Early Sequential Development of Infective Dermatitis, Human T Cell Lymphotropic Virus Type 1–Associated Myelopathy, and Adult T Cell Leukemia/Lymphoma

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We describe a patient with human T cell lymphotropic virus type 1 (HTLV-1)–associated infective dermatitis who developed HTLV-1–associated myelopathy/tropical spastic paraparesis and adult T cell leukemia/lymphoma at 16 years of age. Long inverse polymerase chain reaction was used to demonstrate monoclonal integration of proviral DNA in the lymphomatous skin lesion.

Human T cell lymphotropic virus type 1 (HTLV-1) may cause, among other diseases, HTLV-1–associated myelopathy/tropical spastic paraparesis (HAM/TSP) [1], adult T cell leukemia/lymphoma (ATL) [2], and HTLV-1–associated infective dermatitis (IDH) [3]. HAM/TSP is a severe and incapacitating myelopathy that is more common among female patients. Its onset is insidious, and the neurological symptoms usually appear in the fourth or fift decade of life [4]. ATL is a severe and generally fatal form of leukemia/lymphoma that typically occurs in adults aged >40 years [2]. IDH is a chronic, infectious, relapsing dermatitis with exudative, infected, and crusted lesions that affects children aged >1 year; it always affects the scalp [3, 5].

The pathogenesis of HTLV-1 has been extensively studied. However, the mechanisms of related diseases remain unsolved [6, 7]. After HTLV-1 infection, viral proteins promote the proliferation of infected cells, causing chronic activation of cytotoxic T lymphocytes that leads to inflammato y diseases, such as IDH and HAM/TSP [6]. Repeated clonal expansions of infected cells subsequently increase the chances of additional events required for transformation, resulting in the onset of ATL in some carriers [6]. In this article, we report the early, simultaneous development of ATL and HAM/TSP in a patient who has experienced IDH since she was 3 years of age.

Case report. A 12-year-old girl of African descent was seen in November 2000. The patient had a history of eczema, beginning when she was 3 years of age, and a history of punctiform papules and erythematous, crusted, exudative, infected, and pruriginous lesions all over her body, including the scalp. She had been receiving corticosteroids since she was 10 years of age. At hospital admission, she presented with disseminated, erythematous, crusted, exudative, infected, and pruriginous lesions and punctiform papules all over her body, including the scalp and moon facies. Both the patient and her mother were HTLV-1 positive and HIV negative. The girl had been breastfed for 1 year and had no history of ever having received a blood transfusion.

Routine laboratory examinations yielded normal findings except for mild anemia and a skin culture positive for *Staphylococcus aureus.* The patient had no crusting of the nostrils at admission. However, considering her other clinical symptoms, which are typical of IDH, a diagnosis of this condition was made. Biopsy of the scalp revealed an infiltratio of $CD3^+$, CD45RO $(UCHL-1)^+$, $CD4^-$, $CD8^+$, $CD20^-$, $CD79A^-$, perforin-negative, and granzyme B–negative lymphocytes. She was treated with trimethoprim-sulfamethoxazole, without interruption of corticosteroid therapy.

The patient responded well to treatment, but several relapses occurred after the withdrawal of drugs. In February 2005, in addition to the eczematous lesions, the patient experienced crusting in her nostrils (figu e 1) and small papules on her back. One of these papules was excised for histological examination and molecular analysis. Examination of a biopsy specimen revealed hyperkeratosis, acanthosis, focal epidermotropism, and a dense nodular infiltratio in the upper dermis of small-to-medium–sized lymphocytes, with a few larger cells (figu e 2). In the middermis, the same infiltratio was seen around vessels. The neoplastic cells were $CD3^+$, CD45RO $(UCHL-1)^+$, $CD4^+$, $CD5^+$, $CD7^-$, $CD8^-$, $CD20^-$, $CD25^+$, and $CD30^-$. The proliferative index, as evaluated using Ki-67, was ~20%. A morphological diagnosis of peripheral T cell lymphoma, unspecified was made. Blood cell counts and serum

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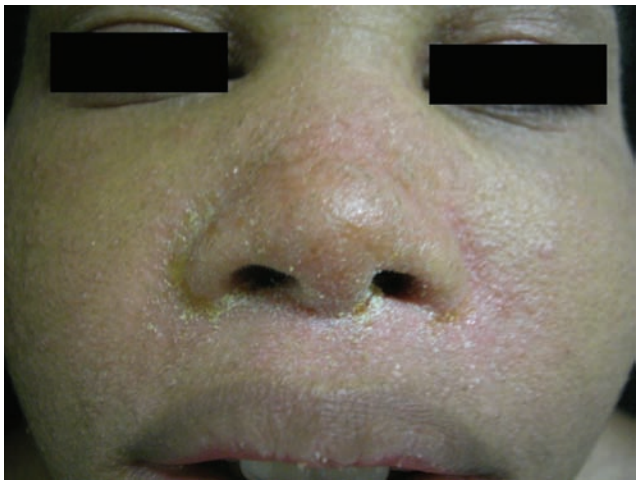

Figure 1. A nasal and perinasal erythematous scaly lesion with crusting of the anterior nares, a classic feature of infective dermatitis associated with human T cell lymphotropic virus type 1 infection.

levels of calcium and lactate dehydrogenase were within normal limits. Physical examination, chest radiography, and abdominal ultrasonography revealed no other sites affected by lymphoma. Monoclonal integration of HTLV-1 was detected in the skin tumor cells by long, inverse PCR (figu e 3) [8], and the presence of HTLV-1 proviral and genomic host DNA sequences was confi med by sequencing. This result confi med the diagnosis of ATL.

After the diagnosis, treatment was initiated with psoralen plus UV light therapy, which completely cleared the lesions. At this time (February 2005), the patient also complained of lumbago, pain in lower limbs, difficult in walking and running, urinary disturbances, and constipation. Neurological examination revealed impaired vibratory sensation in both lower limbs, abnormal gait (spastic paretic gait), and spasticity with pyramidal signs (hyperreflexia ankle clonus, and Babinski sign; Osame motor disability scale, grade 3) [1]. ELISA and Western blot assay revealed HTLV-1 antibodies in the CSF. Investigation of CSF specimens for antibodies to toxoplasmosis, cysticercosis, syphilis, and schistosomiasis yielded negative results. On the basis of these results, the symptomatology, and the finding of the neurological examination, a diagnosis of HAM/TSP was made. In addition to corticosteroid therapy, the patient began receiving baclofen and vitamin C. At the most recent follow-up visit in April 2007, she showed some improvement in urinary incontinence and in the pain in her lower limbs, and the skin lesions had disappeared. Physical examination, chest radiography, and abdominal ultrasonography revealed no lymphomatous infiltration No lymphocytosis, hypercalcemia, or increased lactate dehydrogenase levels were observed, and only 1% atypical lymphocytes were found in the peripheral blood.

Discussion. The diagnoses of HAM/TSP and IDH in the patient we describe were made in accordance with well-established criteria [1, 3, 5]. The presence of HTLV-1 antibodies in CSF specimens confi med the diagnosis of HAM/TSP [1]. Crusting of the nostrils has been considered to be an early characteristic feature of IDH [3]; however, in our patient, this occurred late in her clinical course, as has also been observed elsewhere [5].

The diagnosis of ATL was based on pathological and immunohistochemical features and the presence of monoclonal, integrated HTLV-1 provirus in the DNA of the skin tumor cells [9]. Because lymphocytosis and extracutaneous involvement were not found, the case was classifie as "smoldering ATL," in accordance with the classificatio of Shimoyama [2]. The fact that no relapse of lymphoma occurred may have resulted from treatment with psoralen plus UV light, the efficac of which for clearance of early-stage cutaneous T cell lymphoma has been well established [10]. Moreover, smoldering ATL may result in prolonged survival [11]. An interesting aspect of our case was the change in the phenotypic features between the firs and the second biopsy. Initially, the patient had a $CD4^-$, $CD8^+$ immunophenotype, as has been previously observed in patients with IDH [12]. However, the classic ATL phenotype of $CD4^+$, $CD8^-$, $CD5^+$, $CD7^-$, and $CD25^+$ was found in specimens of the lymphoma lesion [13].

There have been at least 10 well-documented reports of HAM/TSP occurring during childhood and adolescence, and 6 of these cases were associated with IDH [4]. Very few cases of ATL have been observed in children and adolescents [11, 14]. The association of HAM/TSP with ATL is considered rare in adults [15] and has not been reported in adolescents. On the

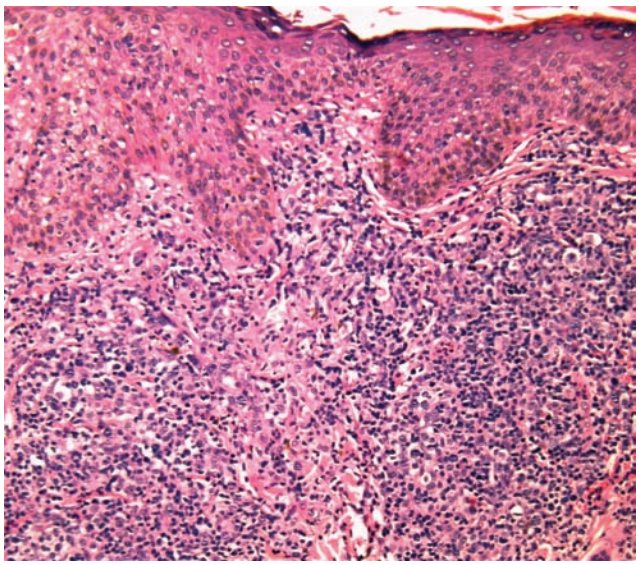

Figure 2. Epidermis with acanthosis. A dense infiltration of small- and medium-sized atypical lymphocytes is present on the upper dermis (hematoxylin and eosin stain; original magnification, ×200).

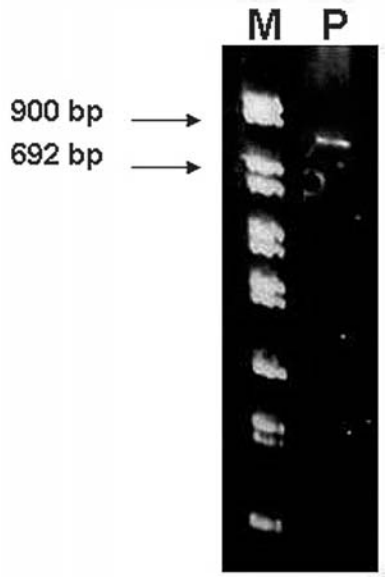

Figure 3. Polyacrylamide gel of long, inverted PCR products. *Lane M,* DNA molecular weight marker VIII (Roche); *lane P,* patient with adult T cell leukemia/lymphoma.

other hand, there have been rare reports of progression of IDH to ATL [3, 16].

Because of the aggressive and relapsing course of IDH in this patient, prolonged corticosteroid treatment was required, and this may have facilitated the development of ATL through immunosuppressive mechanisms, as was recently demonstrated for tacrolimus and prednisolone [17, 18]. To the best of our knowledge, this is the firs report of an early, sequential manifestation of IDH, HAM/TSP, and ATL. The development of HAM/TSP from IDH, as observed in this case, emphasizes the urgent need for new therapeutic options for IDH.

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