Surgical Neurology International

SNI: Unique Case Observations, a supplement to Surgical Neurology International

OPEN ACCESS

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A case of intravascular lymphoma presenting as myelopathy diagnosed with a skin biopsy

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Received: 04 March 15 Accepted: 15 June 15 Published: 20 August 15

This article may be cited as:
Yunoki M, Suzuki K, Uneda A, Yoshino K. A case of intravascular lymphoma presenting as myelopathy diagnosed with a skin biopsy. Surg Neurol Int 2015;6:S367-70.
http://surgicalneurologyint.com/A-case-of-intravascular-lymphoma-presenting-as-myelopathy-diagnosed-with-a-skin-biopsy/

Abstract

Background: Intravascular lymphoma (IVL) is a rare subtype of non-Hodgkin lymphoma with exclusively or predominantly intravascular proliferation. Without therapeutic intervention, the neurologic involvement is rapidly progressive and inevitably fatal. Most of the IVL patients have prominent or exclusive manifestations in the nervous system and there are several reports of patients presenting with spinal symptoms.

Case Description: A 68-year-old male patient admitted with the complaints of progressive paraparesis. T2-weighted magnetic resonance imaging (MRI) of the spinal cord showed hyperintense lesions in the thoracic cord. A diagnosis of myelitis of unknown etiology was assumed, and steroid pulse therapy was administered, which temporarily improved the patient's symptoms. However, the paraparesis recurred, and other symptoms, such as vertigo, psychosis, and seizures, developed 1-month after the initial treatment. Multiple high-intensity lesions were detected in the bilateral subcortical white matter on DW MRI. Based on the patient's clinical course, IVL was suspected; however, obtaining histological confirmation was not possible, as no Gd-enhanced brain or spinal lesions were identified and repeated cerebrospinal fluid examinations were negative for tumor cells. Therefore, a random skin biopsy was performed, and IVL was diagnosed. Obtaining a comparatively favorable outcome was possible owing to the subsequent administration of R-CHOP chemotherapy.

Conclusion: IVL should be included in the differential diagnosis of atypical case of presumed myelitis. An early diagnosis and chemotherapy is crucial for improving the patient's outcome. When obtaining a diagnosis based on tissues other than skin is difficult, a random skin biopsy should be considered in patients with suspected IVL.

Key Words: Intravascular lymphoma, myelopathy, skin biopsy

Access this article online
Website: www.surgicalneurologyint.com
DOI: 10.4103/2152-7806.163316
Quick Response Code:

INTRODUCTION

Intravascular lymphoma (IVL) is a rare subtype of extranodal diffuse large cell lymphoma characterized by the intravascular proliferation of B or T lymphocytes within small blood vessels.[5,8] Up to two-third of patients have neurological symptoms, the frequent findings of which include dementia, aphasia, seizures,

stroke-like episodes, psychosis, etc.[5,8] Typically, the spinal cord is also involved, and there are several reports of patients presenting with spinal symptoms.[9,11,12,15,16] Because IVL produces a variety of clinical findings and the course from onset to death is rapid, obtaining a premortem diagnosis is extremely difficult.[5,8] We herein report a case of IVL presenting as myelopathy that was diagnosed using a skin biopsy and the patient survived for more than 8 months after the administration of chemotherapy. In addition, we review the related literature on IVL, including the antemortem diagnosis and treatment.

CASE REPORT

A 68-year-old previously healthy male was hospitalized for progressive weakness and dysesthesia of the lower limbs associated with urinary dysfunction lasting over 1-month. He was alert and had no other complaints or signs of fever. A clinical examination showed mild weakness and hyporeflexia of the lower limbs, and the plantar reflexes were in extension, although there were no abnormalities in the upper extremities. The results of routine biochemical, immunological, and serological studies were unremarkable, and a cerebrospinal fluid (CSF) analysis showed an increased protein level (205 mg/dl), no oligoclonal bands, a glucose level of 51 mg/dl and a cell count of 41/mm^3 (47 lymphocyte cells/mm^3). A cytological examination for malignant cells was negative. In addition, the findings of cranial magnetic resonance imaging (MRI) and computed tomography (CT) of the thorax and abdomen were unremarkable, whereas whole spine MRI revealed increased signal intensity, which was more pronounced in the gray matter, on a T2-weighted image obtained at the level of Th3 [Figure 1]. A physical examination revealed that no skin lesions or lymphadenopathy, and no mass lesions were found on whole body CT or endoscopy of the gastrointestinal tract. Gallium scanning and spinal Gd-MRI did not disclose any enhanced abnormalities. Therefore, the clinical diagnosis was myelitis of unknown etiology. Immediately after the initiation of treatment with methylprednisolone intravenous (0.5 g/day over 5 days), the patient was able to walk alone and resumed his activities of daily living.

One-month later, however, he was readmitted because the paraparesis recurred and newly appearing symptoms, including bilateral hearing disturbances, severe vertigo, and disorientation, developed. Cranial diffusion-weighted MRI showed several nonenhancing hyperintense lesions in the subcortical white matter [Figure 2a]. MR angiography demonstrated no intracranial arterial stenosis or occlusion [Figure 2b]. At that time, the patient received antiplatelet therapy under a diagnosis of multiple cerebral infarcts. However, his condition continued to deteriorate and he became very drowsy and developed seizures. The bilateral leg weakness was also exacerbated, progressing to flaccid paraplegia and urinary retention. In addition, the patient developed dyspnea, and XP and CT of the chest showed patchy areas of ground-glass opacity in both lungs [Figure 2c and d]. The constellation of these worsening clinical manifestations raised suspicion of IVL, as this condition often lacks lymphadenopathy and preferentially involves the spinal region.[1,2] Repeated CSF examinations were negative for malignant cells. Ultimately, four random biopsies of healthy-appearing skin on the bilateral abdomen and thighs were performed. All skin biopsy specimens

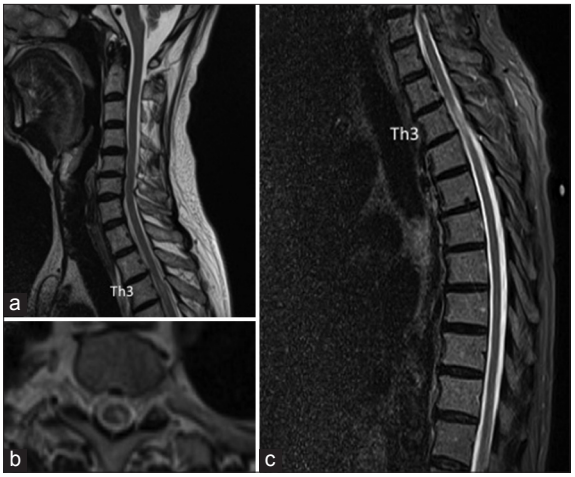

Figure 1: Spinal magnetic resonance imaging performed on the initial presentation demonstrating an increased signal intensity, which was more pronounced in the gray matter, on a T2-weighted image at the level of Th3 (a and b: Sagittal T2-weighted image, c: Axial T2-weighted image at the level of Th3)

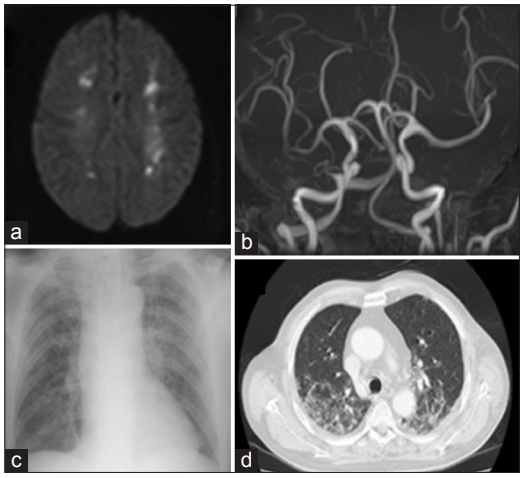

Figure 2: Magnetic resonance imaging of the brain performed on the second presentation showing diffuse bilateral asymmetrical predominantly subcortical hyperintense white matter lesions on diffusion-weighted imaging (a). Cranial magnetic resonance angiography demonstrated no abnormalities (b). XP (c) and computed tomography (d) of the chest showed patchy areas of ground-glass opacity in both lungs

showed obliteration of the small vessels in subcutaneous fat tissue by lymphoma cells, allowing for a diagnosis of IVL [Figure 3]. Chemotherapy with 375 mg/m^2 of rituximab, 750 mg/m^2 of cyclophosphamide, 50 mg/m^2 of doxorubicin and 1.4 mg/m^2 of vincristine on day 1 and 50 mg/m^2 of prednisolone on days 1–5 was started. Although no improvements were noted in the paraplegia, the patient's consciousness level started to recover. A total of six courses were completed within 12 weeks. The patient continues to have complete paraplegia and is wheelchair-bound, although he is well oriented, 8 months after the initial admission.

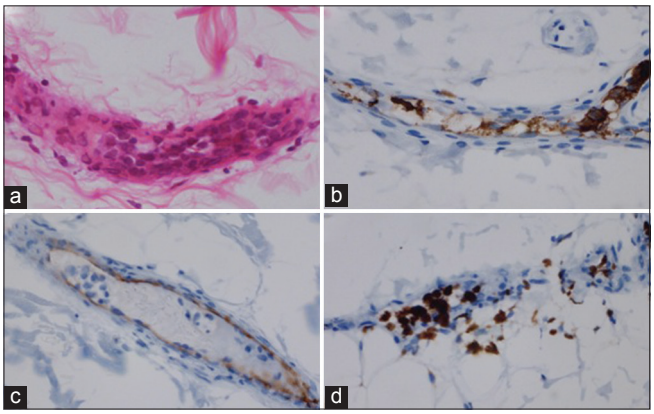

Figure 3: Pathological findings of the random skin biopsy. Large hyperchromatic cells are filling the lumen of the small blood vessels in the subcutaneous adipose tissue (a: H and E, ×400). These cells were positive for CD20 (b: ×400) and negative for CD3 (c: ×400), positive for Ki-67 (MIB-1) (d: ×400) confirming the diagnosis of intravascular large B cell lymphoma

DISCUSSION

IVL is a non-Hodgkin's lymphoma in which the malignant lymphocyte clone is restricted to the lumen of small- and medium-sized blood vessels.[5,8] Although IVL can affect virtually any organ, a distinct pattern of organ involvement has been recognized, with the nervous system, skin and parenchymatous organs (adrenal glands) being most commonly affected.[2,5,8] As in the current case, the CSF in IVL patients typically shows lymphocytic pleocytosis and an elevated protein content, the detection of which usually prompt a primary diagnosis of inflammatory disease.[8] CSF cytology is usually negative for malignancy; there have been only a few case reports of neoplastic cells in the CSF.[16] In contrast to disseminated encephalomyelitis, dementia, aphasia, seizures, and psychosis are frequent findings in cases of IVL.[5,8] In this report, the patient presented with spinal cord symptoms for the first 3 months of the disease course,

Table 1: Reported cases of intravascular lymphoma presenting as myelopathy

Author	Age/ sex	Level of spinal lesion	Subsequent encephalopathy	Interval	Treatment	Diagnosis	Histology	Survival after onset
Dolman *et al.* 1979	79/F	?	-	-	-	Autopsy	Neoplastic angioendotheliosis	3 Mo
Ojeda *et al.* 1983	76/M	?	-	-	-	Autopsy	Neoplastic angioendotheliosis	1 Mo
Dubas *et al*. 1990	78/F	?	-	-	-	Autopsy	Neoplastic angioendotheliosis	
Hamada *et al*. 1991	72/M	T5	+	10 Mo	-	Autopsy	Neoplastic angioendotheliosis	12 Mo
	79/M	C4/5	+	12 Mo	-	Autopsy	-	14 Mo
Takahashi *et al*. 1993	54/F	Th12-L2	+	After spinal biopsy	-	Spinal biopsy	Large B cell	14 Mo
Levin *et al*. 1996	67/M	Th2	-	-	CHOP	Muscle, peripheral nerve biopsy	Large B cel	Alive more than 2 years
Saito *et al* 1998	63/M	CM	-	-	CHOP	Muscle biopsy	Large B cel	Alive more than 10 Mo
Somiya *et al* 1998	84/F	L1-L5	+	3 Mo		Autopsy	Large B cell	4 Mo
Nakahara *et al* 1999	63/M	CM	-	-	CHOP	biopsy	Large B cell	Alive
Vandenheede *et al*. 2002	54/M	No	+	1 week	-	Autopsy	Large B cell	2 Mo
	73/M	No	+	9 Mo	-	Autopsy	Large B cell	11Mo
Savard *et al*. 2008	61/F	CM	+	18 Mo	-	Autopsy	Large B cell	18Mo
Nakao *et al*. 2008	62/F	CM, upper Th	+		Steroid pulse	Autopsy (bone marrow)	Large B cell	16 Mo
Yang *et al*. 2008	70/M	No	+	No	-	Autopsy	Large B cell	3 Mo
Kumar *et al*. 2011	82/F	Th	-	?	Steroid pulse	Autopsy	Large B cell	14 Mo
Shirai *et al*. 2012	45/M	Th	-	-	Steroid pulse	Kidney biopsy	Large B cell	
De Fino *et al*. 2012	76/F	No	?	-	-	Autopsy	Large B cell	2 Mo

after which he developed diffuse cerebral symptoms and cranial neuropathy. To the best of our knowledge, 18 similar cases of IVL with initial spinal symptoms have been reported [Table 1].[6,7,9-13,15,17-22] In most of the 18 reported cases, the disorder remained limited to the spinal cord for no more than 3 months. Subsequently, the patients typically developed a variable combination of symptoms involving subacute encephalopathy, stroke-like events, radiculopathy and cranial neuropathy and survived for no more than 1-year. There are now, however, several reports suggesting that aggressive chemotherapy may be beneficial in IVL patients.[2,10-12] Therapy with a combination of cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone in addition to the recombinant anti-CD20 antibody rituximab (R-CHOP) is the most commonly employed treatment.[10] An early diagnosis is therefore crucial for improving the patient's outcome.[2] The diagnostic work-up should include biopsies of organs known to be frequently involved in patients with IVL, such as the skin, kidneys, adrenal glands, liver, and lungs. It has been reported that brain and skin involvement is more common in Western populations, whereas Asian populations tend to demonstrate more hemophagocytic involvement in association with spleen, hepatic, thrombocytopenic, and bone marrow involvement. As a result, the findings of skin biopsies may therefore be negative in Asians populations and not all skin biopsies may be diagnostic.[4] However, due to the fact that making a diagnosis based on analyses of tissue specimens other than the skin is usually difficult in patients suspected to have IVL, a random skin biopsy should therefore be considered, even in cases without any evident skin lesions.[1,3,14] In order to yield positive results, the biopsy should include the dermis as well as deeper layers, together with the hypodermic adipose tissue, the sample should be relatively large and the procedure should be performed at more than three different locations, including the upper arm, thigh, and abdomen.[14]

Confirming IVL is a diagnostic challenge, not only because the disease rarely presents with nodal or extranodal masses, but also because imaging methods are not always effective in detecting the lesions.[2] There are some reports of IVL with paraplegia accompanying no spinal cord abnormalities on MRI.[21,22] In the current case, spinal MRI revealed a nonenhanced spinal lesion at the level of Th3. The lesion disappeared after the administration of steroid pulse therapy and did not appear after the patient developed flaccid paraparesis. IVL should be taken into consideration in the differential diagnosis in cases involving progressive myelopathy with no apparent etiology.

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