

Cyclosporin A

1 . 1 . 1 . 2 . 3 . 1 . 1
 1 ,
 2 ,
 3

I.

Cyclosporin A(CsA) 33). CsA 1980
 13). 10,39).
 1978 11). 15 - 45mg/kg, 45 - 95mg/kg , CsA

37) , , , , 31). CsA 1983
 28,24,38). 29)
 CsA Tolypocladium Inflatum Gams 11 가 33).
 33) nifedipine
 5) phenytoin 9).
 CsA B - 33).
 T - , 가
 T - 1,9,44).
 6,18).
 CsA , 가 가 8). CsA
 , , 13).
 33). CsA 13,23,43).
 가

13,16,22,23,25,26)

CsA
(plasma cell gingivitis)
21), (1)

(amorphous ground substance)

10%

가

22),

(myofibroblast)

. Microtome 3 - 5µm
hematoxylin - eosin

8,43).

CsA

(2)

CsA

(Transmission Electron
Microscopy, T.E.M.)

CsA

. 0.1M Cacodylate buffer

(PH 7.4) Karnovsky

(2% Glutaraldehyde, 2% Paraformaldehyde, 0.5% CaCl₂) 6

II.

0.1M Cacodylate buffer 2

1.

1.33% OsO₄(0.1M Cacodylate buffer
) 2

0.1M Cacodylate 10

3

propylene oxide 10

CsA

EPON mixture(EPON 812, MNA, DDSA,
DMP30) propylene oxide 1:1

overnight(18)

14 , 25

(embedding - E.M oven 35°C 6 , 45°C
12 , 60°C 24) . E.M oven

, 25

3 , 8 ,

10

CsA

. Ultramicrotome

2

10mg/kg/day

1µm semithin

5 - 6mg/kg/day

1% Toluidin blue

3

CsA

50nm

가 0

uranyl acetate lead citrate
TEM(Philips CM - 10)

. rER(rough endoplasmic reticulum) - cisternae (electron dense granule) (Figure 6).

III.

(1) CsA 3

(rete ridges)가 (Figure 1).

가

가 가

(nodule)

(Figure 2).

(2)

prismatic cell

introflexion 가

plasmatic

columns

plasmatic estroflexions

3). 가 (space)

(Figure (intercellular

가 34).

(Figure 4).

(collagen fiber),

(col -

CsA

lagen fibril)

(Figure 5).

13,21),

22).

CsA

(myofibroblast)가

⁴³⁾
Lubow (1984) ²¹⁾
(plasma cell gingivitis)
가

cell) 가
(intercellular canals) 가
, Mariani

, Yamasaki (1987) ⁴³⁾
(myofibroblast)가

. CsA

, CsA

가
가

Yamasaki

⁴³⁾

가
Deliliers (1986) ¹³⁾ Lubow
CsA

CsA

가
CsA

(endoplasmic reticulum)

가

CsA

Mariani (1993) ²²⁾

(amorphous
ground substance)

가

(basal

가 CsA
CsA가
phenytoin, dihydropyridines, nifedipine

V.

CsA

CsA

3

1.

2.

3.

가

가 CsA

CsA가

VI.

1. Adams, D., Davies, G. : Gingival hyper -

plasia associated with Cyclosporin A:a report of two cases, Br. Dent. J., 157:89, 1983.

2. Barber, M.T., Savage, N.W., Seymour, G.J. : The effect of cyclosporin and lipopolysaccharide on fibroblasts: implications for cyclosporin - induced gingival overgrowth, J. Periodontol., 63:397 - 404, 1992.

3. Barclay, S., Thomason, J.M., Idle, J.R., Seymour, R.A. : The incidence and severity of nifedipine - induced gingival overgrowth, J. Clin. Periodontol., 19:311 - 314, 1992.

4. Bennet, J.A., Christian, J.M. : Cyclosporin - induced gingival hyperplasia: Case report and literature review, J. Am. Dent. Assoc., 111:272, 1985.

5. Borel, J.F., Feurer, C., Gubler, H. U. : Biological effects of cyclosporin A:a new antilymphocyte agent, Agents and actions, 6:468 - 475, 1976.

6. Britton, S., Palacios, R. : Cyclosporin A - usefulness, risks and mechanisms of action, Immunological Review, 65:5 - 22, 1982.

7. Brown, R.S., Beaver, W.T., Bottomley, W.K. : On the mechanism of drug - induced gingival hyperplasia, J. Oral. Pathol., 20:201 - 209, 1991.

8. Buchanaan, J.T., Smith, P. : Cyclosporin and human gingival fibroblasts, J. Dent. Res., 65:789, 1986.

9. Butler, R.T., Kalkwarf, K.L., Kaldahl, W.B. : Drug - induced gingival hyperplasia: Phenytoin, cyclosporin and nifedipine, J. Am. Dent. Assoc., 114:56, 1987.

10. Calne, R.Y., Rolles, K., White, D.J.G., Thiru, S., Evans, D.B., Henderson, R.,

- Hamilton, D.L., Boone, N., McMaster P., Gibby, O., Williams, R. : Cyclosporin - A in clinical organ grafting, *Transplantation Proceedings*, 13:349 - 358, 1981.
11. Calne, R.Y., Thiru, S., McMaster, P., Craddock, G.N., White, D.J.G., Evans, D.B., Dunn, D.C., Pentlow, B.D., Rolles, K. : Cyclosporin - A in patients receiving renal allograft from cadaver donors, *Lancet*, 1:1323 - 1327, 1978.
 12. Daley, T.D., Wysocki, G.P., Day, C. : Clinical and pharmacologic correlations in cyclosporin - induced gingival hyperplasia, *Oral. Sur. Oral. Med. Oral. Pat.*, 62:417 - 421, 1986.
 13. Deliliers, G.L., Santoro, F., Polli, N., Bruno, E., Fumagalli, L., Risciotti, E. : Light and Electron Microscopic Study of Cyclosporin A - Induced Gingival Hyperplasia, *J. Periodontol.*, 57:771 - 775, 1986.
 14. Fischer, R.G., Edwardsson, S., Klinge, B., Attstrom, R. : The effect of Cyclosporin A on the oral microflora at gingival sulcus of the ferret, *J. Clin. Periodontol.*, 23:853 - 860, 1996.
 15. Friskopp, J., Engstrom, P.E., Sundqvist, K.G. : Characterization of mononuclear cells in CsA induced gingival enlargement, *Scand. J. Dent. Res.* 94:443 - 447, 1986.
 16. Hall, B.K., Squier, C.A. : Ultrastructural quantitation of connective tissue changes in phenytoin - induced gingival overgrowth in the ferret, *J. Dent. Res.*, 61:942 - 952, 1982.
 17. Hefti, A.F., Eshenaur, A.E., Hassell, T.M., Stone, C. : Gingival Overgrowth in Cyclosporin A Treated Multiple Sclerosis Patients, *J. Periodontol.*, 65:744 - 749, 1994.
 18. Hess, A.D., Colombani, P.M. : Mechanism of action of cyclosporin: a unifying hypothesis, *Adv. Exp. Med. Bio.*, 213:309 - 330, 1987.
 19. Kahan, B.D., Van Buren, C.T., Lin, S.N., Ried, M., Legrue, S.J. : Pharmacokinetics of cyclosporin A in renal allograft recipients, In, *Cyclosporin A ed.*, 413 - 426, 1982.
 20. Lederman, D., Lumerman, H., Reuben, S., Freedman, P.D. : Gingival hyperplasia associated with nifedipine therapy: report of case, *Oral. Surg. Oral. Med. Oral. Pathol.*, 57:620 - 622, 1986.
 21. Lubow, R.M., Cooley, R.L., Hartman, K.S., McDaniel, R.K. : Plasma - cell gingivitis: report of a case, *J. Periodontol.*, 55:235 - 241, 1984.
 22. Mariani, G., Calastrini, C., Carinci, F., Marzola, R., Calura, G. : Ultrastructural Features of Cyclosporin A - induced gingival hyperplasia, *J. Periodontol.*, 64:1092 - 1097, 1993.
 23. McGaw, W.T., Porter, H., Edmonton, B.S. : Cyclosporin - induced gingival overgrowth: An ultrastructural stereologic study, *Oral. Surg. Oral. Med. Oral. Pathol.*, 65:186 - 190, 1988.
 24. McMaster, P., Gibby, O.M., Calne, R.Y., Loke, M., Luzio, S.D., Rolles, K., White, D.J., Evans, D.B. : Human pancreatic transplantation - preliminary studies of carbohydrate control, *Transplant Proc.*, 13:371 - 373, 1981.
 25. Niimi, A., Tohnai, I., Kaneda, T., Takeuchi, M., Nagura, H. : Immunohistochemical analysis of effects of

- cyclosporin A on gingival epithelium, *J. Oral. Pathol. Med.*, 19:397 - 403, 1990.
26. O'Valle, F., Mesa, F.L., Gomez - Morales, M., Aguilar, D., Caracuel, M.D., Medina - Cano, M.T., Andujar, M., Lopez - Hidalgo, J., Garcia del Moral, R. : Immunohistochemical Study of 30 Cases of Cyclosporin A - induced Gingival Overgrowth, *J. Periodontol.*, 65:724 - 730, 1994.
27. Pernu, H.E., Pernu, L.M., Huttunen, K.R., Nieminen, P.A., Knuuttila, M.L. : Gingival overgrowth among renal transplant recipients related to immunosuppressive medication and possible local background factors, *J. Periodontol.*, 63:548 - 553, 1992.
28. Powles, R.L., Clink, H.M., Spence, D., Morgenstern, G., Watson, J.G., Selby, P.J., Woods, M., Barrett, A., Jameson, B., Sloane, J., Lawler, S.D., Kay, H.E., Lawson, D., McElwain, T.J., Alexander P. : Cyclosporin A to prevent graft - versus - host disease in man after allogeneic bone - marrow transplantation, *Lancet*, 16:327 - 329, 1980.
29. Rateitschak - Pluss, E.M., Hefti, A., Lortscher, R., Thiel, G. : Initial observation that cyclosporin A induces gingival enlargement in man, *J. Clin. Periodontol.*, 10:237 - 246, 1983.
30. Rostock, M.H., Fry, H.R., Turner, J.E. : Severe gingival overgrowth associated with cyclosporin therapy, *J. Peri -*

- odontol., 57:294, 1986.
31. Ryffel, B., Donatsh, P., Mandorin, M. : Toxicological evaluation of cyclosporin A, *Arc. Tox.*, 53:107 - 141, 1983.
 32. Schuller, P.D., Freedman, H.L., Lewis, D.W. : Periodontal status of renal transplant patients receiving immunosuppressive therapy, *J. Periodontol.*, 44:167 - 170, 1973.
 33. Seymour, R.A., Jacobs, D.J. : Cyclosporin and the gingival tissues, *J. Clin. Periodontol.*, 19:1 - 11, 1992.
 34. Seymour, R.A., Thomason, J.M., Ellis, J.S. : The pathogenesis of drug - induced gingival overgrowth, *J. Clin. Periodontol.*, 23:165 - 175, 1996.
 35. Somacarrera, M.L., Hernandez, G., Acero, J., Moskow, B.S. : Factors related to the incidence and severity of cyclosporin - induced gingival overgrowth in transplant patients. A longitudinal study, *J. Periodontol.*, 65:671 - 675, 1994.
 36. Somacarrera, M.L., Hernandez, G., Acero, J., Moskow, B.S. : Localization of gingival overgrowth in heart transplant patients undergoing cyclosporin therapy, *J. Periodontol.*, 65:666 - 670, 1994.
 37. Starzl, T.E., Hakala, T.R., Iwatsuki, S., Rosenthal, T.J., Shaw, B.W., Klintmalm, G., Porter, K. A. : Cyclosporin A and steroid treatment in 104 cadaveric renal transplantation, *Cyclosporin A ed.*, 365 - 377, 1982.
 38. Starzl, T.E., Iwatsuki, S., Klintmalm, G., Schroter G.P.J., Weil, R., Koep, L.J., Porter, K. A. : Liver transplantation, 1980, with particular reference to cyclosporin A, *Transplantation Proceedings*, 13:281 - 285, 1981.
 39. Starzl, T.E., Weil, R., Iwatsuki, S., Klintmalm, G., Schroter G.P.J., Koep, L.J., Iwaki, Y., Terasaki, P.I., Porter, K. A. : The use of cyclosporin A and prednisone in cadaver kidney transplantation, *Sur. Gyn. Obs.*, 151:17 - 26, 1980.
 40. Tipton, D.A., Stricklin, G.P., Dabbous, M.K. : Effect of cyclosporin on gingival fibroblast collagenolytic activity, *J. Dent. Res.*, 66:312, 1987.
 41. Tipton, D.A., Stricklin, G.P., Dabbous, M.K. : Fibroblast heterogeneity in collagenolytic response to cyclosporin, *J. Cell. Bio.*, 46:152 - 165, 1991.
 42. Tyldesley, W.R., Rotter, E. : Gingival hyperplasia induced by cyclosporin - A, *Brit. Dent. J.*, 157:305 - 309, 1984.
 43. Yamasaki, A., Rose, G.G., Pinero, G.J., Mahan, C.J. : Ultrastructure of fibroblasts in Cyclosporin A - induced gingival hyperplasia, *J. Oral. Pathol.*, 16:129 - 134, 1987.
 44. Wysocki, G.P., Gretzinger, H.A., Laupacis, A., Ulan, R.A., Stiller, C.R. : Fibrous hyperplasia of the gingiva. A side effect of Cyclosporin A therapy, *Oral. Surg.*, 55:274, 1983.

Figure 1. (H - E, X 100)

가

(1)

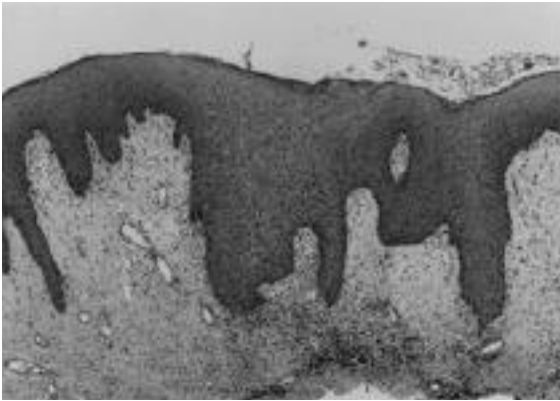


Figure 1

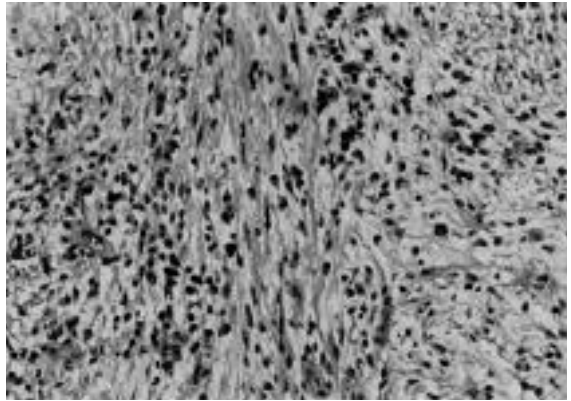


Figure 2

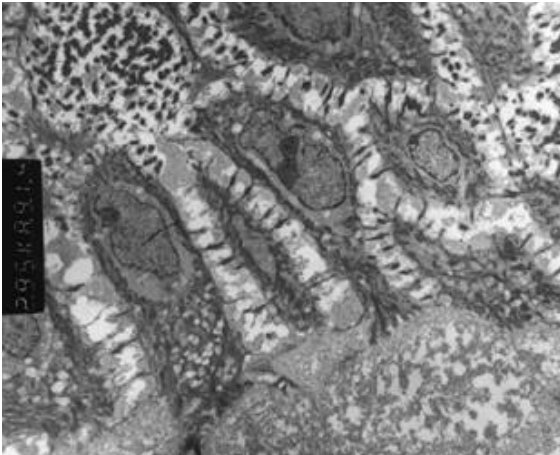


Figure 3

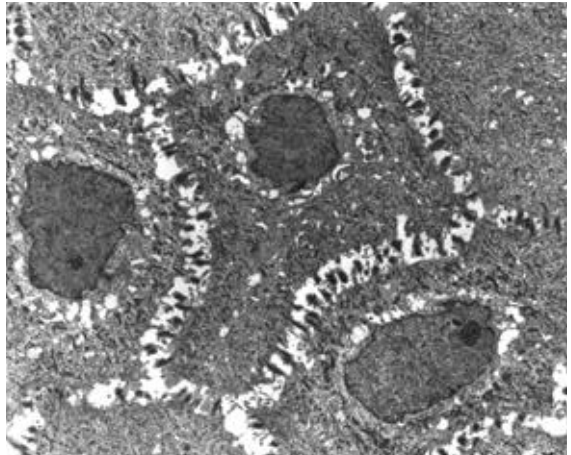


Figure 4

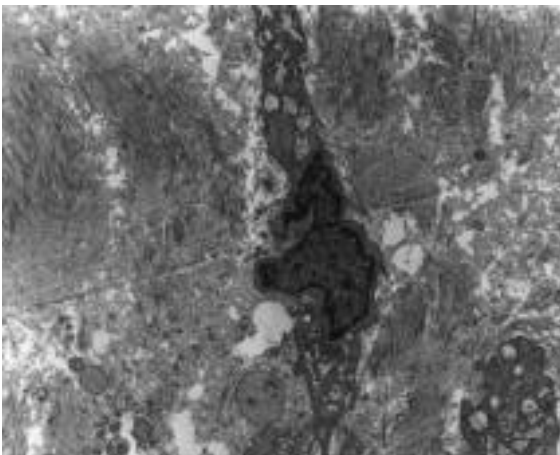


Figure 5

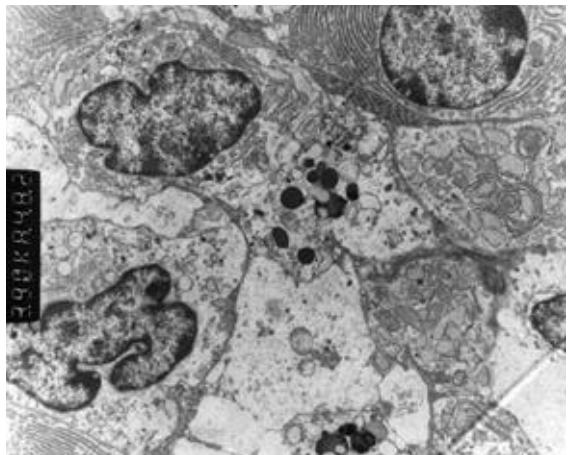


Figure 6

Figure 2. (H - E, X 200)

Figure 3. (TEM, X 5,900)

Figure 4. (TEM, X 5,400)

가가

가

Figure 5. (TEM, X 7,200)

Figure 6. (TEM, X 7,488)

가

- Abstract -

Morphological features of Cyclosporin A - induced Gingival Hyperplasia

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Cyclosporin A (CsA) is now widely used to treat organ transplant recipients. But CsA has various short - and long - term side effects. Especially, gingival hyperplasia is not easy to resolve since its nature is still unknown. This study discusses the pathogenesis of CsA - induced gingival hyperplasia on the basis of data obtained from light and electron microscopic studies of biopsy from patients on CsA treatment after kidney transplantation. Light microscopically, the multilayered squamous epithelium showed an irregular surface of parakeratosis and deep invaginations in the subepithelial tissue. At lamina propria, we

observed bundles of irregularly arranged collagen fiber, some fibroblasts, numerous capillary vessels and a large diffuse infiltration of plasma cells. Ultrastructurally, many fibroblasts, collagen fibers, collagen fibrils were present in lamina propria. On the basis of the data collected, we propose that the morphological features of the dimensional increase in gingival tissue associated with CsA treatment in kidney transplant patients may be considered proliferative fibroblasts, collagen fibers, collagen fibrils in lamina propria.

Key words : Cyclosporin A, gingival hyperplasia, lamina propria, collagen fibers, fibroblasts, collagen fibrils