A Case of Captopril-induced Pemphigus Foliaceus

Ho Sun Jang, M.D., Doo Chan Moon, M.D., Kyung Sool Kwon, M.D.,

Tae Ahn Chung, M.D.

Department of Dermatology, College of Medicine, Pusan National University, Pusan, Korea

A 65-year-old male received captopril therapy (25mg three times a day, for the treatment of congestive heart failure. Seven months after starting the captopril therapy he developed flaccid vesiculobullae and erythematous patches with oozing, crusted surfaces on his trunk and the proximal portion of his extremities. The mucous membranes were not involved. The mucous membranes were not involved.) The histopathologic findings showed subcorneal bulla containing a few acantholytic cells and direct immunofluorescent studies revealed intercellular deposition of IgG and C3 throughout entire epidermis, consistent with pemphigus foliaceus.

After captopril therapy was discontinued, the skin lesions gradually improved within 1 month.

Pemphigus foliaceus is a rare complication of captopril therapy and this is, to our knowledge, the first case report in Korea. (Ann Dermatol 2:(1) 63-67, 1990)

Key Words: Captopril, Pemphigus foliaceus

Captopril (SQ 14,225, 1-(D-3-mercapto-2-methyl-1-oxypropyl)-L-proline) is a potent oral inhibitor of angiotensin-converting enzyme used in treating several forms of hypertension.[1] Cutaneous reactions of diverse morphology are the most common side effects observed during captopril therapy.[2-6] There have been many case reports of pemphigus induced by drugs, especially penicillamine, but captopril-induced pemphigus is very rare. It was first reported in 1980 by Parfrey et al.[7] Since that time, to our knowledge, there have been four case reports implicating captopril as a cause of pemphigus-like eruptions.[8,9] In Korea, so far, there have been no report of captopril-induced pemphigus.

We report a patient with clinical and histopathologic features of pemphigus foliaceus that can be attributed to the administration of captopril.

Received December 30, 1989
Accepted for Publication February 27, 1990

Reprint request to: Ho Sun Jang, M.D., Department Dermatology, College of Medicine, Pusan National University, 1-10, Ami-Dong, Seo-Ku, Pusan, 602-735, Korea.

This case was presented at the 41th Annual Spring Meeting of the Korean Dermatologic Association on April 14, 1989.

REPORT OF A CASE

A 65-year-old man receiving captopril therapy (25mg three times a day) for congestive heart failure visited our department in July 1987 with 1 month history of a vesiculobullous eruption on his trunk and the proximal portion of his extremities. He had a long history of cardiac disease, for which he was receiving therapy with digoxin, decaquinone, laxis and aldactone. Seven months after starting the captopril therapy he developed an eruption on his trunk that slowly spread to involve the proximal extremities. His family history was unremarkable.

On physical examination, flaccid vesiculobullae and erythematous patches with oozing, crusted surfaces were seen on his trunk and proximal extremities (Fig. 1). The mucous membranes were not involved.

The results of the following laboratory tests were within normal limits or negative: complete blood cell count, urinalysis, VDRL, stool examination and

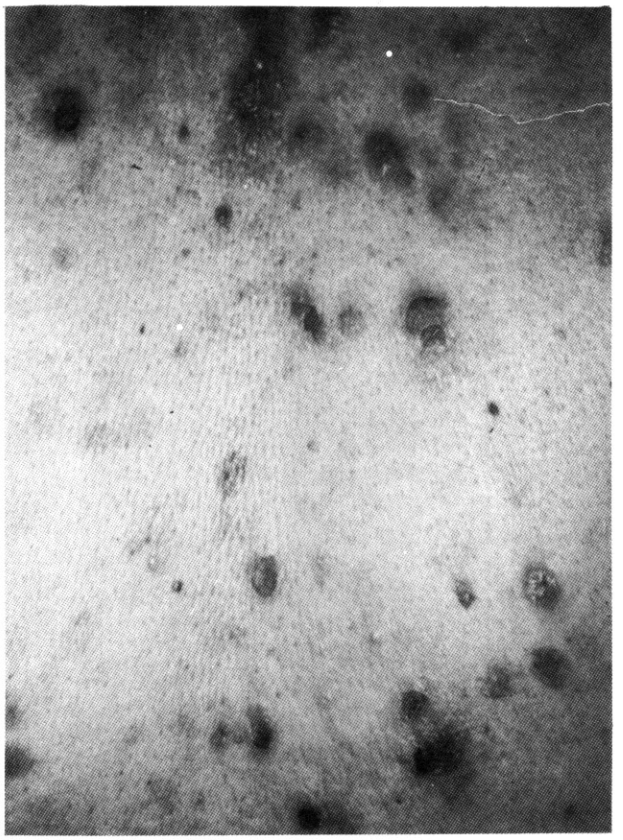


Fig. 1. Erythematous, erosive, crusted patches and bullae on the back.

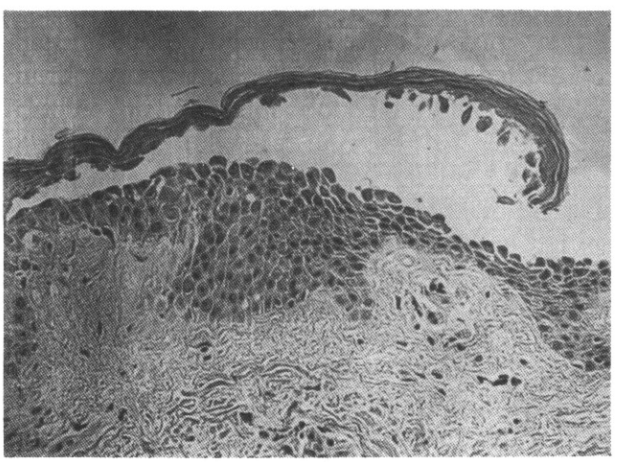


Fig. 2. This biopsy specimen from the back shows subcorneal bulla containing a few acantholytic cells (H&E stain, x200)

liver function tests. Histopathologic examination of the biopsy specimen obtained from a bullous lesion on the back showed a subcorneal bulla containing a few acantholytic cells. The dermis was moderately infiltrated with mononuclear cells with an admixture of a few eosinophils (Fig. 2). Direct immunofluorescent test performed on lesional and perilesional skin showed intercellular deposition of IgG and C3 throughout the entire epidermis (Fig. 3). Indirect immunofluorescent testing of patient's serum, using normal human abdominal skin as the substrate, was negative for circulating intercellular autoantibodies. These findings were consistent with a diagnosis of pemphigus foliaceus.

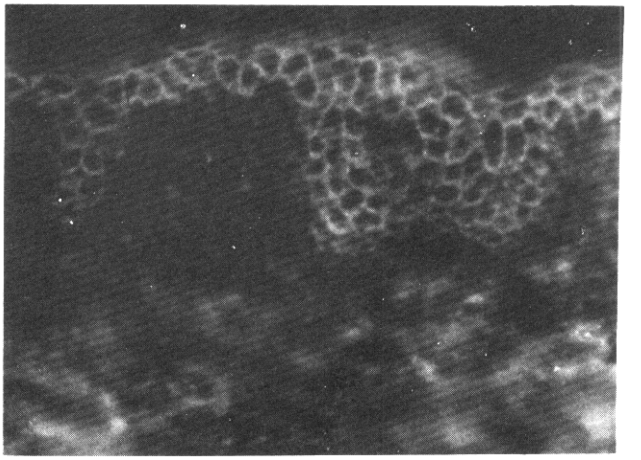


Fig. 3. Direct immunofluorescence of perilesional skin shows intercellular deposion of IgG throughout the entire epidermis (×200)

Captopril therapy was discontinued and with only topical corticosteroid, the skin lesions improved within 1 month. After the lesions had cleared, provocation test with captopril (12.5mg two times a day) was done. Two weeks later, vesicles and erythema with pruritus developed on his back. Thereafter, captopril therapy was discontinued and the skin lesions healed spontaneously and, to date, have not recurred.

DISCUSSION

The angiotensin-converting enzyme inhibitor captopril has been used to treat patient with hypertension since its introduction as a new class of antihypertensive agent in 1979.[1] It inhibits the activity of angiotensin-converting enzyme, thereby blocking the conversion of angiotensin I to the pressor substance angiotensin II.

Cutaneous eruptions are the most common side effects of this therapy and are usually limited to the upper part of the trunk, the arms, the head

and the neck. The reactions vary from edematous and urticarial to erythematous, maculopapular and morbilliform eruptions.[2] Recently, there were also reports of eruptions resembling pityriasis rosea,[3] lupus erythematosus[6] and pemphigus.[7-9] The frequency of cutaneous erptions varies from 8.3% to 58.3% and the average frequency reported when considering all series combined is 15.0%.[2] Other unwanted effected include fever, transient loss of taste, aphthous ulcers of mouth, proteinuria, nephrotic syndrome and reversible renal failure.[10] Most instances of cutaneous eruptions from captopril occurred at high dosage and appeared early in the course of treatment[2,4] but, captopril-induced pemphigus occurred at a relatively low doses and required a more prolonged period.[7,9] In a report of 15 reviews by Wilkin et al.,[2] the average day of onset of the cutaneous eruptions was the ninth day (ranging from the seventh to tenth day) and the average daily dosage was 683mg (ranging from 225mg to 1,000mg). On the other hand, the time of onset of pemphigus from captopril and the daily dosage were the eleventh month and 100mg in the case of Katz et al.,[9] the sixth month and 450mg in the case of Parfrey et al.[7] and in our case, the seventh month and 75mg, respectively.

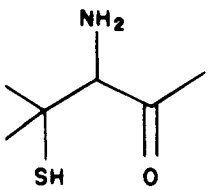
Besides captopril, several other drugs may induce pemphigus. The drugs that so far have been proven to have such an inducing effects are listed in Table 1.[8] Penicillamine, a sulfhydryl amino acid product of the hydrolysis of penicillin, is useful in treatment of Wilson's disease, cystinuria, lead poisoning, rheumatoid arthritis and selected connective tissue diseases. It has been estimated that 7% of patients taking penicillamine for at least six months developed pemphigus and most of them had pemphigus foliaceus.[11]

The mechanism whereby captopril induces pemphigus remains obscure, but the chemical structure of captopril is quite similar to that of penicillamine (Fig. 4).[7,12] The stereochemical position of the sulfhydryl group in both drugs is strikingly similar, they have similar chelating activity and they share many side effects, including apparently a pemphigus-like eruption. Therefore, the mechanisms by which captopril and penicillamine produce eruptoins may be similar, but have not yet been defined. At the present time, in case of penicillamine-induced pemphigus, there are two principal theories. The first proposes that penicillamine may unmask a latent tendency to develop

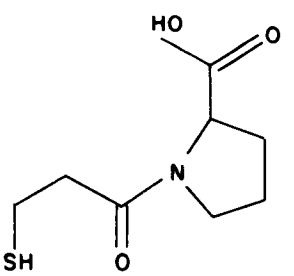
Table 1. Drugs reported to induce pemphigus.

Drug Type	Example
SH-SS drugs	Penicillamine
	Pyritinol
	Thiopronine
	Captopril
	Thiamazole
	Gold sodium thiomalate
Antibiotics	Penicillin
	Rifampicin
Pyrazolon derivatives	Phenylbutazone
	Aminopyrine
	Azapropazone
	Aminophenazone
	Oxiphenylbutazone
Micellaneous	Propranolol
	Progesterone
	Heroin
	Piroxicam
	Levodopa
	Lysine acetylsalicylate

*From Pisani W. Ruocco V: Clin Dermatol 4: 118-132, 1986.



PENICILLAMINE



CAPTOPRIL

Fig. 4. Chemical structures of penicillamine and captopril.

pemphigus.[13] The second suggests that natural epidermal surface proteins are transformed to antigenic structures by the drug,[14] which may bind to epidermal proteins and act as a hapten. It is possible that the capacity of D-penicillamine's sulfhydryl group to react with protein may alter epidermal intercellular cement substance with subsequent antibody formation and these antibodies may produe acantholytic splitting.[11] Recent studies seem to indicate that complement activation may amplify antibody-induced epidermal cell-cell detactement.[15] Which of these theories, if any, proves to be correct remains to be determined. Wilkin et al.[2] ovserved that captopril reactions occured at high dosage schedules and resolved at lower dosage schedules and then suggested a pharmacologic dose-response effect rather than an immunologic mechanism. The fact that cutaneous eruptions occur in a high percentage of patients taking captopril also supports a pharmacologic rather than an immunologic mechanism.[2,4] On one had, captopril is an inhibitor of dipeptidyl-carboxypeptidase, which frequently referred to as angiotensin-converting enzyme, on the other, it is also kininase II, the inactivator of bradykinin. Accordingly, captopril, by inhibiting angiotensin-converting enzyme, not only inhibits the production of angiotensin II, but also inhibits the catabolism of the kinins. Wilkin et al.[2] also demonstrated a considerable potentiation of the histamine flare response, a cutaneous reaction associated with kinins, during captopril therapy. Thus, they also suggested that captopril-induced eruptions might be the result of potentiation of kinin-mediated cutaneous reactions. Recently, Ruocco et al.[16] suggested that the penicillamine might produce lesions by a direct toxic or biochemical effect, without eliciting an immune response, which was evidenced by its ability to produce acantholysis in human skin explants cultured in normal human serum in the presence of th drug. Similar studies have not yet been performed with captopril. In this case, the cutaneous eruption occurred at a relatively low dosage and the immunofluorescent test was positive.Thus we suspected that an immunologic rather than a pharmacologic mechanism might be involved in the pathogenesis of captopril-induced pemphigus foliaceus.

Histopathologically, the earliest changes in pemphigus foliaceus are areas of acantholysis in the upper epidermis, usually in the granular layer or immediate below it, resulting in superficial, often subcorneal bullae.[17] Immunofluorescent test shows that autoantibodies encountered in pemphigus foliaceus are identical with those found in pemphigus vulgaris. They are IgG autoantibodies and are present regularly in the intercellular spaces of the epidermis and usually in the serum.[17] In this case, the above-mentioned histopathologic picture and immunofluorescent findings were demonstrated in the entire epidermis except that no circulating pemphigus autoantibodies were found in the patient's serum. The presence of circulating intercellular antibodies is not constant. When they are found, their titer is often low and does not reflect the severity and extent of the disease, contrary to what occurs in idiopathic pemphigus vulgris,[8] as demonstrated by the case of Matkaluk and Bailin.[18]

Typically, pemphigus foliaceus is mild. Complete resolution may be seen within five to eight weeks after withdrawal of the drug[7,9] Uncommonly, pemphigus induced by penicillamine may persisted for one to two years after discontinuation of therapy and require high-dose steroids plus immunosuppressive drugs for control of the disease.[11,18] In the present case, captopril therpy was discontinued 1 months after the eruption began and all other medications were continued. With only topical corticosteroid therpy, the skin lesions gradually cleared within 1 month. Thereafter, we performed a provocation test with a low dose of captopril (12.5mg, two times a day) and 2 weeks later, vesicles and erythema associated with an itching sensation developed on his back. Thus, we feel this case is a captopril induced pemphigus foliaceus, an uncommon complication of this medication.

REFERENCES

1. Gavras H, Brunner HR, Turini GA, et al: *Antihypertensive effect of the oral angiotensin-converting enzyme inhibitor SQ 14,225 in man. N Engl J Med 298:991-995, 1978.*
2. Wilkin JK, Hammond JJ, Kirkendall WM: *The captopril-induced eruption. Arch Dermatol 116: 902-905, 1980.*

3. Wilkin JK, Kirkendall WM: *Pityriasis rosea-like rash from captopril. Arch Dermatol 118: 186-187, 1982.*
4. Luderer JR, Lookingbill DP, Schneck DW, Demers LM, Cohen C, Hayes AH: *Captopril-induced skin eruptions. J Clin Pharmacol 22: 151-159, 1982.*
5. Daniel F, Foix C, Barbet M, et al: *Captopril-induced eruptions: Occurrence over a three-year period. Ann Dermatol Venereol 110: 441-446, 1983, Cited from ref. 9.*
6. Patri P, Nigro A, Rebora A: *Lupus erythematosus-like eruption from captopril, Acta Derm Venereol 65: 447-448, 1985, Cited from ref. 9.*
7. Parfrey PS, Clement M, Vandenburg MJ, Wright P: *Captopril-induced pemphigus. Br Med J 281:194, 1980.*
8. Pisani w, Ruocco V: *Drug-induced pemphigus. Clin Dermatol 4:118-132, 1986.*
9. Katz RA, Hood AF, Anhalt GJ: *Pemphigus-like eruption from captopril. Arch Dermatol 128: 20-21, 1987.*
10. Atkinson AB, Robertson JIS: *Captopril in the treatment of clinical hypertension and cardiac failure. Lancet 2: 836-839, 1979.*
11. Marsden RA, Ryan TJ, Vanhagen RI, et al: *Pemphigus foliaceus induced by penicillamine. Br Med J 4: 1423-1424, 1976.*
12. Clement M: *Captopril-induced eruptions. Arch Dermatol 117: 525-526, 1981.*
13. Marsden RA, Dawber RPR, Millard PR, Mowat AG: *Herpetiform pemphigus induced by penicillamine. Br J Dermatol 97: 451-452, 1977.*
14. Davies MG, Holt P: *Pemphigus in a patient treated with penicillamine for generalized morphea. Arch Dermatol 112: 1308-1309, 1976.*
15. Ahhalt GJ, Martins C, Rivitti E, Diaz LA: *Endemic pemphigus foliaceus (Fogo Selvagem). Advances in Dermatology. 4:73-93, 1989.*
16. Ruocco V, de Luca M, Pisani M, de Angelis E, Vitale O, Astarita C: *Pemphigus provoked by D-penocillamine: An experimental approach using in vitro tissue culture. Dermatologica. 164: 236-248, 1982.*
17. Lever WF, Schamburg-Lever G: *Histopathology of the Skin. 6th ed. JB Lippincott Co, Philadelphia, 1983, pp 110-112.*
18. Matkaluk RM, Bailin PL: *Penicillamine-induced pemphigus foliaceus: A fatal outcome. Arch Dermatol 117: 156-157, 1981.*