
CASE REPORT

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ADULT T-CELL LEUKEMIA/LYMPHOMA WITH MULTIPLE INTEGRATION OF HTLV-1 PROVIRUS PRESENTING AS AN ISOLATED PARANASAL SINUS TUMOR: A CASE REPORT

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Abstract: *Background.* Adult T-cell leukemia/lymphoma (ATLL) is a highly aggressive T-cell lymphoma and etiologically associated with human T-lymphotropic virus type 1 (HTLV-1). Patients with ATLL commonly present with leukemic changes, systemic lymphadenopathy, and/or extranodal lesion and have very poor prognosis.

Methods and Results. We describe a rare case of ATLL presenting as an isolated paranasal mass. Southern blot analysis of the biopsied specimens demonstrated multiple integration bands of HTLV-1 provirus of different intensities. Chemotherapy resulted in complete resolution of the paranasal mass. Thereafter, the patient showed an indolent clinical course with leukemic changes and pulmonary and cutaneous ATLL lesions and remains alive more than 5 years from diagnosis.

Conclusion. ATLL should be included in the differential diagnosis of sinonasal lymphoma, although the event is rare. Multiple HTLV-1 provirus integrations of different intensities may be indicative of good prognosis for ATLL. © 2007 Wiley Periodicals, Inc. *Head Neck* 30: 815–820, 2008

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Patients with non-Hodgkin's lymphoma (NHL) often present with lymphadenopathy in the head and neck region, whereas extranodal presentation is less common.^{1–3} Among the extranodal head and neck lymphomas, Waldeyer's ring is the most common site of involvement.^{1,2} Other sites, including the sinonasal tract, are less frequently affected. With regard to sinonasal lymphomas, the common histological type is diffuse large B-cell lymphoma (DLBCL) and nasal type natural killer (NK)/T-cell lymphoma.^{4–6} Adult T-cell leukemia/lymphoma (ATLL) is a high-grade T-cell type NHL and etiologically associated with human T-cell lymphotropic virus type 1 (HTLV-1).^{7–10} The majority of ATLL patients present with leukemic changes, systemic lymphadenopa-

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thy, and/or extranodal lesions.^{8–10} The most frequent sites of extranodal involvement are the skin, liver, spleen, bone, and bone marrow,^{8–10} whereas extranodal involvement in the neck and head sites is rare. The diagnosis of ATLL can be established by demonstration of monoclonal integration of HTLV-1 proviral DNA into the host genome by Southern blot analysis.¹⁰ In addition to ordinary single integration, multiple integration of HTLV-1 provirus has been reported in subsets of ATLL patients.¹¹ The clinical significance of multiple integration is not fully elucidated. Here, we report a rare case of primary paranasal ATLL with multiple integration of the HTLV-1 provirus.

CASE REPORT

A 37-year-old Japanese man, who was born in Okinawa, presented with persistent headache at a local hospital in August 2001. He reported a 3-year history of chronic sinusitis and had intermittently received symptomatic treatments. CT scans of the sinuses revealed the presence of a mass lesion in the left ethmoid sinus. He was referred to our hospital for further examination and treatment. Physical examination showed no lymphadenopathy, hepatosplenomegaly, or skin eruptions. A complete blood count showed a leukocyte count of 6600/ μ L with 73% neutrophils, 17% lymphocytes, 6% monocytes, and 4% eosinophil; a hemoglobin concentration of 14.3 g/dL; and a platelet count of 242,000/ μ L. Serum antibody test for HTLV-1 was positive. Results of other laboratory tests were within normal limits. MRI of the sinuses revealed a soft tissue mass in the left ethmoid sinus extending to the left orbit and maxillary sinus (Figure 1). Other work-up including chest X-ray; CT scans of the chest, abdomen, and pelvis; bone marrow examination; lumbar puncture; and upper gastrointestinal endoscopy revealed no evidence of lesions or tumor infiltration. Biopsy of the mass from the paranasal sinus was performed in October 2001. Pathological examination of the biopsied specimens showed a diffuse proliferation of pleomorphic lymphoid cells (Figure 2A). Immunohistochemically, tumor cells were positive for T-cell marker (CD45RO) but negative for B-cell marker (CD20) (Figures 2B and 2C). Monoclonal integration of proviral DNA of HTLV-1 into the host genome was detected by Southern blot analysis (Figure 3A). Two distinct bands over 9 kb were observed in *Eco*RI digestion, indicating biclonal integration of HTLV-1 proviral DNA. Southern blot analysis of the T-cell receptor



FIGURE 1. Non-contrast-enhanced (A) and contrast-enhanced (B) T1-weighted MR image of the sinuses showed a soft tissue mass in the left ethmoid sinus. The mass extended to the left orbit and maxillary sinus. Bone destruction, including ethmoid, palate, and orbital wall, was also seen.

gene was also performed (Figure 3B). Rearranged bands were detected in *Bam*HI and *Hind*III digests, indicating the population was monoclonal. A diagnosis of adult T-cell leukemia/lymphoma (ATLL) originating from the left ethmoid sinus was established. Subsequently, the patient was treated with CHOP chemotherapy (cyclophosphamide [750 mg/m²/day, day 1], doxorubicin

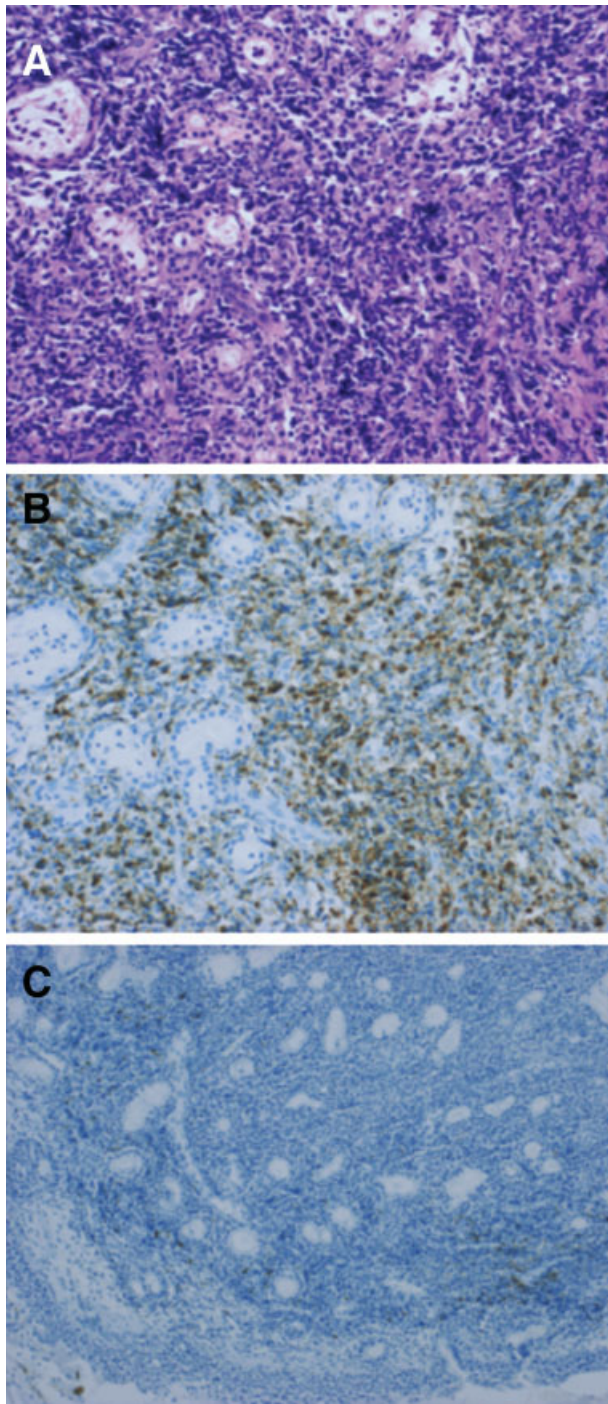


FIGURE 2. Biopsy specimen of the left ethmoid mass stained with hematoxylin-eosin stain. Note diffuse proliferation of pleomorphic lymphoid cells (**A**, original magnification $\times 400$). Immunohistochemically, the tumor cells were positive for CD45RO (**B**, original magnification $\times 400$) and negative for CD20 (**C**, original magnification $\times 400$). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

[50 mg/m²/day, day 1], vincristine [2 mg/day, day 1], and prednisone [100 mg/day, day 1–5]. For central nervous system prophylaxis, methotrex-

ate (15 mg), cytarabine (40 mg), and prednisone (10 mg) were injected together intrathecally during every other course of chemotherapy. After 4 courses of CHOP, however, the patient developed anginal attack possibly induced by doxorubicin. The chemotherapy regimen was modified to COP-E (cyclophosphamide [750 mg/m²/day, day 1], vincristine [2 mg, day 1], prednisone [100 mg/day, day 1–5], and etoposide [100 mg/m²/day, day 1–4]). Additional 4 courses of COP-E were given without recurrence of the angina. This resulted in complete resolution of the ethmoid tumor. However, circulating ATLL cells in the peripheral blood were still detected on completion of the fourth COP-E. In March 2002, the leukocyte count was 3800/ μ L with 9% ATLL cells. Thereafter, the leukocyte count gradually increased over time. In October 2005, the leukocyte count was 23,200/ μ L with 35% ATLL cells. He subsequently developed pulmonary and cutaneous ATLL lesions. Four months later, a regimen of low-dose etoposide (50 mg/day) was started for 4 weeks, which resulted in a decrease in tumor burden. The patient is currently alive more than 5 years after the diagnosis, though with pulmonary and cutaneous lesions as well as circulating ATLL cells.

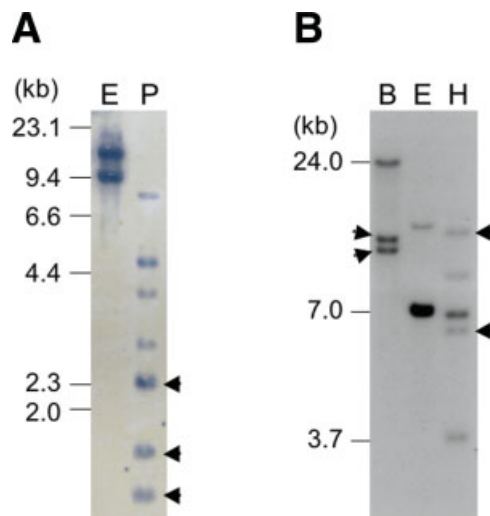


FIGURE 3. (A) Southern blot analysis of human T-lymphotropic virus type 1 (HTLV-1). Integration of HTLV-1 proviral DNA into the host genome was examined by digestion with *EcoRI* (E) or *PstI* (P), and a full length HTLV-1 probe. Arrowheads indicate internal fragments of HTLV-1 provirus. (B) Southern blot analysis using a T-cell receptor C β 1 specific probe after DNA digestion with *BamHI* (B), *EcoRV* (E), and *HindIII* (H). Two rearranged bands were detected in *BamHI* and *HindIII* digests. Arrowheads indicate rearranged bands.

Table 1. Literature survey of reported cases of adult T-cell leukemia/lymphoma with primary or predominant involvement of sinonasal tract.

Case	Age/sex	Involved sites at presentation	Initial treatment	Survival, mo	Ref.
1	39/M	Ethmoid and sphenoid sinuses	Not mentioned	42	4
2	60/F	Ethmoid and sphenoid sinuses, peripheral blood, splenomegaly, cervical, and abdominal lymphadenopathy	Chemotherapy	7	20
3	70/M	Ethmoid, sphenoid and maxillary sinuses, peripheral blood	Chemotherapy	+21	21
4	69/F	Nasal cavity, peripheral blood	Chemoradiotherapy	+20	21
5	50/M	Nasal cavity, left paranasal sinus, orbit, intracranial frontal base	Steroid and radiation	16	22
6	57/F	Nasal cavity, maxillary and ethmoid sinuses, vocal cord, skin, peripheral blood	Tracheotomy and radiation	5	23
Present case	38/M	Ethmoid sinus	Chemotherapy	+60	

DISCUSSION

NHL comprises a heterogeneous group of malignancies that can arise in different nodal and extranodal sites in the head and neck. Approximately 10% of patients with NHL present with extranodal disease in the head and neck.^{1,2} Among extranodal head and neck sites, Waldyer's ring is the most common site of lymphomatous involvement. This is followed by the sinonasal tract (nasal cavity and paranasal sinus), orbit, thyroid gland, salivary gland, oral cavity, and larynx.¹⁻³ Sinonasal lymphomas are an uncommon group of neoplasms that account for 0.2% to 2.0% of all lymphomas in Western countries.^{6,12,13} On the other hand, their incidence has been reported to be higher in Asian and South American countries: sinonasal lymphomas account for 2.6% to 10% of all NHL.^{2,14,15} The common histopathological types are DLBCL and nasal type NK/T-cell lymphoma.¹ Other histopathological types, such as marginal zone B-cell lymphoma, Burkitt or Burkitt-like lymphoma, and peripheral T-cell lymphoma of unspecified type, have been reported but are much less common.⁴ Sinus involvement without nasal disease is common in B-cell lymphoma, whereas the nasal cavity is more frequently involved than paranasal sinuses in T-cell and NK/T-cell lymphomas.^{4,5,14,16-18} Lymphomas of the paranasal sinuses most often involve the maxillary and ethmoid sinuses.^{2,4,17,19,20} Manifestations of sinonasal lymphoma include nasal obstruction, epistaxis, hyposmia, nasal swelling, or mass.^{2,3,6,19} Higher-grade lymphomas such as DLBCL, NK/T-cell lymphoma, and Burkitt lymphoma may display lytic bone destruction, as frequently seen in the head and neck cancers such as

squamous cell carcinoma. Paranasal sinus lymphomas often extend into the orbit.^{1,4}

HTLV-1 is endemic among healthy adults in southwestern Japan (Okinawa and Kyushu), the Caribbean, West Africa, Colombia, Brazil, Peru, Papua New Guinea, and Australia.^{9,10} Several clinical subtypes of ATLL are recognized: smoldering, chronic, acute, and lymphoma.⁷⁻¹⁰ Overall, ATLL is characterized by leukemic change, generalized lymphadenopathy, and/or extranodal lesions. Extranodal presentations are not uncommon and the most frequent sites are the skin, liver, spleen, and bone.⁸⁻¹⁰ Involvement of other extranodal sites is less frequent at presentation. To our knowledge, 6 cases of ATLL presenting with an isolated or predominant lesion in the sinonasal tract, have been documented in the literature (Table 1).^{4,21-24} Therefore, ATLL should be included in the differential diagnosis of sinonasal lymphomas, although the event is rare.

The diagnosis of ATLL is based on the presence of anti-HTLV-1 antibody, a histopathologically or hematologically proven T-cell lymphoid neoplasm, and monoclonal integration of the HTLV-1 provirus into the host chromosomal DNA.¹⁰ Tumor cells commonly show a single integration of the HTLV-1 provirus. Moreover, unusual integration patterns of HTLV-1 proviral DNA have been described.¹¹ These include the multiple integrations of provirus and the integration of defective provirus. In the ordinary integration of 1 complete provirus, Southern blot analysis shows 1 distinct band of over 9 kb in *EcoRI* digestion. By *PstI* digestion, which cleaves at several sites within the proviral DNA, 1 or 2 viral cellular DNA junction bands are clearly detected in addition to the 3

internal fragments of the provirus (bands of 2.4 kb, 1.6 kb, and 1.3 kb). The median survival of ATLL patients with single provirus integration is 8 months.¹¹ Multiple integrations of the provirus have been reported to occur in up to 20% of ATLL patients studied.^{25,26} Two distinct band patterns of multiple integrations have been identified in these patients. These could be demonstrated as multiple bands of the same intensity or different intensities by Southern blot analysis. The clinical significance of multiple integrations of HTLV-1 provirus is not fully elucidated. Shimamoto et al¹¹ studied differences in clinical features between patients with multiple bands of the same and different intensities. The former group (6 cases) exhibited 1 tumor cell clone carrying multiple copies of the provirus, while the latter group (6 cases) exhibited multiple tumor cell clones, each of which carried 1 distinct copy of the provirus. Patients of the former group manifested a highly aggressive clinical course with frequent organ infiltrations, including the lung, pleura, stomach, central nervous system, skin, retina, uvea, and muscle. Their median survival time was only 5.3 months. On the other hand, patients of the latter group had an indolent clinical course and no involvement of extranodal sites except for the skin. Almost all patients survived more than 25 months after the diagnosis.¹¹ Kato et al²⁷ reported a Japanese woman with lymphoma-type ATLL who had a bulky cutaneous tumor on the left thigh. Southern blot analysis showed multiple integration of the provirus. Four bands of slightly differing intensities in *EcoRI* digestion and 8 flanking bands in *PstI* digestion were seen. Taking the results of Southern blot analysis for T-cell receptor gene into account, the patient was considered to have 4 separate tumor cell clones, each of which carried 1 copy of the provirus. The patient received chemotherapy and radiotherapy and was alive 18 months after diagnosis.

In the present case, Southern blot analysis of the biopsied specimens, as demonstrated in Figure 3A, showed 2 distinct bands in *EcoRI* digestion and 4 flanking bands along with 3 internal bands in *PstI* digest. Thus, our patient was considered to have 2 copies of HTLV-1 provirus. Each of the bands detected in *EcoRI* digestion appeared to be of different intensities, suggesting each of the tumor clones carried 1 distinct copy of the provirus. Our patient showed slowly advancing clinical course and unexpectedly survived more than 5 years after diagnosis. Taken together, it is likely that the pattern of multiple

bands with different intensities is associated with slow disease progression and prolonged survival. This integration pattern of the HTLV-1 provirus may be indicative of good prognosis for ATLL. Further studies are required to verify this theory.

In summary, we describe a rare case of primary paranasal ATLL with prolonged survival. ATLL should be included in the differential diagnosis of sinonasal lymphoma; patients may present with an isolated paranasal tumor. Multiple HTLV-1 provirus integrations of different intensities may be indicative of good prognosis for ATLL.

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