Acta Dermatovener (Stockholm) 52: 320–322, 1972

ONYCHOLYSIS DUE TO TOPICAL 5-FLUOROURACIL

Walter B. Shelley

From the Department of Dermatology, University of Pennsylvania School of Medicine, Philadelphia, Pa., USA

Abstract. 5-fluorouracil cream applied under occlusion in a 5% concentration to the fingertips induced a remarkable yet reversible onycholysis. This was not seen when using a 2% concentration.

The singular capacity of 5-fluorouracil to produce onycholysis has not reached the text and monograph level (11, 13, 14, 17, 19). This is possibly due to the fact that the original reports stress either onychodystrophy (6, 18) or the value of this compound in treating paronychial warts (8). Accordingly, we would like to accentuate the growing awareness of this form of iatrogenic onycholysis by the following case report.

CASE REPORT

This 31-year-old white female patient presented the problem of paronychial warts of the right hand which continued to spread despite repeated curettage, electrodesiccation, liquid nitrogen treatments, high dosage vitamin A, as well as topical glutaraldehyde, occlusive iododeoxyuridine therapy and 5-fluorouracil solution (2%) under occlusion.

Occlusive polyvinylidine dressings with 5% 5-fluorouracil cream (Efudex®, Roche Laboratories) each night were then prescribed. Within 1 week the finger tips treated became swollen and tender, and an initial separation of the distal nail plate from the hyponychium was detected. The treatment was continued for three additional weeks during which time the nail became almost completely separated from the bed in each finger treated, and paronychial inflammation was evident. The other finger and toe nails were unchanged and the patient gave no history of previous episodes. Further, there was no relevant history of onycholysis, trauma, oral antibiotics, or the use of nail cosmetics, hardeners, or exposure to chemicals.

The treatment was discontinued and after 1 month the nail plates were re-attaching, although the onycholysis was still clearly evident (Fig. 1). No dystrophy of the plate itself was seen, nor was there any periungual inflammatory change. Four months later nail readherence was complete. Throughout all of this the verrucae remained virtually the same in size and appearance. Patch testing to the Efudex® cream was negative.

DISCUSSION

The attachment of the nail plate to the nail bed is a biologic phenomenon which in certain individuals, especially women, can be easily disturbed. Thus physical *trauma*, such as endured by the poultry plucker, induced by the aggressive nail manicure, or seen in onychotillomania, simply rips the plate from its nail bed moorings. A variant is liquid nitrogen which in the treatment of paronychial warts is also known to induce nail separation (2). Again, any *hyperkeratotic* change in the epidermis of the bed destroys the normally firm attachment of plate to bed. This we observe in psoriasis, in undercoat and nail hardener reactions, as well as following the exposure to the adhesive of artificial nails (9). Likewise *infective* processes are equally disrupting, as in fungal, bacterial or (rarely) viral infection. *Systemic disease* as well as reduction or alteration in peripheral blood flow may be responsible for such dramatic examples of onycholysis as "shell nail" (3). Exposure to *chemicals* such as organic solvents, as well as the commonplace enzyme detergents (7) may also initiate dissolution of the cement adherence system between nail plate and bed. Perhaps the most dramatic examples have been those called *photo-onycholysis* (5). Here the patient's onycholysis reflects the concomitant intake of a phototoxic drug as dechlormethyltetracycline and exposure to sun.

Nevertheless, the average example of fingernail onycholysis seen in dermatologic practice often involves but one nail and is of indeterminate origin. Accordingly the awareness of any specific cause is gratifying and should help us better to

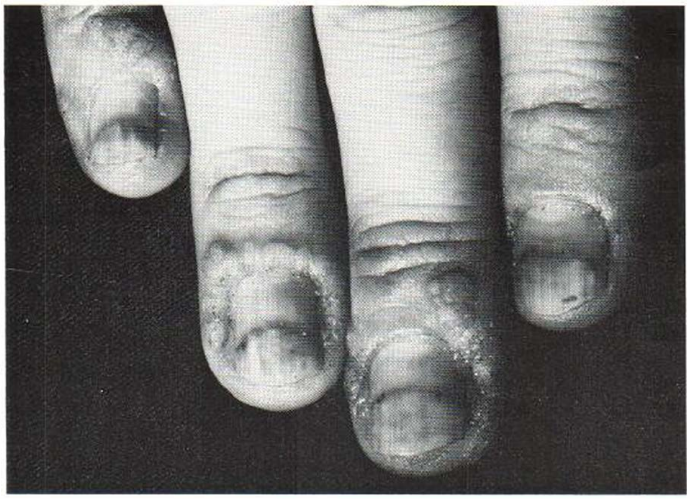

Fig. 1. Onycholysis due to one month of occlusive 5-fluorouracil (5% Efudex® cream) therapy for paronychial warts. Photograph taken 1 month after discontinuing Efudex. Warts remain unaffected. Nails on fingers not treated with fluorouracil showed no change.

perceive the pathogenesis of this common and often puzzling annoyance.

Although 5-fluorouracil is now frequently used in liquid and cream bases for the treatment of active keratoses (15), it is unlikely that onycholysis will be a significant adverse effect under these circumstances. Our patient, as well as those reported previously, stand in contrast since all were apparently using the high concentration of 5%, and furthermore all were applying it to the fingertip under occlusion. A lower concentration of 2%, even under occlusion, did not induce noticeable onycholysis in our patient. Similarly low concentrations produce no histological effect on normal skin (16). Significantly, when 5-fluorouracil is injected under the nail bed itself it produces dramatic onycholysis, indeed, complete nail loss (8). The change is completely reversible, just as it was in our patient, and the new nail grows in with normal reattachment.

Apparently 5-fluorouracil in high concentration under occlusion produces inflammatory change, and inhibition of the growth of the epidermal bed under the nail plate with an ever greater degree of distal nail separation. It is a known inhibitor of thymidylate synthetase and thus blocks DNA synthesis (4). All this is consistent with the early observation that fluorouracil is one of the antimetabolites which when applied locally under occlusion can induce actual erosions in the normal epidermis (10), and the more recent induction of bullous pemphigoid (1). Moreover it is consonant with Robinson's observation (12) of patchy alopecia seen following topical use of 5% 5-fluorouracil. Thus, our patient's experience coupled with those in the literature indicate that fluorouracil must be added to the list of compounds known to induce a striking yet reversible onycholysis.

REFERENCES

1. Bart, B. J. & Bean, S. F.: Bullous pemphigoid following the topical use of fluorouracil. Arch Derm (Chicago) *102:* 457, 1970.
2. Caravati, C. M., Wood, B. T. & Richardson, D. R.: Onychodystrophies secondary to liquid nitrogen cryotherapy. Arch Derm (Chicago) *100:* 441, 1969.
3. Cornelius, C. E. III & Shelley, W. B.: Shell nail syndrome associated with bronchiectasis. Arch Derm (Chicago) *96:* 694, 1967.
4. Eaglstein, W. H., Weinstein, G. D. & Frost, P.: Fluorouracil: Mechanism of action in human skin and actinic kerateses. Arch Derm (Chicago) *101:* 132, 1970.
5. Frank, S. B., Cohen, H. J. & Minkin, W.: Photoonycholysis due to tetracycline hydrochloride and doxycycline. Arch Derm (Chicago) *103:* 520, 1971.
6. Goldman, L., Blaney, D. J. & Cohen, W.: Onychodystrophy after topical 5-fluorouracil. Arch Derm (Chicago) *88:* 529, 1963.
7. Hodgson, G. & Mayon-White, R. T.: Acute onychia and onycholysis due to an enzyme detergent. Brit Med J *3:* 352, 1971.
8. Jaross, R. W.: Treatment of warts with topical and intralesional 5-fluorouracil. *In* Skin Surgery, 3rd ed. (ed. E. Epstein), pp. 374–377. Thomas, Springfield, Ill., 1970.
9. Lazar, P.: Reactions to nail hardeners. Arch Derm (Chicago) *94:* 446, 1966.
10. Nurse, D. S.: Effect of antimetabolites on epidermal structures. Arch Derm (Chicago) *87:* 258, 1963.
11. Ray, L. F.: Onycholysis. A classification and study. Arch Derm (Chicago) *88:* 181, 1963.

12. Robinson, H. M.: Scalp alopecia from Efudex applied to cheeks. *The Schoch Letter,* Item 37, September 1971.
13. Samman, P. D.: The Nails in Disease. Heinemann Medical Books, London, 1965.
14. — The Nails. *In* Textbook of Dermatology (ed. A. Rook, D. S. Wilkinson and F. J. G. Ebling), pp. 1426–1455. F. A. Davis Co., Philadelphia, 1968.
15. Serri, F.: International conference on 5% fluorouracil ointment in dermatology. Dermatologica *140,* Suppl. 1: 1–134, 1970.
16. Simmonds, W. Y.: Histologic effect of fluorouracil on normal skin. Arch Derm (Chicago) *100:* 608, 1969.
17. Taft, E. H.: Onycholysis—A clinical review. Aust J Derm *9:* 345, 1968.
18. Tannenbaum, M. H.: Onychodystrophy after topically applied fluorouracil for warts. Arch Derm (Chicago) *103:* 225, 1971.
19. Zaias, N. & Baden, H. P.: Disorders of nails. *In* Dermatology in General Practice (ed. T. B. Fitzpatrick et al.). McGraw-Hill Book Co., New York, 1971.

Received January 10, 1972

Walter B. Shelley, M.D.
Department of Dermatology
Hospital of the University of Pennsylvania
Duhring Laboratories Bldg
3400 Spruce Street
Philadelphia, Pa. 19104
USA