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Characteristics of the manuscript

Text: 1611 words.

Figures: 2

References: 10

Keywords

Vasculitis; Neurolymphomatosis; Small cell lymphocytic lymphoma; Nerve ultrasound; Magnetic resonance neurography; Nerve biopsy.

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Declarations of interest: none.

Abstract

Neurolymphomatosis is a rare complication of systemic lymphomas, and is classically related to hematogenous spread or intraneural spread of tumor cells from the leptomeninges. Here we report a case of neurolymphomatosis related to direct epineural invasion of superficial peroneal nerve from subcutaneous localization of B-cell lymphoma. Nerve biopsy revealed striking histological features suggestive of contiguous infiltration of superficial peroneal nerve by subcutaneous lymphoma. We think this case report sheds new light on neurolymphomatosis pathophysiology with an unreported mechanism in B-cell lymphoma. It also points out that the clinical spectrum in neurolymphomatosis is really variable, pure sensory mononeuritis being a rare presentation. Finally, our case is also strongly illustrative of the contribution of early nerve ultrasound in patient diagnosis and in guidance of nerve biopsy.

Introduction

Neurolymphomatosis is a rare complication of systemic lymphomas, and is classically related to hematogenous spread or intraneural spread of tumor cells from the leptomeninges.[1] Here we report a case of neurolymphomatosis related to direct epineural invasion of superficial peroneal nerve from subcutaneous localization of B-cell lymphoma.

Case report

A 57-year-old woman was first seen in our neurology department in March 2021. She has been followed in the hematology department since 2018 for a monoclonal B-cell lymphocytosis (CD5/CD19/CD20/CD43+, partial CD23, weak CD79b/FMC7) representing 6% of the total leucocyte population (total lymphocyte count = 2750/mm3). Whole-body CT scan was normal. She also had an IgG-λ monoclonal gammopathy (unquantifiable) and type I cryoglobulinemia. In summer 2020, she developed multiple yellowish-brown plaques on the right thigh following insect stings. Skin biopsy showed a large area of necrobiosis involving full thickness of dermis and superficial hypodermis, surrounded by a palisade of macrophages with giant cells and moderate polyclonal CD5- lymphocyte infiltrates, suggesting necrobiosis lipoidica, with no argument for skin lymphoma localization. In February 2021, after an unusual stretching movement, she experienced sudden pain and numbness at the dorsum of left foot and lateral part of calf. First physical examination one month later revealed induration and hypertrophy of left superficial peroneal nerve (SPN) with hypoesthesia and allodynia (Numeric Rating scale, NRS=7/10) of dorsum of foot, with normal motor strength. Nerve conduction studies revealed absence of sensory nerve action potential (SNAP) of left SPN with normal motor conduction studies of deep peroneal nerve. The rest of motor and sensory nerve conduction studies, ie. tibial, sural, median and ulnar nerves studied bilaterally, was otherwise normal. Standard needle electromyography in both tibialis anterior and

medial/lateral gastrocnemius muscles disclosed no abnormality. Because symptoms occurred during an unusual physical activity, a mechanical cause was considered, but was deemed really atypical. Nerve ultrasound found hypoechogenic thickening of left SPN with loss of fascicular architecture. The abnormalities extended over 5 cm from the ankle to the point where the nerve penetrates the fascia. A focal area of surrounding soft tissue infiltration and edema was observed at mid-leg (**Fig. 1** and **supplementary material**). Magnetic resonance neurography (MRN) was performed and showed a hypertrophic SPN with strong perineural tissue enhancement (**Fig. 1**). Two weeks later, she experienced sudden numbness and neuropathic pain of the dorsum of right foot, with no obvious mechanical factor. Nerve conduction studies revealed alteration of right SPN SNAP, and left SPN SNAP was still inexcitable. Pure sensory mononeuritis multiplex was diagnosed. Total blood count, CRP and fibrinogen were normal. Immunofixation electrophoresis showed IgG-λ monoclonal gammopathy (2 g/l). Cryoglobulin was undetectable, and complement levels analysis showed a significant drop in C4 level (0.01 g/l, N 0.16-0.39) with normal C3 and CH50 levels. LDH (249 IU/ml, N 135-215) and bêta-2 microglobulin (2.26 mg/l, N 0.8-2.2) were moderately elevated. Serum level of angiotensin-converting enzyme was normal. Antinuclear, Anti-SSA/Ro, anti-neutrophil cytoplasmic and onconeural antibodies, rheumatoid factor, hepatitis B and C viruses, HIV and Lyme disease were not found. Whole-body CT scan revealed multiple centimetric mediastinal and coeliomesenteric lymph nodes. Because peripheral nerve imaging was highly suggestive of a vasculitic or infiltrative process, biopsy of left SPN and peroneus brevis muscle was done. On the basis of the significant perineural abnormalities on nerve ultrasound, we also took a large sample of perineural subcutaneous adipose tissue. The main abnormality was a massive mononuclear cell infiltrate in fibroadipose tissue and epineural fascia, consisting predominantly of B lymphocytes (CD20+/CD5+/CD23+/Cycline D1+), with a large area of necrotizing fasciitis and panniculitis (**Fig. 2**). The cell infiltrate was

extending toward nerve, gradually lessening through epineurium and perineurium, and was almost absent of endoneurium. The biopsy also revealed a small-to-medium-sized vessel necrotizing vasculitis in nerve, with moderate perivascular lymphocytic infiltrates. Molecular analysis using polymerase chain reaction on a frozen sample revealed a clonal B-cell population in nerve and subcutaneous tissue, with the same immunophenotypic characteristics and Immunoglobulin Heavy Chain Gene rearrangement than the clonal population in blood. Patient was diagnosed with subcutaneous small lymphocytic lymphoma (SLL) with contiguous infiltration of SPN. Cerebrospinal fluid (CSF) analysis showed 1 white blood cell/mm^3 and 3 red blood cells/mm^3 in conventional cytology, with normal total protein count. Flow cytometry analysis found rare lymphocytes and monocytes but 70% of the lymphocytes were clonal by immunophenotyping. No blood red cell was observed in flow cytometry, ruling out CSF blood contamination. Patient was treated with oral corticosteroids 1 mg/kg/day during four weeks following by progressive tapering over 6 weeks. This treatment was begun just after the nerve biopsy and before final diagnosis was made because vasculitis was highly suspected and rapid deterioration was feared. Neuropathic pain significantly improved in 3 weeks (NRS=4/10) but the patient developed weakness of right foot dorsiflexion. A new electrodiagnostic examination disclosed partial conduction block of right deep peroneal nerve at the fibular head with decreased nerve conduction velocity, with normal distal CMAP and SNAP amplitudes. Electromyographic study disclosed neurogenic pattern in tibialis anterior muscle without active denervation sign. Three weeks later, she had fully recovered and the above-mentioned abnormalities had regressed. She was further treated by 6 cycles of a combination of fludarabine, cyclophosphamide and rituximab according to the French and international chronic lymphocytic leukemia and SLL treatment recommendations.[2] Fludarabine and cyclophosphamide were administered orally for three days at 28-day intervals at the dose of 40 mg/m^2 (70 mg) and 250 mg/m^2 (450 mg). Rituximab

was administered intravenously at 28-day intervals at the dose of 375 mg/m² (700 mg). At last available follow-up (four months after beginning the treatment), patient has only mild residual sensory symptoms and neuropathic pain of the dorsum of both feet (NRS=2/10). She has not developed new neurological symptoms. Nerve conduction studies were stable.

Discussion

Lymphomas affect the peripheral nervous system in many ways: demyelinating neuropathy through a dysimmune mechanism, paraneoplastic microvasculitis, amyloidosis or immunoglobulin deposits, and direct malignant lymphocytic invasion of the peripheral nerves or roots, coined neurolymphomatosis.[1,3,4]

In our patient, nerve biopsy was crucial to determine the mechanism of the neuropathy, especially because her hematological condition was stable for three years so that the link between the monoclonal B-cell lymphocytosis and neuropathy was not obvious. The biopsy found the same monoclonal B-cell population in nerve and blood, consistent with the diagnosis of neurolymphomatosis secondary to systemic SLL. Pathogenesis of neurolymphomatosis is still unclear, but putative mechanisms include hematogenous spread, penetration to the CSF space along spinal roots or direct nerve invasion after binding to neural cell adhesion molecules.[1,5] In those cases, lymphomatous cell are generally located in perineurium and endoneurium, without significant involvement of epineurium or perineural tissues.[3] But against all odds, the monoclonal cell infiltrate in our patient was far more abundant in subcutaneous tissue, and was gradually lessening toward epineurium and perineurium. This pattern was better suggestive of contiguous infiltration of SPN by subcutaneous lymphoma, despite the presence of the monoclonal population in the CSF. Considering the very superficial localization of SPN, direct epineural invasion by monoclonal cells from subcutaneous tissue seems possible, as it has been previously hypothesized in T-

cell lymphoma.[6] Pathogenesis of neurolymphomatosis might be even more complex and new mechanisms might be elucidated in the future, as evidenced by a recent study showing a potential role of the extracellular matrix in malignant lymphoproliferation.[7]

Nerve biopsy also showed necrotizing vasculitis, which is not reported in neurolymphomatosis.[1,3,4] In this context, may other mechanisms participate in the neuropathy of our patient? Necrotizing vasculitis has been reported as a rare paraneoplastic syndrome in the context of hematological malignancies, but only few case reports are available so that the association is not clear.[4] Besides, serum onconeural antibodies were tested negative in our patient. Vasculitis linked to cryoglobulinemia could also be hypothesized, because of low CH50 level and former cryoglobulinemia positivity. However, necrotizing vasculitis of medium-sized vessels is mainly observed in type 2 cryoglobulins secondary to HVC chronic infection.[8] Peripheral nerve vasculitis linked to cryoglobulinemia is frequently a non-necrotizing lymphocytic microvasculitis of the small arteries.[8] Nonetheless, we cannot rule out a role of croyglobulinemia in the vasculitis of our patient.

Nerve imaging was crucial in the management of our patient. Indeed, MRN and nerve ultrasound disclosed enlarged SPN with major perineural tissue abnormalities. In the context of a painful neuropathy and an underlying hematological disease, vasculitis or lymphomatous infiltration was evoked therefore leading to early nerve biopsy.[9,10] Nerve ultrasound also greatly influenced the biopsy procedure: the nerve sample was taken at a lower site than usual, where perineural edema was the greatest. We also took a large amount of perineural subcutaneous adipose tissue for paraffine-embedded section analysis. Ultrasound analysis led to a highly effective biopsy procedure. Only few other papers have reported on nerve ultrasound findings in patients with neurolymphomatosis. Vijayan et al. described consistent findings in three patients with nerve swelling and loss of fascicular architecture associated with increased intraneural and perineural vascularity. They also described a large mass arising

from the ulnar nerve and the sciatic nerve in two patients.[9] Briani et al. reported one patient with increased perineural and intraneural vascularity but otherwise unaltered nerve morphology.[10] Our results are close to those of Vijayan and al. with enlarged cross-sectional area, altered nerve echogenicity and loss of fascicular architecture. Perineural abnormalities were not organized as a mass, but were rather suggestive of an edematous reaction. Unfortunately, we did not perform Doppler sonography. The value of nerve ultrasound study in a neurophysiology department is increasingly recognized, and may speed up the diagnosis of various diseases, such as neurolymphomatosis.

Conclusion

We report a putative mechanism of peripheral nerve involvement in B-cell lymphoma, namely direct epineural invasion from subcutaneous localization of SLL. We also demonstrate the crucial contribution of early nerve ultrasound in patient diagnosis and in guidance of nerve biopsy.

References

1. Baehring JM, Damek D, Martin EC, et al. Neurolymphomatosis. Neuro Oncol. 2003;(April):104–15.

2. Quinquenel A, Aurran-Schleinitz T, Clavert A, et al. Diagnosis and Treatment of Chronic Lymphocytic Leukemia: Recommendations of the French CLL Study Group (FILO). HemaSphere. 2020 Oct;4(5):e473.

3. Tomita M, Koike H, Kawagashira Y, et al. Clinicopathological features of neuropathy associated with lymphoma. Brain. 2013;136(8):2563–78.

4. Viala K, Béhin A, Maisonobe T, et al. Neuropathy in lymphoma: a relationship between the pattern of neuropathy, type of lymphoma and prognosis? J Neurol Neurosurg Psychiatry. 2008;79:778–82.

5. Briani C, Visentin A, Campagnolo M, et al. Peripheral nervous system involvement in lymphomas. J Peripher Nerv Syst. 2019 Mar;24(1):5–18.

6. Puffer RC, Dyck PJB, Paul P, et al. Putative mechanisms for spread and transformation of cutaneous T-cell lymphoma to neurolymphomatosis. Muscle and Nerve. 2019;60(5):E30–3.

7. Brekken RA. Faulty ECM signaling facilitates autoimmune lymphomagenesis. Cancer Discov. 2014 Jan;4(1):25–6.

8. Cacoub P, Comarmond C, Domont F, et al. Cryoglobulinemia Vasculitis. Am J Med. 2015;128(9):950–5.

9. Vijayan J, Chan YC, Therimadasamy A, et al. Role of combined B-mode and Doppler sonography in evaluating neurolymphomatosis. Neurology. 2015;85(9):752–5.

10. Briani C, Visentin A, Cavallaro T, et al. Primary neurolymphomatosis as clinical onset of chronic lymphocytic leukemia. Ann Hematol [Internet]. 2017;96(1):159–61. Available from: http://dx.doi.org/10.1007/s00277-016-2852-2

Figure legend

Figure 1

A, B: nerve ultrasound showing A/ hypertrophic left superficial peroneal nerve with loss of fascicular architecture (cross-sectional area 6 mm², within dotted circle) and perineural tissue edema (white arrows); B/ normal left superficial peroneal nerve at mid-leg underneath fascia (cross-sectional area 2 mm², within dotted circle).

C : magnetic resonance neurography, fat-suppression short T1 inversion recovery, showing hypertrophy of left superficial peroneal nerve with strong nerve and subcutaneous enhancement (white arrow).

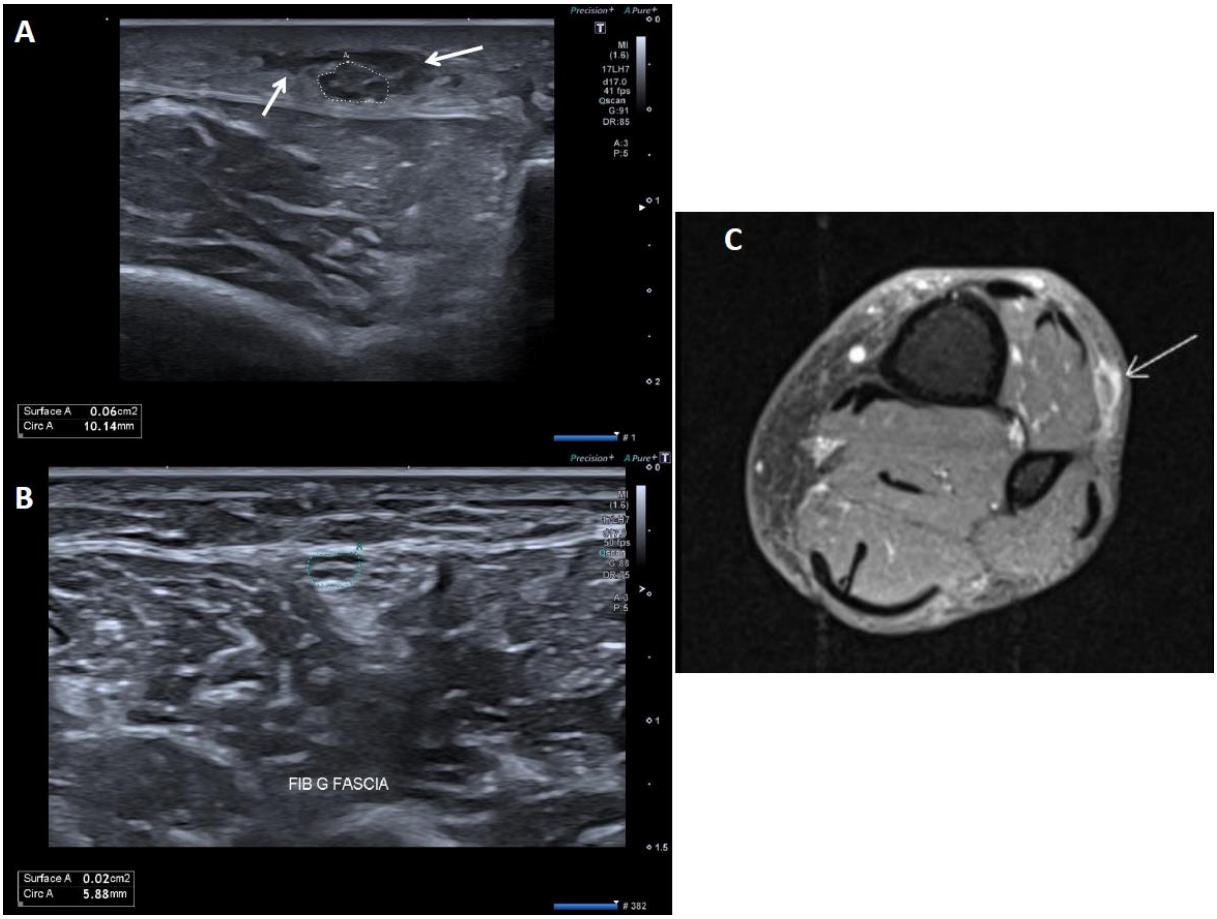
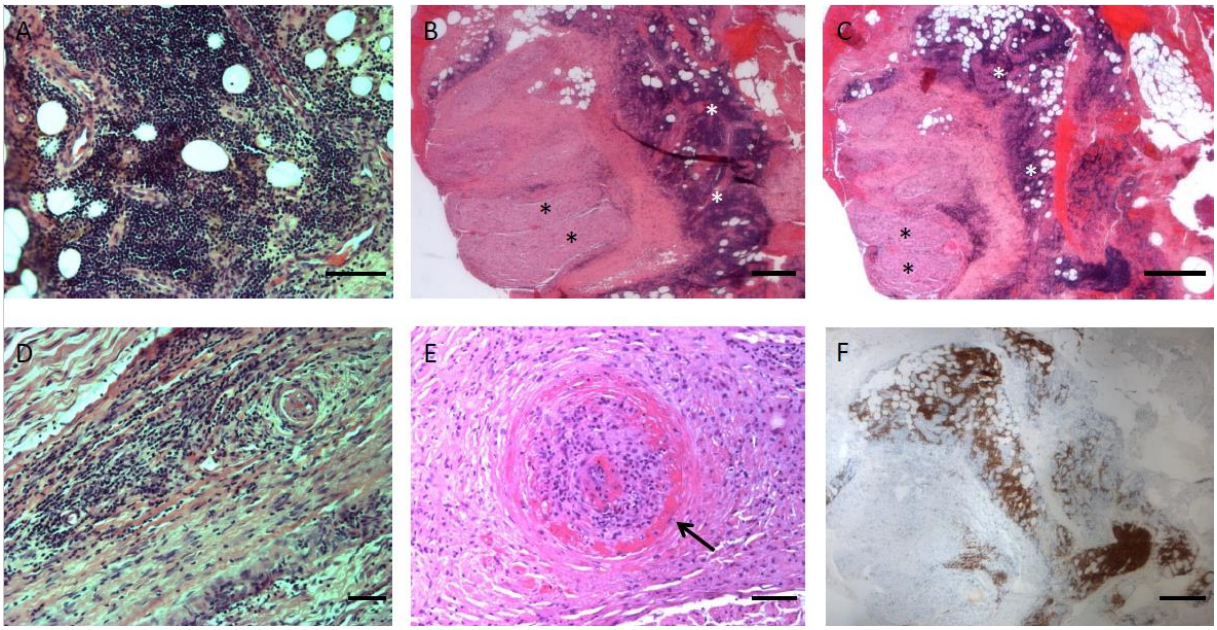


Figure 2

Superficial peroneal nerve biopsy. Longitudinal section of paraffin embedded tissue seen under light microscopy. (A, B, C) Massive mononuclear cell infiltrates in subcutaneous tissue with area of necrotizing panniculitis (white stars). The infiltrate extends toward nerve but is clearly less abundant (B & C, black stars) (Hematoxylin-eosin saffron staining). (D) Mononuclear cell infiltrates in the perineurium (Hematoxylin-eosin saffron staining). (E) Thrombosis of a medium-sized vessel in perineurium with thickened vessel wall and fibrinoid necrosis (black arrow) (Hematoxylin-eosin saffron staining). (F) Marked CD20 expression (B lymphocytes), which is very prominent in the mononuclear cells infiltrate. Scale bars = 100 µm (A, D & E) and 500 µm (B, C & F).



Supplementary material

Dynamic nerve ultrasound study of left superficial peroneal nerve, from ankle to mid-leg. The nerve becomes hypertrophic and hypoechogenic with loss of fascicular architecture a few centimeters above the ankle, with a focal area of subcutaneous edema. The study shows gradual normalization of the nerve appearance by moving up mid-leg, with normal appearance of the nerve under the fascia.