

Cyclosporin-induced Sebaceous Hyperplasia in Renal Transplant Patients

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Abstract

Introduction: Sebaceous hyperplasia is associated with immunosuppressive treatment with cyclosporin in male renal transplant patients. This has not been reported in the local context. **Clinical Picture:** This is a report on 2 Chinese renal transplant patients on cyclosporin who developed sebaceous hyperplasia. **Treatment and Outcome:** One patient was treated with carbon dioxide laser. The result was good and the patient was satisfied with the procedure. **Conclusion:** Cyclosporin-induced sebaceous hyperplasia is likely to be a direct and casual effect of cyclosporin, and to be unrelated to immunosuppressive action. However, further studies are needed to find out whether sebaceous hyperplasia is a dysplastic process or tumour progression in genetically susceptible patients under the effect of immunosuppression.

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Introduction

There are several reports in the literature of sebaceous hyperplasia being induced by cyclosporin in immunosuppression of organ transplant patients. The condition was only found in male transplant patients and not seen in children with renal transplant. Two Chinese renal transplant recipients who developed sebaceous hyperplasia while on cyclosporin are reported in this case report. The mechanism of cyclosporin-induced sebaceous hyperplasia and the treatment of sebaceous hyperplasia are discussed.

Case Reports

The first patient was a 54-year-old Chinese male. He had end-stage renal failure secondary to IgA nephropathy with mesangio-proliferative glomerulonephritis. He had had a cadaveric renal transplant in 1996. He was maintained on cyclosporin 250 mg (4.3 mg/kg body weight) and prednisolone 10 mg. He noticed multiple skin-coloured lesions on his face 3 years after renal transplant. On examination of his face, there were about 100 2-mm to 5-mm skin-coloured umbilicated papules, which were clinically sebaceous hyperplasia (Fig. 1). There were viral warts on the face. He also had tinea cruris, onycholysis and nail dystrophy affecting the fingernails and culture of the

nails grew *Candida albicans*. Skin biopsy of one of the papules showed hyperplasia of the sebaceous gland. He was treated with carbon dioxide laser, and showed improvement.

The second patient was a 40-year-old Chinese male. He had had a renal transplant in 1995 and was maintained on cyclosporin 275 mg (3.6 mg/kg body weight) and prednisolone 8 mg. He noticed multiple skin-coloured lesions on his face 5 years after renal transplant. The caudate lobe of his liver was resected, showing Epstein-Barr virus-associated smooth muscle tumour. On examination, there were about 20 2-mm to 5-mm skin-coloured umbilicated papules on the face, which were clinically diagnosed as sebaceous hyperplasia. Huge viral warts were found on the feet. There was onychomycosis of the fingernails and toenails and culture of the nails grew *Trichophyton rubrum*. Skin biopsy from the face showed several sebaceous glands opening into a common shaft onto the overlying skin (Figs. 2a and 2b). He did not want treatment for the sebaceous hyperplasia.

Discussion

Sebaceous hyperplasia is commonly seen in middle age or older. The causative factors include intrinsic ageing and

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Fig. 1. Sebaceous hyperplasia on the right face.

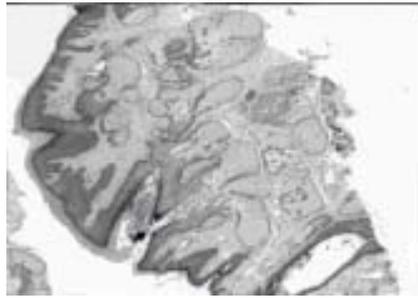


Fig. 2a. Several sebaceous glands opening into a common shaft onto the overlying skin (Haematoxylin and eosin stain, original magnification x50).

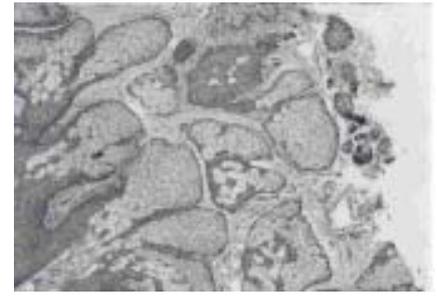


Fig. 2b. Higher magnification showing hyperplasia of sebaceous glands (Haematoxylin and eosin stain, original magnification x100).

extrinsic ageing (photo-ageing). Reduced androgen levels lead to a decreased cellular turnover in aged sebaceous glands of the face, resulting in glandular hyperplasia. Prolonged ultraviolet radiation has been shown to induce marked hyperplasia of sebaceous gland in hairless mice. Ultraviolet A light penetrates deeper into the dermis to reach the sebaceous gland and is probably the spectrum that causes the sebaceous gland hyperplasia to develop in ageing facial skin.¹

Familial sebaceous hyperplasia was first reported by Dupre et al in 1980.² The sebaceous hyperplasia appears during puberty or soon after. The face, neck and upper thorax are affected sparing the periorificial regions. Acneiform lesions are absent. It runs a slowly progressive course.

Muir-Torre syndrome was first reported by Muir and Torre in 1967. It is an autosomal dominant condition. Patients have multiple sebaceous gland carcinoma, multiple keratoacanthomas and visceral tumours. Sebaceous hyperplasia has been reported in association with internal malignancy in the setting of Muir-Torre syndrome. However, it is generally accepted that sebaceous hyperplasia alone does not signify a predisposition to cancer or represent a sign of Muir-Torre syndrome.

Cyclosporin-induced sebaceous hyperplasia has been reported in several series of organ transplant recipients. There were 2 series of renal transplant recipients on cyclosporin who developed sebaceous hyperplasia. Lugo-Janer et al³ reported that 5 of 63 (8%) renal transplant patients on cyclosporin developed sebaceous hyperplasia. Bencini et al⁴ reported that 7 of 67 (10%) renal transplant recipients on immunosuppression developed sebaceous hyperplasia. In every case, the patient had been taking cyclosporin. This association was not observed in an earlier report on kidney transplant recipients who had not received cyclosporin.⁵ The development of sebaceous hyperplasia had previously been observed in patients receiving 5 mg to

10 mg per kg body weight per day and was considered to be dose-dependent.

The 2 patients in this report received a daily dose of 3.6 mg and 4.3 mg per kg body weight. They developed sebaceous hyperplasia 3 to 5 years after cyclosporin treatment. The 2 patients reported by Boschnakow et al⁶ received a low dose of 2 mg to 2.5 mg and presented with sebaceous hyperplasia 9 years and 19 years after cyclosporin treatment. All the recipients who developed sebaceous hyperplasia were male. Sebaceous hyperplasia has not been reported in children due to the immaturity of the sebaceous gland in children.

De Berker et al⁷ reported that 16 of 104 (16%) heart transplant patients had sebaceous hyperplasia, compared to 1% in an age- and sex-matched controlled group. The condition occurred solely in men and affected the face only. All 3 male kidney transplant recipients had sebaceous hyperplasia. In this report, the sebaceous hyperplasia in adults had a greater association with photo-ageing and carcinogenesis than hypertrichosis. This report proposed that sebaceous hyperplasia induced by cyclosporin was related to the process of dysplastic epithelial proliferation in transplant recipients. Experimentally-induced sebaceous hyperplasia in rodents appeared to be influenced by genotype.⁸ In the series by de Berker,⁷ there were no features in the drug and medical history to distinguish those with and without sebaceous hyperplasia suggesting a possible genetic basis to the development of sebaceous hyperplasia after organ transplant. The simplest support for this hypothesis was that only men had sebaceous hyperplasia.

The Muir-Torre syndrome also provided indirect support for a genetic link in sebaceous hyperplasia. Despite the lack of statistical significance, which could be ascribed to the relative small number of patients, the increased severity of hypertrichosis in dark-skinned patients is interesting and might suggest the importance of genetic predisposing factors in regulating individual susceptibility to the drug.⁴

Other immunosuppressive drugs used in renal transplant patients, such as azathioprine and prednisolone, have not been shown to induce sebaceous hyperplasia.^{3,5,9} Sebaceous hyperplasia is considered to be a direct and causal effect of cyclosporin on the sebaceous gland rather than a result of immunosuppressive action.⁷ However, some authors suggest it is impossible to differentiate between the effects induced by cyclosporin and those induced by steroids, since both can modify the pilo-sebaceous unit.⁴ The 2 drugs have synergistic effects because cyclosporin reduces the clearance and potentiates the effect of prednisolone.¹⁰

An association between sebaceous gland carcinoma and immunosuppressive drugs has been reported.¹¹ As in Muir-Torre syndrome, a microsatellite instability in post-transplant sebaceous carcinoma DNA was found together with a loss of mismatch repair genes,¹² indicating a possible interaction between DNA mismatch repair gene proteins and immunosuppressive drugs. Treatment with immunosuppressive drugs may unmask latent Muir-Torre syndrome or promote tumour progression in genetically susceptible patients, leading to the development of sebaceous hyperplasia.

One study showed that the skin is one of the principal sites of accumulation of cyclosporin, in addition to other tissues (in particular fat).¹³ Skin acts as a storage depot for the drug, which may account for the fact that cutaneous manifestations are among the commonest side effects. Since cyclosporin is highly lipophilic, it has been suggested that the sebaceous gland might be the major cutaneous site of its elimination. Cyclosporin is known to cause hypertrichosis. The affinity of cyclosporin for lipids could be important in inducing these modifications of the pilo-sebaceous follicles viz. hypertrichosis and sebaceous hyperplasia.

Isotretinoin is effective in the treatment of sebaceous hyperplasia but recurrence is common after the treatment is stopped. Grimalt et al¹⁴ reported 3 patients with familial sebaceous hyperplasia treated with isotretinoin 1 mg/kg body weight. They showed marked improvement after 6 weeks' treatment. Long-term therapy with a lower dose was given to maintain the improvement. One patient was taking 20 mg every other day.

Other options include electrodesiccation, shave excision and carbon dioxide laser. Walter et al¹⁵ reported the advantage and efficacy of carbon dioxide laser in the treatment of cyclosporin-induced sebaceous hyperplasia in a renal transplant patient. The procedure was less stressful to the patient and provided a dry operative field. The first patient in the report also found good cosmetic effect after carbon dioxide laser. One of the authors has treated other patients with sebaceous hyperplasia with carbon dioxide

laser, and the results have been good, with high patient acceptance.

Conclusion

Cyclosporin induces sebaceous hyperplasia in adult male renal recipients on cyclosporin. Sebaceous hyperplasia is likely to be a direct and causal effect of cyclosporin on the sebaceous gland, and to be unrelated to immunosuppression. However, further studies are needed to find out whether sebaceous hyperplasia is a dysplastic process or tumour progression in genetically susceptible patients under the effect of immunosuppression.

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