BMJ Case Reports

TITLE OF CASE

Diagnostic delay in a case of T-cell neurolymphomatosis.

SUMMARY

A 69-year-old woman presented with severe subacute painful meningoradiculoneuritis. Neurophysiology showed a patchy, proximal axonal process with widespread denervation. Cerebrospinal fluid (CSF) was lymphocytic (normal T-cell predominant) with negative cytology. MRI revealed multiple sites of enhancement but FDG-PET was negative. Bone marrow aspirate and trephine (BMAT) showed no evidence of a lymphoproliferative condition. Right brachial plexus biopsy demonstrated mixed T-/B-cell endoneurial inflammation not fulfilling criteria for vasculitis. She was stabilised with high-dose steroids and cyclophosphamide, followed by mycophenolate for inflammatory myeloradiculoneuritis. However, symptoms recurred when prednisolone was weaned. Although T-cell receptor gene analysis from the initial CSF demonstrated clonal rearrangements, it was only when the same clones were identified on two repeat BMATs and CSF that T-cell neurolymphomatosis, an exceedingly rare condition, was diagnosed. This case highlights the value of repeated investigations when clinical suspicion is high and usefulness of clonality assessment to increase yield when other investigations are non-diagnostic.

BACKGROUND

Peripheral neurolymphomatosis (pNL) is a disorder of lymphomatous infiltration of the peripheral nervous system. Most cases are associated with B-cell non-Hodgkin lymphoma (NHL) of various types, whereas T-cell pNL is exceedingly rare.

Significant diagnostic delay is acknowledged (average 18.7±9.2 months in a case series from our hospital of pathologically proven cases of all types of pNL or those with highly suggestive biopsies over 16 years [S Keddie, unpublished data, 2019]), related to heterogeneity of clinical presentation, non-specific investigations with variable diagnostic yield and difficulties of obtaining diagnostic and treatment-determining tissue from nerves. Without treatment, T-cell lymphoma usually takes an aggressive, frequently fatal course. Despite intensive therapy (chemotherapy +/- high dose therapy and haematopoietic stem cell transplantation), under 50% of patients are disease-free at 5 years.[1] Specific consideration for strategies to treat disease behind the blood-nerve barrier makes such approaches more challenging. Definitive histological diagnosis is usually a pre-requisite to any treatment. This case highlights the diagnostic challenges and value of repeated investigations over time, ideally when immunosuppression is minimised, when clinical suspicion is high.

CASE PRESENTATION

A 69-year-old woman presented with severe lumbar back pain followed by right arm pain without neurological deficit. She initially had a low-grade fever with raised inflammatory markers (C-reactive protein 140mg/L). Ten days later, she developed bilateral leg weakness and difficulty walking. Because of rapid deterioration, she was treated with five days of intravenous immunoglobulin for presumed acute inflammatory demyelinating polyradiculoneuropathy. Medical history included localised breast cancer treated with wide local excision and tamoxifen 13 years prior and normal surveillance mammogram one

year before. She was an ex-smoker of 40-pack-years.

She continued to worsen, and over six weeks developed flaccid tetraparesis, facial weakness, diplopia, ptosis and urinary retention. Examination revealed asymmetric, non-length dependent weakness with reduced pinprick sensation and proprioception (Fig. 1a). Reflexes were present but asymmetric in the arms and absent in the legs. Plantar responses were extensor bilaterally.

INVESTIGATIONS *If relevant*

Initial neurophysiology showed asymmetric reduction in median nerve compound muscle action potentials (CMAP) with normal lower limb motor studies. Sensory nerve action potentials (SNAP) were absent in the right median, attenuated in the right radial and ulnar and left median, left sural and superficial peroneal nerves but normal in the right radial, sural and superficial peroneal nerves. There was florid active denervation throughout the right upper limb, with milder involvement of the left upper and right lower limb muscles. Clinical and electrophysiological characteristics were those of a diffuse right and patchier left brachial plexus and bilateral lower limb radiculoplexopathy (Fig. 1b).

Magnetic resonance imaging (MRI) showed enhancement of bilateral oculomotor, V2 and left V1 trigeminal nerves, right supraclavicular brachial plexus with bilateral diffuse enlargement and hyperintensity and left S1 nerve root with additional nodular thickening of the cauda equina (Fig. 2a). Fluorodeoxyglucose positron emission tomography (FDG-PET) was negative, as were investigations for breast cancer recurrence.

Three cerebrospinal fluid (CSF) samples showed lymphocytic pleocytosis (range 20-74x10^9/L), elevated protein (range 0.84-1.57g/L) and unmatched oligoclonal bands (Fig. 1c). Enterovirus, herpes simplex virus-1 and -2, varicella zoster virus, cytomegalovirus, Epstein Barr virus polymerase chain reaction (PCR) and Lyme serology (CSF and serum) were negative. Cytology and immunostaining of CSF cells was consistent with a lymphocyte population with no atypical cells identified. Flow cytometry showed abundant lymphocytes, predominantly normal CD3+ T-cells (90% of total cellularity) with occasional CD20+ B-cells (Fig. 2b). Immunoglobulin heavy chain (IgH) PCR showed no evidence of clonal rearrangements. However, clonal T-cell receptor (TCR) rearrangements (Vg9+Jg1.3/2.3, and Vg10+Jg1.3/2.3) were detected. pNL was the suspected clinical diagnosis at this stage and histological confirmation was sought.

Left sural nerve biopsy performed initially revealed active axonal degeneration only and was non-diagnostic, as clinical, imaging and neurophysiological findings pointed to more proximal pathology. Subsequent clinical, electrophysiological and MRI targeted right brachial plexus biopsy demonstrated substantial endoneurial inflammation with mixed CD3/CD8+ T, CD20+ B-cell and occasional plasma cell populations with accompanying prominent endoneurial oedema, axonal degeneration and some depletion of myelinated fibres (Fig. 2c). Histological criteria for vasculitis were not met. Detailed immunostaining and review by haemato-histopathologists was unable to confirm malignant infiltration, neoplastic lymphoproliferation or amyloid.

DIFFERENTIAL DIAGNOSIS *If relevant*

The clinical features and neurophysiology and imaging findings were consistent with a subacute onset, painful myeloradiculoneuritis. Differential diagnoses initially included an infective cause, given constitutional symptoms and raised inflammatory markers, but post-infectious, vasculitic, inflammatory,

neoplastic and paraneoplastic causes were also considered, due to the rapid progression and previous history of malignancy and smoking. Following the finding of clonal TCR rearrangements in CSF and histopathological evidence of T-cell infiltrate in clinically affected tissue, strong suspicion of a T-cell mediated pNL was raised.

TREATMENT *If relevant*

Due to sensitivity issues with clonality testing, rarity of T-cell pNL, lack of definitive histopathological diagnosis and advised evidence that transient T-cell clones can occur with infective and inflammatory processes,[2] a decision was made to commence empirical treatment for inflammatory myeloradiculoneuritis. With high dose oral corticosteroids and pulsed intravenous cyclophosphamide, there was demonstrable stabilisation. Ten courses of cyclophosphamide were completed over six months as per the CYCLOPS regimen [3] and mycophenolate mofetil (MMF) was commenced as maintenance therapy, while oral corticosteroids tapered.

With cyclophosphamide, steroids and intensive neurorehabilitation, the patient made meaningful gains. Three months post-cyclophosphamide proximal upper limb strength improved from Medical Research Council (MRC) grade 3/5 to 5/5 and she could stand with assistance (Fig. 1a). Prednisolone was weaned completely by 15 months from presentation and MMF continued. However, a relapse occurred two months later with loss of ability to stand, recurrence of similar meningoradicular pain and rapid regression to quadriplegia. Neurophysiology also confirmed deterioration in motor and sensory parameters, including ongoing active denervation with chronic neurogenic changes (Fig. 1b).

Although repeat investigation revealed some resolution of the cranial nerve and cauda equina enhancement on MRI, two further CSF samples remained lymphocytic (8-11x10^9/L) with elevated protein (0.97g/L). Repeat whole body FDG-PET was negative. Bone marrow aspirate and trephine (BMAT) showed no evidence of an abnormal lymphoid population. However, multiplex PCR was again positive for clonal TCR beta and gamma chain gene rearrangements, identical to those identified in CSF at presentation. Again after multidisciplinary discussion, on the basis of T-cell clones being unstable and ‘non-specific’ and the lack of histological confirmation in clinically affected tissue a diagnosis of T-cell pNL was not confirmed.

Intravenous methylprednisolone resulted in neurological stabilisation but no functional improvement. Cyclosporine was commenced as an alternative immunosuppressant because of its preferential T-cell effect. The patient remained wheelchair-bound with reasonable arm function, no perianal sensation and required a suprapubic catheter. Her degree of disability remained stable over the following two years.

Given lack of definitive diagnosis and ongoing suspicion of the relevance of the clonal T-cell populations, she was once again re-evaluated 12 months later. BMAT again showed no morphological evidence of lymphoma, but the same TCR gene rearrangements were detected as in CSF.

OUTCOME AND FOLLOW-UP

The clinical presentation of subacute onset, painful, steroid-responsive myeloradiculoneuritis, non-diagnostic T-cell infiltrate in affected tissue but persistent identical T-cell clones in bone marrow and CSF suggested a diagnosis of probable T-cell pNL. A more intensive approach including high-dose chemotherapy with agents such as methotrexate, cytarabine and thiotepa were considered but in light of her poor performance status, 40-pack-year smoking history and other comorbidities, less intensive strategies were

adopted. She continued on maintenance prednisolone and cyclosporine and remained neurologically stable until death secondary to urinary sepsis at 46 months from presentation.

DISCUSSION *Include a very brief review of similar published cases*

Lymphoma can affect the nervous system in numerous ways. pNL refers to direct infiltration of malignant lymphocytes into peripheral nerves, cranial nerves, nerve roots and/or plexus. 90% of cases are NHL, most commonly diffuse large B-cell lymphoma, and acute leukaemia accounts for the remaining 10%. Peripheral T-cell lymphoma (PTCL), a form of NHL, is an exceedingly rare cause. pNL may be the first presentation of malignancy in around 25% of patients.[4] This case highlights how diagnostic difficulty contributes to its under-recognition.

Histopathology is the gold standard, but advances in imaging and immunogenetics can support the diagnosis. Although none of these tests are 100% sensitive or specific, their presence in the appropriate clinical context, with neurology and haemato-oncology collaborative expertise, may be deemed adequate to justify toxic treatments.

MRI is not always diagnostically useful but findings can include nerve nodular thickening with or without enhancement, whilst FDG-PET can show abnormal linear uptake along the course of involved nerves.[5] In the International Primary Central Nervous System Lymphoma Collaborative Group case review of 50 patients with pNL, MRI and FDG-PET were abnormal in 77% and 84% of cases respectively. Sural nerve biopsies were diagnostic in only 40% in this series, increasing to 88% of targeted nerve biopsies.[4] As such, both imaging modalities are recommended to increase the likelihood of identifying involved tissue and guide targeted biopsy because of the patchy nature of lymphomatous neuropathy.

Tissue diagnosis of T-cell pNL is particularly challenging because of frequently admixed B-cell components giving the appearance of a mixed inflammatory infiltrate. Furthermore, although suspicion may arise due to abnormal surface T-cell antigenic expression identified on immunophenotyping, there is a lack of surface clonal marker expression, such as Ig light chains, a marker of B-cell lymphoproliferation. Clonality assessment of lymphocytic surface receptor (IgH or TCR subunit for B- and T-cells respectively) gene rearrangement can detect unique rearranged antigen-receptor genes on monoclonal tumour cells.[6] This can help prompt review of the diagnosis if clonality is detected. Duchesne *et al.* tested IgH/TCR multiplex PCR assays on 15 nerve biopsies against standard histopathology in pNL.[7] Of four biopsies showing ‘polyclonal infiltrates’ without clear histopathological evidence of malignant cells and not highly suspicious histologically, clonality studies led to the final diagnosis in three.

Similarly, most CSF samples are given only superficial analysis resulting in non-specific findings of excess lymphocytes. Clonality assessment can increase diagnostic yield. A study of CSF in patients with suspected lymphoproliferative processes found that the sensitivity and specificity of cytology alone was 27% and100%, flow cytometry 10% and 95% and IgH analysis 58% and 85%.[8]

On BMAT, TCR gene rearrangement analysis may help in suggesting a lymphoproliferative disorder. Clonal rearrangements supporting a diagnosis of T-cell lymphoma were detected in 67% of BMATs performed in patients with a clinical suspicion of lymphoma, including 33% where bone marrow histopathology was initially inconclusive.[9] However, caution is required if a diagnosis is based solely on BMAT clonality as false positives occur when there are only small numbers of T-cells or there is a reactive oligoclonal expansion of T-cells.[10] Persistence of clones and their discovery in more than one site increases the likelihood of significance.

A literature review identified eight published cases of PTCL-associated pNL, with additional reports in adult T-cell leukaemia (three cases), extranodal NK/T-cell lymphoma (three) and cutaneous T-cell lymphoma (eight) (Table 1). Age, clinical presentation and imaging findings were heterogeneous across the series but pain was the most common feature. CSF cytology had a low diagnostic yield, with clonality contributing in only 1 of 4 (25%) cases where it was tested. TCR gene rearrangement PCR was reported in nine patients on various samples. Clonality was demonstrated in all five of the skin lesion, lymph node and nerve biopsies but only one of four CSF samples. Biopsy of the affected tissue had the highest diagnostic yield including 9 of 11 (82%) neural tissue biopsies but BMAT demonstrated malignancy in only 3 of 9 (33%) cases. In the majority of remaining cases a diagnosis was made from lymph node or skin lesion biopsies.

Standard first-line therapy of systemic T-cell NHL is usually anthracycline-based, most commonly CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) [11] but a broad range of therapies, incorporating agents that cross the blood-brain barrier, are reported with generally poor prognosis: 15/19 patients (79%) dying at a median of six months after development of neurological symptoms. Development of more effective therapies which penetrate the blood nerve barrier is clearly needed.

Here we present a case of subacute onset, painful myeloradiculoneuritis with constitutional symptoms and lymphocytic pleocytosis as the initial manifestation of T-cell neurolymphomatosis. A diagnosis was established based on the clinical presentation, non-specific pathological T-cell predominant infiltration of affected tissue and persistent T-cell clone detected in multiple sites. Empirical immunosuppression was felt to have modified the disease process contributing to the relatively long survival.

Table 1. Summary of published cases of pNL associated with a T-cell malignancy.

	Age Sex	Prior Dx	Clinical features			CSF			MRI	FDG-PET uptake	BMAT	Histology	Clonality	Diagnosis	Treatment	Outcome
			Neurologic	Pain	Systemic	WBC	Pr	Cytology								
1 [12]	62F	N	CN	None	None	↑	↑	Suspicious, TCRg -	Bilateral CN III enhancement	-	-	CN III biopsy	CSF -	PTCL	1. HD MTX, PCZ, CCNU, IT ARAC 2. IA carboplatin, etoposide	No evidence disease at 36 months
2 [12]	40F	N	CN, MM	None	Uveitis	↑	↑	Suspicious, TCRg +	Leptomeningeal enhancement	-	Normal	Meningeal biopsy	CSF +	PTCL	1. HD MTX, PCZ, CCNU, IT ARAC 2. RTX	Died of disease at 19 months
3 [12]	21M	N	CN, plexus, nerve root	Y	None	N	N	Cytology +, TCRg -	CN VII, C5-6 and cauda equina enhancement	-	Normal	-	CSF -	PTCL	1. HD MTX, IT ARAC 2. RTX	Died of disease at 15 months
4 [12]	31M	N	CN, cord	None	Uveitis	N	N	Cytology -, TCRg -	Normal	-	Normal	Orbit (anterior chamber) biopsy	CSF -	PTCL	1. CYC, doxorub IT MTX 2. DHIP	Died of disease at 19 months
5 [13]	24M	Y	CN	None	LAN	↑	-	-	Bilateral CN III, V, VII, VIII, IX, X thickening, enhancement	Thoracic vertebrae	-	Cervical LN biopsy	-	PTCL	1. EPOCH 2. IDARAM, cranial RTX	Died of disease at 22 days
6 [14]	60M	Y	Nerve root, PN	Y	None	-	-	Cytology +		Multiple lumbosacral roots and sciatic nerves	-	-	-	PTCL	1. IT MTX	Unknown
7 [15]	61M	N	Nerve root, PN	Y	None	↑	↑	-	Left L4-S2 nerve root enlargement	-	-	Left S1 nerve root biopsy (left sural nerve biopsy non-diagnostic)	-	PTCL	Unknown	Unknown
8 [16]	28M	Y	CN	Y	LAN	-	-	-	Bilateral CN V, right CN VII, VIII enlargement and enhancement	Bilateral CN V, right CN VII, VIII, right cervico-thoracic ganglion, 7-10th intercostal nerves	-	Cervical LN biopsy	-	PTCL	CHOP	Unknown
9 [17]	48F	Y	CN, PN	Y	Rash, LAN	-	-	Cytology +	Normal	Sciatic, iliac recurrent laryngeal, nerves, cervical nerve roots, pituitary gland, skin, mammary glands	-	-	-	Adult T-cell leukaemia secondary to HTLV-1	1. CYC, adriamycin, vincristine, vinblastine, ranimustine, etoposide, paraplatin, prednisolone 2. HD MTX	Died of disease at 4 months
10 [18]	56F	Y	CN, nerve root, PN	None	Rash, LAN	N	N	-	Cervical nerve root, radial, median, ulnar nerve enlargement and enhancement	Cervical nerve root, radial, median, ulnar nerve	-	Skin lesion biopsy	-	Adult T-cell leukaemia secondary to HTLV-1	1. Prednisolone, IVIG for MMN 2. Etoposide, prednisolone	Decreased size nerves on MRI
11 [19]	64F	Y	Plexus	Y	Rash	-	-	-	Left brachial plexus thickening	-	-	Skin lesion biopsy	Skin lesion biopsy +	Cutaneous T-cell lymphoma	1. CYC, vincristine, doxorubicin, HD MTX 2. Ifosfamide, cytarabine, etoposide, MTX	Died of disease unknown duration
12 [20]	60M	Y	PN	Y	Rash	-	-	-				Skin lesion biopsy Sural nerve biopsy		Adult T-cell leukaemia secondary to HTLV-1	Died before commencing	Died of disease at 4 years
13 [21]	68F	Y	PN	Y	Rash, LAN	-	-	-		Normal		Skin lesion and inguinal LN biopsy Left sural nerve biopsy	Nerve biopsy +	Cutaneous T-cell lymphoma	CHOP	Clinical improvement in muscle strength and skin lesions

14 [22]	66M	Y	CN, PN		Rash, renal lesion	↑	↑	-	Normal		Normal	Renal lesion biopsy		Cutaneous T-cell lymphoma	1. CHOP 2. Hyper-CVAD	Died of disease at 2 months
15 [23]	73F	Y	CN, nerve root, PN		Rash	-	-	-				Skin lesion, LN biopsy Right superficial peroneal nerve biopsy	Skin lesion, LN biopsy +	Cutaneous T-cell lymphoma	1. CHOP, chlorambucil 2. HD MTX	Died of disease at 14 months
16 [24]	32M	Y	MM	Y	Rash	N	N	-	Common peroneal nerve thickening			Skin lesion biopsy US-guided FNA of common peroneal nerve		Cutaneous pleomorphic small/ medium-sized T-cell lymphoma	CHOP	Improvement and in remission at 3 years
17 [25]	64M	Y	PN	Y	Rash	↑	N	-			Normal	Skin lesion biopsy Right sural nerve biopsy	Skin lesion biopsy +	Cutaneous T-cell lymphoma	1. Prednisolone 2. CYC, etoposide, cytarabine, bleomycin	Functional improvement, complete remission at 2.5 years
18 [26]	76M	Y	Plexus, PN		Rash	-	-	-	Left brachial and sacral plexus diffuse nodular thickening			Ulnar nerve re-exploration		Cutaneous T-cell lymphoma	Palliative RTX	Died of disease 12 months after neurologic symptoms
19 [27]	29M	Y	CN, nerve root, PN	Y	Rash	↑	↑	Cytology +	Left CN V thickening and enhancement, cauda equina thickening, nodular deposits on right side of thecal sac, right psoas and lumbar muscle enlargement		Normal	Skin lesion biopsy	Skin lesion biopsy +	Cutaneous large T-cell lymphoma	1. CHOP 2. HD/IT MTX, cytosine arabinoside, RTX	Died of disease at 3 months after neurologic symptoms
20 [28]	26F	N	Plexus, PN	Y	Rash	N	N	-	Brain white matter lesions	Left brachial plexus, median, ulnar nerves and right tibial nerves, CNS, nasopharynx and skin	Lymph-oma	Skin lesion biopsy		Extranodal NK/T-cell lymphoma	Dexamethasone	Died of disease at 5 months
21 [29]	47M	N	CN, PN	Y	Fever, weight loss, rash	N	N	-	Normal	Right CN III and VII, right tibial, left ulnar and peroneal nerves and spine	Lymph-oma	Nerve and muscle biopsies after steroids: non-diagnostic		Extranodal NK/T-cell lymphoma	1. IVMP, IVIG with transient improvement 2. SMILE 3. Cord blood transplantation 4. Salvage steroid and etoposide	Died of disease at 6 months
22 [30]	61M	N	CN, PN	Y	-	↑	↑	-	Anterior margin T10-12 enhancement, brain white matter disease		Lymph-oma	Sural nerve biopsy		Extranodal NK/T-cell lymphoma	IVMP followed by prednisone taper	Died of disease at 3 months

Light grey shading – diagnostic investigation, dash – data not described

Abbreviations – F: female; M: male. Prior Dx: prior diagnosis of haematological malignancy; N: no; Y: yes. CN: cranial nerve; MM: mononeuritis multiplex; PN: peripheral nerve; LAN: lymphadenopathy. WBC: white blood cell count; Pr: protein level; TCRg: T-cell receptor gene rearrangement. HTLV: human T-lymphotrophic virus; NK: natural killer. HD MTX: high-dose methotrexate; PCZ: procarbazine; CCNU: lomustine; IT: intrathecal; ARAC: cytarabine; IA: intra-arterial; RTX: radiotherapy; CYC: cyclophosphamide; doxorub: doxorubicin; DIHP: dexamethasone, cisplatin, cytarabine; EPOCH: etoposide, adriamycin, vincristine, cyclophosphamide, prednisolone; IDARAM: cytosine arabinoside, dexamethasone, idarubicin, intrathecal methotrexate; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisolone; MMN: multifocal motor neuropathy; hyper-CVAD: hyper-fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, cytarabine; IVMP: intravenous methylprednisolone; SMILE – steroids, methotrexate, ifosfamide, L-asparaginase and etoposide.

LEARNING POINTS/TAKE HOME MESSAGES *3-5 bullet points*

- T-cell peripheral neurolymphomatosis is rare, though likely under-diagnosed.
- Consider the diagnosis in cases with subacute onset, painful, patchy neurological deficits.
- Standard diagnostic tests include cerebrospinal fluid, imaging and nerve biopsy.
- Clonality assessment can increase yield when other tests are non-diagnostic.
- The finding of a persistent, identical clone supports the diagnosis and may justify treatment.

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FIGURE/VIDEO CAPTIONS

Figure 1a. Clinical progression of disease as indicated by change in weakness (MRC sum score [31]) and sensory deficits over time with alterations in oral corticosteroid dose (vertical axes) and various immunomodulatory treatments (horizontal axes). Time points at which neurophysiology was performed are indicated by the red crosses and CSF by the orange crosses below the horizontal axis.
Abbreviations – nerve conduction studies: NCS, cerebrospinal fluid: CSF, bone marrow aspirate and trephine: BMAT, cyclophosphamide: CYC, mycophenolate mofetil: MMF, intravenous immunoglobulin: IVIG, intravenous methylprednisolone: IVMP, Medical Research Council: MRC, costal margin: CM.

Figure 1b. Neurophysiology at initial presentation (May 2015) and relapse (June 2016) .
Abbreviations – compound muscle action potential: CMAP, Sensory nerve action potential: SNAP, conduction velocity: CV, DML: distal motor latency.

Figure 1c. Serial CSF findings following initial presentation (three samples in May 2015) and at relapse (two samples in July 2016). Abnormal results are indicated in bold.
Abbreviations – white cell count: WCC, lymphocyte count: lymph, red cell count: RCC, unpaired oligoclonal bands present in CSF: OCB+, immunoglobulin: Ig, polymerase chain reaction: PCR, T-cell receptor gene rearrangement: TCRg.

Figure 2a. MRI showing enhancement of oculomotor nerves (A), cauda equina (B) and lumbosacral plexuses (C) on post-gadolinium T1 weighted sequences (C) and enlargement and hyperintensity of the brachial plexus on T2 weighted sequences (D).

Figure 2b. The CSF preparation stained with Giemsa method (A) shows frequent small lymphocytes admixed with occasional intact red blood cells. Majority of the lymphocytes are CD3 positive T lymphocytes (B) with rare admixed CD20 positive B lymphocytes (C). Scale bar: 50µm in A-C.

Figure 2c. Haematoxylin and eosin stained section of right brachial plexus biopsy demonstrates widespread endoneural oedema (A) and increased numbers of endoneural freely scattered and loosely arranged perivascular small lymphocytes (B). There is moderate depletion of myelinated fibres across the fascicle demonstrated by SMI94 immunostaining (C) and there is widespread active axonal degeneration with infiltration of CD68 positive macrophages (D). The endoneural inflammatory cell infiltrate is mixed, comprising CD3 positive T lymphocytes (E), CD20 positive B lymphocytes (F) and very rare, isolated CD138 positive plasma cells (not shown). Scale bar: 200µm in A, 20µm in B and 100µm in C-F. All immunostainings shown: CD3 (1:100, LN10, Leica), CD20 (1:200, L26, Leica), CD138 (1:100, MI15, DAKO), CD68 (1:100, PG-M1, DAKO) were carried out on automated immunostainers (Roche Ventana Discovery or Leica BondMax) following manufacturer's guideline.

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Figure 1a.

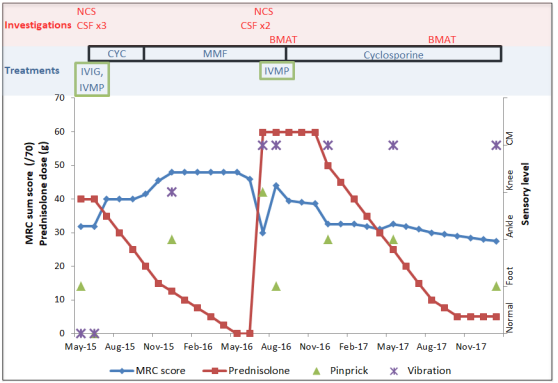

Figure 1b.

	Presentation		Relapse	
	Right	**Left**	**Right**	**Left**
Motor				
Median CMAP (wrist)	1.0mV	2.9mV	1.9mV	2.2mV
Median CV (wrist-elbow)	43m/s	48m/s	45m/s	42m/s
Median DML	3.3ms	3.9ms	5.1ms	4.2ms
Median F wave latency	-	-	34ms	32ms
Common peroneal CMAP (ankle)	2.1mV	-	0.3mV	-
Common peroneal CV(fibular neck-ankle)	43m/s	-	31m/s	-
Common peroneal F wave	Absent	-	-	-
Tibial CMAP (ankle)	16.7mV	15.5mV	7.7mV	7.1mV
Tibial CV(popliteal fossa-ankle)	39m/s	-	35m/s	34m/s
Tibial F wave latency	52ms	55ms	55ms	66ms
Sensory				
Radial (forearm-snuffbox)	1μV	16μV	Absent	10μV
Median (D3-wrist)	Absent	4μV	Absent	-
Ulnar (D5-wrist)	1μV	-	Absent	3μV
Sural (calf-ankle)	22μV	8μV	4μV	Absent
Superficial peroneal (calf-ankle)	7μV	5μV	Absent	Absent

Figure 1c.

Date	Cells ($x10^9$/L)	Biochemistry	Cytology	Flow cytometry
May 2015 (1)	**WCC 33 (lymph 28)** RCC <1	**Protein 1.57g/L** Glucose 3.2g/L (serum 5.8g/L) **OCB+**	CSF is cellular composed mainly of small lymphocytes and macrophages. There are no atypical cells. Immunostains show the majority of the small lymphocytes are CD3+ T-cells and the medium sized occasional lymphocytes are CD20+ B-cells. Features are in keeping with a reactive, chronic inflammatory process (lymphocytic meningitis).	Abundant lymphocytes, predominantly normal T-cells.
May 2015 (2)	**WCC 75 (lymph 74)** RCC 10	**Protein 1.32g/L** Glucose 3.2g/L (serum 5.8g/L)	Not available	Not available
May 2015 (3)	**WCC 23 (lymph 20)**	**Protein 0.84g/L** Glucose 3.2g/L	CSF is cellular composed mainly of small lymphocytes and macrophages. There are no atypical cells. The lymphoid cells are predominantly CD3+ T-cells with scattered CD20+ B-cells. Features are in keeping with a reactive, chronic inflammatory process (lymphocytic meningitis).	No evidence of malignancy. TCRg PCR generates two dominant products (Vg9+Jg1.3/2.3, Vg10+Jg1.3/2.3).
July 2016 (1)	**WCC 8 (lymph 8)** RCC <1	**Protein 0.97g/L** Glucose 4.5g/L (serum glucose not available) **OCB+** IgG 38mg/L IgM 0.23mg/L	Not available	Not available
July 2016 (2)	**WCC 11 (lymph 11)** RCC <1	Protein, glucose not available IgG 37mg/L	CSF is moderately cellular with an increase in white blood cells, mainly small lymphocytes and macrophages. There are no atypical cells. Features are in keeping with a mild chronic inflammatory/ reactive process.	No evidence of a lymphoproliferative disorder. B-cells were not detected.

Figure 2a.

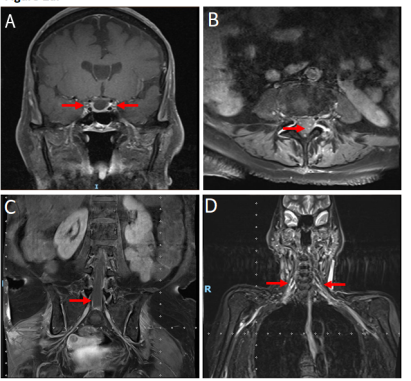

Figure 2b.

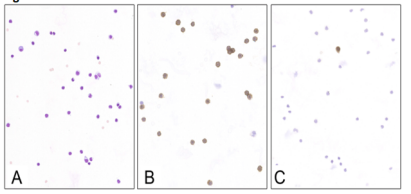

Figure 2c.