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Giant Septic Lymphadenitis with Marked Gas Formation Caused by *Bacteroides fragilis* in a Patient with Adult T-cell Leukemia/lymphoma

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Abstract

Adult T-cell leukemia/lymphoma (ATL) sometimes causes opportunistic infections. A 53-year-old woman with systemic lymphadenopathies was diagnosed with ATL by inguinal lymph node biopsies and underwent oral chemotherapy. Two months later, high grade fever, lower abdominal pain and lymphadenopathy recurred. Computed tomography revealed the presence of lymphadenopathy with marked gas formation in the pelvic lesion. Blood cultures were suggestive of septic lymphadenitis by *Bacteroides fragilis* (*BF*). This represents the first demonstration of giant lymphadenitis with gas formation caused by *BF* in a patient with ATL. Notably, septic lymphadenitis is pivotal in the differential diagnosis of systemic lymphadenopathy in ATL.

Key words: adult T-cell leukemia/lymphoma, lymphadenitis, *Bacteroides fragilis*, gas formation

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Introduction

Adult T-cell leukemia/lymphoma (ATL) provokes a variety of opportunistic infections, especially *Strongyloides stercoralis*, *Pneumocystis jirovecii*, cytomegalovirus, *Toxoplasma gondii*, *Mycobacterium tuberculosis*, *Mycobacterium avium* complex and fungal infections (1). In patients with ATL, the dysfunction of infected T-cells sometimes causes a series of opportunistic infections.

Bacteroides fragilis (*BF*) is an anaerobe, which usually colonizes the colon and female genital tracts. The major types of anaerobic infection are localized in the tissues of the intra-abdominal area, the pelvis, the skin, soft tissue, the pleuropulmonary region, and the female genital tract (2). Anaerobic infections are often associated with tissue necrosis and abscess formation. However, anaerobic bacterial

lymphadenitis is rare. Therefore, to precisely diagnose pelvic lymphadenopathy, we need to explore the possibility of bacterial lymphadenitis, malignancies, autoimmune lymphadenopathy and a variety of inflammatory diseases. After the diagnosis of malignant lymphoma, we sometimes fail to exclude the possibility of bacterial lymphadenitis, in the seeming absence of neutropenia. We herein report an extremely rare case of pelvic lymphadenitis with gas formation caused by *BF* in a 53-year-old Japanese woman with ATL.

Case Report

A 53-year-old Japanese woman represented systemic lymphadenopathy. Anti-human T-cell lymphotropic virus type 1 (HTLV-1) antibody was detected. A pathological investigation via a left inguinal lymph node open biopsy revealed the presence of pleomorphic lymphoma cells which were CD4

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Figure 1. Abdominal CT on day 13 of the first cycle of CHOP showed a lymph node with air bubble-like structures and two cystic lymph nodes. The maximum size of the lymph nodes was around 6×5 cm.

positive and CD8 negative. The prevalence of the ATL cells was over 5% in the peripheral blood. Based on the laboratory findings, the patient was diagnosed with acute-type ATL. Her systemic lymphadenopathy exacerbated and the prevalence of ATL cells in peripheral blood reached around 20% after 5 months. The serum level of lactate dehydrogenase (LDH) was increased from 600 to 2,600 IU/L. After she rejected treatment with intensive combination chemotherapy, because she did not have any symptoms (except for lymphadenopathy), we decided to initiate the administration of oral combined chemotherapy, which included etoposide and prednisolone for 4 months. Three weeks after the initiation of oral combined chemotherapy, the patient's lymphadenopathy was ameliorated and her level of serum LDH decreased from 2,600 to 1,200 IU/L. Her lymphocyte and ATL cells decreased from 40 to 8% and 25 to 3%, respectively. She appeared in the emergency service with high fever and left lower abdominal pain, accompanied by a prominent tender mass in the area of the left lower abdomen. Her white blood cell (WBC) count was within the normal range, while her neutrophil count was elevated (WBC count, $7.7 \times 10^9/L$; neutrophils, 98%) without a left shift. Neither lymphocytes nor ATL cells were detected. The serum levels of LDH and soluble interleukin-2 receptor (IL-2R) were markedly elevated at 2,500 IU/L and 29,000 U/L, respectively. There was no elevation of the patient's C-reactive protein level. As computed tomography (CT) revealed the presence of systemic lymphadenopathy, especially of the pelvic lymph nodes, which were reminiscent of central necrosis without infectious findings. Clinically, she did not present cellulitis and the left inguinal site where lymph node biopsy was performed was stable. Because of the ATL progression, she was received CHOP (cyclophosphamide 750 mg/m² on day 1, doxorubicin 50 mg/m² on day 1, vincristine 1.4 mg/m² on day 1 and prednisolone 60 mg/m² on day 1-5). One week after the chemotherapy, there was a marked improvement of her systemic lymphadenopathy, however, the left lower abdominal pain continued. When her leukocyte count dropped

to $0.5 \times 10^9/L$, she developed a high fever with shivering. Cefepime was administered for febrile neutropenia. *BF* was detected in one of blood culture bottles. The antimicrobial susceptibility test showed resistance to 4th generation cephalosporins, but carbapenem, clindamycin, and quinolone sensitivity. We thus changed the antibiotic therapy to imipenem/cilastatin, clindamycin, and levofloxacin combined with hyperbaric oxygen therapy. CT on day 13 of the first cycle of CHOP detected three enlarged lymph nodes in the pelvic region (Fig. 1). The size of the largest one was 6×5 cm. Air bubble-like structures were observed. Taken together with the pathophysiological findings, she was diagnosed with *BF*-induced pelvic lymphadenitis and resultant sepsis. We attempted to aspirate and drain the lymphadenitis, but did not succeed. The discharge was very limited and no bacteria were detected in the culture. Her fever was reduced, but the inflammation of the three lymph nodes did not improve with antibiotics. She subsequently presented a severe headache and vomiting. ATL cells were detected in her cerebrospinal fluid, but no bacteria were found. Since her persistent headache was attributed to ATL-invasive meningitis, of anticancer drugs (methotrexate 15 mg, cytarabine 20 mg, and prednisolone 20 mg) were administered intrathecally, one month after the first cycle of CHOP. Two days after the IT administration of the anticancer drugs, the three swollen lymph nodes were successfully removed (Fig. 2a). The resected lymph nodes were not adhesive around the tissues and were capsulated without rupture. The cut surfaces of extirpated lymph nodes consisted mainly of solid necrotic tissues and modest lymphoid tissues without a foul smell. The bacterial and fungal cultures of the removed lymph nodes were negative. Pathologic examination of the lymph nodes revealed necrosis and the presence of neutrophil-filled abscesses. ATL cells were not detected (Fig. 2b). She was received a second cycle of CHOP chemotherapy two months after the first cycle CHOP (Fig. 3). The pelvic lymphadenitis was not considered to have recurred during the subsequent chemotherapies, because she did not have persistent febrile abdominal pain.

Discussion

The current patient was a case of ATL represented by septic lymphadenitis with gas formation in the pelvic region due to *BF*. In general, septic lymphadenitis caused by *BF* is diagnosed by CT imaging of the lymph node gas formation and blood culture. In the present case, there were two manifestations to be highlighted. First, the size of lymph nodes in the lymphadenitis was extraordinarily large. Second, the infection was provoked in a patient who was T-cell immunocompromised. It is noteworthy that certain groups of immunocompromised subjects, including patients with diabetes mellitus, the elderly, patients undergoing steroid treatment, patients with HIV-infection, and transplantation recipients sometimes experience infections in unusual anatomical sites (3). An abscess is a unique biologic phenomenon re-

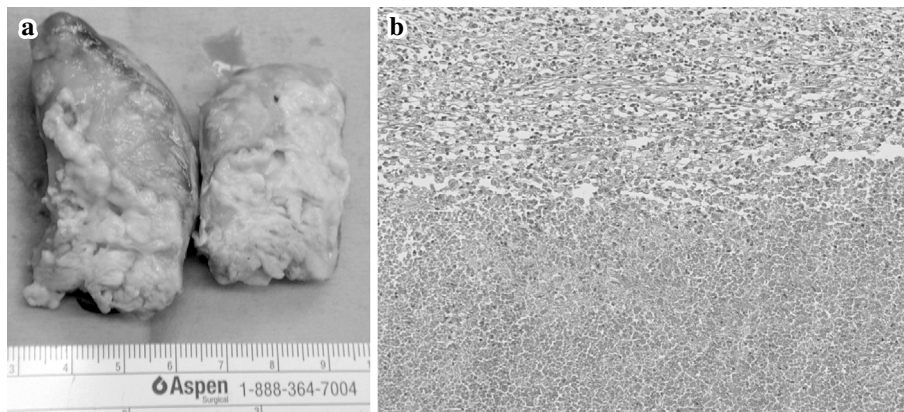


Figure 2. The analysis of the resected lymph nodes: (a) macroscopic findings; yellowish necrotic foci were noted on the cut surface of the nodes, (b) microscopic findings; the lymph nodes were necrotic with neutrophil-filled abscesses. ATL cells were not detected.

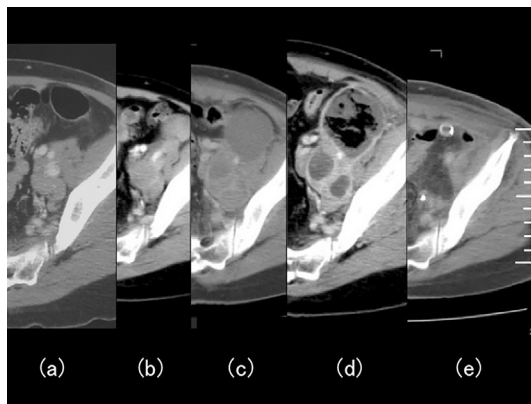


Figure 3. The representative findings on the CT. (a) The initial state, (b) after oral combined chemotherapy, (c) on emergency admission, (d) after CHOP therapy, and (e) after resection of the three affected lymph nodes.

flecting the combination of pathological processes and the host's defensive mechanisms. Within the fibrous capsule of a well-formed abscess, bacteria and neutrophils coexist. The animal models of intra-abdominal sepsis are employed to identify cells responsible for abscess formation. Experiments with $\alpha\beta$ TCR knockout mice have suggested that T-cells play a critical role in abscess formation in response to *BF* (4).

A line of studies suggests that the activation of CD4-positive T-cell and the resultant production of interleukin-17 play a critical role in the formation of abscesses caused by *BF* (5). HTLV-1 infection suppresses the immunity of the host and induces various types of opportunistic infections such as *Strongyloides stercoralis*, *Pneumocystis jirovecii*, cytomegalovirus, *Mycobacterium tuberculosis* (1). Bacterial pathogens of *BF* induce abscess formation by CD4 positive T-cells and neutrophils (6). It should be noted that abscess formation is made not only by neutrophils but also by CD4 positive T-cells. It is likely that in the current case, the abscesses were formed in the lymph nodes for over 2 weeks, because abscess formation requires a long period of time to

inactivate T-cells and neutrophils through HTLV-1 infection and chemotherapy. As the patient's T-cell count was over $0.2 \times 10^9/L$ from day 7 of the first cycle CHOP, the abscess formation on CT was clarified on day 13 of the first cycle CHOP. To our knowledge, the present case is the first demonstration of giant pelvic lymphadenitis with gas formation caused by *BF* in a patient with ATL.

Common types of anaerobic infections occur through endogenous bacterial flora. Anaerobes are involved in infections of the intraperitoneal cavity, thoracic cavity, the female genital organs, the skin/soft tissues, the nervous system (brain, epidural tissue and subdural tissue), the oral cavity and the neck. A comprehensive knowledge of the common sites of anaerobic colonization by anaerobes is critical to determine the pathogens as well as to estimate their routes of invasion. It has been shown that major sites of *BF* colonization include the colon, the oral cavity, the thoracic cavity, the female genital organs, and the urological tract, but not the skin. In accordance with this notion, the major origins of *BF* bacteremia are considered to be the gastrointestinal tract, the female genital tract, the skin/soft tissue, the urological tract, and the respiratory tract (7). Without the occurrence of cellulitis, it is considered unlikely that an inguinal open biopsy caused the pelvic lymphadenitis on the same side as it was performed. Furthermore, the current patient presented no other infectious signs and symptoms.

The predisposing factors for anaerobic bacteremia include malignant neoplasms, hematologic disorders, transplantation of organs, recent gastrointestinal or obstetric surgery, intestinal obstruction, diabetes mellitus, post-splenectomy, the use of cytotoxic agents or corticosteroids, and the presence of an undrained abscess (8). Our patient had multiple risk factors including hematological malignancy, post chemotherapy, and the use of corticosteroids. However she did not have the other major risk factors, especially diabetes mellitus, intestinal obstruction, or HIV infection.

BF is often isolated not only from pus secretions, puncture fluids, and dialysis fluids but also from blood. Anaerobic blood culture-positive patients sometimes have underly-

ing diseases included malignant tumors, gastrointestinal/hepatobiliary diseases, and surgical complications (8). Although we could not identify ATL cells nor *BF* in the resected lymph nodes, it crucial to consider the possibility of opportunistic infections by *BF* in the differential diagnosis of lymphadenopathy in patients with ATL.

The authors state that they have no Conflict of Interest (COI).

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