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# Prurigo Nodularis in a Patient with Anaplastic Large Cell Lymphoma: A Potential Role for M2-Macrophages in Its Pathogenesis

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Dear Editor:

Several pre-existing conditions including malignancy have been reported to be associated with prurigo[1,2]. However, no detailed description of prurigo nodularis (PN) in a patient with anaplastic large cell lymphoma (ALCL) has been published to date. Here we present a novel case of PN in a patient with ALCL in addition to a potential role for M2-macrophages in its pathogenesis.

A 64-year-old male presented with an ulcerated tumor on his left temple (Fig. 1A). A diagnosis of primary cutaneous ALCL without lymphadenopathies was made (Fig. 1B, C). Radiation targeting the tumor eradicated those lesions (Fig. 1D). However, during radiation against ALCL, pruritic papules/nodules had begun to spread. Physical examination showed multiple papules and nodules spread over his trunk and extremities (Fig. 1F). Histopathological examination revealed that a dome-shaped thick crust covered an entire lesion (Fig. 1G). Mild perivascular infiltrates in the superficial dermis were composed of histiocytes, lymphocytes and a few eosinophils (Fig. 1H). At the base of the lesion, lymphocytes were relatively abundant in perivascular infiltrates (Fig. 1I). A diagnosis of PN was made. Topical application of steroid ointments and oral administration of olopatadine hydrochloride (10 mg/day) had initially relieved the pruritis; however the recurrence of ALCL was found (Fig. 1E). Immunohistochemical examination showed a slight positive reaction for CD3 (Fig. 1J) and a strong positive reaction for interleukin (IL)-17 (Fig. 1K) in intravascular lymphocytes. Perivascular inflammatory infiltrates of histiocytes were positive for CD163 (Fig. 1L), PGM1 (Fig. 1M), and FoxP3 (Fig. 1N). Laboratory investigations revealed normal immunoglobulin (Ig) E: 19 IU/ml (normal, 0~295 IU/ml). C(H)OEP (cyclophosphamide–hydroxydaunorubicin–vincristine–etoposide-prednisolone) therapy, excluding hydroxydaunorubicin, had been started. The cervical lymphoadenopathies were eliminated by four courses of C(H)OEP therapies (Fig. 1O). PN disappeared with pigmentation (Fig. 1P). Four months after completion of the therapy, the ALCL had recurred with re-emergence of the PN lesions on the trunk and extremities. Administration of brentuximab relieved the ALCL accompanied by the disappearance of PN.

PN had been considered to be a variation of eczema, while other conditions such as internal malignancies have been reported to be associated with PN[1,2]. We found that macrophages with an M2 phenotype expressing CD163 represented the majority of cells in the lesional skin, as a previous report described that major cellular components of prurigo lesions

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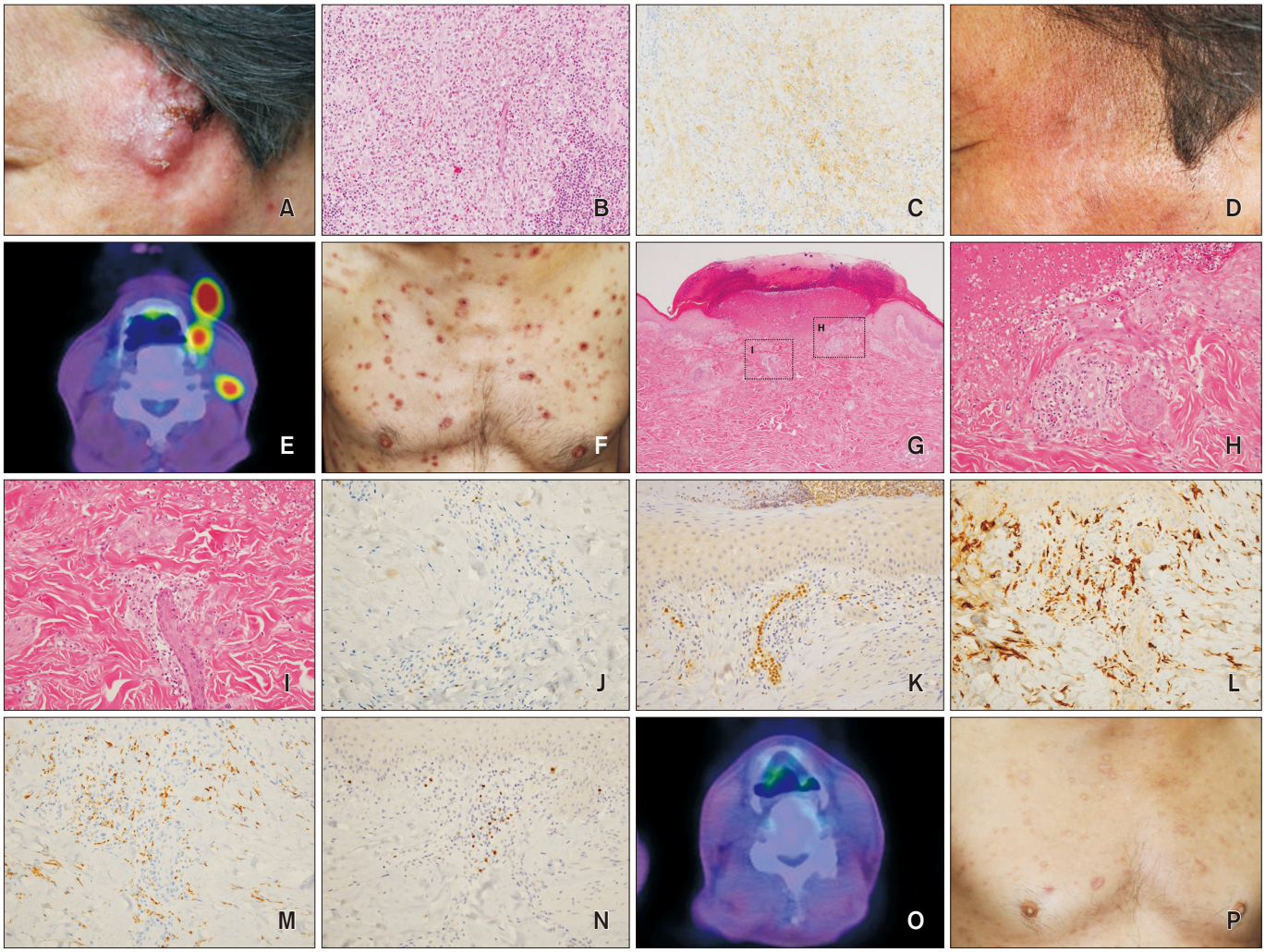


**Fig. 1.** An ulcerated tumor and erythematous plaques on his left temple before (A) and after (D) the radiation. Positron emission tomography/computed tomography (PET/CT) at the patient's cervical nodes before (E) and after (O) treatment. Multiple papules and nodules on his trunk before (F) and after (P) the treatment. (B) Histopathology of an ulcerated tumor showing a proliferation of atypical lymphoid cell in the dermis (H&E stain, ×200). (C) Immunohistochemistry showing a positive reaction for CD30 in most tumor cells in the lesion (×200). (G~I) Histopathology of a nodule showing a dome-shaped thick crust (G: H&E stain, ×40); the dashed boxes labeled 'H' and 'I' indicate the areas shown in Fig. 1H and 1I, respectively. Perivascular infiltrates were composed of histiocytes and lymphocytes (H: H&E stain, ×200). Lymphocytes were relatively abundant in perivascular infiltrates at the base of the lesion (I: H&E stain, ×200). (J~N) Immunohistochemistry of a nodule showing positive reactions for CD3 (J, ×200), IL-17 (K, ×200) and FoxP3 (N, ×200) in lymphocytes, and positive reactions for CD163 (L, ×200) and PG-M1 (M, ×200) in histiocytes. (J, K, M) Immunostainings of the section shown in Fig. 1H. Panels (L) and (N) show immunostainings of the section shown in Fig. 1I.

are CD68(+) macrophages[3]. We also found that IL-17-positive cells were predominant in vessels of the papillary dermis in the lesional skin with nuclear translocation of phospho-STAT3 in epidermal keratinocytes (Fig. 2A, B). These cellular components in the lesions of PN were similar to those of the ALCL lesions (Fig. 2C~F)[4]. Studies of our murine model of prurigo also suggest the significance of STAT6 in the pathogenesis of PN. In that model, which uses IgE-transgenic mice, M2 macrophages have a suppressive role on prurigo reactions[5]. In our patient, who has a normal serum IgE level, M2 macrophages may have a promoting role in the pathogenesis of PN. We speculate that those conflicting data may imply a critical importance of M2 macrophages in the pathogenesis of PN. We received signed consent form from this patient for all images.

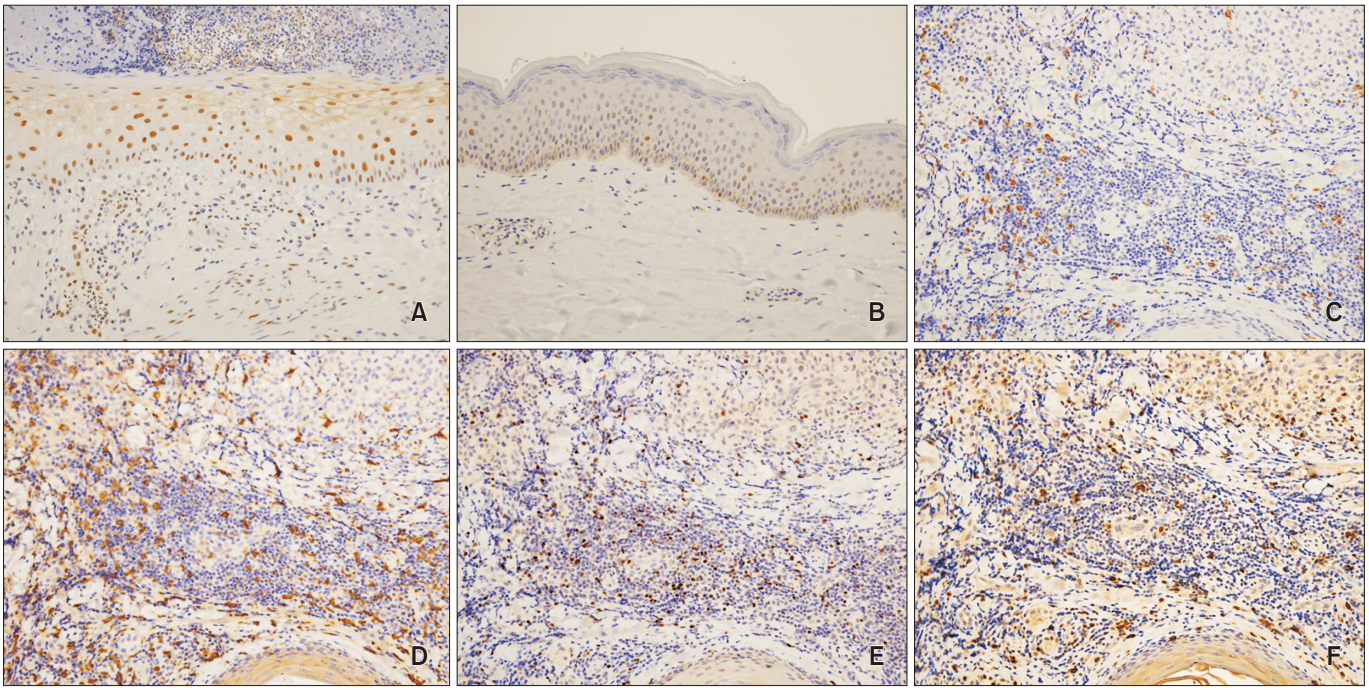


**Fig. 2.** (A, B) Immunohistochemistry showing a positive reaction for Phospho-STAT3 in keratinocytes in lesion skin (A, ×200) and a negative reaction in non-lesional skin (B, ×200). (C~F) Immunohistochemistry of infiltrates in the tumor showing consistent results of staining of PG-M1 (C, ×200), CD163 (D, ×200), FoxP3 (E, ×200), and interleukin-17 (F, ×200) in a nodule.

## CONFLICTS OF INTEREST

The authors have nothing to disclose.

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## REFERENCES

1. Accioly-Filho LW, Nogueira A, Ramos-e-Silva M. Prurigo nodularis of Hyde: an update. J Eur Acad Dermatol Venereol 2000;14:75-82.
2. Iking A, Grundmann S, Chatzigeorgakidis E, Phan NQ, Klein D, Ständer S. Prurigo as a symptom of atopic and non-atopic diseases: aetiological survey in a consecutive cohort of 108 patients. J Eur Acad Dermatol Venereol 2013;27:550-557.
3. Gambichler T, Skrygan M, Werries A, Scola N, Stücker M, Altmeyer P, et al. Immunophenotyping of inflammatory cells in subacute prurigo. J Eur Acad Dermatol Venereol 2011;25:221-226.
4. De Souza A, Tinguely M, Burghart DR, Berisha A, Mertz KD, Kempf W. Characterization of the tumor microenvironment in primary cutaneous CD30-positive lymphoproliferative disorders: a predominance of CD163-positive M2 macrophages. J Cutan Pathol 2016;43:579-588.
5. Hashimoto T, Satoh T, Yokozeki H. Protective role of STAT6 in basophil-dependent prurigo-like allergic skin inflammation. J Immunol 2015;194:4631-4640.