

SHORT COMMUNICATION

Successful Treatment of Adult Onset Langerhans Cell Histiocytosis with Bi-weekly Administration of Pegylated Interferon- α Sadanori Furudate¹, Taku Fujimura^{1*}, Yumi Kambayashi¹, Mitsuko Kawano², Kouetsu Ogasawara², Akira Tsukada¹, Erika Tamabuchi¹, Takahiro Haga¹, Akira Hashimoto¹ and Setsuya Aiba¹¹Department of Dermatology, Tohoku University Graduate School of Medicine, and ²Department of Immunobiology, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan. *E-mail: tfujimura1@mac.com

Accepted Jan 8, 2014; Epub ahead of print Feb 4, 2014

Langerhans cell histiocytosis (LCH) is characterised by the clonal proliferation of Langerhans cells (LC) that predominantly occurs in infants and small children, but LCH is rare in adults (1). Generally in children, local therapy would be an appropriate treatment, since patients with localised disease or disease limited to a single organ system have a good prognosis (1). However, the clinical picture of LCH in adults is not fully understood and the optimal treatment for it is still under discussion. In this report, we describe a case of adult onset LCH successfully treated with bi-weekly pegylated interferon (PEG-IFN)- α 2a and discuss the immunological background focusing on the tumour microenvironment immunologically.

CASE REPORTS

A 57-year-old Japanese man visited our outpatient clinic with a one-month history of multiple papules on his face. On his initial visit, physical examination revealed waxy, normal-coloured small papules on his nose and forehead (Fig. 1A). The size of the papules was approximately 1–3 mm in diameter. A skin biopsy specimen revealed large atypical cells infiltrating throughout the dermis (Fig. 1E). Immunohistochemical staining revealed that these atypical cells were positive for CD1a (Fig. 1G) and S100, but negative for CD68. From these findings, we diagnosed this patient as adult onset LCH. Computed tomography

(CT) scan, magnetic resonance imaging (MRI), bone marrow biopsy, and positron emission tomography (PET) revealed no sign of internal lesions. First, we administered topical steroids for 3 months without any effect. During the initial treatment, newly infiltrated plaques and papules with ulcer appeared on his bilateral groin (Fig. 1C). We performed skin biopsy again, which revealed dense infiltration of CD1a⁺ cells throughout the dermis, resembling the previously described lesion. We then subcutaneously administered 180 μ g of PEG-IFN- α 2a bi-weekly. One month later, the plaques and nodules had disappeared (Fig. 1B, 1D). The biopsy specimen from the groin post-PEG-IFN- α 2a treatment revealed that, although the density of infiltrating cells was similar to that of the pre-treatment specimen (Fig. 1F), CD1a⁺ cells were remarkably decreased (Fig. 2H) and, compared to the specimen from previous specimen (Fig. 1I), CD86⁺ cells were remarkably increased (Fig. 1J). The interval of IFN- α 2a administration was prolonged one month and there was no evidence of recurrence for 9 months.

To further examine the profiles of tumour-infiltrating cells pre- and post-PEG-IFN- α 2a treatment, we employed immunohistochemical staining for CD8, granulysin, TIA-1, Foxp3 (data not shown), CD163 (Fig. S1A, B¹), and CD206 (Fig. S1C, D¹). Immunohistochemical staining revealed that the administration of PEG-IFN- α 2a significantly increased the number of CD8⁺ cells and granulysin-bearing cells (Fig. S2¹). Moreover, to quantify the immunohistochemical staining section for CD163, we per-

¹<http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1807>

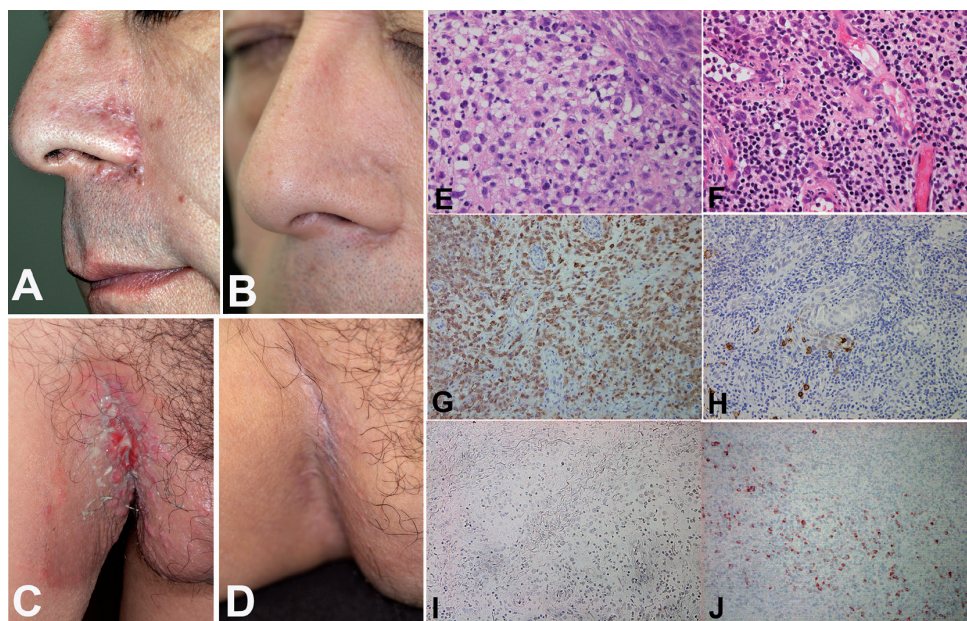


Fig. 1. Physical examination and histological findings pre- and post-PEG-IFN- α 2a therapy. Waxy, normal-coloured small papules on the nose and forehead (A). Infiltrated plaques and papules with ulcer appeared on the bilateral groin (C). The plaques had disappeared after PEG-IFN- α 2a therapy (B, D). Large atypical cells had infiltrated throughout the dermis (E: H&E staining), and were positive for CD1a (G). The infiltrating cells were prominent throughout the dermis (F: H&E staining) but did not include CD1a⁺ cells (H). Paraffin-embedded tissue samples from pre- (I) and post- (J) PEG-IFN- α 2a therapy were deparaffinised and stained using anti-CD86 Ab and developed with liquid permanent red. (Original magnification \times 200 (G, H, I, J), \times 400 (E, F)).

formed TissueFAXS analysis for CD163⁺ cells, as previously described (2), which revealed a decrease in the percentage of CD163⁺ cells (Fig. S1G¹, H¹). To quantify the other staining for CD8, granulysin, TIA-1 and Foxp3, the number of immunoreactive cells was counted using an ocular grid of 1 cm² at a magnification of ×400 (Fig. S2¹). Staining of the infiltrated leucocytes was examined in more than 3 random, representative fields from each section.

DISCUSSION

In this report, we describe a case of adult onset LCH successfully treated with bi-weekly PEG-IFN- α 2a. Immunohistochemical staining revealed that the administration of IFN- α 2a decreased the number of CD1a⁺ tumour cells and, in contrast, CD86⁺ cells were increased around the tumour. In addition, the histoFAXS analysis revealed that the ratio of CD163⁺ M2 macrophages in the tumour was significantly decreased. Moreover, the number of granulysin-bearing cells was significantly increased though there was no effect on the number of TIA-1⁺ and Foxp3⁺ cells in the tumour. Our present study sheds light on the possibility of IFN- α 2a therapy for adult onset LCH and its effect on the tumour microenvironment of LCH.

LCH is characterised by the clonal proliferation of LC that predominantly occurs in infants and small children, but LCH in adults is rare (1). Therefore, the clinical picture of LCH in adults is not fully understood and its optimal treatment is still under discussion. Interestingly, Geissmann et al. (3) previously reported that LCH cells, which have an immature dendritic LC phenotype, could be induced to mature by CD40L and attain allostimulatory activity to a level similar to that of mature dendritic cells (DCs). They concluded that LCH cells might be induced to differentiate toward mature DCs, and drugs that enhance the *in vivo* maturation of these immature phenotype cells might be of therapeutic benefit. In addition, as we previously reported, human monocyte-derived DC (MoDC) could be induced to mature by IFN- α (4). From the above findings, we hypothesised that PEG-IFN- α 2a might induce the maturation of LCH and could be an optimal therapy for adult LCH. Indeed, the eruptions on the nose and bilateral groin rapidly disappeared with complete remission for 9 months.

To further confirm our hypothesis, we employed immunohistochemical staining for the biopsy specimens pre- and post-IFN- α 2a treatment. The tumour infiltrating CD86⁺ cells in the specimen were prominent only post-treatment. As a previous report suggested, the upregulation of the expression of CD86 increased the antigen presenting function of LCH cells (3), suggesting the proliferation of effector cells in the tumour microenvironment. Indeed, in parallel with the CD86⁺

cells, the number of CD8⁺ cells and granulysin-bearing cells was significantly increased, though there was no significant increase in TIA-1⁺ cells and Foxp3⁺ cells. Granulysin has homology to other cytotoxic molecules of the saponin-like protein family (5), and several reports have suggested that granulysin lyses various tumours which may be related to the prognosis of tumour patients (6–8). In addition, the ratio of CD163⁺ M2 macrophages, which were reported as tumour-associated suppressive macrophages together with CD206 (9–11), was decreased by IFN- α 2a treatment. In summary, the results of the present study suggest that the administration of PEG-IFN- α 2a induces an anti-tumour immune response in the tumour microenvironment, which might contribute to a therapeutic effect on LCH.

REFERENCES

1. Matsuki E, Tsukada Y, Nakaya A, Yokoyama K, Okamoto S. Successful treatment of adult onset Langerhans cell histiocytosis with multi-drug combination therapy. *Intern Med* 2011; 50: 909–914.
2. Tojo GI, Fujimura T, Kawano M, Ogasawara K, Kambayashi K, Furudate S, et al. Comparison of IL-17 producing cells in different clinical types of alopecia areata. *Dermatology* 2013; 227: 77–82.
3. Geissmann F, Lepelletier Y, Fraitag S, Valladeau J, Bodemer C, Debré M, et al. Differentiation of Langerhans cells in Langerhans cell histiocytosis. *Blood* 2001; 97: 1241–1248.
4. Fujimura T, Yamasaki K, Hidaka T, Ito Y, Aiba S. A synthetic NOD2 agonist, muramyl dipeptide (MDP)-Lys (L18) and IFN- β synergistically induce dendritic cell maturation with augmented IL-12 production and suppress melanoma growth. *J Dermatol Sci* 2011; 62: 107–115.
5. Krensky AM, Clayberger C. Granulysin: a novel host defense molecule. *Am J Transplant* 2005; 5: 1789–1792.
6. Pagès F, Berger A, Camus M, Sanchez-Cabo F, Costes A, Molitor R, et al. Effector memory T cells, early metastasis, and survival in colorectal cancer. *N Engl J Med* 2005; 353: 2654–2666.
7. Kitamura N, Katagiri YU, Itagaki M, Miyagawa Y, Onda K, Okita H, et al. The expression of granulysin in systemic anaplastic large cell lymphoma in childhood. *Leuk Res* 2009; 33: 908–912.
8. Kambayashi Y, Fujimura T, Tsukada A, Hashimoto A, Aiba S. Extranodal T-cell/histiocyte-rich large B-cell lymphoma presenting primarily on the skin. *Acta Derm Venereol* 2012; 92: 637–639.
9. Tiemessen MM, Jagger AL, Evans HG, van Herwijnen MJC, John S, Taams LS. CD4+CD25+Foxp3+ regulatory T cells induce alternative activation of human monocytes/macrophages. *Proc Natl Acad Sci USA* 2007; 104: 19446–19451.
10. Kambayashi Y, Fujimura T, Furudate S, Hashimoto A, Haga T, Aiba S. Comparison of immunosuppressive and cytotoxic cells in angiosarcoma: Development of a possible supportive therapy for angiosarcoma. *Dermatology* 2013; 227: 14–20.
11. Fuentes-Duculan J, Suárez-Fariñas M, Zaba LC, Nograles KE, Pierson KC, Mitsui H, et al. A subpopulation of CD163-positive macrophages is classically activated in psoriasis. *J Invest Dermatol* 2010; 130: 2412–2422.