CASE REPORT

Rare case of T-cell lymphoma presenting as acute myelopathy

Verena Clarissa Samara, Adam de Havenon

Department of Neurology,
University of Utah, Salt Lake
City, Utah, USA

Correspondence to
Dr Verena Clarissa Samara,
verena.samara@hsc.utah.edu

Accepted 7 October 2016

SUMMARY

Acute myelopathy is a rare presentation of systemic T-cell lymphoma. We present the case of a man aged 68 years with a diffuse erythematous maculopapular rash, followed by lower extremity paresthesias and progressive lower extremity weakness. Spinal MRI showed longitudinally extensive T2 hyperintensity with diffuse contrast enhancement. An atypical clonal T-lymphocyte population was identified in cerebrospinal fluid, peripheral blood and bone marrow aspirate, indicating a malignant T-cell lymphoproliferative disorder. The patient was treated with intrathecal and systemic chemotherapy. Unfortunately, he was not responsive to chemotherapy.

BACKGROUND

Lymphomas can be associated with neurological symptoms if they are primary central nervous system (CNS) lymphomas, intravascular lymphomas, if they infiltrate the CNS (eg, leptomeningeal disease), or are associated with a paraneoplastic syndrome or opportunistic infection. Spinal cord compression causing acute myelopathy can occur due to spinal lymphoma (uncommon) or due to mass effect from a lymphoma growing just outside the meninges. It is important to recognise myelopathy as the presenting symptom of lymphomas to urgently initiate adequate treatment and thus improve the chances of recovery. We present a case report of a patient with an unusual T-cell lymphoma myelopathy and a review of the available literature.

CASE PRESENTATION

A man aged 68 years presented with lower extremity weakness and sensory loss which was preceded 1 month earlier by a case of sinusitis, for which he was treated with penicillin. Several days after starting the penicillin, he developed a diffuse rash involving the trunk and all four extremities. His primary care provider suspected a drug reaction and prescribed a 1-week course of prednisone. This resulted in resolution of the rash. However, the patient continued to have pruritus, and then started to develop paresthesias in his feet, followed by anaesthesia and difficulty with balance. He then became weak in his lower extremities, which led to an inpatient admission for suspected acute inflammatory demyelinating polyneuropathy (AIDP). Initial cerebrospinal fluid (CSF) studies showed 57 RBCs, 100 white cell counts (WCCs) (92% lymphocytes), glucose 70 mg/dL and protein 75 mg/dL. He was treated with high-dose intravenous steroids with rapid improvement in his symptoms.

However, following steroid pulse therapy, his neurological symptoms again worsened and his rash recurred, so he was transferred to our tertiary care centre.

His medical history was pertinent for hypertension, prostate cancer treated with combination external beam radiotherapy and seed implantation, a left femur fracture and GERD, status post *Helicobacter pylori* eradication. He took lisinopril, losartan potassium/hydrochlorothiazide (Hyzaar), omeprazole and aspirin daily. He did not drink alcohol or smoke. Family history revealed that his father died from Hodgkin's lymphoma at age 38. A brother died from colon cancer at age 40. General medical examination showed a blood pressure of 151/80 mm Hg, poor dentition and a generalised, erythematous maculopapular rash over the entire trunk, all four extremities, and his genitals but largely sparing the soles and entirely sparing palms, face and mucous membranes (figure 1). In areas, the rash was confluent, but the papules were still individually distinguished, and borders were poorly defined. The rash did not blanch and there was no discharge, tenderness to palpation, warmth or

Figure 1 Generalised erythematous maculopapular rash.

CrossMark

To cite: Samara VC, de Havenon A. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2016-217944

induration. Neurological examination demonstrated some difficulty with word finding, bilateral lower extremity weakness (3–4/5), lower extremity hyperreflexia with clonus but negative Babinski signs, impaired sensation to light touch, proprioception and temperature sensation below the midabdomen, mild asterixis, impaired rectal tone, dullness to sensation in the perianal area and loss of anal wink.

INVESTIGATIONS

Laboratory investigation revealed an elevated WCC of 18K/ μ L (42% polymorphonuclear leucocytes, 47% lymphocytes), haematocrit 33%, platelet count 171K/ μ L, sodium 135 mmol/L, potassium 4 mmol/L, creatinine 0.75 mg/dL, liver function tests within normal limits, C reactive protein 1.0 mg/L, sedimentation rate 4 mm/hour, ACE inhibitors 17 U/L, antinuclear antibodies 1:64, Vitamin B12 466 pg/mL and lactate dehydrogenase 1231 U/L. Serum protein electrophoresis showed a decreased albumin level (3.37 g/dL) but no monoclonal protein. HIV-PCR, HSV-PCR, Mycoplasma-PCR, hepatitis panel, HTLV-I/II DNA and antibodies, *Bartonella henselae* antibodies, Rickettsia antibodies, RPR, haemagglutinin, cryoglobulin, cyclic citrullinated peptide, rheumatoid factor, antineutrophil cytoplasmic antibodies (ANCA), neuromyelitis optica (NMO) antibodies, anti-SSA/SSB antibodies, antidouble-stranded DNA antibodies, anti-Hu/Ri/Yo/amphiphysin antibodies and paraneoplastic Mayo panel were all negative.

CSF studies showed 142 WCC/ μ L (80% lymphocytes), protein 108 mg/dL, glucose 54 mg/dL. Infectious tests (Gram stain, aerobic, anaerobic and fungal cultures, *Borrelia burgdorferi* antibodies, Colorado tick fever antibodies, Cryptococcus antigen, CMV-PCR, Ehrlichia-PCR, Anaplasma-PCR, Enterovirus-PCR, EBV-PCR, HSV-PCR and antibodies, Measles antibodies, Mumps antibodies, VZV-PCR and antibodies, WNV antibodies, California encephalitis antibodies, Eastern Equine Encephalitis antibodies, Western Equine Encephalitis antibodies, St Louis encephalitis antibodies, lymphocytic choriomeningitis virus antibodies, Mycobacteria culture, *Mycoplasma pneumoniae*-PCR and antibodies, *Coxiella burnetii* antibodies, Rickettsia antibodies, *Treponema pallidum* VDRL) and oligoclonal bands were negative. Immunoglobulin G was 4.7 mg/dL, albumin was 46 mg/dL, and IgG/albumin ratio was 0.10. CSF cytology did not identify abnormal cells. However, CSF cytometry showed evidence of a monoclonal T-cell population (figure 2).

Brain MRI showed diffuse T2/FLAIR hyperintensities consistent with white matter disease but no acute findings. MRI of the spinal cord revealed diffuse T2 hyperintensities with diffuse contrast enhancement (figure 3).

Histology of a skin biopsy demonstrated perivascular lymphocytic infiltration in the dermis, normal epidermis and no abnormal lymphocytes within blood vessels (no evidence of intravascular lymphoma; figure 4).

A peripheral blood smear showed atypical and enlarged lymphocytes with irregular nuclear contours and condensed chromatin. Immunophenotypic analysis of peripheral blood showed an atypical mature CD4-positive T-cell population (brighter than normal CD5, partial CD57+) which represented ~20% of the total leucocytes (figure 5A), consistent with a lymphoproliferative disorder. This population demonstrated monoclonal

Source:	CD2	CD3	CD5	CD4:CD3	CD8:CD3	CD4:CD8	CD20	CD30
CSF	99%	99%	99%	97%	2%		1%	

Figure 2 Cerebrospinal fluid flow cytometry.

Figure 3 MRI of the spinal cord: scattered T2-hyperintensities with diffuse patchy enhancement.

Figure 4 Skin biopsy: lymphocytic perivascular infiltration.

TCR (T-cell receptor) V β 16 expression. A bone marrow aspirate (figure 5B) showed rare atypical lymphocytes (~5% of nucleated cells) and a monoclonal population similar to that in peripheral blood.

Staging work-up also disclosed multiple solid tumour deposits involving the liver as well as the bony pelvis. Biopsy from the pelvis disclosed an adenocarcinoma of unknown primary (potentially lung or thyroid; online supplementary figure S1). The liver was not biopsied.

DIFFERENTIAL DIAGNOSIS

The atypical CD4-positive clonal T-lymphocyte population identified in multiple specimens (figure 6) indicates a malignant T-cell lymphoproliferative disorder. The morphology and immunophenotype are not typical for any specific subtype, so this was considered a peripheral T-cell lymphoma, not otherwise specified (peripheral T-cell lymphomas (PTCL)-NOS).

TREATMENT

The patient's T-cell lymphoma was initially treated with methotrexate chemotherapy, alternating high-dose intravenous

Figure 5 (A) Peripheral smear.
(B) Bone marrow.

Figure 6 Full flow cytometry profile.

Source:	CD2	CD3	CD5	CD4:CD3	CD8:CD3	CD4:CD8	CD20	CD30
Skin	100%	100%	100%	80%		4:1	<1%	0%
Bone marrow	92%	90%	79%	72%	19%			
Blood	95%	94%	85%	76%	15%	5:1	4%	
CSF	99%	99%	99%	97%	2%		1%	

methotrexate and high-dose intrathecal methotrexate. As his neurological status and skin rash failed to improve significantly, he was given an additional dose of intrathecal cytarabine, also without appreciable improvement in his symptoms. The patient's T-lymphocyte count failed to diminish substantially following these chemotherapy administrations but rather continued to rise. As such, the patient's T-cell lymphoma was determined to be unresponsive to chemotherapy. Of note, the patient received no specific treatment for his incidental adenocarcinoma other than as needed pain medication.

OUTCOME AND FOLLOW-UP

As the patient's T-cell lymphoma was unlikely able to be treated successfully, end-of-life options were discussed with the patient. He discharged to an inpatient hospice facility near his home and passed away shortly thereafter.

DISCUSSION

Spinal cord compression is a medical emergency and usually presents with back or neck pain, followed by radicular symptoms and eventually myelopathy manifesting as weakness and ascending sensory loss. Bowel and bladder dysfunction occur later in the disease course.¹ The diagnosis of soft tissue involvement is usually established with MRI imaging, whereas CT is better at detecting bony metastases.²

There are few case reports in the literature of myelopathy associated with lymphomas. Primary intramedullary spinal cord lymphoma is uncommon,³ and primary epidural spinal lymphomas⁴ as well as primary spinal intradural extramedullary lymphomas⁵ are exceedingly rare. Myelopathy is more commonly caused by compression of the spinal cord due to metastases of lymphomas, which usually occur in the epidural or leptomeningeal space.⁶ Intradural-extramedullary⁷ or intramedullary metastases⁸ are less common causes of lymphoma-related spinal cord injuries.^{9 10} Neurological symptoms can also be caused indirectly via paraneoplastic syndromes¹¹ or opportunistic infections of the nervous system in patients with immunosuppression.

Our patient presented with the typical symptoms of myelopathy: lower extremity weakness and ascending numbness.

The initial diagnostic process was clouded as he had received high-dose oral steroids for a presumed drug rash, followed by high-dose intravenous steroids for presumed AIDP. Following administration of steroids, he experienced improvement both times but symptoms quickly recurred. After recurrence of his symptoms, spinal MRI showed scattered T2 hyperintensities with diffuse, patchy contrast enhancement. Extensive infectious work-up remained negative. As CSF studies showed a clonal T-cell population, a peripheral smear and bone marrow biopsy were obtained, which confirmed the presence of atypical monoclonal lymphocytes. The monoclonal population was identical in all three specimens, confirming a lymphoproliferative disorder. Biopsy of the maculopapular skin rash showed an atypical lymphoid infiltrate, which was likely also a manifestation of his disease.

The presence of cluster of differentiation (CD) molecules CD2, CD3 and CD5 on the surface of all monoclonal cells as well as a CD4 predominance helped classify the disease process as a T-cell lymphoma.¹² The presence of TCR V β 16 expression confirmed the presence of clonality.¹³ CD 30 negativity helped rule out certain subtypes of anaplastic and cutaneous T-cell lymphomas.^{12 14} The partial presence of CD 57, a marker of natural killer cell maturation, might indicate a likely higher likelihood of 'B' symptoms and bone marrow involvement as CD 57 expression has been proposed as a prognostic marker related to immune dysfunction.¹⁵ Overall, the morphology and phenotype of the clonal T-lymphocyte population was not consistent with a specific subtype of T-cell lymphomas, so that our patient was eventually diagnosed with a PTCL-NOS.

PTCL are rare and usually aggressive with a poor prognosis. Clinical characteristics and outcome vary depending on the subtype. PTCL-NOS is the most common type, making up about one-quarter of all PTCL.¹⁶ It typically occurs in adult males with a median age of 55–60 years and is often diagnosed in advanced stages of the disease.¹⁷ Treatment regimens usually consist of aggressive chemotherapy, but there is currently no standard of care treatment regimen of chemotherapeutic agents. The most common combination chemotherapy is CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone).¹⁸ Patients with CNS involvement are usually treated with

Figure 7 Diagnostic approach to acute myelopathy (after 21). CSF, cerebrospinal fluid; NMO, neuromyelitis optica; MS, multiple sclerosis; IgG, immunoglobulin G; SS-A, Sjogren's syndrome antibody (anti-RO).

high-dose methotrexate, either systemically or intrathecally.¹⁹ Unfortunately, the majority of patients relapse rapidly, so that 5-year survival rates are only 10–30%. Numerous agents are currently being evaluated in clinical trials with the hope that more effective treatment strategies will improve overall outcomes in the future.²⁰

As outlined above, acute myelopathy is a medical emergency requiring not only urgent and appropriate diagnostic steps as outlined in figure 7²¹ but also urgent initiation of treatment to improve chances of recovery. This usually includes the empiric administration of high-dose steroids.²² It is, however, important to understand that administering steroids to a patient with an undiagnosed spinal mass might delay diagnosis and appropriate treatment as lymphomas can temporarily remit after steroid administration.²³

Learning points

- ▶ Patchy enhancement of the spinal cord is suspicious for malignancy.
- ▶ Systemic lymphomas can present with neurological symptoms as the initial manifestation.
- ▶ Lymphocytes on a skin biopsy are concerning for malignancy, particularly when they are not in the blood vessel wall or associated with immune complexes (vasculitis).
- ▶ Steroids (particularly pulse doses) cloud the diagnosis of lymphoma or leukaemia.
- ▶ Do not rely on PET/CT to make your diagnosis as it can cloud the picture with incidental findings.

Contributors VCS drafted the article. AdH edited the article.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Cole JS, Patchell RA. Metastatic epidural spinal cord compression. *Lancet Neurol* 2008;7:459–66.
- 2 Shah LM, Salzman KL. Imaging of spinal metastatic disease. *Int J Surg Oncol* 2011;2011:769753.
- 3 Flanagan EP, O'Neill BP, Porter AB, *et al.* Primary intramedullary spinal cord lymphoma. *Neurology* 2011;77:784–91.
- 4 Cugati G, Singh M, Pande A, *et al.* Primary spinal epidural lymphomas. *J Craniovertebr Junction Spine* 2011;2:3–11.
- 5 Cugati G, Singh M, Symss NP, *et al.* Primary spinal intradural extramedullary lymphoma causing cauda equine syndrome. *J Craniovertebr Junction Spine* 2012;3:58–61.
- 6 Grier J, Batchelor T. Metastatic neurologic complications of non-Hodgkin's lymphoma. *Curr Oncol Rep* 2005;7:55–60.
- 7 Carra BJ, Sherman PM. Intradural spinal neoplasms: a case based review. *J Am Osteopath Coll Radiol* 2013;2:13–21.
- 8 Mathur S, Law AJ, Hung N. Late intramedullary spinal cord metastasis in a patient with lymphoblastic lymphoma: case report. *J Clin Neurosci* 2000;7:264–8.
- 9 Giglio P, Gilbert MR. Neurologic complications of non-Hodgkin's lymphoma. *Curr Hematol Malign Rep* 2006;1:214–19.
- 10 Grimm S, Chamberlain M. Hodgkin's lymphoma: a review of neurologic complications. *Adv Hematol* 2011;2011:624578.
- 11 Graus F, Ariño H, Dalmau J. Paraneoplastic neurological syndromes in Hodgkin and non-Hodgkin lymphomas. *Blood* 2014;123:3230–8.
- 12 Campbell SM, Peters SB, Zirwas MJ, *et al.* Immunophenotypic diagnosis of primary cutaneous lymphomas. A review for the practicing dermatologist. *J Clin Aesthet Dermatol* 2010;3:21–5.
- 13 Hodges E, Krishna MT, Pickard C, *et al.* Diagnostic role of tests for T cell receptor (TCR) genes. *J Clin Pathol* 2003;56:1–11.
- 14 Bisig B, Gaulard P, de Leval L. New biomarkers in T-cell lymphomas. *Best Pract Res Clin Haematol* 2012;25:13–28.
- 15 Focosi D, Petrini M. CD57 expression on lymphoma microenvironment as a new prognostic marker related to immune dysfunction. *J Clin Oncol* 2007;25:1289–91.
- 16 Vose J, Armitage J, Weisenburger D. International T-Cell Lymphoma Project. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. *J Clin Oncol* 2008;26:4124–30.
- 17 Phillips AA, Owens C, Lee S, *et al.* An update on the management of peripheral T-cell lymphoma and emerging treatment options. *J Blood Med* 2011;2:119–29.
- 18 Moskowitz AJ, Lunning MA, Horwitz SM. How I treat the peripheral T-cell lymphomas. *Blood* 2014;123:2636–44.
- 19 Pui CH, Thiel E. Central nervous system disease in hematologic malignancies: historical perspective and practical applications. *Semin Oncol* 2009;26(Suppl 2):S2–16.
- 20 Coiffier B, Federico M, Caballero D, *et al.* Therapeutic options in relapsed or refractory peripheral T-cell lymphoma. *Cancer Treat Rev* 2014;40:1080–8.
- 21 Jacob A, Weinschenker BG. An approach to the diagnosis of acute transverse myelitis. *Semin Neurol* 2008;28:105–20.
- 22 Schmalstieg WF, Weinschenker BG. Approach to acute or subacute myelopathy. *Neurology* 2010;75(Suppl 1):S2–8.
- 23 Kan E, Levi I, Benharroch D. Alterations in the primary diagnosis of lymphomas pretreated with corticosteroid agents. *Leuk Lymphoma* 2011;52:425–8.

Copyright 2016 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow