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【 CASE REPORT 】

A Unique Case of Sarcoid-associated Myelopathy Accompanied by Lung Cancer

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Abstract:

The differential diagnosis of myelopathy in patients with malignancies may be challenging, as a spinal biopsy is not always applicable. A 66-year-old woman who had shown transient double vision and nausea developed spasticity and impaired deep sensation in both feet. Magnetic resonance imaging showed abnormal gadolinium enhancement of the brainstem, spinal meninges, and nerve root. Cerebrospinal fluid (CSF) revealed mild pleocytosis and elevated protein and decreased glucose levels, although CSF cytology was normal. Lung carcinoma was simultaneously detected, and noncaseating granuloma was detected from the hilar and axillary lymph nodes, so she was diagnosed with sarcoid-associated myelopathy. Her symptoms were kept stable by intravenous methylprednisolone, oral prednisolone, and methotrexate. This is the first case of sarcoid-associated myelopathy accompanied by lung cancer, suggesting the importance of clinical course, repetitive CSF cytology, and a biopsy of the lymph nodes to distinguish sarcoid-associated myelopathy from meningeal metastasis in patients with malignancies.

Key words: sarcoidosis, myelopathy, lung cancer

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Introduction

Sarcoidosis is a systemic inflammatory disease that is pathologically characterized by granulomatous changes (1). Although sarcoidosis mainly affects the lungs, skin, eyes, liver, and lymph nodes, the nervous system is affected in 5-15% of patients (2), causing cranial neuropathy, aseptic meningitis, hydrocephalus, myelopathy, and peripheral neuropathy (3). A biopsy of the affected organs is preferred for the diagnosis of sarcoidosis, but this is not always practical in the case of neuro-sarcoidosis, which is often diagnosed based on neuro-inflammation and systemic sarcoidosis (4), and where a careful differential diagnosis is required.

Patients with sarcoidosis are at a high risk of developing malignancies, including lung cancer (5). Conversely, malignancies can elicit a systemic granulomatous response, which is virtually indistinguishable from sarcoidosis (6). Therefore, theoretically, when patients with malignancies develop neurological symptoms, neuro-sarcoidosis should be considered, although brain metastases or a paraneoplastic syndrome are more frequent (7). However, malignancy-accompanied sarcoidosis in the nervous system is rarely reported, possibly due to the difficulty of its histological diagnosis. Thus, the clinical presentation of neuro-sarcoidosis in patients with malignancies remains poorly understood.

We herein report a unique case of neuro-sarcoidosis presenting with myelopathy accompanied by a lung nodule and lymphadenopathy.

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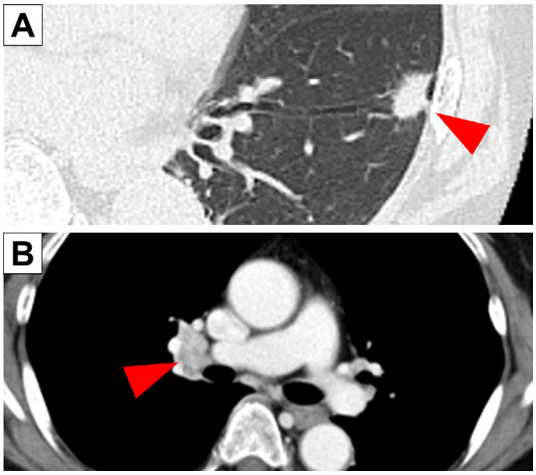

Figure 1. Chest computed tomography, showing (A) a 14-mm lung tumor in the left lower lobe (arrowhead) and (B) hilar lymphadenopathy (arrowhead).

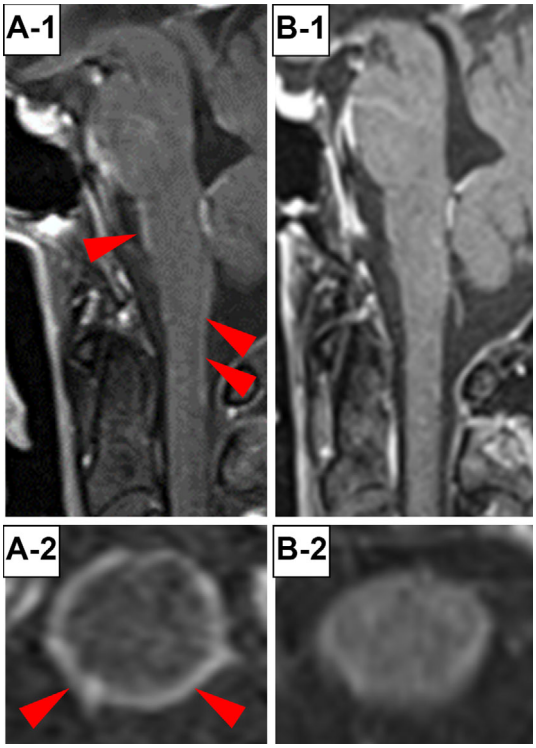

Figure 2. Magnetic resonance imaging, demonstrating abnormal gadolinium enhancement of the meninges at the brainstem and cervical spine (A-1, 2), which was resolved after intravenous mPSL administration (B-1, 2).

Case Report

A 66-year-old woman was admitted to our hospital due to difficulty walking and numbness. At 61 years old, she had developed double vision which became more severe when she looked to her bottom right. Although she had not visited a hospital then, her double vision had spontaneously resolved within a month. At 64 years old, she walked with difficulty and was continuously nauseous. Although gastrointestinal endoscopy was performed in a clinic, the findings were normal. Her difficulty walking gradually worsened, and she required a walking cane at 65 years old. At 66 years old, she felt numbness in her feet. She was diagnosed with lumbar canal stenosis in an orthopedic clinic, and laminoplasty (L2-L4) was performed. However, her difficulty walking and numbness in her feet persisted, and she felt instability while standing when washing her face. Four months after laminoplasty, she was admitted to our hospital.

On admission, an assessment of her physical condition was normal. She was alert. Her cranial nerve functions, including extraocular movement, were normal. Her muscle strength was intact, and she showed no limb ataxia. However, her gate was ataxic, and her tandem gait was impaired. Although her superficial and position sense were intact, she felt numbness in her feet with sacral sparing and showed a reduced sense of vibration and positive Romberg's sign. Her deep tendon reflexes were hyperactive in all extremities, while her jaw jerk reflex was normal. She showed positive bilateral Trömner, Wartenberg, Babinski and Chaddock signs. Her muscle tonus was spastic in all extremities. Meningeal irritating signs were absent. She showed urinary disturbance and constipation, but orthostatic hypotension was absent. An ophthalmic examination and transthoracic echocardiography were normal. These symptoms suggested a pathological lesion in the upper cervical spine, but we speculated that the brainstem was also involved because she had developed double vision and nausea as described.

Serum analysis findings were normal, including her white blood cell count (8,030/μL), erythrocyte sedimentation rate (17/38 mm), glucose (91 mg/dL), vitamin B12 (809 pg/mL), folate (5.78 ng/mL), angiotensin-converting enzyme (18.1 U/L), and soluble interleukin-2 (IL-2) receptor (338.2 U/mL). Serum anti-aquaporin 4 antibody was negative. Her interferon γ-releasing assay was negative. A cerebrospinal fluid (CSF) analysis revealed mild pleocytosis (9/μL, mononucleosis 100%), increased protein (158 mg/dL), decreased glucose (27 mg/dL), and a normal IgG index (0.536). Oligoclonal bands were negative, and repetitive CSF cytology was normal.

Computed tomography (CT) revealed a lung tumor in the left lower lobe (Fig. 1A) and hilar lymphadenopathy (right > left, Fig. 1B). Magnetic resonance imaging (MRI) demonstrated abnormal gadolinium enhancement of the meninges at the brainstem and cervical spine (Fig. 2A-1, 2) as well as at the lumbar nerve root (L4, Fig. 3B), while cerebral MRI showed mild periventricular hyperintensity without gadolinium enhancement (Fig. 3A); no intramedullary lesion was found by spinal MRI (Fig. 3C). ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) showed abnormal uptakes in the lung tumor [maximum standardized uptake value (SUVmax): 5.71] and hilar and axillary lymph nodes (SUVmax: 6.74/6.81 for right/left hilar lymph nodes, 4.88/6.67 for the axillary lymph nodes, Fig. 4A, B) (8, 9). A CT-guided lung biopsy from the left lower lobe revealed adeno-

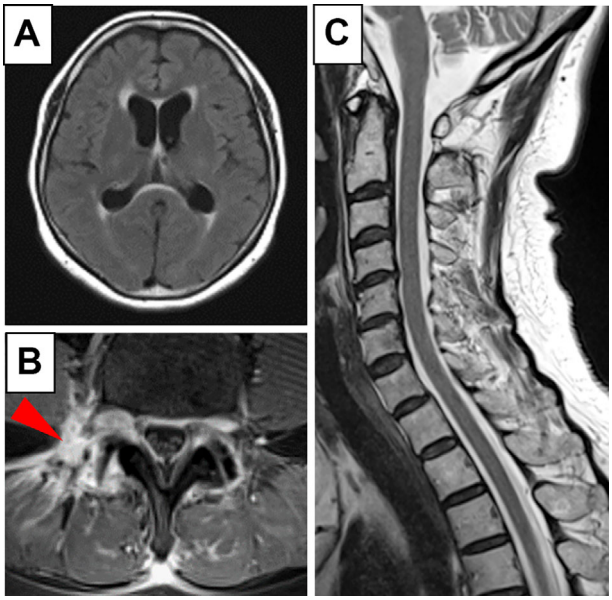

Figure 3. **Magnetic resonance imaging, also showing cerebral periventricular hyperintensity on a fluid attenuated inversion recovery image (A), and abnormal lumbar nerve root gadolinium enhancement (B, arrowhead), while intramedullary spinal lesion was not found (C).**

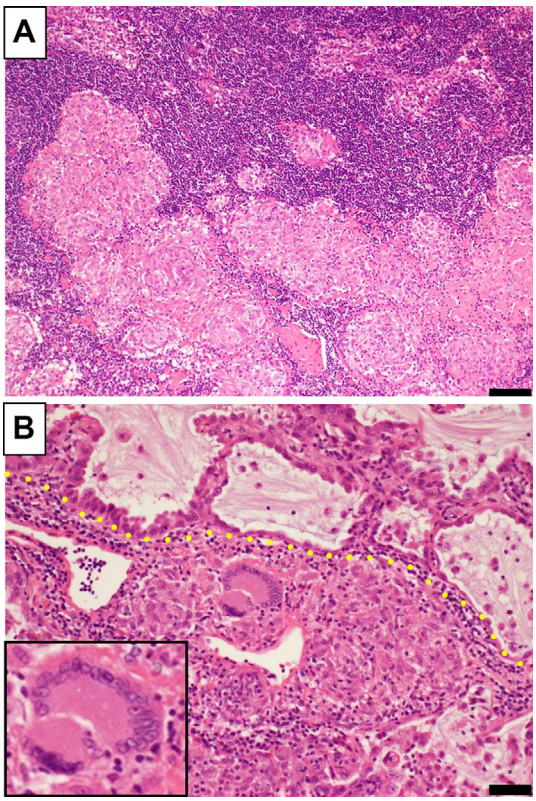

Figure 5. **A left axillary lymph node biopsy showing a collection of noncaseating granuloma by Hematoxylin and Eosin staining (A). Scale bar: 100 μm. Resected lung, showing both adenocarcinoma (upper) and granulomatous change (B). Scale bar: 50 μm.**

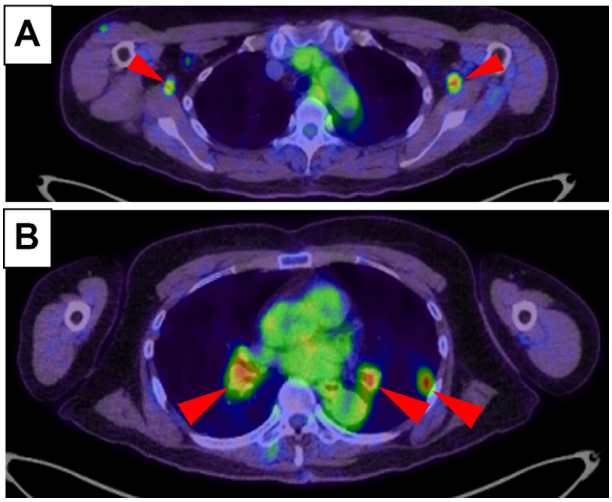

Figure 4. **^{18}F-fluorodeoxyglucose positron emission tomography showing an abnormal uptake in the axillary lymph node (A, arrowheads), hilar lymph node, and lung tumor (B, arrowheads).**

carcinoma, while a biopsy from the left axillary lymph node showed a collection of noncaseating granuloma (Fig. 5A). The results of her nerve conduction study of her bilateral median, tibial, and sural nerves were normal.

Due to a complication of early lung cancer, and since sarcoidosis was suspected, video-assisted partial resection of the left lung was performed, demonstrating adenocarcinoma with a granulomatous change (Fig. 5B). The left hilar lymph node showed granuloma without cancer metastasis. Two months after lung resection, when her difficulty walking worsened slightly, she was intravenously treated with methylprednisolone (mPSL; 1 g×3 days; 2 courses), followed by oral prednisolone (PSL; started at 60 mg/day for 4 weeks, then tapering) and methotrexate (MTX; 4 mg/week). The abnormal gadolinium enhancement of the meninges diminished after intravenous mPSL (Fig. 2B-1, 2), but her symptoms remained unchanged, even after starting oral PSL and MTX intake.

Discussion

The present patient showed transient double vision and nausea and developed slowly progressive myelopathy showing spasticity and impaired deep sensation. MRI revealed abnormal gadolinium enhancement of the brainstem, spinal meninges, and nerve root. Although lung carcinoma was simultaneously detected, noncaseating granuloma was detected from hilar and axillary lymph nodes, so she was diagnosed with sarcoid-associated myelopathy.

There are two granulomatous reactions that are linked to malignancies: sarcoidosis and sarcoid-like reactions. Sarcoidosis is a systemic disease affecting multiple organs, such as the lungs, skin, eyes, and nervous system (10). In the present case with sarcoidosis, granulomatous changes were observed around the lung adenocarcinoma, suggesting a rela-

tionship between lung adenocarcinoma and sarcoidosis (Fig. 5B). Chronic inflammation and immune dysfunction are observed in sarcoidosis (11), and the immune response against tumor cells may be suppressed in patients with sarcoidosis (12). Although a clinical study showed some conflicting evidence (13), meta-analyses showed that the relative risk of developing cancer in patients with sarcoidosis was 1.19-1.21 (11, 14). Lung cancer is three times more common in individuals with sarcoidosis than in those without it (15). The coexistence of sarcoidosis and lung cancer is most common in squamous cell lung cancer (16), although the present case displayed adenocarcinoma. Conversely, sarcoid-like reaction is a noncaseating granulomatous reaction that does not meet the diagnostic criteria for sarcoidosis, occurring in association with malignancy, drugs, radiation, infection or foreign bodies (17). In patients with malignancy, sarcoid-like reactions may be the result of a strong immune response to tumor cells and be associated with a better prognosis (18). Recent studies have shown that immune checkpoint inhibitors, such as pembrolizumab and nivolumab, can cause a sarcoid-like reaction (5).

Myelopathy was observed in about 20% of neurosarcoidosis cases (2). Meningeal gadolinium enhancement without parenchymal hyperintensity on MRI, as was the case with the present patient, was observed in 23% of cases of sarcoidosis-associated myelopathy without malignancy (19). However, sarcoidosis-associated myelopathy in a patient with malignancy is rarely reported, and this is the first reported case of sarcoid-associated myelopathy accompanied by lung cancer.

In addition to neuro-sarcoidosis, leptomeningeal metastases (LMs) of lung cancer were also suspected in the present case due to the complication of lung adenocarcinoma and the CSF findings, which showed pleocytosis and decreased glucose. LMs were observed in 3-5% of patients with advanced non-small-cell lung cancer (NSCLC) (20), which may be a similar gadolinium enhancement of spinal meninges on MRI (21), and were associated with a poor survival (2-4 months) (22). Although a meningeal biopsy was not performed, slow disease progression, noncaseating granuloma of lymph nodes without metastasis, negative CSF cytology, and a good response to steroid therapy suggested sarcoidosis-associated myelopathy.

In conclusion, the present case showed a unique complication of lung adenocarcinoma and sarcoid-associated myelopathy. The clinical course, repetitive CSF cytology, and a biopsy of the lymph nodes are important for distinguishing sarcoid-associated myelopathy from meningeal metastasis in patients with malignancies.

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

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