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Eosinophilic Fasciitis Preceding Relapse of Peripheral T-Cell Lymphoma

Although eosinophilic fasciitis (EF) may precede hematologic malignancy or Hodgkin's disease, association with peripheral T-cell lymphoma (PTCL) is extremely rare. Only four cases of EF preceding or concomitant PTCL have been reported in the world literature. We experienced the first Korean case of EF complicated by the later relapse of peripheral T-cell lymphoma. A 63-year-old Korean male has been followed at our outpatient clinic periodically after treatment for stage IV PTCL. He had been in complete remission for seven and a half years when he developed edema of both lower extremities followed by sclerodermatous skin change in both hands with peripheral eosinophilia. Biopsy from the left hand showed fibrous thickening of the fascia with lymphoplasmacytic and eosinophilic infiltrate, consistent with EF. Twenty-five months later, a newly developed lymph node from the left neck showed recurrence of PTCL. EF may occur as a paraneoplastic syndrome associated with the relapse of PTCL. Therefore, in a patient with EF, the possibility of coexisting and/or future occurrence of hematologic neoplasm should be considered.

Key Words: *Eosinophilic Fasciitis; Lymphoma, T-Cell, Peripheral; Paraneoplastic Syndromes*

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INTRODUCTION

Eosinophilic fasciitis (EF) was first introduced by Shulman as diffuse fasciitis with hypergammaglobulinemia and eosinophilia. It was named as Shulman's syndrome by Rodnan et al. (1, 2). It is characterized by scleroderma-like skin lesions, peripheral eosinophilia and hypergammaglobulinemia, and has been associated with aplastic anemia and immune thrombocytopenia. EF can precede or be concomitant to internal malignancies such as a paraneoplastic syndrome. In the world literature, eosinophilic fasciitis have been associated with malignancies such as myelomonocytic leukemia, Hodgkin's disease, peripheral T-cell lymphoma (PTCL), and carcinomas (3-12). Among the 15 previously reported malignancy-associated cases, a case of EF concurrent with mycosis fungoides was described and PTCL was developed in three cases months or years after the diagnosis of EF.

We experienced a 63-year-old Korean male with EF who developed clinical relapse of original PTCL. We report this case with review of literature.

CASE REPORT

A 63-year-old male complained of swelling of both lower extremities and sclerodermatous skin changes of two months duration in both hands. He had been treated and followed periodically for stage IV PTCL, which had been confirmed by a left supraclavicular lymph node biopsy performed in 1989 and showed PTCL, mixed medium and large cell by revised European-American classification of lymphoid neoplasms (REAL) (Fig. 1) (13). He had been in complete remission for the past seven and a half years without evidence of relapse. He denied any histories of arthralgias, Raynaud's phenomenon, febrile sensation, night sweat, weight loss or L-tryptophan ingestion. Physical examination did not show peripheral lymphadenopathy or organomegaly. There was no evidence of heart failure. Both hands showed tightening of the skin and he was unable to extend his fingers. Both lower extremities showed pitting edema.

Laboratory data showed hemoglobin of 10.7 g/dL, WBC count of 6,300/μL with 22% eosinophils. Blood chemistry showed serum albumin of 2.8 g/dL and normal serum lactate dehydrogenase value. Antinuclear antibody and rheumatoid factor were negative.

Possibility of the tumor recurrence was thought but findings of chest radiograph and abdominal computed tomogram were normal. Bone marrow aspiration and biopsy showed increased mature eosiophils but no evidence of lymphoma was noticed.

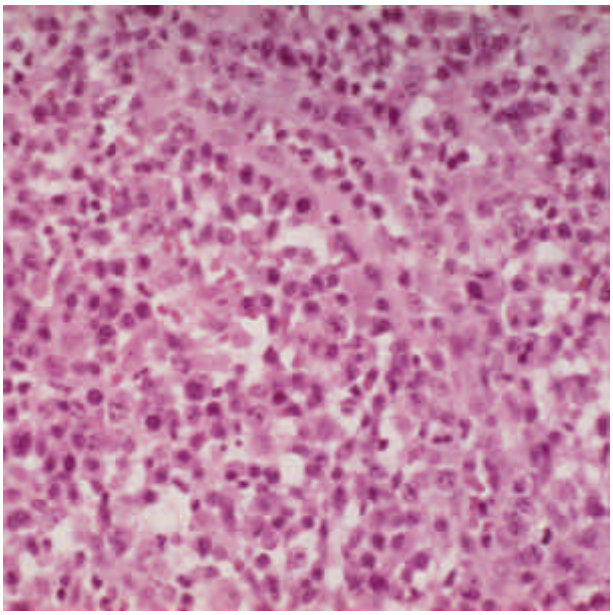

Fig. 1. Left supraclavicular lymph node biopsy performed in 1989 shows total effacement of lymph node architecture with diffuse mixed infiltration of atypical medium and large lymphoid cells (H&E, ×200).

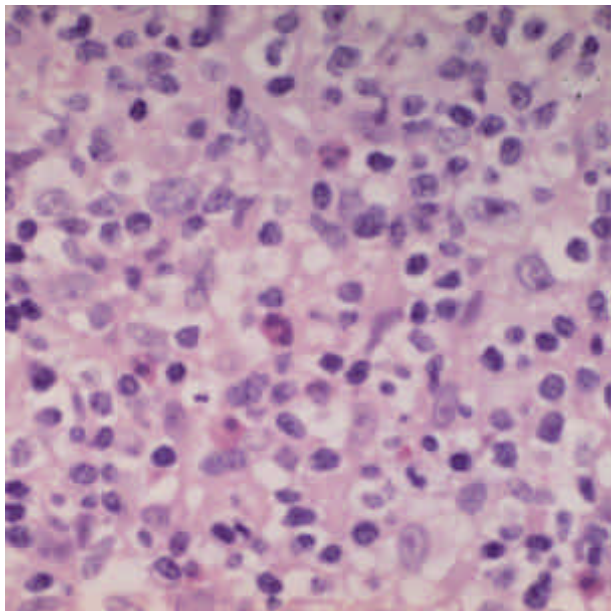

Fig. 3. Light microscopic findings of recurrent right cervical lymph node show similar histologic findings of original peripheral T cell lymphoma. In addition to atypical medium and large lymphocytes, aggregates of epithelioid cells and eosinophils were frequently seen (H&E, ×200).

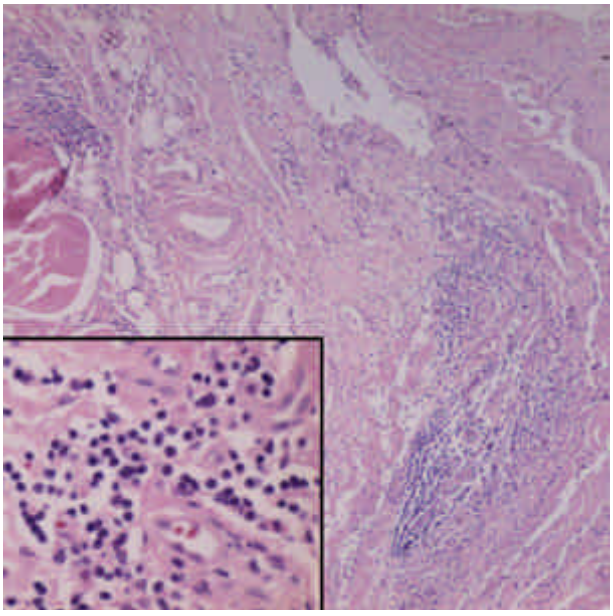

Fig. 2. Skin biopsy shows diffuse fibrous thickening of the fascia with chronic inflammatory infiltrate. Inflammatory cells were composed mostly of lymphocytes intermingled with plasma cells and occasional eosinophils (H&E, ×100). Inflammatory cells are clearly recognized (Inlet, H&E, ×200).

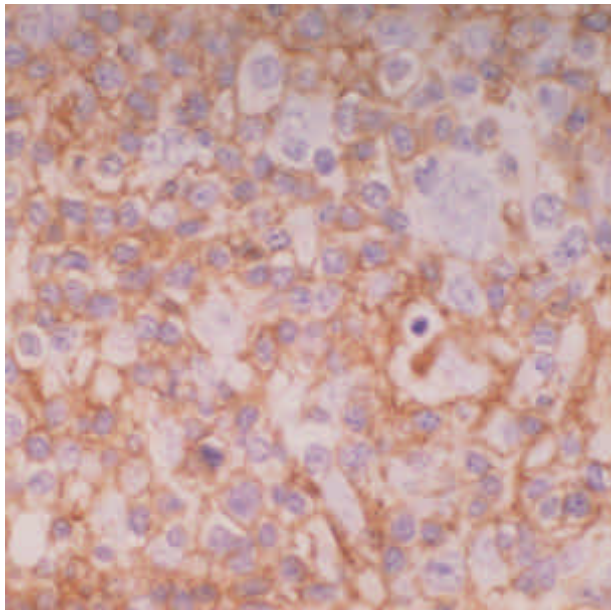

Fig. 4. Immunohistochemical staining of Fig. 3 shows positivity for T cell marker, CD45RO (×400).

Biopsy from the left hand (Fig. 2) showed diffuse fibrous thickening of the fascia with chronic inflammatory infiltrates. The inflammatory infiltrates were mostly lymphpocytes and some plasma cells were intermingled with occasional eosinophils. The epidermis appeared normal. The reticular dermis showed mild perivascular lymphocytic infiltrate without fibrosis. The subcutis showed thickening of the interlobular fibrous septum

with sparse infiltration of lymphocytes and eosinophils. The attached skeletal muscle fibers showed no significant pathologic changes. He was managed with oral prednisone and D-penicillamine with gradual symptomatic improvement. He was tapered off of his medications.

Twenty-five months after the diagnosis of EF, a painless right cervical lymph node was found. Excisional biopsy confirmed the relapse of PTCL, mixed medium and large cell (Fig. 3). The lymph node architecture was totally effaced with diffuse mixed infiltration of atypical medium-sized and large cells. Admixed eosinophils, aggregates of epithelioid histiocytes were frequently seen in addition to plasma cells. Proliferations of small blood vessels were also present. Immunostaining with pan-T cell markers, CD45RO (UCHL-1) and CD43 (MT-1) showed positivity in neoplastic lymhocytes (Fig. 4). B cell markers [CD20 (L-26) and MB-2] were negative.

DISCUSSION

After the first description by Shulman (1) as diffuse fasciitis with hypergammaglobulinemia and eosinophilia, Rodnan et al. (2) proposed the term EF because of the striking changes present in both the superficial and deep fascia, and the prominence of eosinophils in the inflammatory reaction. Despite sclerodermatous skin changes in EF, Raynaud's phenomenon was rare in EF. Other common findings in EF not frequently found in scleroderma were peripheral eosinophilia, hypergammaglobulinemia, elevated sedimentation rate, normal nail-fold microscopy, sparing of the epidermis and dermis on skin biopsy, and connection to exercise as the initiating event in many patients (6). Clinically, the arms and legs are the most common sites of involvement, with many patients having simultaneous hand and foot involvement.

EF can be associated with many hematologic diseases such as acute leukemia, aplasic anemia, Hodgkin's disease, pure red cell aplasia, and non-Hodgkin lymphoma (3-5, 14-16). The overall frequency of hematological disorders in EF may be close to 10% (6). EF can be associated with malignancies other than hematologic malignancy such as mammary carcinoma or prostatic carcinoma. In the world literatures, 15 cases of malignancies were reported months or years after the diagnosis of EF and two cases concomitant to EF (Table 1).

EF displays some characteristics of paraneoplastic syndrome (9). First, it occurs at a distance from the tumor. Second, it evolves in concert with the neoplasm at a median lag time of one year. Third, it is preferentially associated with certain tumors (lymphohematologic malignancies). Finally, it sometimes remits after successful cancer surgery. Our patient fulfils these characteristics of paraneoplastic syndrome.

Murata et al. (17) reported that the eosinophilias in adult T-cell leukemia/lymphomas, T-cell lymphomas and B-cell lymphomas were 21%, 11.1% and 10.5%, respectively. It has been hypothesized that immune complexes deposited in the fascia of the patients with EF may attract eosinophils either directly or via activation of complement system, which may in turn stimulate the fibroblasts to proliferate, resulting in sclerosis (18). Although the exact mechanisms of the eosinophilias associated with lymphomas remain unclear, one possibility is cytokines released by activated immunocytes, either malignant or normal leukocytes reacting to malignant cells, which may

Table 1. Summary of 15 previously reported cases of cancer-associated eosinophilic fasciitis

Patient No.	Author	Year	Sex	Age (yr)	Cancer	Precedence	Lag time
1	Michet et al.	1981	F	49	Myelomonocytic leukemia	EF	7 months
2	Doyle et al.	1985	F	48	Myelomonocytic leukemia	EF	3 years
3	-		M	55	Chronic lymphocytic leukemia	EF	12 months
4	-		F	69	Myeloproliferative process	EF	12 months
5	Rodat et al.	1982	F	70	Hodgkin's disease	EF	3 years
6	Michaels	1982	F	53	Hodgkin's disease	EF	3.5 years
7	Lakhanpal et al.	1988	F	?	Mammary carcinoma	?	?
8	Chan et al.	1991	M	73	Mycosis fungoides	Concomitant	0
9	Diez-Martin et al.	1991	M	69	PTCL	EF	2 months
10	Naschitz et al.	1994	F	72	Tubular carcinoma, breast	EF	3 months
11	idem		M	82	Prostatic carcinoma	Concomitant	2 years
12	idem		F	60	Hodgkin's disease	EF	1 year
13	Junca et al.	1994	F	69	PTCL, lymphoepithelioid cell	EF	2 years
14	Chevalier et al.	1995	F	51	Angioimmunoblastic T-cell lymphoma	EF	6 months
15	Masuoka et al.	1998	F	51	PTCL, mixed medium and large cell	Concomitant	0
16	Current study	1999	M	55	PTCL, mixed medium and large cell	EF	25 months

EF, eosinophilic fasciitis; PTCL, peripheral T-cell lymphoma

be responsible for the eosinophilia and sclerosis seen in these associated hematological malignant neoplasm. The expansion of T-cell clone with the unusual phenotype CD3-CD4+ is able to produce high levels of IL-4 and IL-5 and low levels of IL-2 and interferon-gamma. T-cell proliferations associated with eosinophilia are generally characterized by cells with a mature phenotype and most often belong to the helper (CD4 positive) subset of mature T cells (19). Currently, three lymphokines i.e. granulocyte/macrophage colony-stimulating factor, IL-3, and IL-5 are known to induce eosinophilia (20-22). Brugnoni et al. (23) emphasized the relationship between hypereosinophilic syndrome, IL-5, and T-cell lymphoproliferative diseases.

Despite the initial report, which suggested that EF was a cortisone-responsive condition with a benign course, only 59% had a satisfactory response to prednisolone alone (24). Polypharmacy using prednisolone and azathioprine with either hydroxychloroquine or D-penicillamine has been reported to be effective in patients with EF (25).

Our patient is interesting in that when he first presented with lymphoma, there were no signs of eosinophilia and EF, but these occurred 25 months prior to the recurrence of the original lymphoma. It could be postulated that a patient may have subclinical malignant T-cell lymphoma which produces various cytokines such as IL-3, IL-5 or granulocyte/macrophages colony-stimulating factor before showing overt clinical manifestations of recurrence. In a patient with newly onset EF, the possibility of coexisting and/or future occurrence of hematologic neoplasm should be considered.

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