Elevated Serum Tissue Polypeptide Antigen in a Patient with Mycosis Fungoides

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Tissue polypeptide antigen (TPA) is a tumor marker which has been found to be elevated in various solid tumors, including cancers of the lung, breast, and bladder. However, there have been very limited reports regarding the association of this tumor marker with hematologic malignancies. We here report a patient with mycosis fungoides (MF), presenting with generalized scaling involving >90% of the total body surface area, erythema of buttocks and thighs, bilateral inguinal lymphadenopathy, and atypical lymphocytes found in the peripheral blood. A series of tumor markers were found to be within normal limits except TPA, which was elevated three times above the upper normal limit. The presence of another primary tumor was excluded by history taking, physical examination, blood tests, and various radiological and nuclear imaging. Following two courses of chemotherapy, the patient’s skin condition improved, and her serum TPA level returned to normal. These findings suggest that serum TPA may prove to be clinically significant in a subset of patients with mycosis fungoides. (Dermatol Sinica 25: 67-72, 2007)

Key words: Tissue polypeptide antigen, Mycosis fungoides, Tumor marker
INTRODUCTION

Cutaneous T cell lymphoma (CTCL) is a T cell neoplasm that first manifested in the skin. Mycosis fungoides is the classic form of CTCL, and is an epidermotropic neoplasm composed of T helper (CD4+) cells. The clinical presentation of mycosis fungoides is varied, and it can simulate many different dermatoses. The term ‘the great imitator’ is therefore applied to this disease.1

Historically, various tumor markers have been used in the screening, diagnosis, and follow-up of patients with cancer. The most well-known examples include the tumor marker alpha-fetoprotein (AFP) for hepatocellular carcinoma, prostate specific antigen (PSA) for prostate cancer, and CA-125 for ovarian cancer. Tumor markers, however, have been rarely used in patients with cutaneous T cell lymphoma. This report describes, for the first time, a case of mycosis fungoides with extensive skin involvement, in which the clinical course parallels serum levels of the tumor marker tissue polypeptide antigen (TPA).

CASE REPORT

A 55-year-old Taiwanese female complained of generalized scaling of the skin on her trunk and four limbs, with erythema of her buttocks and thighs. This presentation was associated with pruritus and a sensation of warmth in the affected skin. She denied any fevers, chills, loss of appetite, loss of weight, or any other symptoms. Her skin complaint started 10 years ago, but only involved her thighs initially. Over the next few years, however, extension of the skin lesions with progressive involvement of her trunk and four limbs was noted.

Physical examination revealed generalized scaling of her trunk and four limbs, with patches of erythema particularly involving her buttocks and thighs (Fig. 1, 2). The only areas spared were her face, hands, and feet. The extent of skin involvement was estimated to be >90% total body surface area. Abdominal examination showed no evidence of hepatosplenomegaly, and there were no palpable breast lumps. Lymph node examination revealed multiple enlarged non-tender inguinal lymph nodes bilaterally.

Skin biopsy specimens taken from her back and right thigh were both diagnostic of mycosis fungoides (Fig. 3). They showed small to medium sized atypical lymphocytes infiltrat-
ing the upper dermis, displaying a predominantly perivascular and lentiginous pattern (linear accumulation associated with the basement membrane zone). There is prominent epidermotropism to the lower and medium layers of the epidermis, with formation of Pautrier microabscesses (Fig. 4). The lymphocytes showed nuclear hyperchromasia and indented nuclei, and were CD3+, CD5+, and CD20-, with occasional CD30+ cells.

A complete blood count and differential counts were normal. However, a peripheral blood smear was performed which showed an increased number of atypical lymphocytes. Subsequent bone marrow aspiration and biopsy were negative for atypical cells. A series of tumor markers were evaluated, including squamous cell carcinoma antigen (SCC), carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), CA 19-9, CA-125, and TPA. All tumor marker levels were within normal limits except serum TPA, which was found to be markedly elevated (211 U/L, normal <70 U/L).

A plain radiography of the chest was normal. Computed tomography scans of the chest and abdomen showed enlarged bilateral inguinal lymph nodes (about twelve in number). Positron emission tomography and gallium scans confirmed the presence of bilateral inguinal lymphadenopathy with low grade radionuclide uptake, with no evidence of visceral involvement. Inguinal lymph node biopsy showed reactive hyperplasia with no atypical lymphocytes identified.

Clinically, this patient presented with generalized erythematous scaly patches with bilateral inguinal lymphadenopathy (negative for atypical lymphocytes), and with no evidence of visceral involvement. Using the TMN classification, the patient is T2 (generalized plaques, papules, or erythematous patches covering >10% of skin surface), N1 (clinically abnormal peripheral lymph nodes, pathology negative for mycosis cells), and M0 (no visceral organ involvement). She is therefore classified as Stage IIA (T2N1M0) according to the International Union Against Cancer (UICC) staging system.2

Due to the presence of atypical lymphocytes in the blood and lymphadenopathy, she was transferred to the Hematology and Oncology ward for further management. Systemic chemotherapy was discussed and the EPOCH regimen (etoposide, prednisone, oncovin [vincristine], cyclophosphamide, and epirubicin) was subsequently administered. Following two courses of chemotherapy, her skin erythema and scaling improved (Fig. 5), and her serum TPA level dropped to within normal limits (<50 U/L).
DISCUSSION

Mycosis fungoides is the most common form of cutaneous T-cell lymphoma and is characterized as an epidermotropic neoplasm composed of CD4+ (helper) cells. It is an uncommon disease with an annual incidence of 4.5 cases/million in the United States. Although a number of factors (eg, infectious agents, oncogenes, cytokines, occupational or environmental exposures) have been hypothesized as causative agents, none has been definitively confirmed.

Mycosis fungoides primarily involves the skin at early stages of the disease, but progression of disease may occur with eventual dissemination to the lymph nodes, spleen, and internal organs. Sézary syndrome is an erythrodermic variant associated with a leukemic form of the disease. Mycosis fungoides has a wide variety of clinical presentations, and may resemble many benign dermatoses, including chronic eczematous or atopic dermatitis, psoriasis, nummular dermatitis, or tinea corporis. It has therefore been called “the great imitator”, a term that has previously been applied to syphilis. Early lesions are often confused with other dermatoses, and it is not unusual for the diagnosis to remain elusive for years. The patient described in this report had visited various dermatology clinics for years but was not given the diagnosis of mycosis fungoides until skin biopsy was performed in our hospital this year.

Tumor markers have been useful in patient management in certain tumors. Some tumors produce or elicit the production of markers that can be measured in the serum. In a given patient, rising and falling levels of the marker are usually associated with increasing or decreasing tumor burden, respectively. Examples include human chorionic gonadotropin (gonadal germ cell tumor), alphafetoprotein (hepatocellular carcinoma, gonadal germ cell tumor), prostate-specific antigen and prostatic acid phosphatase (prostate cancer), lactate dehydrogenase (lymphoma and other tumors), CA-125 (ovarian cancer), CA 19-9 (colon, pancreatic and breast cancer), and carcinoembryonic antigen (adenocarcinomas of the colon, pancreas, lung, breast, and ovary).

Tissue polypeptide antigen is a protein antigen identified immunologically by Bjorklund and Bjorklund (1957) in tumors using horse sera raised against the insoluble residues remaining after successive extractions of pooled human tumors. Using immunofluorescence microscopy, Weber et al. found a subset of epithelial cells to stain positively with TPA antibodies, including uterine epithelium, bile duct cells in liver, and tumor cells in breast carcinoma. Cells of the stratified squamous epithelia of skin, hair follicle and tongue as well as cells of non-epithelial origin (fibroblasts,
skeletal and smooth muscle cells, neurones) were negative. In addition, TPA antigenicity was not demonstrated in lymph nodes or the bone marrow. Subsequently, TPA was found to be a molecular complex containing cytokeratins 8, 18 and 19, which were typical of various simple and non-squamous epithelia and in carcinomas derived from these epithelia. Cytokeratins 8, 18 and 19 were not present in the normal epidermis or other types of squamous epithelium.

Elevated levels of circulating TPA were present in the sera of patients with certain tumors, which are often used to monitor tumor progression and therapeutic response, and provide early prognostic information. The release of TPA from tumor cells into patient sera may be a result of apoptosis and destruction of tumor cells. Serum TPA was not elevated in patients with benign processes such as eczematous skin conditions.

It might be expected that since cytokeratins 8, 18 and 19 are not present in the normal epidermis or other types of stratified squamous epithelium, TPA may not be used as a tumor marker in malignancies derived from stratified epithelial cells. However, recent studies have shown that certain squamous cell carcinomas are associated with elevated serum TPA, including squamous cell carcinomas of the uterine cervix, larynx, and esophagus. In addition, the human epidermoid squamous cell carcinoma A-431 cell line showed positive staining for TPA. These studies suggest that normal squamous epithelial cells may develop the ability to secrete TPA when they become malignant.

TPA level was usually not elevated in the sera of patients with hematologic malignancies. However, a study by Sadamori et al. found serum TPA to be elevated in certain patients with acute nonlymphocytic leukemia, and serum TPA level was closely correlated to therapeutic response and length of survival in these patients. Since normal hematopoietic cells have negative TPA antigenicity, these findings suggest that hematopoietic cells may acquire the ability to secrete TPA when they undergo malignant change. On the other hand, another study by Sadamori found no correlation between serum TPA and clinical and histological data in adult T-cell leukemia (ATL) patients. Therefore, only a subgroup of patients with hematologic malignancies may exhibit elevated serum levels of TPA. To date, there has been no report describing the association of serum TPA with mycosis fungoides.

In this report, a patient with mycosis fungoides was found to exhibit elevated serum levels of TPA. All other tumor markers tested were not elevated. The presence of another primary tumor was excluded by history taking, physical examination, and a series of investigations including blood tests, chest/abdominal computed tomography scan, gallium scan, and positron emission tomography scan. Following two courses of chemotherapy, clinical improvement in her skin erythema and scaling was seen, in parallel with normalization of serum TPA level.

There are several possible explanations for the source of increased TPA in this patient. The mycosis fungoides cells may produce TPA, or they may elicit TPA production by interaction with other cells. Hypothetically, epidermotropism of atypical lymphocytes may stimulate transformation of epidermal keratinocytes, which might then develop the ability to secrete TPA. Although it is possible that this patient may have another TPA-producing tumor, extensive clinical investigations speak against this possibility.

In conclusion, we present a case of mycosis fungoides with extensive skin involvement, atypical lymphocytes in the blood, and inguinal lymphadenopathy, which is associated with elevated serum levels of TPA. This case is extraordinary, since that elevated serum TPA level returned to normal after treatment with chemotherapy, which parallels the improvement in skin condition. There is therefore a definite correlation between TPA level and the clinical course in this particular patient. We hypothesize that serum TPA may be clinically useful in a subset of patients with mycosis fungoides, and further studies are warranted to address this
important question.

REFERENCES


