http://dx.doi.org/10.5021/ad.2015.27.5.618

CD56-Negative Extranodal NK/T-Cell Lymphoma, Nasal Type, with Extranasal Cutaneous Involvement

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Dear Editor:

Extranodal NK/T-cell lymphoma (ENTCL), nasal type, is a well-defined aggressive cytotoxic lymphoma[1]. Although immunophenotyping with CD56 is known to be positive in practically all cases, CD56-negative cases have also been reported, particularly in the upper respiratory tract. However, there are very few reports of skin involvement[2]. Here, we report a unique case of a CD56-negative, Epstein-Barr virus (EBV)-positive ENTCL, nasal type, with cutaneous involvement.

A 35-year-old Korean female patient presented with a tender violaceous crusted indurated plaque on the right thigh and a light brown ill-defined induration on the right upper arm (Fig. 1). Histopathologic examination showed an atypical lymphocytic infiltration composed of small- to medium-sized cells with irregular folded nuclei, and inconspicuous nucleoli. The infiltrate demonstrated angiocentric growth with frequent mitoses. Focal epidermal and dermal necrosis were also noted (Fig. 2A, B). The infiltrated cells stained positively for antibodies against surface CD3, CD8, and granzyme B, whereas they were negative against CD4, CD56, and CD20 (Fig. 2C～E). EBV-encoded RNA (EBER) *in situ* hybridization was positive in many infiltrated cells (Fig. 2F). Three months before, the patient had been diagnosed with ENTCL, nasal type, for her recurrent nasopharyngeal ulcer. The microscopic evaluation of the uvula showed similar findings to that of the skin. Bone marrow biopsy, computed tomography and whole body 18-fluoro-2-deoxyglucose positron emission tomography scan revealed no systemic invasion of the lymphoma. Despite cisplatin-based concurrent chemoradiation therapy, there was only a partial reduction of the tumor.

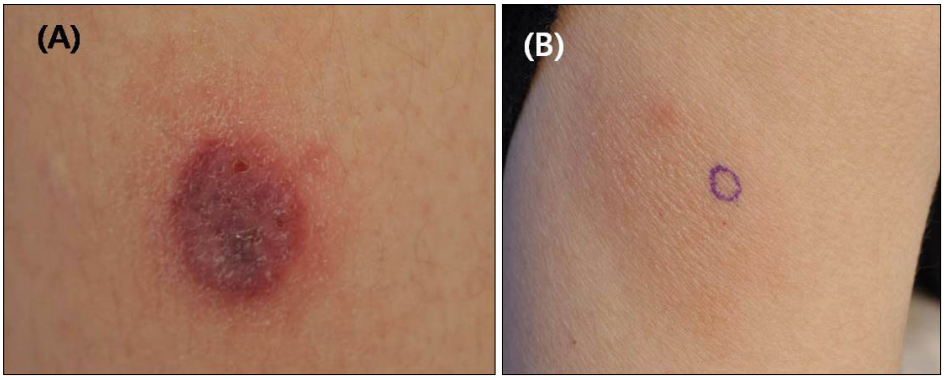

Fig. 1. Clinical manifestation of the skin lesions. (A) A tender dark erythematous scaly indurated plaque with oozing on the right thigh. (B) A tender light brown, ill-defined induration with cigarette-paper-like fine scales on the right upper lateral arm.

Received September 18, 2014, Revised October 10, 2014, Accepted for publication November 6, 2014

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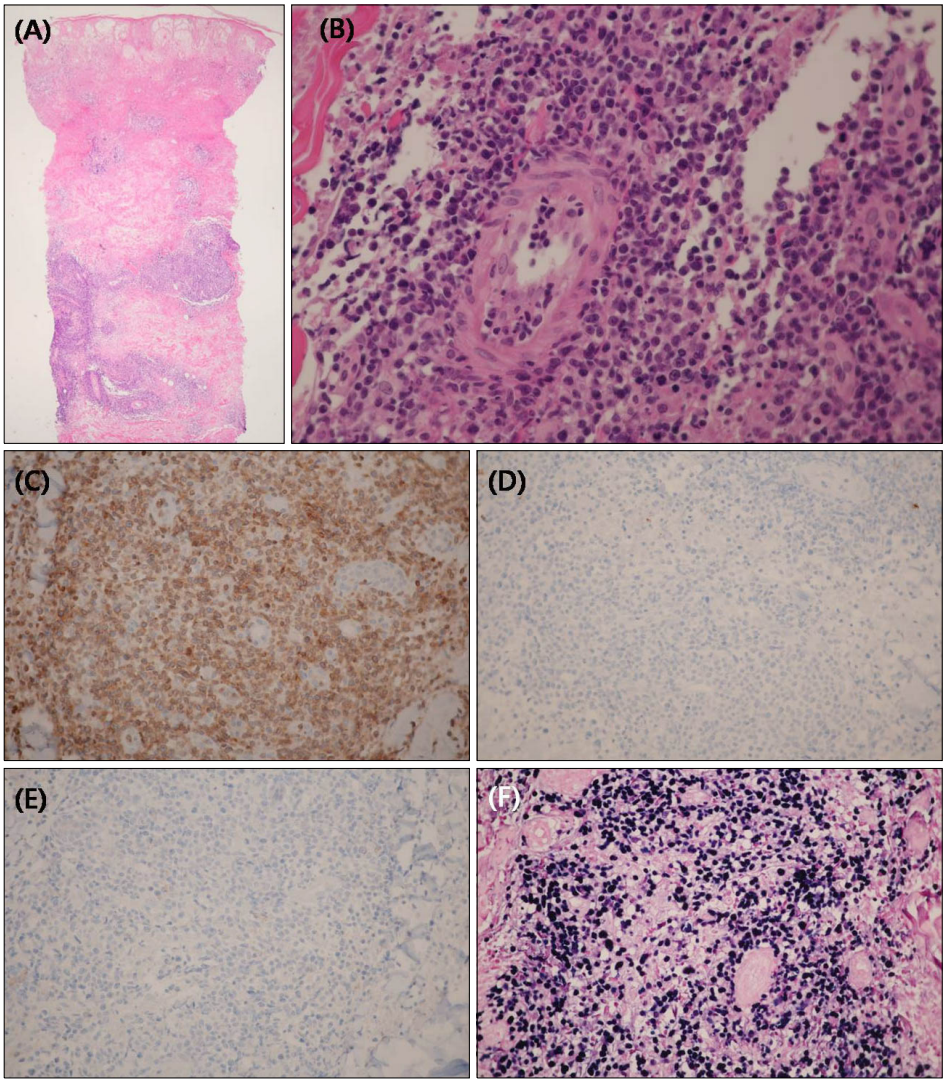

Fig. 2. Microphotograph of the lesion on the right thigh. (A) Dense cellular infiltrates involving the deep dermis. Angiocentricity is conspicuous and epidermal necrosis is visible (H&E, ×12). (B) Atypical lymphocytes composed of small- to medium-sized cells with irregular folded nuclei, inconspicuous nucleoli, and moderate, pale to clear cytoplasm demonstrating angiocentric growth and angiodestruction. Frequent mitoses are seen (H&E, ×400). (C) Positive immunohistochemical staining with surface CD3 in atypical lymphoid cells (×400). (D) CD20 is not stained (×400). (E) CD56 is completely absent in the tumor (×400). (F) Epstein-Barr virus-encoded RNA *in situ* hybridization showing many positive cells (×400).

ENTCL, nasal type, is a rare aggressive lymphoma that occurs more commonly in East Asia. Patients are typically middle-aged adults and have a male predominance[3]. The prognosis is poor regardless of therapeutic strategies, with a median survival no more than 12 months. The skin is known to be the second most common site of involvement and the disease usually manifests as multiple ulcerated plaques or tumors on the trunk or extremities. Histopathologically, ENTCL is characterized by dense infiltrates involving the dermis and often the subcutis. The cells have irregular or oval nuclei, moderately dense chromatin, and a pale cytoplasm. Prominent angiocentricity and angiodestruction often accompany extensive necrosis[1]. Immunophenotypically, the neoplastic cells typically stain for antibodies against CD2, CD56, cytoplasmic CD3, and cytotoxic proteins (TIA-1, granzyme B, and perforin), but lack surface CD3[4]. However, rare cases are CD56 negative, and they stain positively for surface CD3, CD5 and CD8. Detection of EBV and expression of cytotoxic proteins are required for the diagnosis of these CD56-negative cases[4].

Most of the reported CD56-negative cases occurred in the upper respiratory tract[5]. Concerning skin involvement, to our knowledge, there have only been three cases recorded in the literature[2]. CD56-negative cases seem to be as aggressive as CD56-positive cases, and are usually unresponsive to conventional chemotherapy, with poor prognosis and a short median survival[2].

This case emphasizes that CD56 might not be invariably positive in ENTCL even in cases with extranasal cutaneous involvement. The immunohistochemistry and EBER in situ hybridization would be important ancillary studies for the accurate diagnosis of this rare aggressive cytotoxic lymphoma.

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http://dx.doi.org/10.5021/ad.2015.27.5.620

Development of Vitiligo during Treatment with Adalimumab: A Plausible or Paradoxical Response?

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Dear Editor:

Adalimumab is a complete human monoclonal anti-tumor necrosis factor α (anti-TNF α) that is generally well tolerated. With increasing use of adalimumab and other anti-TNF α therapies, several cutaneous adverse events have been reported during the therapy, including immune-mediated skin lesions[1]. A 39-year-old woman who had an 11-year history of Crohn's disease and was treated with adalimumab (40 mg administered subcutaneously every other week) presented at our clinic with multiple achromic macules and patches on the extremities (Fig. 1). The lesions developed abruptly about 12 months after the initiation of adalimumab therapy. The diagnosis of vitiligo was made after the patient's skin turned blue under a Wood's lamp. Laboratory tests were also performed to check for other autoimmune conditions, including thyroid disorders, and no abnormality was diagnosed. The patient denied any family history of vitiligo. She has been treated with a combination therapy of excimer laser and topical tacrolimus without stopping the adalimumab therapy for about 1 year, and has shown minimal response thus far.

The role of anti-TNF α inhibitors in the development of vitiligo is complicated and contradictory. There have been several case reports that showed improvement in vitiligo in patients receiving anti-TNF α therapy for other diseases[2]. The therapeutic effect of anti-TNF α inhibitors on vitiligo might result from stopping the physiological effect of TNF α on melanogenesis. Concretely, it has been reported that TNF α decreases the level of tyrosinase, a rate-limiting enzyme in melanin biosynthesis *in vitro*[3]. The melanocytotoxic effect of TNF α in vitiligo has also been demonstrated[2]. On the contrary, anti-TNF α inhibitors have been

Received September 19, 2014, Revised November 6, 2014, Accepted for publication November 12, 2014

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