CASE REPORT

Cytomegalovirus-related transverse myelitis in an immunocompetent host: a subacute onset of an immune-mediated disease?

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SUMMARY

We report a case of transverse myelitis in an immunocompetent host with an atypical long onset of symptoms. A 56-year-old man was admitted to the hospital reporting 5 months of progressive ascending lower extremity weakness and numbness, inability to walk, bowel incontinence, urinary retention and several episodes of nausea and vomiting. MRI showed moderate spinal swelling and multiple hyperintense signal changes on cervical levels C2–C5 and thoracic levels T1–T3. Cerebrospinal fluid (CSF) showed pleocytosis and was positive for anti-cytomegalovirus (CMV) IgG intrathecal antibodies, but the CSF PCR for CMV was negative. The diagnosis of immune-mediated CMV-related transverse myelitis was established and the patient was treated with methylprednisolone and valgancyclovir. The patient had poor recovery and remained paraplegic at discharge.

BACKGROUND

Transverse myelitis (TM) is a progressive neurological disorder resulting from inflammation of the spinal cord.¹ This disease has an estimated incidence of one to eight cases per million people per year.²

Clinical features of TM include autonomic, sensory and motor disturbances at the level of the spinal cord lesion. Segmental weaknesses with upper motor neuron signs, sensory deficit on a spinal level on the torso, spinal tract findings and urinary retention strongly suggest the diagnosis.³

A large number of etiological entities have been found to be related to myelitis including multiple sclerosis, neuromyelitis optica, dural arteriovenous fistula, spinal cord infarction, systemic diseases such as sarcoidosis, systemic lupus erythematosus, Sjögren's and Behcet's syndromes, and infectious pathogens as *Chlamydia psittaci*, *Mycoplasma pneumoniae*, *Borrelia*, *Bordetella*, herpes simplex virus (HSV), Epstein-Barr virus and cytomegalovirus (CMV).

CMV infection is a very rare cause of inflammatory myelopathy, with only 13 well-documented cases reported to date in immunocompetent patients.^{4–5} The pathophysiological mechanism involved in CMV-related myelopathy is not well understood, although it has been postulated that damage to the spinal cord could be the result of a direct attack of the virus⁶ or a series of immune mechanisms including the deposition of circulating immune complexes or the activation of lymphocytes

by superantigens.⁷ Furthermore, the clinical course of CMV-related myelopathy has been reported so far as an acute illness presentation.^{4–11} We present a case of CMV-related TM with subacute onset of symptoms, likely immune-mediated followed by acute worsening of symptoms, likely due to secondary CMV reactivation of the immune system.

CASE PRESENTATION

A 56-year-old man with a history of hypertension, type 2 diabetes mellitus and obesity was admitted to our hospital reporting 5 months of progressive ascending lower limb weakness and numbness, urinary retention, bowel incontinence and several episodes of nausea and vomiting. He decided to present to the hospital because of inability to walk that started 24 hours prior to admission. Initially, his vital signs were stable and within normal limits. Pertinent physical examination revealed clear sensorium and normal cranial nerves, asymmetric paraparesis (proximal muscle strength: right 1/5, left 2/5), symmetric distal upper limbs paresis (4/5), hypoesthesia, apallesthesia and akinesia below T8 dermatome, with L4, L5 and S1 levels being spared. Patellar and ankle tendon reflexes were increased and there was bilateral lower extremity spasticity. The bilateral Babinski sign was positive.

INVESTIGATIONS

On admission, MRI T2-weighted sequence, *fluid attenuation inversion recovery* (FLAIR) sequence and contrast-enhanced images showed moderate spinal swelling and multiple hyperintense signal changes on cervical levels C2 to C5, and thoracic levels T1, T2 and T3 (figure 1). Brain MRI was normal. Serum anti-CMV IgG was very elevated (250 UA/mL, normal range 0–6), but anti-CMV IgM was negative (0.38 UA/mL, normal: 0–0.85). Cerebrospinal fluid (CSF) analysis showed 149 cells/mm³ (85% neutrophils), increased protein levels (573.9 mg/dL) and normal glucose. CSF/serum IgG index was high at 1.36 (normal range 0.0–0.68) and CSF/serum albumin index was 48.1 (normal range 0–7).

During the first 2 weeks of hospitalization, while the infectious etiology was ruled out, the motor deficit progressed and further affected the upper limbs and respiratory function. On examination, upper extremity muscle strength was 3/5 bilateral symmetric and sensation was absent below L3 level.

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Figure 1 Contrast-enhanced MRI demonstrating moderate spinal cord swelling and signal changes on cervical and thoracic levels (arrows).

A diagnosis of acute TM was established and intravenous methylprednisolone 1 g/day was administered for 5 days. On day 18 of hospital stay, the patient was transferred to the intensive care unit. Two days later, he developed three small genital ulcers, which eventually spontaneously resolved. HSV PCR from the ulcers was not performed because there was no clinical suspicion of typical ulcers. Epstein-Barr virus (EBV) serology was negative and HSV serology was not performed. A skin biopsy reported perivascular and interstitial infiltrate composed by histiocytic and plasmacytic lymphocytes.

The patient's respiratory and motor functions gradually improved, and a new MRI revealed persistence of focal hyperintensities at the same cervical and thoracic levels, but only discrete contrast enhancement. Repeat anti-CMV serology showed positive IgM titres (1.68 AU/mL; normal range 0–0.85) while IgG remained stable (>250 AU/mL). We evaluated intrathecal antigen-specific IgG synthesis, as described by Reiber^{12 13} and detected high CSF anti-CMV IgG (IgG index 2.29, normal value up to 1.50). The IgM index could not be calculated because the total IgM in CSF was not an available test at our institution. The PCR method for CMV DNA detection was negative.

DIFFERENTIAL DIAGNOSIS

Normal brain MRI and lack of oligoclonal bands excluded multiple sclerosis and acute disseminated encephalomyelitis, whereas serological tests ruled out connective tissue diseases, systemic diseases and acute infections as the cause of myelitis. Routine chemistry tests, vitamin B₁₂, ceruloplasmin and serum copper levels were within normal range. Autoimmune panel and serological tests for HIV-1–2, EBV, human T-lymphotropic virus, *Brucella*, *Borrelia* and syphilis were negative. CSF gram stain and aerobic culture were both negative.

TREATMENT

On diagnosing CMV-related TM, the patient was started on valgancyclovir 900 mg orally two times a day for 21 days. After the initial 5 days of intravenous methylprednisolone, the patient was continued on prednisone 60 mg daily for 1 week and then gradually tapered over the next 3 weeks.

OUTCOME AND FOLLOW-UP

The patient was discharged home with normal respiratory function and normal upper limbs' strength; however, paraplegia persisted, as well as the inability to control the sphincters' function. The patient did not get any additional clinical improvement after treatment with valgancyclovir. One year later, his neurological deficits did not change. He subsequently died secondary to sepsis from an infected pressure ulcer.

DISCUSSION

CMV is a lymphotropic pathogen belonging to the Beta-herpesviridae subfamily and it can establish a persistent or latent infection in mononuclear lymphocytes and other cells such as macrophages, bone marrow stroma and epithelial cells. In the USA, approximately 50%–85% adults are infected with CMV.¹⁴ However, in immunocompetent patients, the infection is usually asymptomatic or manifests itself as an undifferentiated mononucleosis-like syndrome.¹⁵

Clinical features of CMV-related TM are non-specific and indistinguishable from other causes of myelopathy. The disease usually has a rapidly progressing onset,^{4 6–11} beginning with back pain followed by paraparesis, sphincter dysfunction and ascending sensitive deficit.⁷ Nevertheless, in our case, the patient had an unusual subacute onset with symptoms developing slowly throughout months and then rapidly progressing over 2 weeks.

It is also remarkable the lack of systemic symptoms and findings of severe CMV infection such as fever, retinitis, transaminitis, thrombocytopenia or leucopenia.¹⁵ Genital ulcers, although clinically similar to those described in CMV cutaneous infection,¹⁶ cannot be attributed directly to the virus, neither other infectious agents, as the skin biopsy showed unspecific inflammatory infiltrate and sexual-transmitted diseases serology was negative.

Repeated T2-weighted, FLAIR and contrast-enhanced MRI showed transient multiple hyperintensities on spinal cord C2–C5 and T1–T3, indicating spinal cord inflammation and blood–brain barrier disruption. These findings are usually required to establish the diagnosis of TM; therefore, they are present in the majority of reported CMV-related myelitis cases.^{4 6 8 9} However, injury is usually confined to one single spinal level, unlike our case.

The initial determination of anti-CMV antibodies revealed markedly high IgG titres with normal IgM titres, this is compatible with a report from Fux *et al*⁷ who found similar antibodies values in a patient with CMV TM after an alike period (140 days) since symptoms onset. CSF demonstrated intrathecal synthesis of IgG antibodies specific for CMV, nevertheless, no viral DNA was detected by PCR, which is consistent with most cases reported,⁴ except for two.^{5 6} These findings suggest that the spinal cord injury may be a consequence of postinfectious immune response due to the abnormal deposition of immune complexes formed by circulating IgG antibodies.⁹ Our case had an acute worsening of symptoms after a 5-month subacute onset of TM that we speculate could be explained by an increase in a previous abnormal immune response triggered by CMV reactivation. One prior case report⁵ described for the first time a potential two-stage attack, with initial viral attack causing TM and secondary immune-mediated attack that caused encephalitis. The CMV TM in our case could be related to either reactivation of a previous CMV infection or to reinfection with a different CMV strain as the IgM titres became elevated once his clinical condition deteriorated. We cannot tell with certainty the difference in between the two possible etiologies. CMV IgM is considered to be very sensitive

but not very specific for initial infection as the levels can increase during CMV reactivation as well. In this case, the CMV IgM can mean either reinfection with a different CMV strain or reactivation of the previous CMV infection.¹⁷ The CMV reinfection rate in immunocompetent women was reported to be about 10% annualized rate, similar to the frequency of primary CMV infection in the population.¹⁸

The possibility for CMV IgM crossreactivity with EBV was considered. This has been reported in the setting of acute EBV infection when the IgM EBV are positive and also the IgM CMV become falsely positive.¹⁹ The consistent serological findings of CMV IgG positivity (twice) and the CSF findings of IgG positivity strengthen the likelihood of a real CMV infection and make the likelihood of EBV crossreactivity very low.

Treatment options for CMV-related myelitis include glucocorticoids and antiviral agents; however, the efficacy of those approaches is still uncertain, with different response rates among reported cases. Our patient was initially treated with only high doses of intravenous methylprednisolone, resulting in slight recovery. Subsequent administration of valgancyclovir did not result in additional improvement. All similar reported cases in the literature described concomitant antiviral therapy along with the glucocorticoid therapy,^{4 5 7-9} making it impossible for any conclusion to be drawn regarding the impact of each individual treatment.

Learning points

- Cytomegalovirus (CMV)-related transverse myelitis (TM) is rare in immunocompetent patients and the pathophysiological mechanism is not well understood. Nonetheless, some events described in this case, such as intrathecal synthesis of anti-CMV antibodies, absence of viral DNA in cerebrospinal fluid and lack of response to ganciclovir, suggest a postinfectious immune-mediated response. The clinical picture with acute worsening of the symptoms on a subacute presentation supports the possibility of CMV reactivation or reinfection that could worsen the previous abnormal immune response.
- CMV infection should be investigated in all patients presenting with TM, regardless of their immunocompetence status and of their clinical presentation. TM can present with subacute symptoms.
- Early initiation of glucocorticoid treatment is very important in clinical recovery. Clinicians might consider early concomitant treatment with glucocorticoids and antivirals to possibly prevent CMV reactivation on already active TM, with consideration to possible side effects related to antiviral therapy initiation.

Contributors All authors: certify that they have participated sufficiently in the work to take public responsibility for the content. XM: took care of the patient while in the hospital and drafted the case report. AH provided extensive intellectual feedback for the case report draft. XM and AH: conducted independent literature search and individually reviewed and summarised the entire referenced literature.

Disclaimer Furthermore, each author certifies that this material or similar material has not been and will not be submitted to or published in any other publication.

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REFERENCES

- 1 West TW. Transverse myelitis—a review of the presentation, diagnosis, and initial management. *Discov Med* 2013;16:167–77.
- 2 Gómez-Argüelles JM, Sánchez A, López E, *et al*. Mielitis transversa aguda: revisión clínica y algoritmo de actuación diagnóstica. *Revista de Neurología* 2009;49:533–40.
- 3 Schmalstieg WF, Weinshenker BG. Approach to acute or subacute myelopathy. *Neurology* 2010;75(18 Suppl 1):S2–8.
- 4 Arslan F, Yilmaz M, Paksoy Y, *et al*. Cytomegalovirus-associated transverse myelitis: a review of nine well-documented cases. *Infect Dis* 2015;47:7–12.
- 5 Daida K, Ishiguro Y, Eguchi H, *et al*. Cytomegalovirus-associated encephalomyelitis in an immunocompetent adult: a two-stage attack of direct viral and delayed immune-mediated invasions. case report. *BMC Neurol* 2016;16:223.
- 6 Karunarathne S, Govindapala D, Udayakumara Y, *et al*. Cytomegalovirus associated transverse myelitis in an immunocompetent host with DNA detection in cerebrospinal fluid; a case report. *BMC Res Notes* 2012;5:364.
- 7 Fux CA, Pfister S, Nohl F, *et al*. Cytomegalovirus-associated acute transverse myelitis in immunocompetent adults. *Clin Microbiol Infect* 2003;9:1187–90.
- 8 Karacostas D, Christodoulou C, Drevelengas A, *et al*. Cytomegalovirus-associated transverse myelitis in a non-immunocompromised patient. *Spinal Cord* 2002;40:145–9.
- 9 Rigamonti A, Usai S, Ciusani E, *et al*. Atypical transverse myelitis due to cytomegalovirus in an immunocompetent patient. *Neurol Sci* 2005;26:351–4.
- 10 Miles C, Hoffman W, Lai CW, *et al*. Cytomegalovirus-associated transverse myelitis. *Neurology* 1993;43:2143–5.
- 11 Baig SM, Khan MA. Cytomegalovirus-associated transverse myelitis in a non-immunocompromised patient. *J Neurol Sci* 1995;134:210–1.
- 12 Reiber H, Lange P. Quantification of virus-specific antibodies in cerebrospinal fluid and serum: sensitive and specific detection of antibody synthesis in brain. *Clin Chem* 1991;37:1153–60.
- 13 Reiber H. Knowledge-base for interpretation of cerebrospinal fluid data patterns. Essentials in neurology and psychiatry. *Arq Neuropsiquiatr* 2016;74:501–12.
- 14 Murray P, Rosenthal K, Pfaller M. Human Herpes Virus. In: Murray P, Rosenthal K, Pfaller M, *Medical Microbiology*. 5th eds. Madrid, Spain: Elsevier, 2006.
- 15 Rafailidis PI, Mourtzoukou EG, Varbobitis IC, *et al*. Severe cytomegalovirus infection in apparently immunocompetent patients: a systematic review. *Viral J* 2008;5:47.
- 16 Chisholm C, Lopez L. Cutaneous infections caused by Herpesviridae: a review. *Arch Pathol Lab Med* 2011;135:1357–62.
- 17 Ross SA, Arora N, Novak Z, *et al*. Cytomegalovirus reinfections in healthy seroimmune women. *J Infect Dis* 2010;201:386–9.
- 18 Stagno S, Pass RF, Cloud G, *et al*. Primary cytomegalovirus infection in pregnancy. Incidence, transmission to fetus, and clinical outcome. *JAMA* 1986;256:1904–8.
- 19 Miendje Deyi Y, Goubau P, Bodéus M. False-positive IgM antibody tests for cytomegalovirus in patients with acute Epstein-Barr virus infection. *Eur J Clin Microbiol Infect Dis* 2000;19:557–60.

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