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CASE REPORT

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A severe case of neuroleukemiosis caused by B cell chronic lymphocytic leukemia, presenting as mononeuritis multiplex

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Abstract

Aims: To report an exceptional case of nerve infiltration by an otherwise benign chronic B cell leukemia, inducing severe mononeuritis multiplex.

Methods: The patient underwent extensive evaluation, including nerve conduction study and myography, brain and plexus MRI, and nerve biopsy.

Results: The clinical and electrophysiological diagnosis was a mononeuritis multiplex with severe motor and sensory involvement; only the nerve biopsy allowed definite diagnosis and introduction of chemotherapy, leading to resolution of sensory deficit and progressive motor improvement.

Discussion: Neuroleukemiosis caused by chronic lymphoid leukemia is an exceptional diagnosis. The presence of other possible causes like cryoglobulinemia could induce avoidance of nerve biopsy thus undertreating patient, since steroid treatment is not expected to be efficient on lymphocytic proliferation. Our case stretches the importance of nerve biopsy and raises neuromuscular specialist's awareness of this rare entity.

KEYWORDS
chronic lymphoid leukemia, mononeuritis multiplex, neuroleukemiosis, neurolymphomatosis

1 | BACKGROUND AND AIMS

Infiltration of peripheral nerve by leukemia has been defined as neuroleukemiosis,[1] to distinguish this entity from the more common neurolymphomatosis.

Neurologic involvement's severity and outcome are influenced by the characteristics of the leukemia, and it has been described almost exclusively in relation to acute forms.

Neuroleukemiosis caused by chronic leukemia (CL) is exceedingly rare, but severe involvements of the peripheral nervous system are described. Due to notion of CL being a "benign" disease, which often requires follow-up alone without specific treatment, this etiology of peripheral neuropathy can be easily overlooked, potentially causing misdiagnosis and insufficient treatment.

Here, we report the case of neuroleukemiosis caused by chronic lymphoid leukemia, inducing a severe mononeuritis multiplex.

2 | CASE REPORT

A 58-year-old woman was diagnosed in March 2020 with B cell chronic lymphocytic leukemia (CLL), stage RAI I, Binet A, with lymphocytosis and cervical adenopathies. She secondarily developed leukemic infiltration in her left breast, granulomatous rosacea (both histologically proven), and

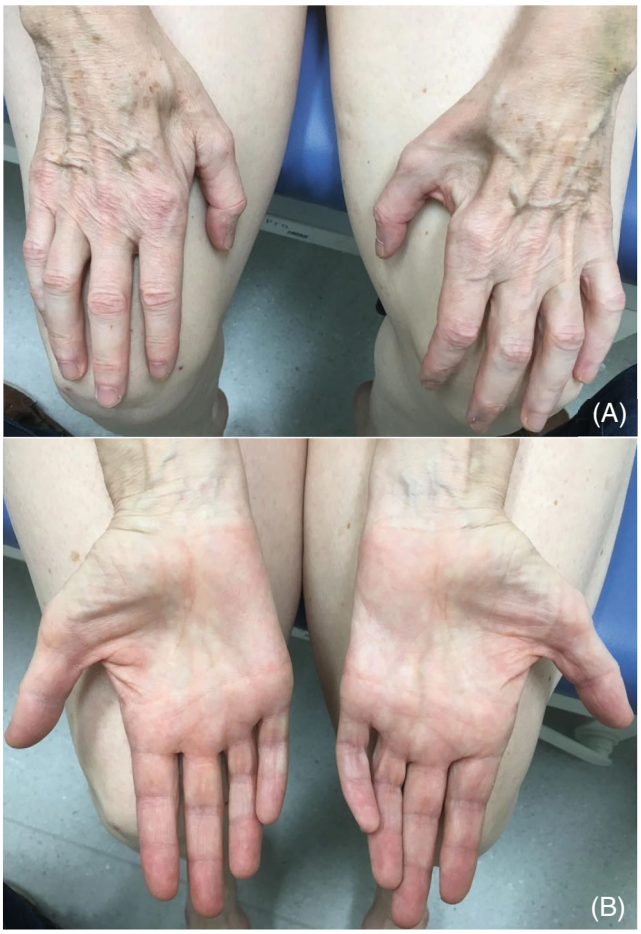

FIGURE 1 Hand muscles amyotrophy (A: dorsal view; B: palmar view).

bilateral ear chondritis. Blood work-up disclosed type I cryoglobulinemia with hypocomplementemia and severe hypogammaglobulinemia.

In August 2021, she experienced rapidly progressing painful dysesthesias in her left hand, and a few days later, in her right hand encompassing median, ulnar, and radial sensory territories. In the two following weeks, she noticed progressive weakness and atrophy in both hands (with left predominance, Figure 1), limiting daily activities as bottle-opening or shirt-buttoning.

Neurological examination showed left predominant amyotrophic weakness of hand muscles (abductor pollicis brevis MRC 4/5 on both sides, dorsal interossei MRC 2/5 on the left, and 3/5 on the right side).

Strength was normal in all other muscle groups, with normal symmetrical reflexes. Toes were downgoing. Sensory examination showed bilateral glove-pattern hypoesthesia up to the wrists.

Nerve conduction studies (Table S1) were compatible with mononeuritis multiplex with predominantly axonal, non-length dependent and asymmetrical sensorimotor neuropathy in the upper limbs. Brachial plexi MRI was normal, but brain MRI showed diffuse hypertrophic pachymeningitis; CSF examination disclosed a moderate pleiocytosis (10 leucocytes/mm^3) with 2 erythrocytes/mm^3 and normal protein level. CSF cytology showed 59% of white cells with the same immunophenotype as the known CLL. Radial nerve biopsy (Figure 2) showed segmental and focal perineural B cell infiltrate ($CD20^+$, $CD79a^+$, $CD5^+$), with the same characteristics as identified in the previous breast biopsy, allowing the diagnosis of neuroleukemiosis. We considered all previous systemic manifestations (chondritis, rosacea, cryoglobulinemia type I) as paraneoplastic consequences of CLL. The cytogenetic in blood revealed a deletion 13q and a trisomy 12 without negative prognostic factors (del 11q, 17p, or TP53 mutation). Immunoglobulin variable heavy chain (IGHV) genes were mutated. The lymph node involvement was stable on CT. She was initially treated with oral steroids. In order to limit the neurological complications and to increase the effectiveness of treatment, an association of acalabrutinib 100 mg twice/day and obinutuzumab for the six first cycles was introduced. At 4 weeks from treatment onset, the patient showed complete remission of dysesthesias and slight motor improvement. Motor function gradually improved: serial handgrip strength measured with Jamar grip dynamometer showed a progressive improvement from baseline to 7 months follow-up of 19% for the right hand (18.7–23 kg) and 24% for the left hand (10.7–14 kg).

3 | INTERPRETATION

Infiltration of nerve structures by leukemia is defined as neuroleukemiosis[1] and can manifest with mononeuropathy (isolated or multiplex), polyneuropathy, or plexopathy.[2] Neuroleukemiosis is an exceptional diagnosis, occurring mostly in acute leukemia. Only five cases have previously been described in CLL,[3–6] one presenting as lumbosacral plexopathy and the others as mononeuritis multiplex. When performed,[4] nerve immunohistochemistry showed positive CD20 and CD5 staining, as in our case. Nerve and other tissues involvements are utmost unusual and challenge the notion of CLL being a "benign" hematological disease, even when CLL does not show negative hematological predictive factors and does not require treatment per se. Beyond direct nerve infiltration, other types of peripheral neuropathy (including demyelinating polyneuropathies) have been rarely described in association with CLL.[7] Tissue infiltration by monoclonal B cells is frequently found but nerve involvement is unusual. In our case, given the multisystemic infiltration of CLL, a mechanism by hematogenous spread seems plausible. As described in neurolymphomatosis, the apparently random targeting of different tissues in neuroleukemiosis could also depend on the different expression of adhesion receptors.[8] A secondary spreading after CSF penetration is another possible explanation in our case, given the CSF cytology evidence of the CLL clone and meningeal involvement signs in brain MRI.

Should we had considered the diagnosis of peripheral nerve vasculitis based only on the positive cryoglobulinemia and omitted the nerve biopsy, we would have treated the patient with steroids alone, which are not expected to be efficient on the lymphocytic proliferation. Indeed, from the sole hematological point of view, the patient had no indication for CLL treatment.

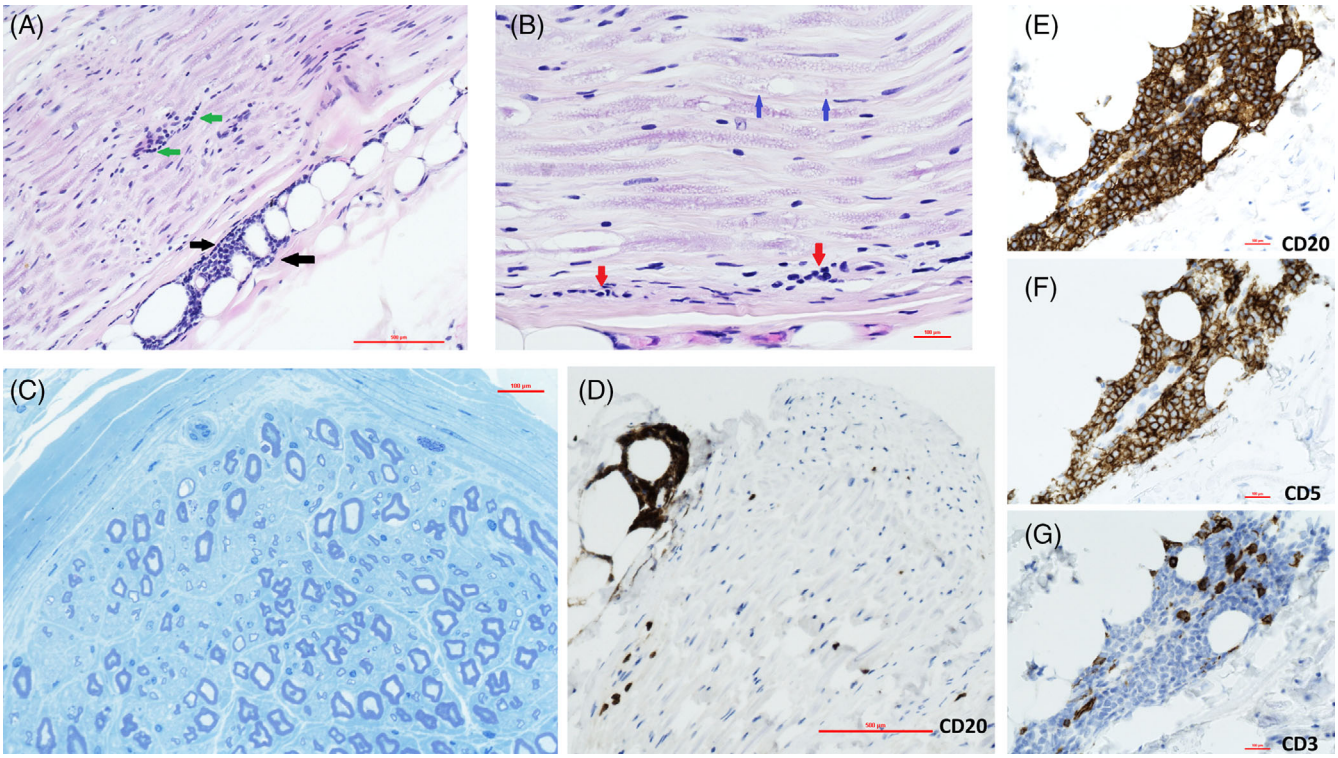

FIGURE 2 Superficial (sensory) radial nerve biopsy. Histological examination of longitudinal sections on H&E (A,B) revealed focal lymphoid infiltrates located in epineurium (black arrows), perineurium (red arrows) and endoneurium (green arrows), and rare features of axonal degeneration as "digestion chambers" (blue arrows). Immunophenotyping (D–G) of lymphoid infiltrates (ABC-peroxidase/DAB) confirmed that most lymphoid cells were B-cells of same phenotype ($CD20^+$, $CD5^+$) (E,F) as the known CLL without significant T-cell ($CD3^+$) infiltration (G). On nerve cross section, the leukemia cells were well detected by CD20 immunohistochemistry in the endoneurium and appeared rare and sparsed. Elsewhere, leukemia cells were mostly located in perivascular area without occlusion of blood vessel lumens. On semithin cross section (C), the distribution of the large myelinated fibers was variable with a loss in number in some areas, without obvious clusters of regeneration.

The strength of this study lies in the description of a rare but severe neurologic complication of a theoretical benign hematological disease, with challenging diagnosis and favorable outcome. It also demonstrates the usefulness of nerve biopsy in such unusual patients. We are aware of the limitation of a single case report, especially regarding treatment response.

Although rare, neuromuscular specialists in reference centers should be aware of this possible complication and promptly order a nerve biopsy in case of mononeuritis multiplex in patients with CLL.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest related to this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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