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Various Neurological Symptoms by Neurolymphomatosis as the Initial Presentation of Primary Testicular Lymphoma

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Key Words
Neurolymphomatosis · Primary testicular lymphoma · Diffuse large B-cell lymphoma · Central nervous system infiltration

Abstract
Neurological symptoms induced by the infiltration of malignant lymphoma into the nervous systems are subsumed under the term neurolymphomatosis (NL). Here, we report the case of a 30-year-old Japanese man with primary testicular lymphoma complicated, as seen in various neurological findings, by secondary NL prior to testicular swelling. Painless right scrotal enlargement was noticed more than 1 month after the appearance of neurological complications such as right upper extremity numbness, dysarthria, facial palsy, and diplopia. Proactive investigation and biopsies of extranodal sites at high risk of central nervous system infiltration of malignant lymphoma, such as the testes, should be considered when secondary NL is suspected based on imaging findings.
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Introduction

Neurological symptoms induced by the infiltration of malignant lymphoma into the peripheral nerves, nerve roots, plexus, and cranial nerves are subsumed under the term neurolymphomatosis (NL) [1, 2]. NL is a rare complication and is only seen in 0.85–2.9% of non-Hodgkin's lymphoma cases [1]. The manifestation of NL includes multiple mononeuropathy, polyneuropathy, radiculopathy, and cranial neuropathy, which causes muscular weakness,

KARGER 125

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sensory disturbance, spontaneous pain, and autonomic failure [3]. The majority of NL cases exhibit multiple mononeuropathy patterns, whereas some cases show a symmetrical polyneuropathy pattern, mimicking Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and other types of neuropathy [4–6]. Therefore, the diagnosis of NL is difficult and often elusive even though early recognition of NL has contributed to successful treatment [2]. Here, we report a case of atypical primary testicular lymphoma (PTL) that was complicated with NL prior to testicular swelling.

Case Report

A 30-year-old Japanese man was admitted to our hospital complaining of right upper extremity numbness, dysarthria, facial palsy, and diplopia. Six days after the admission, high-dose intravenous immunoglobulins were started under a suspicion of inflammatory polyclonal neuropathy since the neurological symptoms were progressing. However, the patient's neurological symptoms did not improve. Steroid pulse therapy (methylprednisolone 1 g/day for 3 days) and continuous administration of prednisolone (1 mg/kg/day) were immediately initiated, but these treatments were not effective either.

Eventually, artificial respiratory ventilation was required because of respiratory muscle paralysis. Gadolinium-enhanced magnetic resonance imaging (MRI) of the cervical spine detected swelling of the cervical roots (C5/6) and cauda equina (fig. 1a, b). Brain MRI showed enhancement in the bilateral roots of the facial nerve (fig. 1c, d). Although these findings were suggestive of central nervous system (CNS) infiltration by a malignant tumor as well as acute phase of Guillain-Barré syndrome, cerebrospinal fluid analysis did not detect any evidence of malignancy, including malignant lymphoma. Nerve biopsy was not performed out of concern for nerve injuries. We could not find any evidence of malignancy, including enlarged lymph nodes, in the systemic computed tomography (CT). In addition, complete blood count and laboratory examination showed no abnormalities, including normal level of lactate dehydrogenase and soluble interleukin-2 receptor. Bone marrow examination and whole-body fluorodeoxyglucose-positron emission tomography (FDG-PET) could not be performed due to the patient's poor physical status concerning neurological symptoms.

One month after the admission, painless right scrotal enlargement was noticed. A total right orchiectomy was performed immediately. Pathological findings revealed diffuse infiltration of CD20-positive large atypical lymphocytes (fig. 2). These cells were positive for CD79a, paired box protein 5 (PAX5), B-cell lymphoma (BCL)2 and BCL6, and multiple myeloma oncogene 1 (MUM1) and negative for CD5, CD10, CD23, CD30, cyclin D1, and Epstein-Barr virus-encoded small RNA (EBER). Thus, a diagnosis of diffuse large B-cell lymphoma was made. When we reevaluated the CT and gallium scintigraphy at the time of admission, we found irregular contrast enhancement and faint uptake of the right scrotum, even though testicular swelling was not observed. Together with these imaging findings and clinical courses, we concluded that the various neurological symptoms were due to secondary NL.

Although treatment with 3 courses of high-dose methotrexate, 6 courses of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), whole brain/cervical spinal cord irradiation (total 30 Gy), and intrathecal chemotherapy (methotrexate, cytarabine, prednisone) were administered, his neurological symptoms did not improve. He chose to receive palliative care and died 6 months later.

Discussion

This report describes a case of PTL with a rare clinical course in which various neurological symptoms were complicated by secondary NL prior to painless scrotal enlargement. The most common clinical presentation of PTL is unilateral painless scrotal swelling. It is reported that about 80% of patients are in the limited stage at the time of diagnosis, and CNS involvement is only presented in 3% of patients at diagnosis [7]. On the other hand, PTL has an extremely high CNS recurrence rate (5-year risk, 20%; 10-year risk, 35%), and thus, CNS prophylaxis is highly recommended [7, 8]. Secondary NL as the primary presentation of malignant lymphoma is rare [9]. Moreover, we could not find any previous reports of PTL presenting with neurological findings by secondary NL prior to testis enlargement, although steroid therapy might have influenced the progression of PTL and NL. Investigation of the testes and CNS before the initiation of steroids might have led to the earlier diagnosis of PTL and secondary NL, even though inflammatory polyclonal neuropathy was suspected.

The pathological diagnosis of NL is difficult due to the risk of nerve injuries during biopsy examinations. Furthermore, MRI and cerebrospinal fluid examinations do not exhibit high sensitivity for diagnosing NL. Recently, FDG-PET has been reported to be a useful diagnostic modality that exhibits high sensitivity and specificity for NL [2, 10–12]. Further, whole-body diffusion-weighted MRI has also been proposed to be a useful tool for detecting NL lesions [13]. Consistent with our case, the treatment response of NL is poor. Previous reports have demonstrated that the median survival period of patients with primary NL is 20 months and that of patients with secondary NL is only 8 months [2]. Further studies are needed to identify factors that affect response of NL to treatment, outcome, and prognosis [14].

In summary, we report a case of PTL complicated by secondary NL prior to testicular swelling. This case suggests that extranodal sites such as the bone marrow, skin, testes, breasts, epidural space, retroperitoneum, orbit, nasal/paranasal sinuses, and lungs are at high risk of CNS involvement and should be investigated thoroughly in cases in which CNS infiltration by malignant lymphoma is suspected based on imaging findings [15]. Moreover, proactive biopsies of these sites should be considered.

Disclosure Statement

None of the authors has any conflict of interests to declare.

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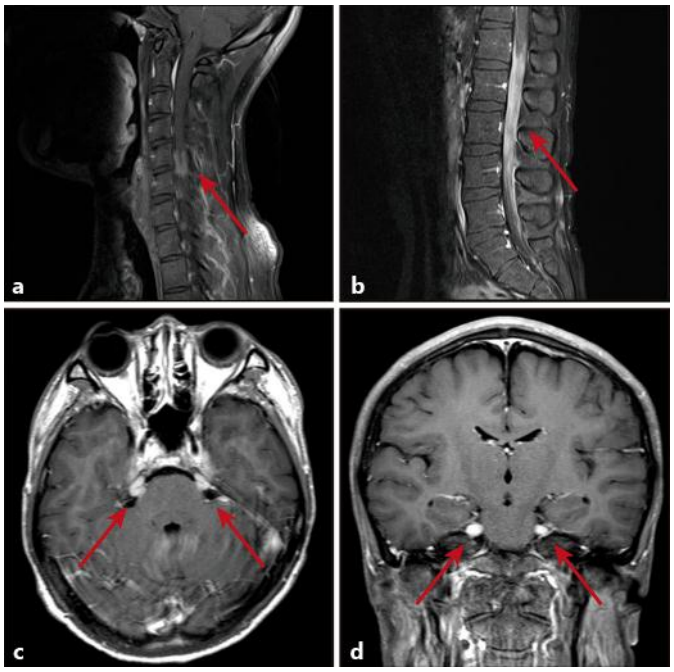

Fig. 1. MRI findings of the CNS. **a**, **b** Gadolinium-enhanced MRI of cervical spine showed swelling of the cervical 5/6 roots on day 14 (**a**) and the cauda equina on day 20 (**b**). **c**, **d** Brain MRI on day 21 detected gadolinium enhancement in the bilateral roots of the facial nerve (**c** transverse section, **d** coronal section).

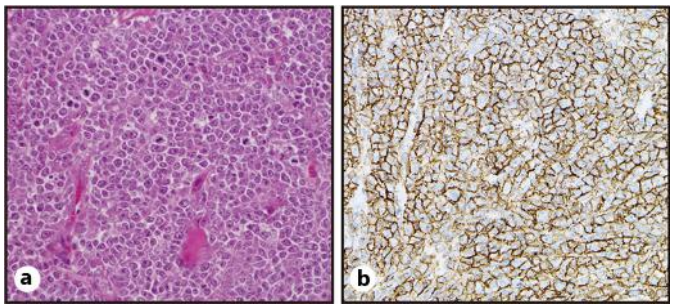

Fig. 2. Pathological findings of the testis. **a** Histopathological examination detected diffuse infiltration of the right testis by large atypical lymphocytes (HE, ×400). **b** These cells were positive for CD20 (×400).