

Case Report

Adult T-cell leukemia/lymphoma accompanying follicular mucinosis: a case report with review of the literature

Mitsuaki Ishida, Muneo Iwai, Keiko Yoshida, Akiko Kagotani, Hidetoshi Okabe

Department of Clinical Laboratory Medicine and Division of Diagnostic Pathology, Shiga University of Medical Science, Shiga, Japan

Received September 30, 2013; Accepted October 23, 2013; Epub November 15, 2013; Published December 1, 2013

Abstract: Follicular mucinosis is recognized as one of the histopathological reaction patterns characterized by the accumulation of mucin within follicular epithelium. It is induced by various causes including inflammatory diseases, and more than half of the cases are associated with malignant lymphoma, mainly mycosis fungoides. Herein, we describe the third documented case of adult T-cell leukemia/lymphoma (ATLL) accompanying follicular mucinosis. A 72-year-old Japanese male presented with persistent erythema in his arm and neck. Laboratory tests demonstrated positivity for human T-cell leukemia virus (HTLV)-1 antibodies. Histopathological study of the biopsy specimen from the neck revealed superficial perivascular, nodular, and intrafollicular lymphocytic infiltrations. These lymphocytes were small- to medium-sized and had convoluted nuclei. Mucoïd material deposition was observed within the hair follicles, and it was digested by hyaluronidase. Immunohistochemically, these lymphocytes were positive for CD3, CD4, CD25, and Foxp3. Accordingly, an ultimate diagnosis of ATLL accompanying follicular mucinosis was made. The skin is the most common extralymphatic site of involvement of ATLL. The present case clearly demonstrated that albeit extremely rare, ATLL can cause follicular mucinosis. Therefore, ATLL should be included in the differential diagnostic consideration of follicular mucinosis.

Keywords: Adult T-cell leukemia/lymphoma, follicular mucinosis, skin

Introduction

Adult T-cell leukemia/lymphoma (ATLL) is a distinct subtype of T-cell lymphoma and is defined as a peripheral T-cell neoplasm caused by human T-cell leukemia virus type-1 (HTLV-1) [1]. This disease is endemic in several regions of the world, such as Japan, the Caribbean basin, and parts of Central Africa, which is closely linked to the prevalence of HTLV-1 [1]. Various organs are affected by this disease, and the skin is the most common extralymphatic site of involvement [1]. The characteristic histopathological feature of skin involvement of ATLL is perivascular lymphocytic infiltration with or without nodular formation in the dermis and/or subcutis [2, 3]. Epidermal involvement may be seen, namely Pautrier-like microabscess [2, 3]. The morphological features of the neoplastic cells are typically small- to medium-sized or

medium to large lymphocytes with pronounced nuclear polymorphism [2, 3].

Follicular mucinosis is currently recognized as one of the histopathological reaction patterns characterized by the accumulation of mucin within follicular epithelium [4]. It is induced by various causes and has two main clinicopathological variants [4]. Primary follicular mucinosis is a benign idiopathic form, mainly occurring in children and young adults and shows spontaneous remission. The secondary form is also referred as to lymphoma-associated follicular mucinosis, occurring in elderly patients mainly associated with mycosis fungoides. Up until now, only a few cases of ATLL accompanying follicular mucinosis have been reported [5, 6]. Herein, we describe the third documented case of ATLL accompanying follicular mucinosis, and review the clinicopathological features of this extremely rare variant of follicular mucinosis.

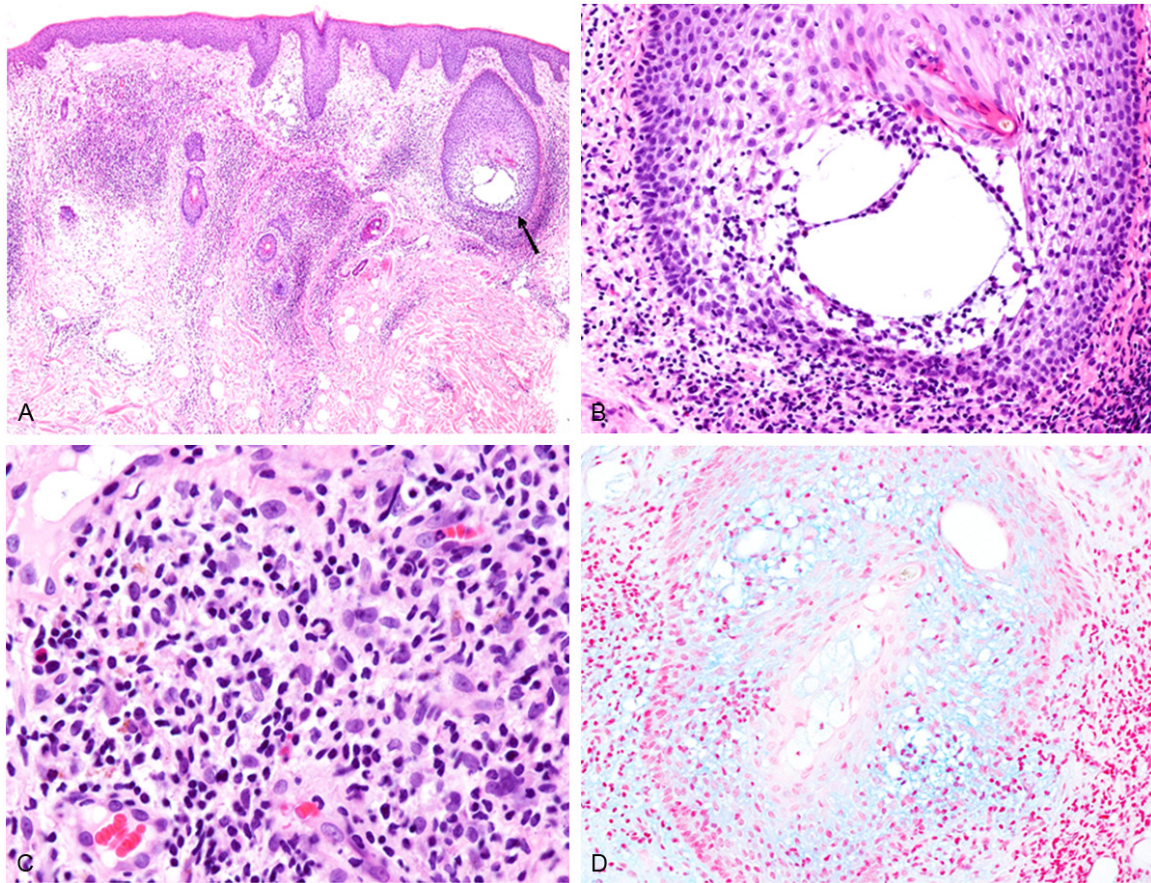


Figure 1. Histopathological features. A: Superficial perivascular, nodular, and intrafollicular lymphocytic infiltrations are observed. Mucoïd material deposition is also noted within the hair follicle (arrow), HE, x 40. B: Lymphocytic infiltration and mucoïd material deposition within the hair follicle, HE, x 200. C: Infiltrated lymphocytes are small- to medium-sized and have convoluted nuclei, HE, x 400. D: The mucoïd material within the hair follicle is positive for Alcian blue staining, Alcian blue stain, x 200.

Case report

A 72-year-old Japanese male with a past history of brain infarction at the age of 57 presented with persistent erythema in his arm and neck. Physical examination showed that erythema was present mainly in the sun-exposed regions including the arm and neck. Neither lymph node swelling nor hepatosplenomegaly was observed. Laboratory tests revealed that the white blood cell count was slightly elevated ($8.2 \times 10^9/L$, range 3.0-8.0) and soluble interleukin-2 receptor was within normal range (371 U/mL, range 220-530). HTLV-1 antibody was positive in serology (x 2048). Moreover, anti-HTLV-1 envelop (gp46) and core protein (p19, p24, and p53) antibodies were positive. Biopsy from the neck was performed.

The biopsy specimen revealed superficial perivascular and nodular lymphocytic infiltrations

in the dermis (**Figure 1A**). Lymphocytic infiltration was also observed within the follicular epithelium, and mucoïd material deposition was noted (**Figure 1A, 1B**). Infiltrated lymphocytes were small- to medium-sized and had convoluted nuclei (**Figure 1C**). A few eosinophilic infiltrates were also observed. Further, mild epidermotropism was noted. The mucoïd material within the follicular epithelium was positive for Alcian blue staining (**Figure 1D**) and was digested by hyaluronidase.

Immunohistochemical studies were performed using an autostainer (Ventana) by the same method as previously reported [7-10]. Infiltrated lymphocytes in the upper dermis and follicular epithelium were both CD3- and CD4-positive (**Figure 2A, 2B**). These lymphocytes had also infiltrated into the epidermis (**Figure 2A**). These T lymphocytes were CD25- and Foxp3-positive

ATLL accompanying follicular mucinosis

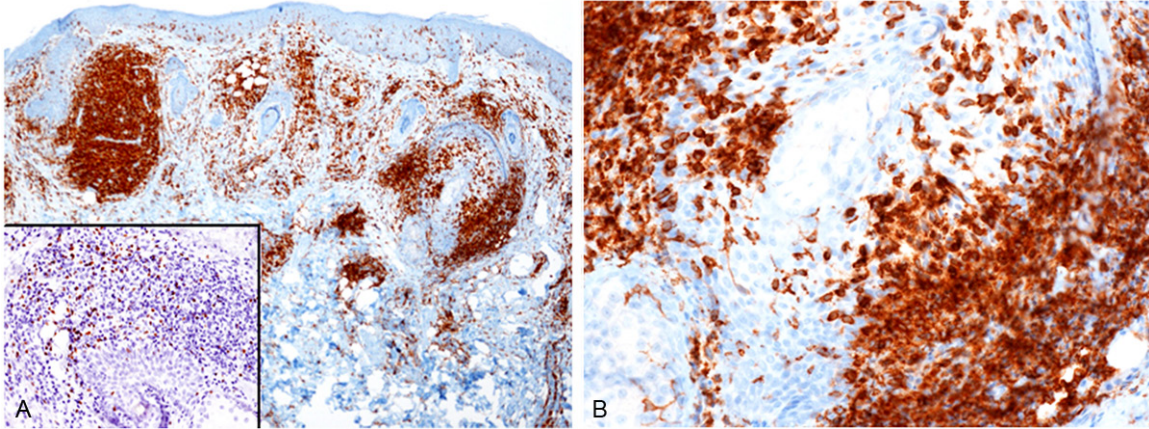


Figure 2. Immunohistochemical features. (A, B) CD4-positive lymphocytes have infiltrated into the upper dermis and within the hair follicle, x 40 (A), x 200 (B). Foxp3-positive cells have infiltrated into the hair follicles (A, inset), x 100.

Table 1. Clinicopathological features of adult T-cell leukemia/lymphoma accompanying follicular mucinosis

Case No.	Age/Gender	Origin	Location	Immunohistochemical characteristics	Reference
1	49/Male	Japanese	Neck	CD3(+), CD45RO(+)	[5]
2	68/Female	Jamaica	Abdomen	CD3(+), CD4(+), CD25(+), CD30(-)	[6]
Present case	72/Male	Japanese	Neck	CD3(+), CD4(+), CD25(+), Foxp3(+), CD30(-)	

as well (**Figure 2A**, inset), but negative for CD8, CD20, and CD30.

According to these results, an ultimate diagnosis of ATLL accompanying follicular mucinosis was made.

Discussion

Follicular mucinosis is considered as an epithelial reaction pattern characterized by the accumulation of mucin within the outer root sheath of the hair follicles [4, 11]. It can occur in a number of inflammatory conditions, such as eczematous dermatoses, lupus erythematosus, side effects of imatinib, and insect bite [12], however, more than half of the cases with follicular mucinosis is lymphoma-associated [4, 11]. The most common subtype of malignant lymphoma in association with follicular mucinosis is mycosis fungoides, following Sézary syndrome [4, 11]. Cerroni *et al.* analyzed the clinicopathological features of 44 cases of follicular mucinosis [11]. In their series, 16 cases were idiopathic primary follicular mucinosis, and the remaining 28 cases were lymphoma-associated [11]. Twenty-six of 28 cases were mycosis fungoides, and the remaining 2 cases were

Sézary syndrome [11]. They claimed that follicular mucinosis might represent a form of localized cutaneous T-cell lymphoma [11]. Moreover, it has been reported that follicular mucinosis can be associated with various types of malignant lymphoma other than mycosis fungoides and Sézary syndrome, such as Hodgkin lymphoma and anaplastic large cell lymphoma [12-24]. Further, a case of follicular mucinosis associated with metastatic clear cell renal cell carcinoma has also been documented [25].

There have been only two reports of ATLL accompanying follicular mucinosis [5, 6]. **Table 1** summarizes the clinicopathological features of the previously reported two cases as well as the present one. Wada *et al.* described the first documented case of ATLL accompanying follicular mucinosis in a 49-year-old Japanese male [5], and subsequently Camp *et al.* reported the second case in a 68-year-old Jamaican female [6]. Neoplastic cells in all three cases were CD3-positive, and were CD4- and CD25-positive in two cases, in which these markers were examined (**Table 1**).

Foxp3 has been recently used as a useful immunohistochemical marker for regulatory T

cells (Treg) and are thought to be a more specific marker for Treg cells than other markers such as CD4 and CD25 [26]. Recent studies have indicated that the neoplastic ATLL cells showed positive immunoreactivity for Foxp3 [26, 27]. This marker is thought to be useful for diagnosis of ATLL because mycosis fungoides is consistently negative for Foxp3. In the present case, the neoplastic cells were CD3-, CD4-, and Foxp3-positive, which are typical immunohistochemical characteristics of ATLL, and this is the first report to show positive immunoreactivity for Foxp3 in the neoplastic cells of ATLL accompanying follicular mucinosis.

The mechanism of mucin deposition in follicular mucinosis is thought to be the response of follicular keratinocytes to a specific T-cell infiltrate [28]. Albeit extremely rare, this case clearly demonstrated that the neoplastic cells of ATLL can occur in follicular mucinosis. Therefore, ATLL should be included in the differential diagnostic consideration of follicular mucinosis.

Disclosure of conflict of interest

None

Address correspondence to: Dr. Mitsuaki Ishida, Department of Clinical Laboratory Medicine and Division of Diagnostic Pathology, Shiga University of Medical Science, Tsukinowa-cho, Seta, Otsu, Shiga, 520-2192, Japan. Tel: +81-77-548-2603; Fax: +81-77-548-2407; E-mail: mitsuaki@belle.shiga-med.ac.jp

References

- [1] Ohshima K, Jaffe ES, Kikuchi M. Adult T-cell leukaemia/lymphoma. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW, eds. *World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues*. Lyon: IARC Press, 2008. pp: 281-284.
- [2] DiCaudo DJ, Perniciaro C, Worrell JT, White JW Jr, Cockerell CJ. Clinical and histologic spectrum of human T-cell lymphotropic virus type-I-associated lymphoma involving the skin. *J Am Acad Dermatol* 1996; 34: 69-76.
- [3] Nagatani T, Miyazawa M, Matsuzaki T, Iemoto G, Ishii H, Kim ST, Baba N, Miyamoto H, Minato K, Motomura S. Adult T-cell leukemia/lymphoma (ATL)-clinical, histopathological, immunological and immunohistochemical characteristics. *Exp Dermatol* 1992; 1: 248-252.
- [4] Rongioletti F, De Lucchi S, Meyes D, Mora M, Rebora A, Zupo S, Cerruti G, Patterson JW. Follicular mucinosis: a clinicopathologic, histochemical, immunohistochemical and molecular study comparing the primary benign form and the mycosis fungoides-associated follicular mucinosis. *J Cutan Pathol* 2010; 37: 15-19.
- [5] Wada T, Yoshinaga E, Oiso N, Kawara S, Kawada A, Kozuka T. Adult T-cell leukemia-lymphoma associated with follicular mucinosis. *J Dermatol* 2009; 36: 638-642.
- [6] Camp B, Horwitz S, Pulitzer MP. Adult T-cell leukemia/lymphoma with follicular mucinosis: an unusual histopathological finding and a commentary. *J Cutan Pathol* 2012; 39: 861-865.
- [7] Ishida M, Iwai M, Yoshida K, Kagotani A, Okabe H. Sarcomatoid carcinoma with small cell carcinoma component of the urinary bladder: A case report with review of the literature. *Int J Clin Exp Pathol* 2013; 6: 1671-1676.
- [8] Ishida M, Mori T, Umeda T, Kawai Y, Kubota Y, Abe H, Iwai M, Yoshida K, Kagotani A, Tani T, Okabe H. Pleomorphic lobular carcinoma in a male breast: case report with review of the literature. *Int J Clin Exp Pathol* 2013; 6: 1441-1444.
- [9] Nakanishi R, Ishida M, Hodohara K, Yoshida T, Yoshii M, Okuno H, Horinouchi A, Iwai M, Yoshida K, Kagotani A, Okabe H. Prominent gelatinous bone marrow transformation presenting prior to myelodysplastic syndrome: a case report with review of the literature. *Int J Clin Exp Pathol* 2013; 6: 1677-1682.
- [10] Ishida M, Mochizuki Y, Iwai M, Yoshida K, Kagotani A, Okabe H. Pigmented squamous intraepithelial neoplasia of the esophagus. *Int J Clin Exp Pathol* 2013; 6: 1868-1873.
- [11] Cerroni L, Fink-Puches R, Back B, Kerl H. Follicular mucinosis. A critical reappraisal of clinicopathologic features and association with mycosis fungoides and Sezary syndrome. *Arch Dermatol* 2002; 138: 182-189.
- [12] Hempstead RW, Ackerman AB. Follicular mucinosis: A reaction pattern in follicular epithelium. *Am J Dermatopathol* 1985; 7: 245-257.
- [13] Bittencourt AL, de Oliveira RF, Santos JB. Primary cutaneous folliculotropic and lymphohistiocytic anaplastic large cell lymphoma. *J Cutan Med Surg* 2011; 15: 172-176.
- [14] Lee KK, Lee JY, Tsai YM, Chao SC. Follicular mucinosis occurring after bone marrow transplantation in a patient with acute lymphoblastic leukemia. *J Formos Med Assoc* 2004; 103: 63-66.
- [15] Sumner WT, Grichnik JM, Shea CR, Moore JO, Miller WS, Burton CS. Follicular mucinosis as a presenting sign of acute myeloblastic leukemia. *J Am Acad Dermatol* 1998; 38: 803-805.
- [16] Alagheband M, Cairns ML, Chuang TY. Xanthoerythrodermia perstans and alopecia mucinosa in a patient with CD-30 cutaneous T-cell lymphoma. *Cutis* 1997; 60: 41-42.

ATLL accompanying follicular mucinosis

- [17] Benchikhi H, Wechsler J, Rethers L, Aubry F, Bouzouita A, Farcet JP, Revuz J, Bagot M. Cutaneous B-cell lymphoma associated with follicular mucinosis. *J Am Acad Dermatol* 1995; 33: 673-675.
- [18] Mehregan DA, Gibson LE, Muller SA. Follicular mucinosis: histopathologic review of 33 cases. *Mayo Clin Proc* 1991; 66: 387-90.
- [19] Thomson J, Cochran RE. Chronic lymphatic leukemia presenting as atypical rosacea with follicular mucinosis. *J Cutan Pathol* 1978; 5: 81-87.
- [20] Rashid R, Hymes S. Folliculitis, follicular mucinosis, and papular mucinosis as a presentation of chronic myelomonocytic leukemia. *Dermatol Online J* 2009; 15: 16.
- [21] Gibson LE, Muller SA, Leiferman KM, Peters MS. Follicular mucinosis: clinical and histopathologic study. *J Am Acad Dermatol* 1989; 20: 441-446.
- [22] Ramon D, Jorda E, Molina I, Galan A, Torres V, Alcacer J, Monzo E. Follicular mucinosis and Hodgkin's disease. *Int J Dermatol* 1992; 31: 791-792.
- [23] Stewart M, Smoller BR. Follicular mucinosis in Hodgkin's disease: a poor prognostic sign? *J Am Acad Dermatol* 1991; 24: 784-785.
- [24] Plotnick H, Abbrecht M. Alopecia mucinosa and lymphoma; report of two cases and review of literature. *Arch Dermatol* 1965; 92: 137-141.
- [25] Derancourt C, Blanc D, Agache P. Follicular mucinosis associated with a Grawitz tumour. *Clin Exp Dermatol* 1993; 18: 391.
- [26] Roncador G, Garcia JF, Garcia JF, Maestre L, Lucas E, Menarquez J, Ohshima K, Nakamura S, Banham AH, Piris MA. FOXP3, a selective marker for a subset of adult T-cell leukaemia/lymphoma. *Leukemia* 2005; 19: 2247-2253.
- [27] Karube K, Aoki R, Sugita Y, Yoshida S, Nomura Y, Shimizu K, Kimura Y, Hashikawa K, Takeshita M, Suzumiya J, Utsunomiya A, Kikuchi M, Ohshima K. The relationship of FOXP3 expression and clinicopathological characteristics in adult T-cell leukemia/lymphoma. *Mod Pathol* 2008; 21: 617-625.
- [28] Ishibashi A. Histogenesis of mucin in follicular mucinosis. An electron microscopic study. *Acta Derm Venereol* 1976; 56: 163-171.