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Case Report

Sarcoidosis-Lymphoma Syndrome Associated with Folliculotropic Peripheral T Cell Lymphoma Not Otherwise Specified

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Keywords

Sarcoidosis-lymphoma syndrome · Tumor-associated macrophages · Folliculotropic PTCL-NOS

Abstract

Sarcoidosis is occasionally accompanied by hematologic malignancies, including cutaneous T-cell lymphoma, called sarcoidosis-lymphoma syndrome. Although the mechanism underlying the induction of lymphomas is still unknown, understanding the immunological background of sarcoidosis could help explain the possible mechanisms of the induction of lymphomas. In this report, we describe a case of sarcoidosis-lymphoma syndrome associated with folliculotropic peripheral T cell lymphoma not otherwise specified, which caused dense infiltration of CD30+ CD163+ tumor-associated macrophages (TAMs) only in the lesional skin. Our present case might suggest the significance of TAMs in developing sarcoid-lymphoma syndrome.

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Introduction

Sarcoidosis-lymphoma syndrome is a rare disease in which lymphoma develops in patients with sarcoidosis [1, 2]. Although the etiology of sarcoidosis is still unknown and the concept of sarcoidosis-lymphoma is controversial, previous reports suggest the coexistence of sarcoidosis and hematologic malignancies, such as Hodgkin disease, non-Hodgkin lymphoma, cutaneous T-cell lymphoma (CTCL), and leukemia [1]. In this report, we describe a case of sarcoidosis-lymphoma syndrome associated with folliculotropic peripheral T cell lymphoma not otherwise specified (PTCL-NOS), which caused dense infiltration of CD30+ CD163+ tumor-associated macrophages (TAMs) only in the lesional skin. Our present case might suggest the significance of TAMs in developing sarcoid-lymphoma syndrome.

Case Report

A 60-year-old Japanese woman with a 10-year-history of prominent edema with subcutaneous nodules on the right lower leg visited our outpatient clinic. She had been diagnosed as having erythema induratum, and administered oral prednisolone for 10 years. On her initial visit, physical examination revealed multiple pigmented follicular papules (Fig. 1a) and widespread ulcers on the right lower leg (Fig. 1b). Histological findings revealed dense infiltrate of atypical lymphocytes throughout the dermis with Langhans type giant cells and epithelioid cells (Fig. 1c, d). Immunohistochemical staining revealed that these atypical lymphocytes, which were infiltrated throughout the dermis, were positive for CD3, CD4, CD5, and CD45, and negative for CD7, CD8, and CD30. In addition, a dense infiltration of CD30+ cells (Fig. 2a) and CD163+ macrophages (Fig. 2b), both of which possessed dendritic-shaped cytoplasm, was observed. Assessment of the T cell receptor (TCR) gene rearrangement by Southern blot analysis confirmed the monoclonality of the TCRβ chain. We screened for possible metastatic lesions with positron emission tomography and found lymph node swelling in the left inguinal lymph node, left axillar lymph node, and right chest wall lymph node. The lymph node biopsy from the left inguinal lymph node revealed prominent masses of epithelioid cells with giant cells and a dense infiltrate of atypical lymphocytes (Fig. 2c). The profiles of the atypical cells were similar to those in the skin lesions, and assessment of the TCR gene rearrangement of lymph node confirmed the monoclonality of the TCRβ chain. From the above findings, we diagnosed this patient as having sarcoidosis-lymphoma syndrome associated with folliculotropic PTCL-NOS. We administered oral prednisolone 30 mg/day, and the skin ulcers and lymph node were under control, though the folliculotropic papules remained.

Discussion

Sarcoidosis is occasionally accompanied by hematologic malignancies, including CTCL [1]. Previous reports suggested that patients with sarcoidosis developed lymphoma a few years after the onset of sarcoidosis, called sarcoidosis-lymphoma syndrome [1, 2]. Although the mechanism underlying the induction of lymphoma is still unknown, understanding the immunological background of sarcoidosis might reveal the possible mechanisms of the induction of lymphomas. For example, von Bubnoff et al. [3] reported that the indoleamine 2,3-dioxygenase expression in myeloid cells contributes to the onset of tolerance in adaptive

immunity in sarcoidosis. In another report, the number of Foxp3+ regulatory T cells (Tregs) in sarcoidosis was higher than in other granulomatous disorders [4], suggesting the immunosuppressive microenvironment of granuloma in sarcoidosis. Notably, macrophages could produce various chemokines to recruit immunoreactive and immunosuppressive cells by the stimulation of stromal factors [5]. These reports suggested the significance of immunosuppressive cells, especially tissue-associated macrophages, in the development of lymphomas in patients with sarcoidosis.

TAMs play a role in the formation of CTCL by the production of various chemokines [5–8]. As we have previously reported, stromal factors in CTCL (periostin, IL-4) are expressed in the cancer stroma of the lesional dermis after the plaque stage of mycosis fungoides (MF) [7]. Notably, these macrophage stimulatory factors induce the production of specific chemokines that correlate with the recruitment of CTCL cells [6–8], suggesting that TAMs could be a target for CTCL treatment [5]. Indeed, recently Kim et al. [9] reported the efficacy of brentuximab vedotin, anti-CD30 Ab, for the treatment of advanced MF and Sézary syndrome by targeting not only CTCL cells but also CD30+CD163+ TAMs in the lesional skin of MF. In addition, Furudate et al. [8] reported the therapeutic and immunomodulatory effects of IFN-α_2a on TAMs in patients with advanced MF. These clinical and research studies suggested that TAMs play a crucial role in CTCL development.

In this report, we describe a case of sarcoidosis-lymphoma syndrome associated with folliculotropic PTCL-NOS. In our present case, dense infiltration of CD30+ CD163+ macrophages was detected only in the lesional skin but not in the lymph nodes; Langhans giant cells and atypical lymphocytes were detected in both the lesional skin and lymph nodes. This phenomenon might suggest that the populations of atypical lymphocytes in the skin and lymph nodes were different in our case. Indeed, the efficacy of prednisolone was different in the skin lesions and lymph nodes in our case. These observations suggested that CD30+ CD163+ TAMs might play roles in the clonal recruitment of CTCL cells in the lesional skin. This report presents only a single case, but further cases may provide fundamental insights into the mechanisms of the coexistence of sarcoidosis and CTCLs.

Statement of Ethics

The patient gave written informed consent.

Disclosure Statement

The authors declare no conflicts of interest.

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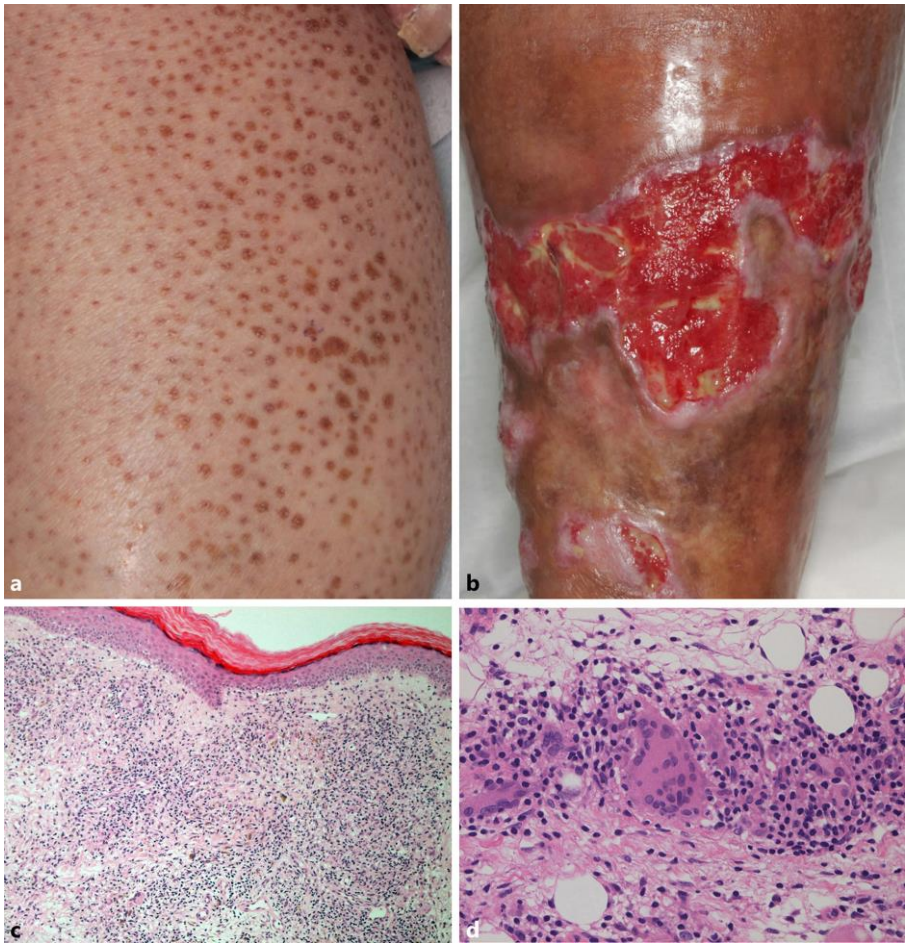

Fig. 1. Multiple pigmented follicular papules (**a**) and widespread ulcers on the right lower leg (**b**). **c**, **d** Dense infiltrate of atypical lymphocytes throughout the dermis with Langhans giant cells and epithelioid cells. Original magnification ×100 (**c**) and ×400 (**d**).

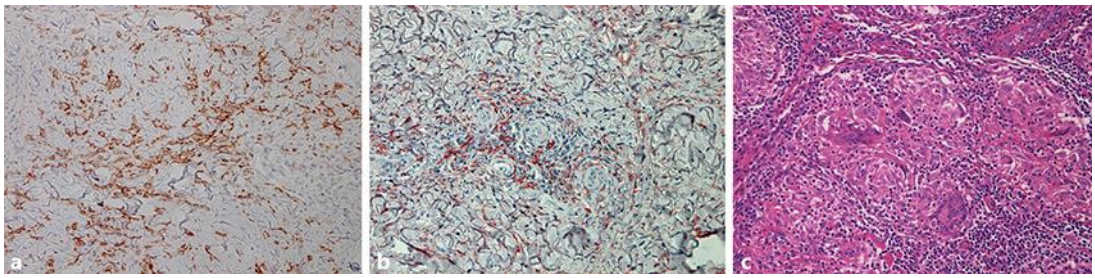

Fig. 2. Paraffin-embedded tissue samples were deparaffinized and stained with anti-CD30 Ab (**a**) and anti-CD163 Ab (**b**). The sections were developed with 3,3′-diaminobenzidine tetrahydrochloride (**a**) or liquid permanent red (**b**). **c** Biopsy from the left inguinal lymph node revealed prominent masses of epithelioid cells with giant cells and a dense infiltrate of atypical lymphocytes. Original magnification ×200 (**a**, **b**) and ×100 (**c**).