exclusion of other causes of paronychia, the presence of other manifestations of retinoid-like effect, and the temporal relationship with the drug administered.[4,20] It follows a chronic or recurrent clinical course with fluctuating intensity. At different times the same patient may have paronychia in different digits.[4,20] Positive bacterial cultures of periungual exudate do not rule out the diagnosis, as there may be bacterial superinfection.[2,4,11,13,20]

Table II. Frequency of clinical manifestations in a series of 21 patients with indinavir-induced retinoid-like effects[20]

Findings	No. of cases (%)	95% CI
Cutaneous xerosis	16 (76.19)	52.45–90.88
Cheilitis	16 (76.19)	52.45–90.88
Pruritus	9 (42.86)	22.59–65.56
Paronychia	7 (33.33)	15.48–56.89
Asteatotic eczema	6 (28.57)	12.19–52.31
Ingrown toenails	4 (19.05)	6.29–42.58
Skin excoriations	3 (14.29)	3.76–37.36
Nail plate dystrophy	1 (4.76)	0.25–25.87
Acquired ichthyosis	1 (4.76)	0.25–25.87

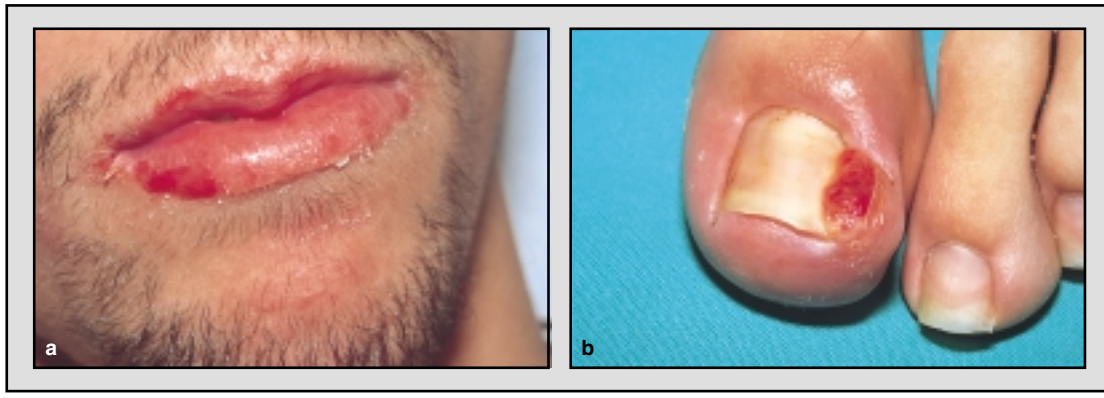

Fig. 1. (**a**) Erosive and desquamative cheilitis, and (**b**) paronychia and ingrowing toe nail with swelling and hypertrophic granulation tissue in a patient treated with indinavir-containing antiretroviral therapy.

5.4.2 Ingrown Nails

Ingrown nail affects the large toes (figure 1b) and less frequently other toenails, but does not occur on fingers. It is clinically indistinguishable from ordinary ingrown toenail, which is not related to administration of drugs, except for the almost constant presence of hypertrophic granulation tissue and the possible simultaneous occurrence of paronychia on other toenails and fingernails and other manifestations of retinoid-like effect. Some authors[11] consider that the condition is not a true ingrown nail, but pharmacologically induced granulation tissue covering the nail plate. In our experience both events occur and a vicious cycle takes place; ingrown nail stimulates the production of granulation tissue by acting as a foreign body while hypertrophic granulation tissue and inflammation in turn worsen ingrowing nail. Pyogenic granuloma-like lesions, located on skin other than the perionychium, is an adverse effect of systemic retinoids that has not been related to antiretroviral therapy to date.

5.4.3 Nail Plate Alterations

Softening of the nail plate has been reported,[10] as well as dystrophy secondary to paronychia[14,20] with pitting, Beau's lines, longitudinal striation and onychorrhexis in patients treated with indinavir.[20]

5.5 Hair Alterations

Indinavir-induced alopecia affects the body surface (limbs, chest, pubis, axillae) more frequently than the scalp.[10,18] It is characterised by diffuse hair loss clinically indistinguishable from body or scalp effluvium due to other causes, except for the possible presence of other retinoid-like effect manifestations. Two cases of alopecia attributed to indinavir[24] had features of alopecia areata. Such cases are doubtful, as alopecia areata is an autoimmune condition not related to oral retinoid therapy. Nevertheless, it has been described as a manifestation of the immune reconstitution

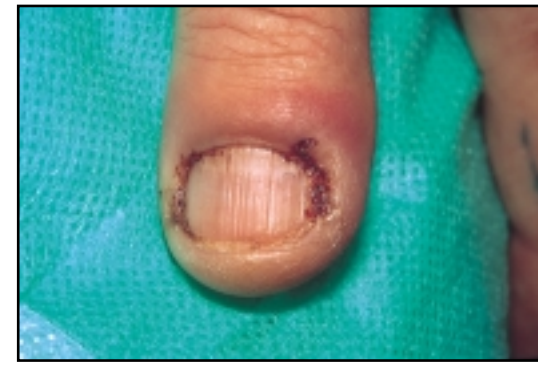

Fig. 2. Paronychia of a finger with erythema, exudation and crusts in a patient receiving indinavir.

syndrome related to highly active antiretroviral therapy (HAART).[44]

Curling of previously straight hair seems to be very infrequent, as to our knowledge only two cases have been reported,[27,28] and besides indinavir plus ritonavir one of themreceived isotretinoin for acne.[27] This phenomenon was known as an adverse effect of oral retinoids.[45]

5.6 Hyperlipidaemia

Hyperlipidaemia is an adverse effect of both systemic retinoids and protease inhibitors, and it is a manifestation of both retinoid-like effect and lipodystrophy syndrome. Alterations in the serum lipid profile are similar in both conditions, being characterised by increased levels of tryglycerides and very low density lipoproteins (LDL) and less frequently of total cholesterol and LDL-cholesterol and a decreased high density lipoprotein (HDL)/LDL ratio.

5.7 Other Possible Retinoid-Like Manifestations

5.7.1 Mood Changes

There are a number of reports concerning a possible relationship between the systemic retinoid isotretinoin and depression and suicide. Such a relationship is controversial and a causal connection has been not demonstrated to date.[46] A case was reported concerning an HIV-infected individual who 6 months after starting indinavir therapy developed body alopecia together with mood disturbance in the form of irritability, anxiety and depression. Both alopecia and mood disturbance regressed after discontinuing indinavir.[25]

5.7.2 Tendinitis

Tendon and ligament calcification is a known long-term retinoid therapy-induced adverse effect.[47] Indinavir has been related to tendinitis and frozen shoulder. However, it is improbable that this complication is related to retinoid-like effects and is more likely the result of intratissue indinavir crystallisation.[48,49]

6. Effect of Indinavir Withdrawal on Clinical Symptoms

Cheilitis and cutaneous dryness usually regress within the first week after indinavir withdrawal.[20,21] Paronychia of fingers usually resolves within 3 months. Ingrown toenails may be persistent because of self-perpetuation. Nail plate dystrophy completely resolves after the replacement of the plate by a new one, which takes about 6 months in fingers and 1 year in toes. Alopecia resolves within 4–6 months.[18,25]

7. Histopathology

Histopathology in a case of paronychia attributed to lamivudine showed only granulation tissue;[1] similar findings were reported in a case of paronychia attributed to indinavir[5] and in three cases of paronychia attributed to lamivudine plus indinavir.[11]

Biopsy of indinavir-induced asteatotic eczema performed in five patients showed epidermal psoriasiform acanthosis, hypergranulosis with focal parakeratosis and scale-crusts, and dermal vasodilation and perivascular lymphocytic infiltrates.[10,19]

Lip biopsy in six cases of exfoliative cheilitis, attributed to combination antiretroviral therapy including indinavir, showed epidermal ulcerations and dermal oedema with diffuse lymphocytic infiltration.[22] In another case of indinavir-induced cheilitis, biopsy showed acanthosis and parakeratosis without inflammation.[21]

Biopsy of indinavir plus ritonavir-induced alopecia in one patient showed hairs in the telogen phase.[26]

The histopathological features described in this section are rather unspecific, as they are also found in ordinary ingrown toenails, asteatotic eczema and irritative cheilitis not related to antiretroviral therapy. However, biopsy is useful to exclude other diseases requiring differential diagnosis, such as psoriasic paronychia, herpetic whitlow, actinic cheilitis, allergic contact cheilitis and psoriasis.

8. Management

In most cases, symptoms of indinavir-induced retinoid-like effects are mild and do not usually require withdrawal of the medication, as in the case with oral retinoids.[4] Nevertheless, in an Italian series[10] retinoid-like effects led to the discontinuation of therapy in 8 out of 84 (9.5%) indinavir-treated patients. Curiously, some of those patients, who tolerated pruritus, troublesome cheilits, lipodystrophy, nausea, vomiting and even renal colic, demanded that therapy be stopped when they realised they were losing hair. In a prospective study concerning patient nonadherence to antiretroviral therapy[50] it was found that pruritus was associated with a higher risk of nonadherence persisting over time, resulting in treatment failure.[51]

In patients receiving indinavir, caution must be taken with concurrent administration of oral retinoids or retinol supplements, as well as to use of contact lenses, which is associated with conjunctivitis and ocular discomfort in patients experiencing retinoid-induced eye dryness.[52]

Cheilitis and skin dryness improve with topical emollients and asteatotic eczema with topical corticosteroid ointment.[10,20]

Paronychia may be kept minimally symptomatic with topical application of corticosteroids and antibacterials.[3-5,13] If there is superimposed bacterial infection, systemic antibacterials are necessary;[3-5] they must be active against *Staphylococcus aureus*. Although surgical treatment has often been reported to be useful,[1,2,7,13,17] it seems preferable to avoid aggressive procedures, as recurrences are common.[3,5] However, we consider that partial nail plate extraction besides phenol matrixectomy is a minimally invasive technique that produces immediate relief in patients with ingrown toenails.

There are other possible approaches to the management of indinavir-induced retinoid-like effects. Regression of indinavir-induced ingrown toenail was observed in a patient following reduction of the drug dosage from 800mg three times daily to 400mg twice daily, together with ritonavir 400mg twice daily.[15] James et al. reported a patient with indinavir/ritonavir combination therapy-related ingrown toenail who did not experience recurrences after phenol matrixectomy and dosage change from indinavir 800/ritonavir 200mg twice daily to 400/400mg twice daily.[17] However, in another patient such a dosage change did not avoid recurrences of ingrown toenail.[17]

Therapeutic drug monitoring of minimun plasma concentrations followed by dose adjustment has been suggested as a means of managing optimal exposure to antiretroviral therapy, to limit the risk of toxicity and maximise efficacy.[38,53]

There are no reports of the use of tocopherol (vitamin E) for treating or preventing antiretroviral-related retinoid-like effects.

If necessary, the best treatment is replacement of indinavir with an alternative protease inhibitor or by an antiretroviral regimen not containng indinavir, which resolves retinoid-like manifestations without recurrences.

9. Conclusions

Indinavir is the most frequent cause of paronychia in HIV-infected patients. It occurs in the context of retinoid-like effects, which is the most frequent mucocutaneous adverse manifestation related to indinavir administration. Indinavir is indeed the only antiretroviral drug that produces these adverse effects *in vivo*, although ritonavir enhances indinavir-induced retinoid-like effects in a dose-dependent manner. It is improbable that lamivudine induces paronychia. Indinavir-induced retinoid-like effects must be separated from lipodystrophy syndrome. Replacement of therapy by an antiretroviral regimen not containing indinavir but containing other protease inhibitors and even lamivudine, lead to regression of retinoid-like manifestations.

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