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NET LETTER

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Primary cutaneous CD30+ lymphoproliferative disorder in an atopic dermatitis patient on cyclosporine therapy

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Sir,

The risk of lymphoma in atopic dermatitis (AD) is controversial, and both positive and negative correlation has been reported. The relation may rather be related to its therapy. Additionally, increment of middle-aged AD might be related. The age of 9.6% of AD in Japan was over 46 years. Recently, beneficial effect of cyclosporine for AD has been established. However, after using cyclosporine for AD, primary cutaneous CD30+ lymphoproliferative disorder (including lymphomatoid papulosis (LyP), primary cutaneous anaplastic large cell lymphoma (ALCL), and borderline lesion) is sporadically observed. [1],[2],[3],[4] Recent report indicated that CD30+ T lymphocytes are up-regulated in the lesional skin of AD by mast cells which show the regulatory roles on both innate and acquired immunities. [5]

A 57-years-old man was treated by topical corticosteroid ointment and antihistamine by a local dermatologist because of itchy chronic eruptions under a diagnosis of AD for about 20 years. He had no methotrexate administration or PUVA therapy. It was not clear whether he received steroid administration treatment. Because of the lack of response, he was referred to our hospital [Figure 1a]. Total body analyses including CT and Ga scintigraphy did not disclose any systemic manifestations including mycosis fungoides or cutaneous lymphoma. Histopathology of the skin lesion was consistent with AD [Figure 1b and c].

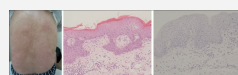


Figure 1: (a) Lichenified, scaly, erythematous plaques on the back. (b) Histopathological findings. (H and E, ×100). Inflammatory infiltrate is observed on the upper dermis. Hyperkeratosis, acanthosis, and parakeratosis. Epidermal spongiosis and lymphoid cell infiltration. (c) CD30+ lymphocytes were scarce

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We started pre-prandial administration of cyclosporine (150 mg/twice a day; 2.2 mg/kg/day). The concentration of trough level was 65 ng/ml. The maximum concentration of cyclosporine was got at 1 h and showed 770 ng/ml. Atopic erythema and itching were decreased dramatically. After eight weeks of treatment, exudative erythematous

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plaque was detected on his right thigh [[Figure 2]a]. Topical application of betamethasone 17-valerate ointment was not effective and peripheral reddish nodules were developed. Cyclosporine was discontinued and skin biopsy was performed for the tumor [[Figure 2]b]. Superficial lymph nodes were not palpable. Skin biopsy disclosed dense lymphoid cell infiltrate in the upper dermis [[Figure 3]a] and anaplastic large cells with bizarre morphology [[Figure 3]b]. The anaplastic cells were CD3+ and CD30+ [[Figure 3]c]. Anaplastic lymphoma kinase (ALK) 1 protein and EB virus were negative. T cell receptors gene rearrangement of the skin nodule was negative. CT, Ga scintigraphy, MRI, PET-CT, bone marrow aspiration, gastric and colon endoscopies did not detect any systemic manifestations. Peripheral blood analyses disclosed no abnormality, either. Liver function tests, BUN and serum creatinine levels were also normal. Serum soluble interleukin-2 receptor and thymidine kinase activity were 294 U/ml (normal:149-519 U/ml), and 4.8 U/l (<5 U/ml), respectively. Serum IgE was 37.1 IU/ml (0-170 IU/ml). Thymus and activation-regulated chemokine (TARC; chemokine of Th2) was 1,455 pg/ml (<450 pg/ml). We diagnosed this case as a CD30+ lymphoproliferative disorder (Type A LyP) by those histological examinations, laboratory examinations, and clinical features. Skin nodules subsided spontaneously without any specific treatment. His AD has been favorably treated by corticosteroid ointment, skin emollients and antihistamine administration.

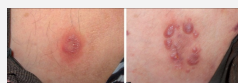


Figure 2: Clinical presentations on the right thigh. (a) Exudative erythematous plaque was detected. (b) The nodules were still enlarging following the discontinuation of cyclosporine

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Figure 3: Histopathological findings. (a) Low magnification (x20). Numerous mononuclear cell infiltrates are noted in the upper dermis. (b) Bizarre-shaped cells with conspicuous nucleolus (x200). (c) Most of the infiltrated cells were CD30+ (x200)

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CD30+ lymphoproliferative disorder in AD patients during cyclosporine therapy is rare and only four cases have been described [Table 1]. [1],[2],[3],[4] Cyclosporine is also used for psoriasis, which is accompanied by similar lymphoproliferative disorder. While some reports suggest no significant relation between AD and lymphoma, others suggest the positive correlation between cutaneous lymphoproliferative disorder and AD. [1] As shown in [Table 1], CD30+ lymphoproliferative disorder in AD patients treated by cyclosporine, three of the five reported cases showed the LyP type histopathology and four of the five cases showed resolution of the lesion without progression to genuine lymphoma.

Case	Reference	Age	Sex	Duration of AD	Duration of Cyclosporine	Lesion	Response
1	[1]	45	M	10 years	1 year	CD30+ lymphoproliferative disorder	Resolution
2	[2]	45	M	10 years	1 year	CD30+ lymphoproliferative disorder	Resolution
3	[3]	45	M	10 years	1 year	CD30+ lymphoproliferative disorder	Resolution
4	[4]	45	M	10 years	1 year	CD30+ lymphoproliferative disorder	Resolution
5	[5]	45	M	10 years	1 year	CD30+ lymphoproliferative disorder	Resolution

Table 1: Cutaneous CD30+ lymphoproliferative disorder in atopic dermatitis treated by cyclosporine

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Recent reports indicate that CD30+ T lymphocytes are up regulated in the lesional skin of AD. This is induced by interleukin-8, macrophage inflammatory protein (MIP)-1 α , and MIP-1 β derived from mast cells. This novel activation pathway does not depend on the classical IgE pathway and this pathway may be observed in psoriasis as well as in Hodgkin lymphoma. [5] Mast cells may have a regulatory role on both innate and acquired immunity. [5] In our case, numerous CD30+ T lymphocytes were detected in skin tumors after cyclosporine administration, which was not apparent in the pre-existing AD lesion. We could not get the samples and not detect the change in the number of mast cells or cytokines derived from mast cells of the skin during the tumor progression and regression in this case. Cyclosporine, besides its well-known immunosuppressive effect, might have changed the cytokine balance including mast cell-derived cytokines.

Our case indicates the potential risk of cutaneous CD30+ lymphoproliferative disorder in cyclosporine-treated AD. Cyclosporine-induced lymphoproliferative disorder, albeit rare, should be kept in mind during the cyclosporine treatment of AD.

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Figures

[Figure 1], [Figure 2], [Figure 3]

Tables

[Table 1]

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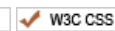
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Sex	Age	Clinical appearance	Therapy and periods of improvement	Cyclosporine dose and treatment period	Histologic feature	References
Male	39	Large ulcerated erythematous nodule on back	Cyclosporine was discontinued/ Subsided in 6 months	100 mg/day for 2 years	Dermal tumor with large atypical cells with abundant cytoplasm and prominent nucleoli. CD30 positive.	Kirby <i>et al.</i> ^[2]
Male	25	Crusted nodules on right flank, trunk, and right hand.	Cyclosporine was discontinued and extracorporeal photophoresis was performed/ Subsided in 5months	2 to 2.5 mg/kg for 3 years	Confluent lymphoid infiltrate occupying the dermis with ulceration. Mixed lymphoid infiltrate containing a proportion of large anaplastic cells. CD30 positive, lymphomatoid papulosis type A.	Fletcher <i>et al</i> ^[1]
Male	36	Numerous 1-2 cm ulcerated and tumid nodules on the neck, trunk and extremities.	Cyclosporine was discontinued and methotrexate treatment was performed./ Improved after methotrexate treatment	3 mg/kg for 4 years	Wedge-shaped polymorphic lymphoproliferative infiltrate in the dermis consisting of large atypical cells with irregular nuclei, prominent nucleoli, frequent mitoses and eosinophilic cytoplasm. CD30 positive, lymphomatoid papulosis type A.	Laube <i>et al</i> ^[3]
Male	37	Purplish 10cm-sized tumor on the right hip.	Cyclosporine was discontinued. CHOP therapy and allogeneic hematopoietic stem cell transplantation was performed/ Not described	2.5-4 mg/kg for 1 year before eruption occurred	Dense infiltrate of large lymphocytes. No epidermotropism was observed. The infiltrate was dense, mononorphous and composed of large non-anaplastic cells. CD30 positive.	Mougel <i>et al</i> ^[4]
Male	57	Ulcerated 5cm-sized nodule on the thigh.	Cyclosporine was discontinued/ Subsided in 6 months	150 mg/twice a day. For 2 months	Dense cell infiltrate in the upper dermis consisting CD30-positive bizarre mononuclear cells consistent with lymphomatoid papulosis type A.	Our case