Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.3093-19
Intern Med 59: 573-576, 2020
http://internmed.jp

【 CASE REPORT 】

T-cell Lymphoma Presenting Neutrophilic Inflammation in the Cerebrospinal Fluid

Takaaki Nakamura[1], Yoshiki Takai[1], Kimihiko Kaneko[1], Hiroshi Kuroda[1], Tatsuro Misu[1], Kiyotaka Asanuma[2], Ryoko Saito[3] and Masashi Aoki[1]

Abstract:
A 66-year-old woman presented with upper abdominal pain and weakness in the limbs. She had bilateral uveitis and gastric ulcers. A neurological examination revealed tetraparesis and sensory disturbance in the right arm. A cerebrospinal fluid (CSF) examination showed polymorphonuclear pleocytosis with elevated pro-inflammatory cytokine levels. Magnetic resonance imaging showed brain lesions and a long spinal cord lesion. She was initially diagnosed with neuro-Behçet's disease and was treated with corticosteroids, resulting in no improvement. A gastric mucosa biopsy indicated T-cell lymphoma colocalizing with neutrophils. The cytokine-mediated neutrophilic inflammation probably caused characteristic CSF and histopathological features. It is noteworthy that T-cell lymphoma may present with CSF neutrophilic inflammation.

Key words: polymorphonuclear leukocyte, neuro-Behçet's disease, neuro-neutrophilic disease, interleukin-6, interleukin-8, interleukin-17

(Intern Med 59: 573-576, 2020)
(DOI: 10.2169/internalmedicine.3093-19)

Introduction

Neutrophilic inflammation in the cerebrospinal fluid (CSF), represented as polymorphonuclear pleocytosis, is a characteristic feature of bacterial meningitis and less frequently of neuro-neutrophilic diseases (NND), including neuro-Behçet's disease (NBD) and neuro-Sweet disease (1). Other pathological conditions in the central nervous system (CNS), including those of infectious, inflammatory, or neoplastic origin, generally present with normal cell counts or mononuclear pleocytosis in the CSF (2, 3). Therefore, when clinicians see patients with neutrophilic inflammation in the CSF, they first assess the condition as bacterial meningitis or NND.

We herein report a patient with disseminated T-cell lymphoma in the CNS whose CSF showed neutrophilic inflammation.

Case Report

A 66-year-old woman with no remarkable medical history presented with upper abdominal pain and gradually progressive weakness in all 4 limbs. She first noticed mild paresthesia in the right arm, followed by weakness in the right arm and leg. One month later, she felt difficulty walking due to weakness in the four limbs, suggesting that the lesions developed first in the right cervical nerve root, then in the left frontal lobe, and finally in the spinal parenchyma.

A physical examination revealed bilateral active uveitis and tenderness in the upper abdomen. A neurological examination revealed mild tetraparesis prominent in the right leg and generalized hyperreflexia without apparent pathological reflexes, as well as paresthesia in the right arm without segmental distribution. A confrontation visual field test did not detect any apparent visual field defect. Laboratory tests showed mild anemia (hemoglobin concentration: 9.8 g/dL) and mildly elevated serum C-reactive protein (1.9 mg/dL). Serum antibodies against aquaporin-4, myelin oligodendro-

[1]Department of Neurology, Tohoku University School of Medicine, Japan, [2]Department of Gastroenterology, Tohoku University Graduate School of Medicine, Japan and [3]Department of Pathology, Tohoku University Graduate School of Medicine, Japan
Received: March 26, 2019; Accepted: August 18, 2019; Advance Publication by J-STAGE: October 7, 2019
Correspondence to Dr. Hiroshi Kuroda, dakuro@med.tohoku.ac.jp

cyte glycoprotein, and human T-cell leukemia virus type 1 were all negative.

Gastrointestinal endoscopy revealed multiple gastric ulcers. A CSF examination showed polymorphonuclear pleocytosis without malignant cells (Table). The initial CSF examination was performed in an emergency setting; a fraction of the CSF sample was stored at -80℃, and cytokine assays were performed using the stored sample. CSF cytology was assessed using the sample obtained after corticosteroid administration, showing neither atypical lymphocytes nor neutrophils (Fig. 1). Brain magnetic resonance imaging (MRI) showed hyperintense lesions on fluid-attenuated inversion recovery in the right occipital lobe and left frontal lobe with gadolinium enhancement (Fig. 2a-d). Spine MRI showed a longitudinally extensive lesion in the C6-Th10 vertebral segments (Fig. 2e-g).

Table. Cerebrospinal Fluid Data of the Patient.

Item	value	Normal range or reference value
Cell count, /mm^3	81	<6
Polymorphonuclear cells	74	<1
Mononuclear cells	7	<6
Protein, mg/dL	251	<45
Glucose, mg/dL	35	>40
Plasma glucose, mg/dL	152	N.A.
CSF/plasma glucose ratio	0.23	>0.4
soluble IL-2 receptor, U/mL	433	<100
IL-6, pg/mL	1,128	<4.0
IL-8, pg/mL	969	<2.0
IL-10, pg/mL	11.2	<5.0
IL-17A, pg/mL	3.2	<0.2
Cytology*	Class II (no malignancy)	

CSF: cerebrospinal fluid, IL: interleukin, N.A.: not applicable, *CSF obtained after corticosteroid administration

She was initially diagnosed with NBD because she had uveitis, gastric ulcers, and multiple CNS lesions with neutrophilic inflammation in the CSF. She was treated with corticosteroids but showed no improvement. The reassessment of the spine MRI findings revealed a poorly marginated mass in the right paraspinal muscle (Fig. 2f, g). A gastric mucosa biopsy of adjacent ulcers indicated lymphoid cells presenting nuclear atypia (Fig. 3a, b). The cells were positive for CD2, CD3, CD4, CD7, CD45, and T-cell intracytoplasmic antigen-1 (TIA-1); very weakly-positive for CD56; and negative for CD5, CD8, CD20, and CD30, indicating T-cell lymphoma (Fig. 3c). Neutrophils colocalized with lymphoma cells in part of the specimen, indicating neutrophilic inflammation (Fig. 3a). A paraspinal mass biopsy showed lymphoid cells presenting with nuclear atypia and positive surface markers for T-cell lymphoma, similar to the gastric mucosa biopsy findings. The paraspinal mass biopsy also showed the infiltration of inflammatory cells, including neutrophils and mononuclear cells. 18-fluorodeoxyglucose positron emission computed tomography (FDG-PET) showed an elevated standardized uptake value (SUV) in stomach (SUV_{max}: 7.1), paraspinal mass (SUV_{max}: 2.7), and spinal cord (SUV_{max}: 4.5). The levels of interleukin (IL)-6, IL-8, IL-10, and IL-17A were elevated in the CSF, as measured by a bead-based assay (Bio-Plex Pro Human Cytokine GI 27-

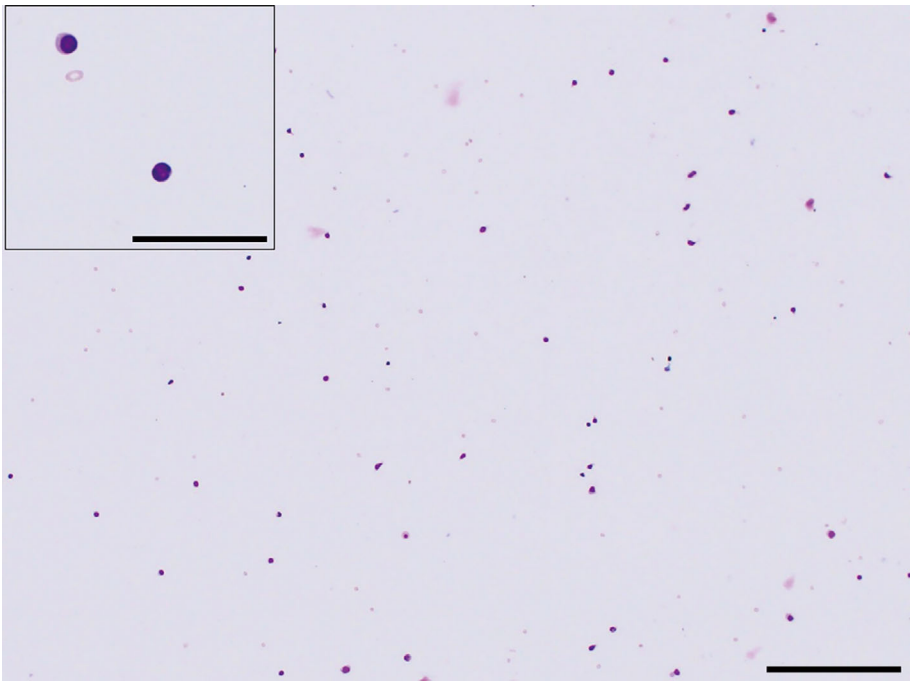

Figure 1. Cytology of the cerebrospinal fluid (Giemsa staining). Neither atypical lymphocytes nor neutrophils were detected in the cytology of the cerebrospinal fluid obtained after corticosteroid administration. Scale bars: 200 μm, 50 μm (insert).

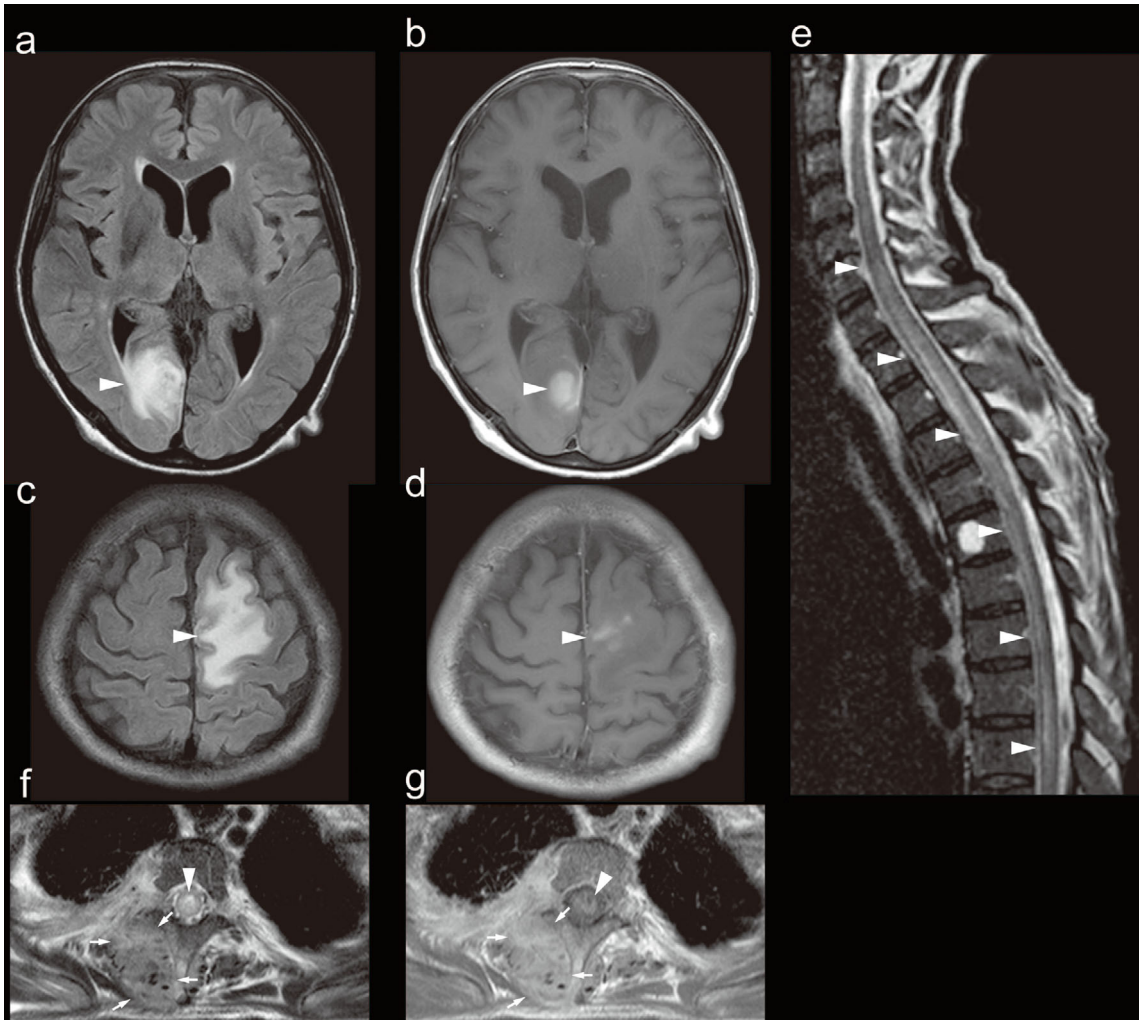

Figure 2. **Magnetic resonance imaging findings of the patient. Brain magnetic resonance imaging (MRI) shows high-signal-intensity lesions in the right occipital lobe and left frontal lobe with partial gadolinium enhancement (a-d, arrowheads; a, c: fluid-attenuated inversion recovery; b, d: T1-weighted image with gadolinium administration). Spine MRI shows a longitudinally extensive spinal cord lesion in the C6-Th10 vertebral segments with partial gadolinium enhancement (e-g, arrowheads; e, f: T2-weighted image; g: T1-weighted image with gadolinium administration). Spine MRI also shows a poorly marginated, enhanced mass in the right paraspinal muscle (f, g, arrows).**

Plex Panel; Bio-Rad, Richmond, USA) (Table). She was ultimately diagnosed with T-cell lymphoma with neutrophilic inflammation.

She was administered chemotherapy but died of sepsis shortly after starting treatment. Based on the clinical course, results of the biopsies, and FDG-PET findings, we assumed that all of the lesions were associated with T-cell lymphoma.

Discussion

We encountered a patient with disseminated T-cell lymphoma in the CNS whose CSF showed neutrophilic inflammation. The difficulty in making an early diagnosis in this case was due to the organ involvement and CSF findings that mimicked NBD. Uveitis and multiple intestinal ulcers are common clinical features of NBD, although malignant lymphoma may also present with such organ involvement.

Neutrophilic inflammation in the CSF with the elevation of pro-inflammatory cytokines, including IL-6, IL-8, and IL-17A, was the characteristic feature of the present case. These cytokines have the potential to induce neutrophilic inflammation via cell adhesion molecules and other chemokines. Such neutrophilic inflammation presenting with the same cytokine profile has been also reported in NND (4, 5). These findings suggest that the elevation of pro-neutrophilic cytokines is a common mechanism of neutrophilic inflammation in the CSF. In addition to the CSF, biopsies of the gastric mucosa and paraspinal mass in this case also showed neutrophilic inflammation. Neutrophilic inflammation in the tissue associated with T-cell lymphoma has been reported in the skin and lymph nodes (6-10). Based on the present findings, the cytokine-mediated neutrophilic inflammation probably caused the characteristic CSF and histopathological findings in our case.

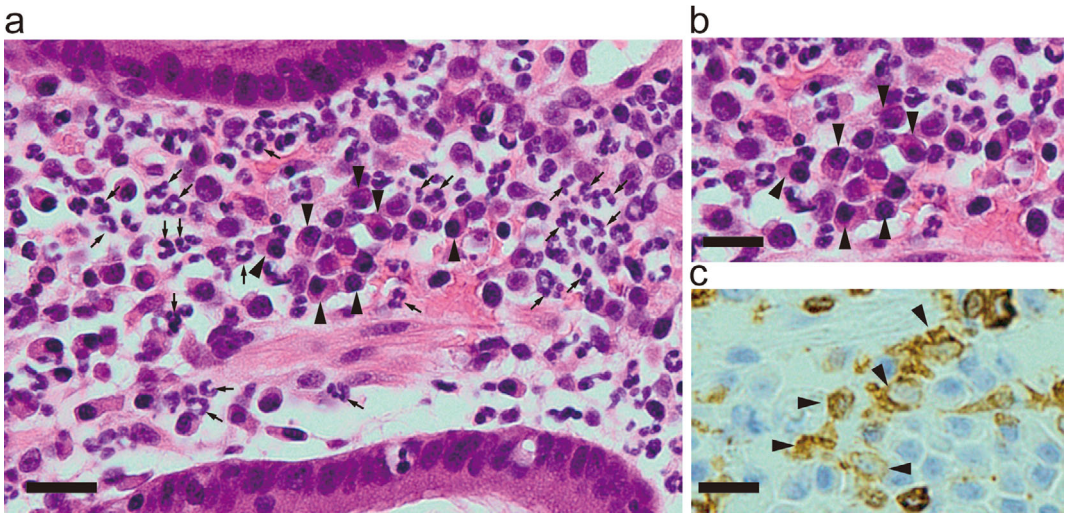

Figure 3. **The histopathological findings of the gastric mucosa biopsy. The biopsy specimens show infiltration of lymphoid cells with nuclear atypia (a, b, arrowheads) and colocalizing neutrophils (a, arrows). The lymphoid cells are positive for CD3 (c, arrowheads) and negative for CD20 (data not shown), indicating T-cell lymphoma. (a, b: Hematoxylin and Eosin staining; c: anti-CD3 immunostaining). Scale bars: 20 μm.**

There are two possible sources of pro-neutrophilic cytokines: lymphoma cells, and non-lymphoma cells, such as activated lymphocytes, macrophages, and endothelial cells. Regarding lymphoma cells, it has been reported that neutrophil-rich anaplastic large-cell lymphoma induces neutrophilic inflammation via CD30 and IL-8 (7); however, this is not applicable to the present case because of the lack of CD30 expression. Further studies are therefore needed in order to clarify the detailed mechanisms underlying neutrophilic inflammation associated with T-cell lymphoma.

In conclusion, it is noteworthy that T-cell lymphoma may present with neutrophilic inflammation in the CSF. Although the early diagnosis of T-cell lymphoma with neutrophilic inflammation is difficult, the existence of intractable skin and soft tissue lesions may be indicating this disease. A careful evaluation and readiness to perform a biopsy are needed when clinicians suspect patients of having NND based on neutrophilic inflammation in the CSF.

Written informed consent was obtained from the patient. The institutional review board approved the use of human subjects for this study. This study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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

Acknowledgement

We thank Dr. Ryo Ichinohasama, a professor of Division of Hematopathology, Tohoku University Hospital, for his valuable advices about the histopathological diagnosis.

References

1. Kimura A, Sakurai T, Koumura A, et al. Longitudinal analysis of cytokines and chemokines in the cerebrospinal fluid of a patient with Neuro-Sweet disease presenting with recurrent encephalomeningitis. Intern Med **47**: 135-141, 2008.
2. Matsuda M, McMurria H, VanHale P, Miller CA. CSF findings in primary lymphoma of the CNS. Arch Neurol **38**: 397, 1981.
3. Scott BJ, Douglas VC, Tihan T, Rubenstein JL, Josephson SA. A systematic approach to the diagnosis of suspected central nervous system lymphoma. JAMA Neurol **70**: 311-319, 2013.
4. Hirohata S, Kikuchi H. Changes in biomarkers focused on differences in disease course or treatment in patients with neuro-Behçet's disease. Intern Med **51**: 3359-3365, 2012.
5. Belghith M, Bahrini K, Kchaou M, Maghrebi O, Belal S, Barbouche MR. Cerebrospinal fluid IL-10 as an early stage discriminative marker between multiple sclerosis and neuro-Behçet disease. Cytokine **108**: 160-167, 2018.
6. Fontao L, Brembilla NC, Masouye I, et al. Interleukin-17 expression in neutrophils and Th17 cells in cutaneous T-cell lymphoma associated with neutrophilic infiltrate of the skin. Br J Dermatol **166**: 687-689, 2012.
7. Boudova L, Kazakov DV, Jindra P, et al. Primary cutaneous histiocyte and neutrophil-rich CD30+ and CD56+ anaplastic large-cell lymphoma with prominent angioinvasion and nerve involvement in the forehead and scalp of an immunocompetent woman. J Cutan Pathol **33**: 584-589, 2006.
8. Badve S, Blumstein A, Wiernik P, Ratech H. Non-hodgkin malignant lymphoma with tissue neutrophilia: a report of 3 cases. Arch Pathol Lab Med **124**: 735-738, 2000.
9. Romano M, Sironi M, Toniatti C, et al. Role of IL-6 and its soluble receptor in induction of chemokines and leukocyte recruitment. Immunity **6**: 315-325, 1997.
10. Hammond ME, Lapointe GR, Feucht PH, et al. IL-8 induces neutrophil chemotaxis predominantly via type I IL-8 receptors. J Immunol **155**: 1428-1433, 1995.