

## Case Report

# Mycosis fungoides in plaque stage with pronounced eosinophilic infiltration, folliculotropism, and concomitant invasive squamous cell carcinoma

Tadashi Terada

*Departments of Pathology, Shizuoka City Shimizu Hospital, Shizuoka, Japan*

Received January 30, 2013; Accepted February 20, 2013; Epub March 15, 2013; Published April 1, 2013

**Abstract:** Mycosis fungoides (MF) is a relatively rare cutaneous T-cell malignancy. Only two cases of MF with marked eosinophilia have been reported. In addition, MF with concomitant squamous cell carcinoma (SCC) occurring in the site of MF has not been reported. The author reports herein a very rare case of MF in the plaque stage showing pronounced eosinophilic infiltration, folliculotropic pattern, and in situ development of poorly differentiated squamous cell carcinoma (SCC). A 75-year-old man was found to show high prostate specific antigen (PSA, 13 hg/ml) and prostatic biopsy showed well differentiated prostatic adenocarcinoma of Gleason score 6. Imaging techniques showed no metastatic lesions. He was treated by estrogen therapy. At 80 years, he consulted our hospital because of erythematous patch in the trunk. Biopsy showed mild infiltrations of lymphocyte and eosinophils. The lesion disappeared spontaneously. At 82 years, he consulted our hospital of because of erythematous patch at the back, and biopsy showed mildly atypical lymphocytes positive for CD20 and CD45, but negative for CD30, CD45RO, S100 protein, and cytokeratin (CK). Lymphoma was suspected but not definite. The lesions spontaneously disappeared. At 86 ages, he also consulted our hospital because of plaques in the face. Biopsy showed proliferation of atypical lymphocytes, marked infiltration of mature eosinophils, marked infiltration of these cells in the fair follicles (folliculotropism), and poorly differentiated invasive SCC arising from follicular cells. An immunohistochemical analysis showed that the atypical lymphocytes are T-lymphoma cells with T-cell markers, cyclinD1, p53, and high Ki67 labeling (50%) but without B-cell markers, NK-cell markers and plasma cell markers. The eosinophils were mature, and lacked p53 and showed low Ki67 labeling (4%). The carcinoma was positive for CK, p53, cyclinD1, and high Ki67 labeling (35%). A diagnosis of MF in the plaque stage with marked non-neoplastic eosinophilic infiltration, marked folliculotropism, and coexistent poorly differentiated invasive SCC was made by the author. Post-biopsy imaging techniques showed no metastasis or lymphadenopathy in the body. The patient was now treated by chemotherapy.

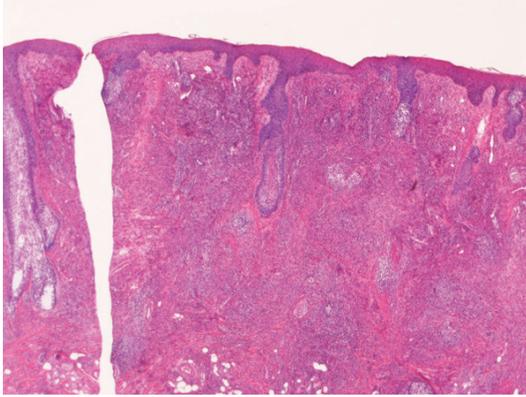
**Keywords:** Mycosis fungoides, eosinophils, squamous cell carcinoma

## Introduction

Mycosis fungoides (MF) is well known but relatively rare T-cell lymphoma of the skin [1]. MF is defined as an epidermotropic, primary cutaneous T-cell lymphoma (CTCL) characterized by infiltrates of small to medium-sized T lymphocytes with cerebriform nuclei. The term MF should be used only for the classical cases characterized by the evolution of patches, plaques, and tumors, or for variants showing a similar clinical course [1]. MF is the most common type of CTCL and account for almost 50% of all primary lymphoma [1]. MF is, as a rule, limited to the skin, with wide spread distribu-

tion, for a protracted period. Extracutaneous dissemination may occur in advanced stages. Clinically, MF has an indolent clinical course with slow progression over years or sometimes decades, from patches to more infiltrated plaques and eventually tumors.

Morphologically, the histological features of MF vary with the stages of the disease [1]. Early patch lesions show lymphocytic infiltrations are seen mildly and atypical lymphocytes with cerebriform nuclei are few. In typical plaque, epidermotropism is more pronounced. The presence of intraepidermal collection of atypical cells (Pautrier microabscesses) is a highly character-



**Figure 1.** Low power view of mycosis fungoides in the plaques state. Numerous infiltrations of atypical lymphocyte and eosinophils are seen. The epidermis shows minimal to mild changes. There are many folliculotropic cells of eosinophils and atypical lymphocytes. The follicular epithelial cells show marked atypia, regarded as squamous cell carcinoma. HE, x40.

istic feature, but it is observed in only a minority of cases. With progression of tumor stage, the dermal infiltrates become more diffuse and epidermotropism may be lost. The tumor cells increase in number and size, showing various proportions of small, medium-sized, to large cerebriform cells, blast cells with prominent nuclei and intermediate form [1]. MF is a T cell neoplasm, and postulated normal counterpart is mature skin-homing CD4+ T-cell. The single most important prognosis factor in MF is the extent of cutaneous and extracutaneous disease as reflected in the clinical stage. Patients with MF limited disease have excellent prognosis. In more advanced stages, the prognosis is poor. Folliculotropic MF is a variant of MF, which is characterized by the presence of follicular infiltrates atypical cerebriform CD4+ T lymphocytes often sparing the epidermis. Most cases show numerous degenerations of the hair follicles (follicular mucinosis) but cases without follicular mucinosis have been reported. Pagetoid reticulosis is a variant of MF is characterized by the presence of patches and plaques with an intraepidermal proliferation of neoplastic T-cells. The term should only be used for localized type. Granulation slack skin is also a variant of MF, but it is extremely rare.

In general, eosinophils are not major components of MF [2-4]. MF with pronounced mature eosinophilic infiltration is exceptionally rare, only two cases of MF with blood or tissue eosin-

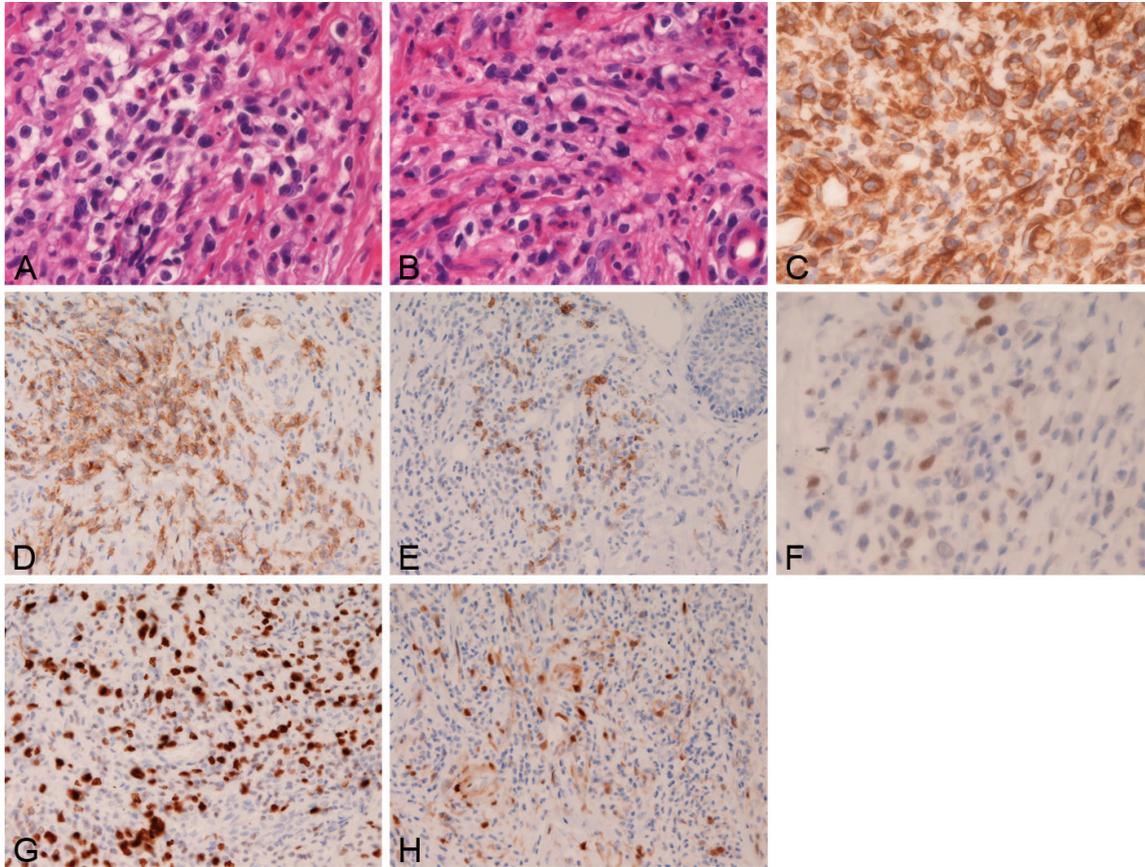
ophilia have been reported [5, 6]. There have been no reports of MF associated with in situ squamous cell carcinoma (SCC) occurring in the site of MF.

The author herein report a case of MF of the plaque stage showing pronounced eosinophilic infiltration, in situ occurrence of SCC at the site of MF, and relatively severe folliculotropism.

### Case report

A 75-year-old man was found to show high prostate specific antigen (PSA, 13 ng/ml; normal 0-4.0 ng/ml) and prostatic biopsy showed well differentiated prostatic adenocarcinoma of Gleason score 6. Imaging techniques including CT and MRI showed no metastatic lesions. He was treated by estrogen therapy. The serum PSA markedly decreased into the normal ranges; this situation has been persisted now. At 80 years, he consulted our hospital because of erythematous patch in the trunk. Biopsy showed mild infiltrations of lymphocyte and eosinophils. No atypical cells or cerebriform cells were seen. The lesion disappeared spontaneously. At 82 years, he again consulted our hospital of because of erythematous patch at the back, and biopsy showed mildly atypical lymphocytes positive for CD20 and CD45, but negative for CD30, CD45RO, S100 protein, and cytokeratin (CK). No apparent lymphoma cells and cerebriform cells were seen. Lymphoma was suspected but not definite. The lesions also spontaneously disappeared. At 86 ages, he thirdly consulted our hospital because of plaques in the face. A blood laboratory data revealed marked peripheral blood eosinophilia (white blood cell count, 63,00/ $\mu$ l; eosinophils 25%, normal 2.0-4.0%), mild anemia (red blood cell count, 324 x 10<sup>4</sup>/ $\mu$ l; normal 450-550), and increased LDH (242 IU/l, normal 106-211). Soluble IL-2 receptor (289 U/ml, normal 122-496) and serum PSA (0.04 ng/ml, normal 0.0-4.0) were normal. Biopsy showed proliferation of atypical lymphocytes, marked infiltration of mature eosinophils, marked infiltration of these cells in the fair follicles (folliculotropism), and poorly differentiated SCC. Low power field showed severe infiltrates of lymphoid cells in from the shallow dermis into the shallow subcutaneous tissue (**Figure 1**). Higher magnification showed that the infiltrates were composed of four elements; atypical medium-sized lymphocytes regarded as lymphoma cells, numerous

## Mycosis fungoides



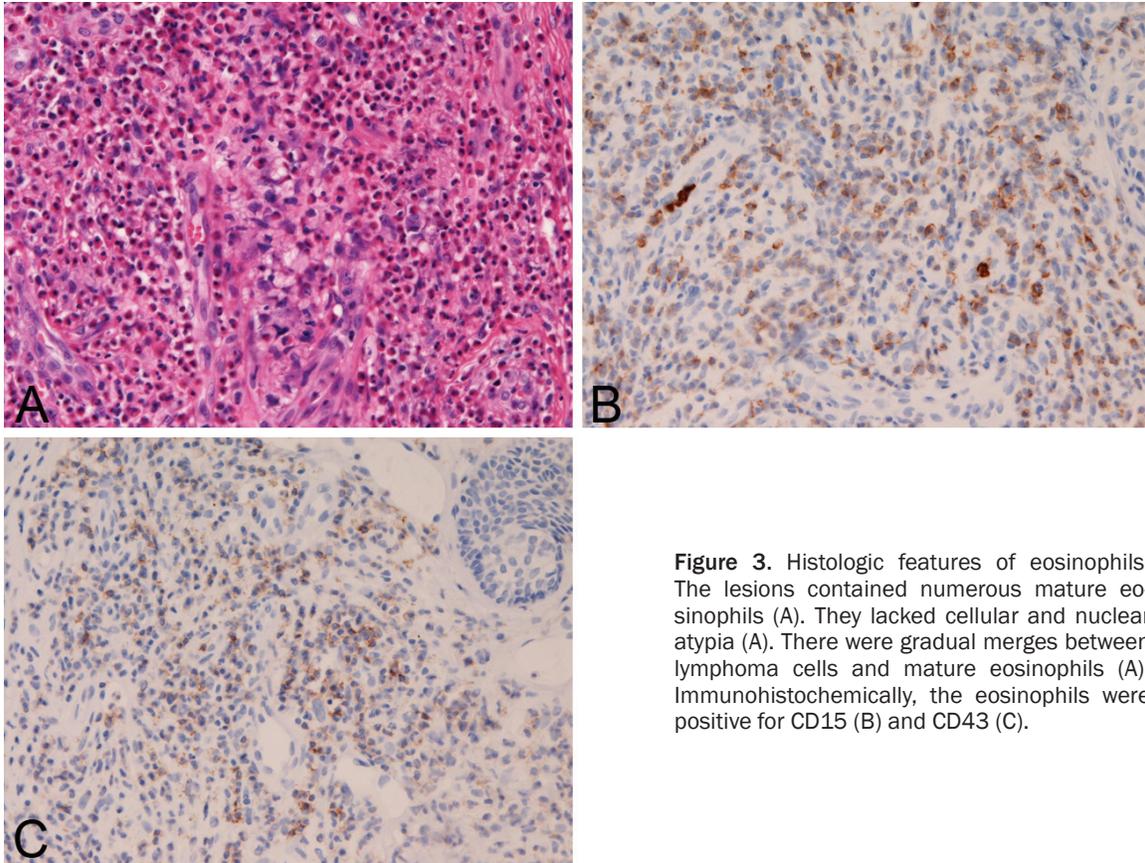
**Figure 2.** Histology of mycosis fungoides cells. They are composed of atypical lymphoma cells with hyperchromatic nuclei (A and B). Many mitotic figures were scattered (A and B). Cerebriform cells and large lymphoid cells with prominent nucleoli were also seen (A and B). Immunohistochemically, the lymphoma cells were positive for vimentin (C), CD3 (D), CD4 (E), and 53 (F). Ki-67 labeling index is 54% (G). They were positive for cyclin D1 (H). A-H: x200.

mature eosinophils, hair follicles infiltrated by these atypical lymphoid cells and mature eosinophils, and atypical follicular epithelial cells and atypical cells in the deep dermis. The epidermal infiltrates are not severe, but mild to minimal (**Figure 1**). An immunohistochemical analysis was performed by the Dako Envision method (Dako Corp, Glostrup, Denmark) as previously reported [7, 8].

The atypical lymphoid cells were composed of atypical lymphoma cells with hyperchromatic nuclei (**Figure 2A** and **2B**). Many mitotic figures were scattered (**Figure 2A** and **2B**). Cerebriform cells and large lymphoid cells with prominent nucleoli were also seen (**Figure 2A** and **2B**). Immunohistochemically, the lymphoma cells were positive for vimentin (**Figure 2C**) and CD45, and positive for T-cell antigens including CD3 (**Figure 2D**), CD4 (**Figure 2E**), CD5, CD43, and CD45RO. P53 was strongly expressed

(**Figure 2F**) and its labeling index was 23%, and the Ki-67 labeling index was 54% (**Figure 2G**). They were positive for cyclin D1 (**Figure 2H**). The lymphoma cells were negative for B-cell antigens including CD10, CD20, CD21, CD23, CD79 $\alpha$ , and bcl-2, were negative for NK-cell markers (CD56 and CD57), and were also negative for plasma cell markers (CD138,  $\kappa$ -chain, and  $\lambda$ -chain), They were negative for CD15, CD30, TdT, CK AE1/3, CK CAM5.2, and KIT. KIT (CD117) was only expressed in scattered mast cells.

The lesions contained numerous mature eosinophils (**Figure 3A**). They lacked cellular and nuclear atypia (**Figure 3A**). There were gradual merges between lymphoma cells and mature eosinophils. Immunohistochemically, the eosinophils were positive for vimentin (**Figure 2C**), CD15 (**Figure 3B**), CD45, and CD43 (**Figure 3C**). P53 was negative and Ki-67 labeling index was



**Figure 3.** Histologic features of eosinophils. The lesions contained numerous mature eosinophils (A). They lacked cellular and nuclear atypia (A). There were gradual merges between lymphoma cells and mature eosinophils (A). Immunohistochemically, the eosinophils were positive for CD15 (B) and CD43 (C).

6%. The eosinophils were negative for CK AE1/3, CK CAM5.2, CD68, CD45RO, CD20, CD30,  $\kappa$ -chain,  $\lambda$ -chain, KIT, CD56, CD57, bcl-2, CD3, CD79 $\alpha$ , TdT, CD138, CD4, CD5, CD21, CD23, and cyclin D1.

The hair follicles were infiltrated by eosinophils (**Figure 4A**) and by lymphoma cells (**Figure 4B**). Follicular mucinosis was occasionally seen (**Figure 4A** and **4B**), particularly in areas of eosinophilic folliculotropism. Although the recognition of folliculotropism by eosinophils was very easy, that MF cells was difficult to distinguish from carcinoma cells. However, immunohistochemical stainings for T-cell marker could detect MF cells (**Figure 4C**) in the follicular epithelial cells with SCC atypia. The immunohistochemical profiles of the lymphoma cells and eosinophils were the same as those of extra-follicular areas.

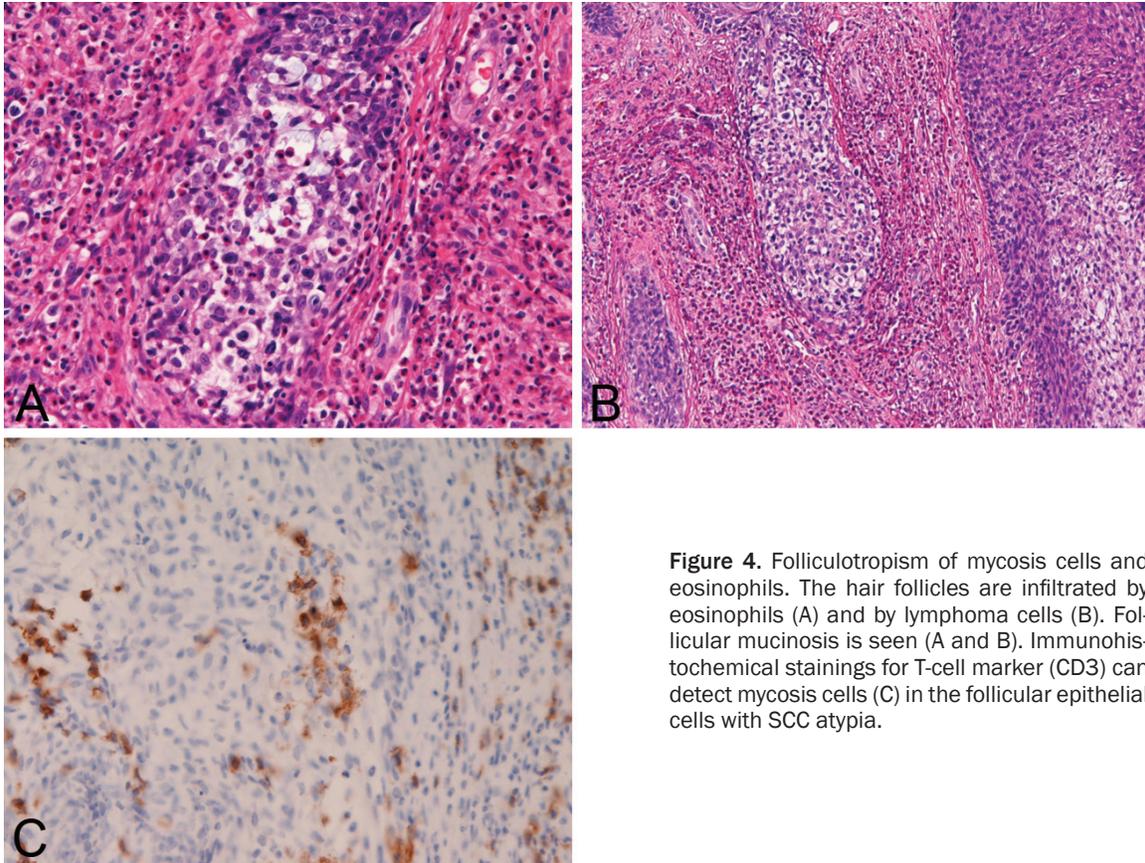
There were atypical epithelial cells in the hair follicles and dermis (**Figure 5A** and **5B**). The dermis showed invasive SCC (**Figure 5C**). These atypical epithelial cells were positive for CK AE1/3 (**Figure 5D**), CK CAM5.2, CD138 (**Figure**

**5E**), cyclin D1 (**Figure 5F**), p53 (labeling=23%) (**Figure 5G**) and high Ki-67 labeling index (37%) (**Figure 5H**). They were negative for CD68, CD45, CD45RO, CD20, CD30, CD15,  $\kappa$ -chain,  $\lambda$ -chain, KIT, CD56, CD57, bcl-2, CD3, CD79 $\alpha$ , TdT, CD4, CD5, CD21, CD23, and CD43. The CK immunostaining highlighted the many islands of infiltrating carcinoma cells in the deep dermis (**Figure 5I** and **5J**). CD138 (**Figure 5E**) was expressed in the non-neoplastic epithelial cells of the skin including epidermis and appendages in addition to the carcinoma cells.

### Discussion

The main HE histology of the present case is proliferation of atypical lymphocytes. They showed nuclear atypia, large cell with prominent nucleoli, cerebriform cells, and many mitotic figures. The features can be diagnosed as malignant lymphoma possible of MF by only HE histology. Immunohistochemical study revealed that the tumor cells had many T-cell antigens including CD3 and CD4. Markers of B-cell, plasma cells, NK-cells were negative.

## Mycosis fungoides



**Figure 4.** Folliculotropism of mycosis cells and eosinophils. The hair follicles are infiltrated by eosinophils (A) and by lymphoma cells (B). Follicular mucinosis is seen (A and B). Immunohistochemical stainings for T-cell marker (CD3) can detect mycosis cells (C) in the follicular epithelial cells with SCC atypia.

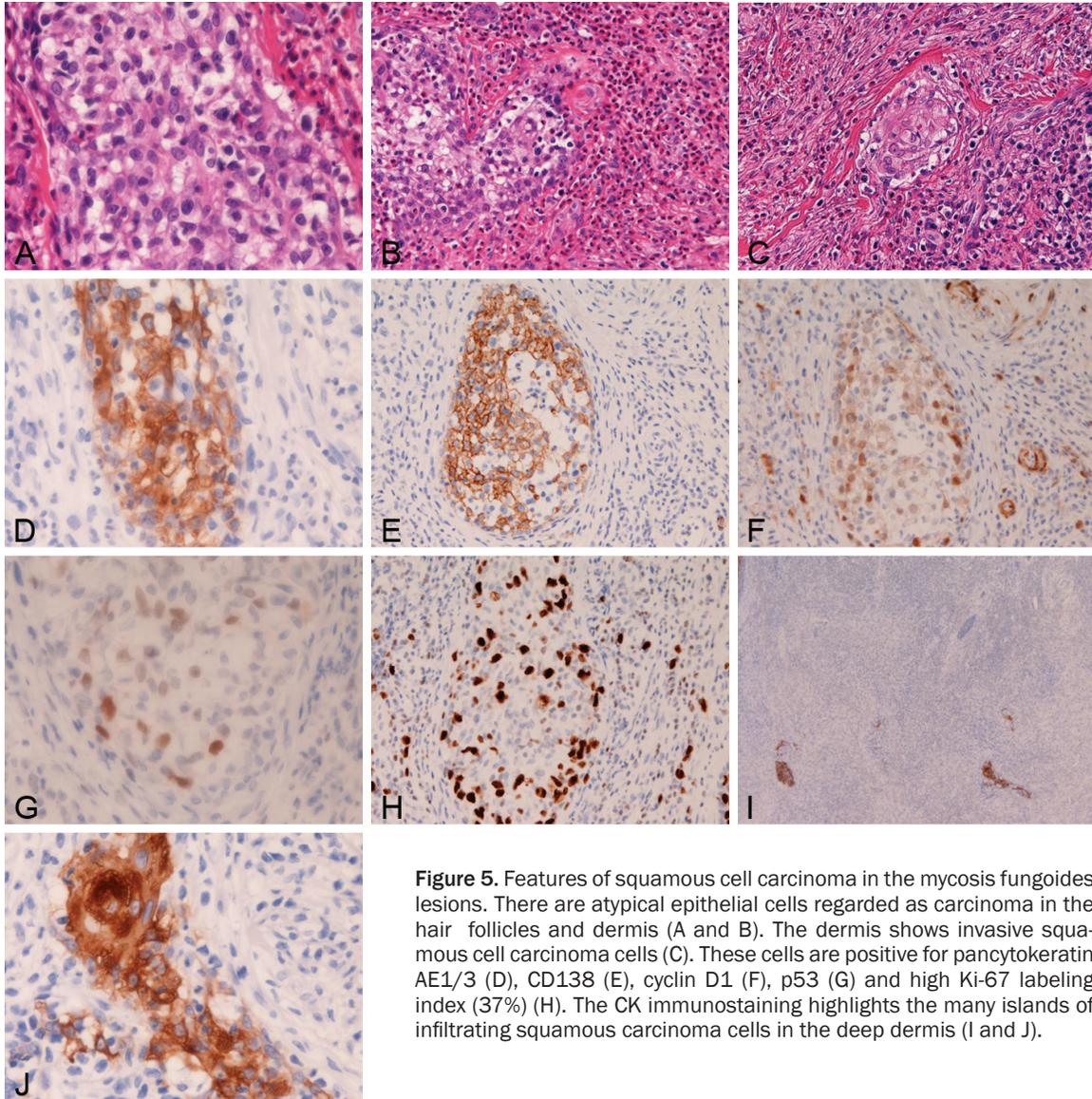
P53 was positive, indicating p53 gene mutations. The Ki-67 labeling index was high (54%). The status of p53 and Ki-67 indicates that the tumor is malignant. Taken together, the present case is regarded as primary CTCL (MF). Curiously, cyclinD1 was expressed in the MF cells. A PubMed search revealed no MF cases with cyclinD1 expression in the literature. In the lymphoma, it is thought cyclin D1 expression is confined to mantle cell lymphoma (B-cell lineage) and plasmacytic neoplasms. The present tumor is T-cell tumor; therefore the present case is not mantle cell lymphoma. The expression of cyclinD1 in this MF needs further studies. It is suggested that MF can express cyclinD1.

In general, pathological diagnosis of MF in early patch and plaque stages is very difficult. It is often diagnosed as inflammatory process because of little atypia of lymphocytes. The diagnosis of MF requires time. At tumor stages, the pathological diagnosis of MF is relatively easy. The present case consulted three times our hospital. First biopsy of the patch stage

revealed only mature lymphocytes and eosinophils. The second biopsy suggested low grade B-cell lymphoma positive for CD20 and negative for CD45RO, but no definite diagnosis of lymphoma was made because the cellular atypia is little for lymphoma. The third biopsy for the first time revealed that the patient has MF. Thus, the diagnosis of MF required much time also in the present case.

It is very interesting that numerous eosinophilic infiltrations were seen in the lesions. This phenomenon was reported in only twice [5, 6]. In general, there are few eosinophils in MF [1-4]. The eosinophils in the current case were mature and free from atypia. The immunohistochemical study including p53 and Ki-67 also suggested the benign nature of the eosinophils. The presence of pronounced mature benign eosinophilic infiltration in MF lesions of the present study may indicate that lymphoma or carcinoma cells aberrantly secrete eosinophilic factors such as eosinophilic colony stimulating factor and eosinophilic chemotactic factor. In this patient, eosinophilia of the peripheral blood

## Mycosis fungoides



**Figure 5.** Features of squamous cell carcinoma in the mycosis fungoides lesions. There are atypical epithelial cells regarded as carcinoma in the hair follicles and dermis (A and B). The dermis shows invasive squamous cell carcinoma cells (C). These cells are positive for pancytokeratin AE1/3 (D), CD138 (E), cyclin D1 (F), p53 (G) and high Ki-67 labeling index (37%) (H). The CK immunostaining highlights the many islands of infiltrating squamous carcinoma cells in the deep dermis (I and J).

was also recognized. Therefore, alternatively, eosinophilic disorders such as hypereosinophilic syndrome and eosinophilic leukemia/lymphoma are separately occurred, although there have been no data of these other eosinophilic diseases were seen. The immunohistochemical findings suggest that the cells are compatible with eosinophils. CD15 and CD43 were expressed in the eosinophils in the current tumor. The expression of CD15 in eosinophils is well recognized [9]. CD15 is also expressed in neutrophils, monocytes, Reed-Sternberg cells in Hodgkin's disease, and some cells of T-cell neoplasm, and some epithelial cells [9]. However, expression of CD43 (MT1), which is a ligand of ICAM-1, is expressed mainly in T-cells,

T-cell neoplasm, glandular epithelium, and neuronal cells. A PubMed search done by the author could not detect the link between eosinophils and CD43. This, however, suggests that CD43 may be expressed in mature eosinophils.

It is also very interesting that folliculotropic infiltration of MF cells and eosinophils was relatively strong in the present case. The folliculotropism of eosinophils were very easily recognized in only the HE section. However, the folliculotropism of MF cells was difficult to discern because it was difficult to differentiate from SCC cells. However, immunohistochemical staining of T-cell markers such as CD3, CD4 and CD5

showed the presence of MF-cells in the hair follicles. Since the MF cells were largely located in the dermis in the present study, the present MF is not a variant of folliculotropic MF, in which folliculotropism is much more severe than in the present case.

In the present study, severe atypia was seen in the follicular epithelial cells. The determination whether these follicular cell atypia was due to the MF cell folliculotropism or due to follicular epithelial malignant neoplasm was difficult. The atypical cells of hair follicles contained T-cell markers-positive MF cells. However, they were mainly composed of CK-positive atypical epithelial cells. P53 was positive and Ki67 labeling index was very high (37%) in these atypical cells, suggesting that they are malignant epithelial cells (SCC). The demonstration of invasive nests of SCC in the deep dermis (**Figure 5C**) definitely indicates that the atypical epithelial cells are invasive SCC cells probably arising from follicular squamous epithelium. Further, CK immunostaining revealed many infiltrating islands of atypical cells positive for CK. Taken together, these findings strongly suggest that the atypical epithelial cells are poorly differentiated invasive SCC arising from the hair follicles. The author concluded this and believes now this interpretation with regard to SCC. In general, inflammatory or neoplastic lymphocytes frequently cause epithelial atypia. Such situations are seen in all organs. For examples, regenerative atypia of foveolar epithelium is frequently seen in gastric ulcer and chronic gastritis as well as in lymphoepithelial lesions in MALT lymphoma. In the skin also, it is very famous that inflammatory infiltrates, for instance in lichen planus, cause epithelial atypia. Although it is possible in the current case that the folliculotropism caused by eosinophils and MF cells gave rise to epithelial reactive atypia, the epithelial atypia is so severe and immunohistochemically p53 was positive and Ki-67 labeling was very high. In addition, CK immunostaining showed many invasive islands of atypical epithelial cells. The author believes that SCC is present in these MF lesions in the plaque stage. A PubMed search and meticulous search of books including WHO blue books could not find the case of concomitant carcinoma within MF lesions. In the present case, CD138 was expressed in the SCC cells and epithelial cells of the skin including epidermis and

appendages. CD138 (Syndecan-1), a 33,000 MW transmembranous proteoglycan whose gene is mapped to 2p24.1; *SDC1*, is known to be also expressed in pre-B-cell, epithelial cells, vascular smooth muscle cells and neuronal cells. Therefore the present finding is a common one. Also in the present case, cyclinD1 is expressed in the carcinoma cells; this phenomenon is common in some carcinomas such as breast and esophageal carcinomas. Thus, the positivity of cyclinD1 in the present SCC cells suggests that cyclinD1 may be expressed in SCC developed from MF. The cyclinD1 was also expressed in vascular endothelial cells and epidermal and follicular epithelial cells.

In conclusion, the author reported an extremely rare case of MF of the plaque stage with pronounced eosinophilic infiltration. This finding is the third report in the world literature. In this MF, there was poorly differentiated invasive SCC originating from hair follicles, a new finding. These interpretations were confirmed by the extensive immunohistochemical study.

**Address correspondence to:** Dr. Tadashi Terada, Department of Pathology, Shizuoka City Shimizu Hospital, Miyakami 1231 Shimizu-Ku, Shizuoka 424-8636, Japan. Tel: +81-54-336-1111; Fax: +81-54-334-1173; E-mail: piyo0111jp@yahoo.co.jp

### References

- [1] Ralfkiaer E, Cerroni L, Sander CA, Smoller BR, Willemze R. Mycosis fungoides. In Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW. Eds. WHO classification of tumours of haematopoietic and lymphoid tissues. IARC: Lyon. 2008. pp: 296-298.
- [2] Dalton SR, Chandler WM, Abuzeid M, Hossler EW, Ferringer T, Elston DM, LeBoit PE. Eosinophils in mycosis fungoides: an uncommon finding in the patch and plaques stages. *Am J Dermatopathol* 2012; 34: 586-591.
- [3] Gerami P, Guitart J. The spectrum of histopathological and immunohistochemical findings in folliculotropic mycosis fungoides. *Am J Surg Pathol* 2007; 31: 1430-1438.
- [4] Nickoloff BJ. Light-microscopical assessment of 100 patients with patch/plaque-stage mycosis fungoides. *Am J Dermatopathol* 1988; 10: 469-477.
- [5] Ishibashi M, Ohshima K, Chen KR. Folliculotropic mycosis fungoides with eosinophilia and CD30+ large-cell transformation: a case with fatal outcome presenting with multifocal le-

## Mycosis fungoides

- sions and leonine facies. *Clin Exp Dermatol* 2010; 35: e133-136.
- [6] Palermo A, Moretti S, Difonzo EM, Fattorossi A. Mycosis fungoides with monoclonal gammopathy, hypereosinophilia, and hyper-IgE. *Dermatologica* 1984; 169: 194-196.
- [7] Terada T, Kawaguchi M, Furukawa K, Sekido Y, Osamura Y. Minute mixed ductal-endocrine carcinoma of the pancreas with predominant intraductal growth. *Pathol Int* 2002; 52: 740-746.
- [8] Terada T, Kawaguchi M. Primary clear cell adenocarcinoma of the peritoneum. *Tohoku J Exp Med* 2005; 271: 271-275.
- [9] Satoh T, Knowles A, Li MS, Sun L, Tooze JA, Zambucchi G, Spry CJ. Expression of lacto-N-fucopentaose III (CD15)- and sialyl-Lewis X-bearing molecules and their functional properties in eosinophils from patients with the idiopathic hypereosinophilic syndrome. *Immunology* 1994; 83: 313-318.