# Mononeuropathy Multiplex as An Uncommon Presentation of Intravascular Lymphoma: A Case Report

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**Abstract**

A 64-year-old man presented with asymmetric paresthesia and subsequent weakness of his feet and a 10-kg weight loss over 40 days. Electrodiagnostic studies revealed distal axonal sensory-motor polyneuropathy with ongoing axonal loss. A peroneal nerve biopsy showed intravascular proliferation of CD-20 positive lymphocytes, which suggested intravascular large B-cell lymphoma.

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## List of abbreviations:

MM: Multiple Mononeuropathy

ONLS: Overall neuropathy limitations scale

IVLBCL: Intravascular large B-cell lymphoma

IVL: Intravascular lymphoma

Abstract:

**Case Presentation:** A 64-year-old man presented with asymmetric paresthesia and subsequent weakness of his feet and a 10-kg weight loss over 40 days. Electrodiagnostic studies revealed distal axonal sensory-motor polyneuropathy with ongoing axonal loss. A peroneal nerve biopsy showed intravascular proliferation of CD-20 positive lymphocytes, which suggested intravascular large B-cell lymphoma.

**Clinical Message:** Although intravascular lymphoma rarely presents with peripheral neuropathy, learning about this presentation can lead to timely diagnosis and improved prognosis in patients with intravascular lymphoma.

**Keywords: Intravascular large B-cell lymphoma, Mononeuritis Multiplex, Neuropathy, diagnosis, case report.**

# Introduction

Mononeuropathy multiplex (MM) is a painful neuropathy involving the sensory and motor peripheral nerves in two separate nerve areas simultaneously [1, 2].

The differential diagnoses associated with MM include a wide range of systemic disorders such as diabetes mellitus, vasculitis, amyloidosis, systemic lupus erythematosus (SLE), viral infections such as AIDS (acquired immunodeficiency syndrome), hepatitis, parvovirus B19, multiple compression neuropathies and paraneoplastic syndromes [3-6]. One possible, albeit rare, cause is lymphoma [7].

Intravascular lymphoma(IVL), a rare B-cell lymphoma, involves an aggressive intravascular overgrowth of neoplastic B-lymphocytes in small to medium-sized vessels [8]. The resulting deficits in vascular supply to organs produce a range of systemic and neurologic symptoms that often overlap with those of other diseases, especially vasculopathies[9]. The most common symptoms include skin lesions and fever/chills. The majority of patients with intravascular lymphoma who develop neurologic symptoms show central nervous symptoms such as cognitive or motor deficits [9]. A systematic review of reported cases estimated that the peripheral nervous system was involved in a minority of 9.5% of patients who experienced some degree of involvement as a late finding discovered only after diagnosis[9].

Diagnosing intravascular lymphoma is challenging because it is rare and it presents with a wide variety of symptoms[11]. Moreover, its diagnosis relies on clinical suspicion and tissue biopsy [10]. On the other hand, this type of non-Hodgkin lymphoma is lethal within a year unless diagnosed and treated early [11]. These issues highlight the importance of early accurate diagnosis and treatment and the role of a high index of suspicion for this life-threatening disease in patients presenting with symptoms suggesting vascular involvement [11-13].

Since intravascular lymphoma and its neurologic manifestations are rare; and the disease course is short with a fatal outcome, the study of their clinical course is limited to case reports and case series[11]. Previous case reports have reported patients with intravascular lymphoma presenting with peripheral neuropathy; However, MM as the primary presentation is extremely rare [7, 14-18]. Previously reported patients were diagnosed in post-mortem autopsies after an initial misdiagnosis of vasculitis [18, 19].

We report a case in which MM was the core manifestation of intravascular large B-cell lymphoma(IVLBCL) and was diagnosed based on a nerve biopsy.

# Case Presentation

A 64-year-old Iranian man presented to our outpatient neurology clinic with paresthesia of distal lower extremities that had started in the left lower extremity and progressed to the right side. Within one week, he developed asymmetrical weakness in distal lower extremities that sequentially involved both proximal lower extremities over one month.

He also reported a loss of appetite and a 10-kg weight loss within one and a half months.

He did not take any medications, did not smoke or use illicit drugs, and had no history of exposure to chemicals or toxins. He had no history of autoimmune or neoplastic diseases and his family history was unremarkable.

Upon physical examination, he was a middle-aged man with average body habitus. His general physical examination, including examination of the skin and lymph nodes, was unremarkable. The neurologic exam was significant for decreased muscle force in lower extremities that was more severe on the left side and absent deep tendon reflexes in the lower limbs. He had asymmetric distal hypoesthesia in both upper and lower limbs. His first dorsal interosseous muscle was atrophic on both sides.

The patient was admitted to the neurology ward for further workup and emergency treatment with a clinical diagnosis of multiple mononeuropathy. Electrophysiologic studies revealed distal axonal sensory-motor polyneuropathy with ongoing axonal loss and multiple mono-neuropathy. Initial lab tests revealed microcytic anemia. He underwent chest and abdominopelvic CT with contrast and left superficial peroneal nerve biopsy. Moreover, laboratory investigations were done in search of an underlying systemic disease that could cause anemia and multiple mononeuropathy (table 1).

Table 1: **Table 1 Para-clinical work-up for our patient who presented with mononeuropathy multiplex.** CBC: Complete blood count; ESR: Erythrocyte sedimentation rate; ANA: Anti-nuclear antibody; RF: Rheumatoid factor; p-ANCA: perinuclear anti-neutrophil cytoplasmic antibodies; CEA: Carcinoembryonic antigen; PSA: Prostate-specific antigen; AFP: Alpha-fetoprotein; βHCG: Beta-Human Chorionic Gonadotropin; HCV: Hepatitis C virus; HIV: Human Immunodeficiency virus; VDRL: venereal disease research laboratory (VDRL); Pb: Lead; PPD: Purified protein derivative; HbA1C: glycated hemoglobin; CT: Computed tomography. Cell counts were performed using the automated cell counter Sysmex® KP300, Biochemistry analyses were done using the Roche Hitachi 917 Rack Chemistry Analyzer, Japan; Serologic markers were checked using the ELISA kits from AUTOBIO DIAGNOSTICS CO. and Liason Autobio A 2000 automated ELISA reader.

| Para-clinical Assessment | Para-clinical Assessment | Para-clinical Assessment | Para-clinical Assessment | Normal range |
|---|---|---|---|---|
| Hematologic | CBC | Hb | 9.9 | M:14-18 F:12-16 |
| | | WBC | 4.6 | 4-10 |
| | | Plt | 236000 | 140-440 |
| | | MCV | 69.4 | 77-97 |
| | | RDW | 21 | 11.8-14.5% |
| | Retic Count | 2.8% | 2.8% | 0.5-2.5% |
| | Serum iron | 10 | 10 | 65-175 |
| | Ferritin | 600 | 600 | 30-300 |
| | Transferrin | 170 | 170 | 200-360 |
| | ESR | 45 | 45 | 0-22 |
| | Serum electrophoresis | Monoclonal IgA negative | Monoclonal IgA negative | |
| | Urine electrophoresis | Monoclonal IgA negative | Monoclonal IgA negative | |

| Para-clinical Assessment | Para-clinical Assessment | Para-clinical Assessment | Para-clinical Assessment | Normal range |
|---|---|---|---|---|
| Para-clinical Assessment | Para-clinical Assessment | Para-clinical Assessment | Para-clinical Assessment | Normal range |
| Rheumatologic and Vasculitis | ANA | Normal | Normal | |
| | Anti-Ro | Normal | Normal | |
| | Anti-La | Normal | Normal | |
| | RF | Normal | Normal | |
| | C3 | Normal | Normal | |
| | C4 | Normal | Normal | |
| | p-ANCA | Normal | Normal | |
| | c-ANCA | Normal | Normal | |
| Paraneoplastic | CA19-9 | Negative | Negative | |
| | CA15-3 | Negative | Negative | |
| | CEA | Negative | Negative | |
| | PSA | Negative | Negative | |
| | AFP | Negative | Negative | |
| | βHCG | Negative | Negative | |
| Infectious | HCV Ab | Negative | Negative | |
| | HIV | Negative | Negative | |
| | Viral markers | Negative | Negative | |
| | VDRL | Negative | Negative | |
| | PPD | Negative | Negative | |
| Toxins | Serum Pb | Normal | Normal | |
| Metabolic | $HbA_1C$ | Normal | Normal | |
| Neoplastic | Abdominopelvic CT | splenomegaly | splenomegaly | |
| | Endoscopy and colonoscopy | No significant abnormalities | No significant abnormalities | |
| | Bronchoscopy | No malignant cell in biopsy; | No malignant cell in biopsy; | |
| | Bone marrow aspiration and biopsy | Normocellular marrow with mild megaloid changes in erythroid series. | Normocellular marrow with mild megaloid changes in erythroid series. | |

He was treated empirically with 5 gr of IV methylprednisolone followed by 50 mg daily oral prednisolone for two weeks.

The histopathological assessment of peroneal nerve biopsy revealed intravascular proliferation of large atypical lymphocytes. The cells were positive for CD-20 on IHC staining (figure 1). Further IHC specification was not feasible due to the few number of available cells.

The final diagnosis was intravascular large B-cell lymphoma, presenting as mono-neuritis multiplex. The patient was referred to an oncology clinic where he received chemotherapy with a combination of doxorubicin, rituximab, cyclophosphamide, and vincristine for about 6 months. Along with chemotherapy, the patient continued receiving oral prednisolone at a dose of 100 mg per day.

### Outcome and Follow-up

We visited the patient for follow-up 4 months after he completed his first cycle of chemotherapy. His weakness had subjectively improved and his Overall Neuropathy Limitations Scale (ONLS) had improved from 1 to 0 in arms and from 4 to 2 in legs.

However follow-up electrodiagnostic studies showed progression in axonal loss and worsening of polyneuropathy. We postulate that the reason was disease progression and chemotherapy-induced axonal damage.

He came back to the clinic after 2 years of his first symptoms complaining of worsening weakness; his ONLS had improved to 2 in arms and 3 in legs. We performed a head-to-toe examination and found new skin lesions in his abdomen (*Figure 2* ); The skin lesion was biopsied and the histopathologic study confirmed the recurrence of intravascular Large-B-cell lymphoma. The timeline in *figure 3* summarizes the disease course in our patient.

## Discussion and Conclusion

We report a 64-year-old Iranian man with intravascular large B cell lymphoma who was referred to our clinic with paresthesia of distal lower extremities and motor symptoms that developed subsequently. These findings and later electromyography and nerve conduction studies were clinically compatible with a multiple mononeuritis pattern of involvement. The patient underwent a thorough work-up, the results of which were inconclusive. A nerve biopsy was done, and the findings led to a diagnosis of intravascular lymphoma.

Notably, our patient did not have any specific symptoms that specifically pointed to a diagnosis of lymphoma. A few cases of intravascular B-cell lymphoma have been reported that were associated with multiple mononeuropathy during the course of the illness. However, in most of these cases, MM was a late finding in the course of the disease, following weeks to months after the diagnosis that is usually based on other symptoms such as skin lesions, fever, or rigors [7, 15, 16]. Another case received an inaccurate diagnosis of vasculitis, which was revealed only after autopsy [7].

Patients with intravascular lymphoma most commonly present with symptoms related to the involvement of the central nervous system (39 percent) and skin (39 percent). Fever and skin lesions are common [5, 8, 20]. Bone marrow (32 percent), spleen (26 percent), and liver (26 percent) are less frequently involved [17]. Our patient did not have any evidence of CNS involvement at presentation, nor did he have fever or skin lesions. Also, bone marrow biopsy and aspiration did not show any significant pathological changes. However, splenomegaly was seen in his abdominal CT scan. Previous reports of similar cases are compatible with associated infiltration of the spleen and liver [7].

More importantly, our patient presented with mononeuropathy multiplex and weight loss without other symptoms. This is a rare presentation in IVLBCL but has been previously reported [13, 16]. In a case series of 26 patients with lymphoma-associated neuropathy, six patients had an MM pattern [7, 21, 22]. Most of these patients had a favorable hematological prognosis except for one patient who did not respond to chemotherapy and died as a result of infectious complications of bone marrow transplantation. Half of the patients experienced neurological improvement after chemotherapy [16]. In general, the prognosis is very poor for patients with intravascular lymphoma, with most of them dying within one year of their diagnosis [7, 9, 15, 16]. Although our patient's neurological disability did not completely respond to chemotherapy and he experienced a relapse of IVLBCL in the skin, he had a favorable survival of more than two years after the initial presentation, partly due to timely diagnosis and early treatment.

Our case report, in line with previous reports, highlights the importance of considering neurolymphomatosis and intravascular lymphoma as possible causes of MM. Specifically, a nerve biopsy with an assessment of clonal perivascular infiltrates may aid clinicians in differentiating between intravascular neoplastic infiltration from vasculitis.

## Declarations

## Ethics approval and consent to participate

The patient provided written informed consent for publication of this case report.

### Consent to publish

The patient provided written informed consent for publication of this case report.

## Data Access statement:

Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

## Authors' contributions

BHA and MAD were the attending physicians who participated in patient assessment and made the final diagnoses. PM and FB gathered and organized the patient data, searched the literature, and composed the manuscript. AZM was the attending pathologist who assessed the tissue specimens and provided the diagnosis. All authors contributed to editing the manuscript. All authors have read and approved the submitted version of the manuscripts.

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# Figure Legends:

Figure 1 Histopathologic assessment of peroneal nerve biopsy; Sections show unremarkable nerve bundles. Adjacent vessels are stuffed with large pleomorphic lymphoid cells. Cells have a high N/C ratio and hyperchromatic nuclei, and scant cytoplasm. Immunohistochemical(IHC) staining shows positive reactivity for CD20, and the diagnosis was reported as intravascular large B-cell lymphoma(CD20+).

Figure 2 (color)The abdominal skin lesion and the biopsy specimens of abdominal skin lesions; Left: Patient's abdomen upon examination on follow-up two years post-presentation. The skin shows scattered violaceous telangiectasiae and retiform purpurae. Middle and Right: Sections show intravascular proliferation of atypical lymphocytic cells inside the dermis. Left: Low magnification Right: High magnification.

Supplementary Figure: The case presentation timeline.