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Case Report

The First Case of Concomitant *Mycobacterium Genavense* Lymphadenitis and EBV-Positive Lymphoproliferative Disorder

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Abstract. This is the first case of concurrent *Mycobacterium genavense* lymphadenitis and Epstein-Barr virus (EBV)-positive lymphoproliferative disorder (LPD) in the same lymph node with no immunocompromised history. *M. genavense* infection is a rare opportunistic infection mainly for human immunodeficiency virus (HIV)-infected patients. Although no immunodeficiency was detected in our patient, our case indicates that the immunodeficiency in the background of EBV latency type III and the immunosuppression by malignant lymphoma itself might induce the *M. genavense* lymphadenitis. This case highly alerts clinicians to the immunosuppressive state of EBV-positive LPD with latency type III even if any immunodeficient serological factors are not detected.

Keywords: *Mycobacterium genavense*; Epstein-Barr virus-positive lymphoproliferative disorder (EBV-LPD); Programmed cell death 1 ligand 1 (PD-L1).

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Introduction. *Mycobacterium genavense* is a non-tuberculous mycobacterium (NTM), first isolated from 18 HIV-infected patients with CD4-positive T cell counts below 100 /μL in 1992.[1] The infection against non-HIV patients is extraordinarily unusual, and only 46 cases have been reported.[2] Most cases are immunocompromised hosts, and the common underlying complications are solid organ transplantation, sarcoidosis, and hematopoietic stem cell transplantation. As for the relation with malignant lymphoma, three cases have been reported, and all developed the infection under the immunocompromised conditions due to chemotherapy or immunosuppressive agents. Herein, we report the first non-HIV case of concurrent *M. genavense* lymphadenitis and Epstein-Barr virus (EBV)-positive lymphoproliferative disorder (LPD) with no apparent immunocompromised history.

Case Report. The patient was a 53-year-old male with no significant past medical history. Since December 2017, the fever up to 40°C emerged intermittently, followed by weight loss and right inguinal lymphadenopathy. In February 2018, a CT scan

showed multiple subphrenic lymphadenopathies. A blood culture detected the bloodstream infection of methicillin-resistant *Staphylococcus aureus* (MRSA), and a gastrointestinal endoscopy revealed the widespread esophageal candidiasis. In March, he was complicated by herpes zoster infection. The right inguinal lymph node biopsy showed mycobacterium infection with malignant lymphoma, and he was transferred to our hospital.

On admission, laboratory data showed a white blood cell count of 14,400 /μL (band cell 3.0%, segmented cell 81.0%, monocyte 8.5%, lymphocyte 7.5%), hemoglobin level of 9.0 g/dL, platelet count of 18.3 x 10^4 /μL, CD4-positive T cell count of 678 /μL (50.3% of T cells), aspartate transaminase (AST) of 16 U/L, alanine aminotransferase (ALT) of 15 U/L, blood urea nitrogen (BUN) of 5.3 mg/dL, creatine of 0.60 mg/dL, C-reactive protein (CRP) of 26.52 mg/dL, immunoglobulin G of 1764 mg/dL, and soluble IL-2R of 16,523 U/mL. HIV antibody, HTLV-1 antibody, *mycobacterium avium* complex (MAC) antibody, candida antigen, aspergillus antigen and Interferon-Gamma release assay were negative. Polymerase chain reaction (PCR) assays for the detection of clonally rearranged T cell receptors in the peripheral blood showed no clonality,[3] and lymphocyte blastoid transformation test by phytohemagglutinin (PHA) was 29,300 count per minute (cpm) (normal range: 20,500-56,800 cpm), which suggested no apparent T cell dysfunction.

PET-CT demonstrated multiple enlargements of subphrenic lymph nodes (SUVmax 11.1 in the right inguinal lymph node) (**Figure 1a-b**). The histopathological examination of the right inguinal lymph node biopsy showed the destruction of normal structure and the mixture of the proliferation of abnormal large lymphoma cells and epithelioid cell granuloma. With small T cells and histiocytes as a background, Hodgkin cells, Reed-Sternberg cells and Lacunar cells invaded. These malignant cells were positive for CD30 and PD-L1, partially positive for CD15, and negative for CD3, CD4, CD8, and CD20 in immunohistochemistry. EBER-ISH was positive, and LMP-1 and EBNA-2 were also partially positive, which suggested EBV infection with latency type III (**Figure 2a-e**). This case showed more atypical and various cell appearance than Hodgkin lymphoma (HL). EBV-associated HL typically shows EBV infection with latency type II. Based on these pathological findings, EBV-positive LPD with Hodgkin lymphoma-like features was diagnosed.

PCR tests of the right inguinal lymph node were negative for *Mycobacterium tuberculosis* and MAC, and culture tests of bacteria, fungi, and mycobacterium species were also negative. However, Ziehl-Neelsen staining of the biopsy specimen showed acid-fast bacilli in granulomas (**Figure 2a**). In PCR, we revealed 100% sequence identity of both 16s ribosomal RNA and heat shock protein 65 (hsp65) of *M. genavense*,[4] targeting 710 base pair (bp) sequences out of 1500 bp and 361 bp sequences out of 1623 bp respectively. The detection of *M. genavense* infection by culture is troublesome due to its fastidious growth requirements;[2] therefore, negative culture result cannot exclude *M. genavense* infection. Consequently, EBV-positive LPD and *M. genavense* lymphadenitis were concomitantly diagnosed. We treated him with rifampicin, ethambutol and clarithromycin against *M. genavense,*[5] and adriamycin, vinblastine and dacarbazine for EBV-positive LPD. We excluded bleomycin due to emphysema. Although fever and lymphadenopathy promptly subsided with these double therapies, PET-CT after six cycles showed multiple lymphadenopathies. The right inguinal lymph node

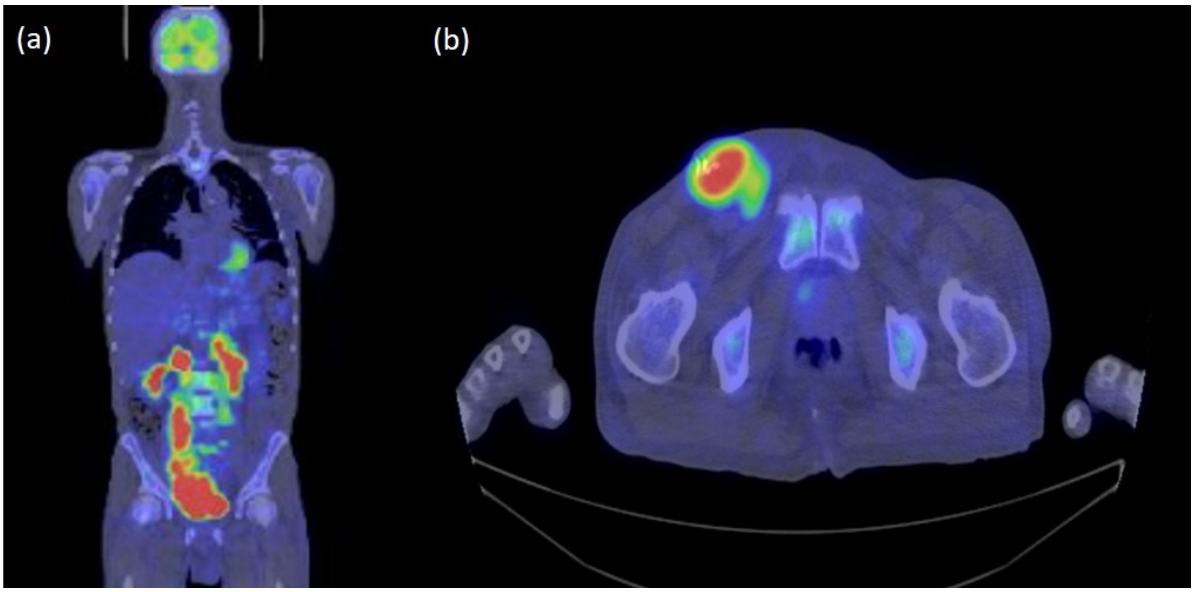

Figure 1. PET-CT images on admission. PET-CT on admission shows (**a**) multiple enlargement of subphrenic lymph nodes and (**b**) SUVmax 11.1 in the right inguinal lymph node.

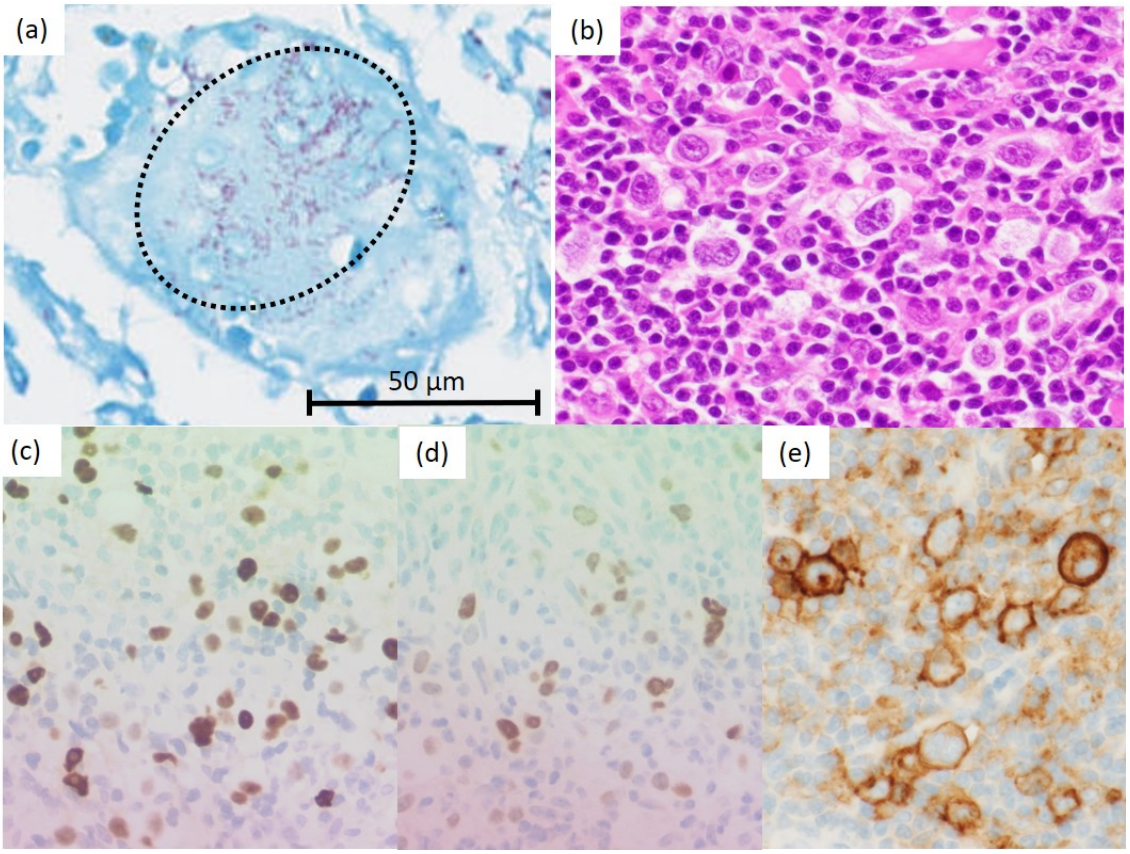

Figure 2. Pathological findings of the inguinal lymph node biopsy. (**a**) Ziehl-Neelsen staining of the right inguinal lymph node biopsy specimen shows acid-fast bacilli in granuloma (dashed-line circle). (**b**) HE staining shows atypical large lymphoma cells with T cells in the background. (**c**) In-situ hybridization for Epstein-Barr virus-encoded small RNA (EBER-ISH) is positive. Immunohistochemical staining shows (**d**) EBNA-2 partially positive, and (**e**) PD-L1 positive (x400 (**b, e**), x200 (**c, d**) at original magnification).

re-biopsy demonstrated the relapse of EBV-positive LPD with no signs of mycobacterium infection. We started salvage chemotherapy and continued triplet antibiotics. The optimal treatment duration against *M. genavense* remains unclear, and we continued the triplet therapy for more than one year.[2] We stopped the triplet antibiotics after 17 months' duration, and subsequently, the patient has had NTM free follow-up for 14 months.

Discussion. Our case is the first case with concomitant *M. genavense* lymphadenitis and malignant lymphoma in the same lymph node. *Mycobacterium genavense* is a rare pathogen named after Geneva, which was first reported in a series of 18 patients with acquired immune deficiency syndrome (AIDS).[1] *M. genavense* infection used to be an opportunistic infectious disease for HIV-infected patients with CD4-positive T cell counts less than 100/µL.[1] However, 46 non-HIV cases have been reported.[2] Most of them were immunocompromised hosts, and the common underlying conditions were solid organ transplantation (40%), sarcoidosis (14%), autoimmune diseases (13%) and hematopoietic stem cell transplantation (7%). 60% were on at least two immunosuppressants, and the median CD4-positive T cell counts were 105/µL. The main symptoms were weight loss, fever, lymphadenopathy and hepatosplenomegaly, which were similar to those of malignant lymphoma.

Three cases reported the relation between *M. genavense* infection and lymphoma (**Table 1A**). An 80-year-old female patient with chronic lymphocytic leukemia,[6] a 51-year-old female patient with peripheral T cell lymphoma,[7] and a 63-year-old male patient with non-Hodgkin lymphoma (NHL)[8] caused *M. genavense* infection. All cases were under chemotherapy or immunosuppressive therapy when *M. genavense* infection was detected; thus, the situation is different from our patient with concurrent *M. genavense* infection and EBV positive LPD with no immunosuppressive therapy.

Meanwhile, a simultaneous diagnosis of NTM infection and malignant lymphoma has been reported in four cases (**Table 1B**). Two of them were patients with AIDS, a 27-year-old male patient with MAC infection and HL,[9] and a 31-year-old male patient with NTM infection and NHL.[10] Since NTM infection and malignant lymphoma are both included in AIDS-defining diseases, the possibility of simultaneous onset may be relatively high in AIDS patients. The other two cases were a 13-year-old male with *M. avium* infection and HL,[11] and a 5-year-old male with MAC infection and HL.[12] These cases were compatible with the evidence that NTM lymphadenitis has mainly occurred in children, and MAC accounts for 80-90%.[13] Consequently, our patient is the first adult non-HIV

Table 1(A). The summary of patients with *M. genavense* infection and malignant lymphoma.

	Case 1 (This case)	Case 2 (Krebs et al., 2002)	Case 3 (Numbi et al., 2014)	Case 4 (Hoefsloot et al., 2013)
Age/sex	53/M	80/F	51/F	63/M
Phenotype of lymphoma	EBV-LPD	B-CLL	PTCL	NHL
Clinical presentation	Lymphadenopathy, fever, weight loss	Lymphadenopathy, splenomegaly, anemia	Lymphadenopathy, weight loss	N/A
Other underlying conditions	None	None	Steroid-dependent polyarthritis	N/A
Immuno-suppressants	None	Chlorambucil + predonisone for B-CLL	Methotrexate, leflunomide, steroid for polyarthritis	Chemotherapy including Rituximab 3 months before isolation
CD4 positive T cell count	678 /μL	N/A	346 /uL	N/A
Biopsy sites for lymphoma	Right inguinal LN	Bone marrow	Inguinal LN	N/A
Infection sites of Mycobacterium	Right inguinal LN	Bone marrow, blood	Right supraclavicular LN, subcutaneous nodules	Bone marrow, disseminated
Treatment of mycobacterium	RFP, EB, CAM	RFP, EB, CAM	RFP, EB, CAM, AMK	RFP, EB, CAM
Treatment of lymphoma	AVD 6 course	None	ICE, auto SCT	N/A
Outcome	Relapse of LPD	Recurrent infection	CR	N/A

AMK, amikacin; auto SCT, autologous stem-cell transplantation; AVD, adriamycin, vinblastine and dacarbazine; B-CLL, B cell chronic lymphocytic leukemia; EB, ethambutol; EBV-LPD, EBV positive lymphoproliferative disorder; CAM, clarithromycin; CR, complete remission; ICE, ifosfamide, cisplatin and etoposide; LN, lymph node; N/A, not available; NHL, non-Hodgkin lymphoma; PTCL, peripheral T cell lymphoma; RFP, rifampicin

Table 1(B). The summary of patients with concomitant NTM infection and malignant lymphoma.

	Case 5 (Brousset et al., 1994)	Case 6 (Kenali et al., 2004)	Case 7 (Yaxsier et al., 2011)	Case 8 (Gupta et al., 2011)
Age/sex	27/M	31/M	13/F	5/M
Phenotype of lymphoma	EBV-associated HL (MC type)	NHL (unknown phenotype)	HL (MC type)	NLPHL
Mycobacterium species	MAC	Not identified	*M. avium*	MAC
Clinical presentation	Intermittent fever, lymphadenopathy	Right facial swelling	Supraclavicular mass	Cervical lymphadenopathy
Other underlying conditions	AIDS	AIDS	None	None
Immuno-suppressants	None	None	None	None
CD4 positive T cell count	<50	N/A	N/A	N/A
Biopsy sites of lymph node	Left cervical LN	Intranasal ulcerating lesion	Supraclavicular LN	Lung, left supraclavicular LN
Infection sites of Mycobacterium	Left cervical LN	Intranasal ulcerating lesion	Supraclavicular LN	Lung, gastric aspirates
Treatment of mycobacterium	N/A	EB, RFP, INH, PZA	EB, RFP, AZM	EB, RFP, AZM
Treatment of lymphoma	N/A	None	VCR, ADR, ETP	ABVE/PC
Outcome	Die of the perforated intestine	Die before starting treatment	CR	CR

ABVD, adriamycin, bleomycin, vinblastine and dacarbazine; ABVE/PC, adriamycin, bleomycin, vincristine, etoposide, prednisone and cyclophosphamide; ADR, adriamycin; AIDS, acquired immune deficiency syndrome; AZM, aztreonam; CAM, clarithromycin; CR, complete remission; EB, ethambutol; ETP, etoposide; HL, Hodgkin's lymphoma; INH, isoniazid; MC, mixed cellularity; NLPHL, nodular lymphocyte predominant Hodgkin lymphoma; MAC, mycobacterium avium complex; N/A, not available; PZA, pyrazinamide; RFP, rifampicin; VCR, vincristine

case with concomitant NTM lymphadenitis and lymphoma.

This patient presents with an EBV latency type III. It is typically observed in immunodeficiency-associated LPD and a part of EBV-positive diffuse large B cell lymphoma (DLBCL), not otherwise specified (NOS), which indicates the highly immunodeficient background.[14] Furthermore, this

patient suffered from *M. genavense* lymphadenitis, MRSA bacteremia, widespread esophageal candidiasis, and herpes zoster infection. These bacterial, fungal, and viral infections further suggest an immunocompromised condition. However, this case did not have primary immune disorders, HIV infection, or another iatrogenic immunodeficiency, or pathological features of DLBCL. White blood count, CD4-positive T cell count, and immunoglobulin levels were normal. T cell receptors in the peripheral blood were polyclonal, and the lymphocyte blastoid transformation test by phytohemagglutinin (PHA) was normal, which suggested no apparent T cell dysfunction. Mycobacterial, fungal, and viral infections can be caused by monocytopenia and mycobacterial infection (MonoMAC) syndrome.[15] However, the differential blood count, including the monocyte count of this patient was normal, which exclude the possibility of MonoMAC syndrome. Furthermore, we analyzed the sequence of GATA binding protein 2 (*GATA2*) using DNA extracted from peripheral blood and found a single-nucleotide polymorphism c.490 G>A (p.A164T) and a silent mutation c.15 C>G. In addition, our case did not have the age like suffering from severe immunosenescence, which is critical for the pathogenesis of EBV-positive DLBCL, NOS.[14] Based on these results, no immunodeficiency could be detected in our patient.

Patients with HL are often complicated with tuberculosis.[16] HL cells are known to highly express PD-L1 and cause intratumoral T cell exhaustion, leading to T cell dysfunction.[17] Generally, high PD-L1 expression on malignant lymphoma cells is due to either the amplification of the PD-L1 locus on chromosome 9p24.1, which is a recurrent abnormality seen in HL, or EBV infection.[18] EBV infection upregulates PD-L1 expression via EBNA2, the characteristic of EBV latency type III.[18] In our case, EBNA2 induced PD-L1 expression on the lymphoma cells and might activate PD-1/PD-L1 signaling on the surrounding T cells. Immune checkpoint players such as PD-1, cytotoxic T lymphocyte antigen 4 (CTLA-4), and T cell immunoglobulin and mucin domain-containing molecule 3 (TIM-3) have been well known for the role of not only cancer immune escape but also immunosuppression during chronic infection.[19,20] For example, during chronic *Mycobacterium tuberculosis* infection, T cells express multiple inhibitory receptors, including PD-1 and TIM-3, which cause T cell exhaustion.[21] It promotes impairment of T cell function and impairs host resistance to *M. tuberculosis*.[21] These reports suggest that T cell exhaustion may induce the exacerbation of infections against mycobacterium species. Therefore, the immunosuppressive effect through the PD-1/PD-L1 axis might promote the simultaneous *M. genavense* infection in our case. Consequently, our case indicates that the immunodeficiency in the background of EBV latency type III and the immunosuppression by malignant lymphoma itself might induce the *M. genavense* lymphadenitis and other bacterial, fungal, and viral infections. Our case highly alerts clinicians of the immunosuppressive state of EBV-positive LPD with latency type III even if any immunodeficient serological factors are not detected.

Conclusions. This is the first case of simultaneously diagnosed *M. genavense* lymphadenitis and EBV-positive LPD with no immunocompromised history. As patients with EBV-positive LPD with latency type III may be highly susceptible to mycobacterium species and other opportunistic infections, there should be increased awareness of their marked immunocompromised condition regardless of the existence of any immunodeficient serological findings.

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