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Case Report

Internal Medicine Section

Fever in a Young Female Patient- A Diagnostic Dilemma

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ABSTRACT

A young female patient on chronic steroid therapy developed Cytomegalovirus gastritis with suspected dissemination. With no other identifiable cause of immune suppression, diagnosis of this unlikely infection under this circumstance proved a challenge. Her non-compliance to treatment further complicated matters. This case highlights the importance of having a high degree of suspicion in diagnosing an unlikely infection in an unforeseen circumstance. It also brings to the limelight the need for clear guidelines on initiating antiviral therapy in non-transplant patients.

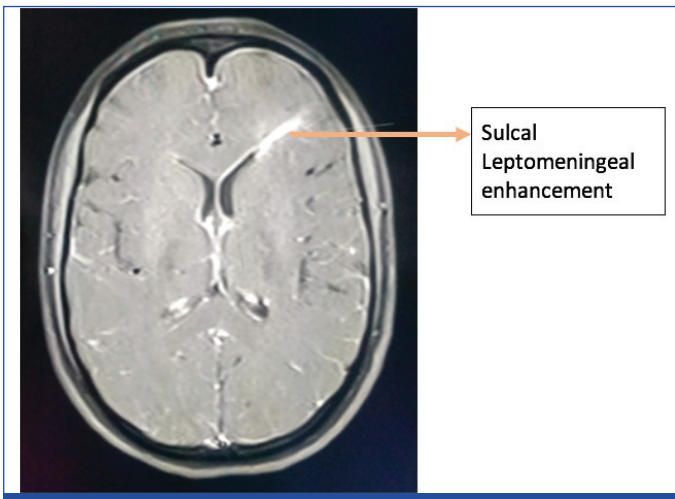
Keywords: CNS viral infection, Cytomegalovirus, Immunocompromised, Non-transplant

CASE REPORT

A 24-year-old female with no known co-morbidities or relevant past history or family history or drug history presented with history of high grade fever and chills for five days, headache for three days non bilious vomiting for two days and an episode of generalised tonic clonic seizures one day prior to presentation. There was no history of immunosuppression, weight loss, cough or expectoration.

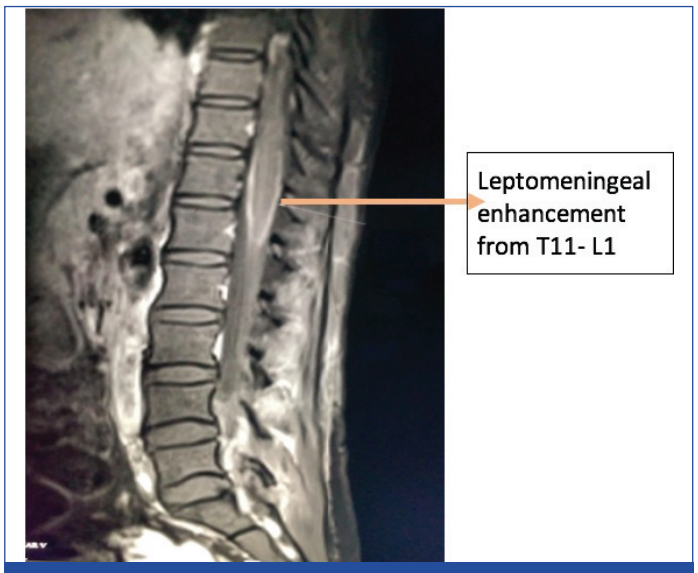
On examination she had low grade fever with altered sensorium and neck stiffness with no focal neurological deficit or lymphadenopathy. Other clinical examination was unremarkable. Chest and abdomen were clinically normal. On baseline laboratory investigations she had WBC count of 14,100 cells per cumm with lymphocytic predominance, while the other tests including biochemical investigations for kidney and liver functions, electrolytes, lipids, chest X Ray and ultrasound abdomen were normal. She was started on Inj.Ceftriaxone 2g IV BD, Inj. Acyclovir 500 mg IV TDS and Inj. Vancomycin 1g IV TDS for a total of 14 days with a working diagnosis of meningitis (?) bacterial/(?) viral.

CSF analysis revealed protein of 176 mgs%, sugar 38 mgs% and cell count of 48 cells/cumm with lymphocytes 65%. Adenosine deaminase level was 17 IU/L. GeneXpert for *Mycobacterium tuberculosis* was negative. CSF gram stain showed few pus cells but no organisms. CSF culture for bacteria was sterile. India ink stain for *Cryptococcus* and Ziehl Nielson for tuberculosis was negative. HSV I, II, IgM, IgG were negative. MRI brain showed patchy meningeal enhancement [Table/Fig-1].



[Table/Fig-1]: MRI brain with contrast showing sulcal leptomeningeal enhancement.

On the basis of the CSF findings anti-tuberculous therapy (ATT) was started along with anti-epileptic anti-oedema measures (intravenous mannitol inj. Dexamethasone and injection Levetiracetam). Her sensorium initially showed improvement but worsened by day three with development of total paraplegia and bilateral papilloedema. MRI of spine with brain screening showed leptomeningeal enhancement [Table/Fig-2]. There was no mass lesion. Repeat CSF analysis showed sugar of 36 mgs% and protein of 256 mgs%. Her virology screen for HIV, HbsAg and HCV was negative. ATT was continued with steroid cover. Power of both lower limbs showed improvement from 0/5 to 2/5. Papilloedema resolved. Patient was discharged with a working diagnosis of Tuberculous Meningitis with probable secondary vasculitis on the basis of CSF Adenosine deaminase levels. She was advised to continue ATT (Rifampicin 450 mg, Isoniazid 300 mg, Ethambutol 800 mg, Pyrizinamide 750 mg), Phenytoin 200 mg and a tapering dose of steroids. As both Phenytoin and Rifampicin are cytochrome P450 inducers and both ATT, phenytoin can cause hepatotoxicity, patient was counselled in detail about the possible adverse effects, was monitored in hospital for possible interaction and treatment failure before being certified fit for discharge. She was told to report immediately in case of adverse reaction.



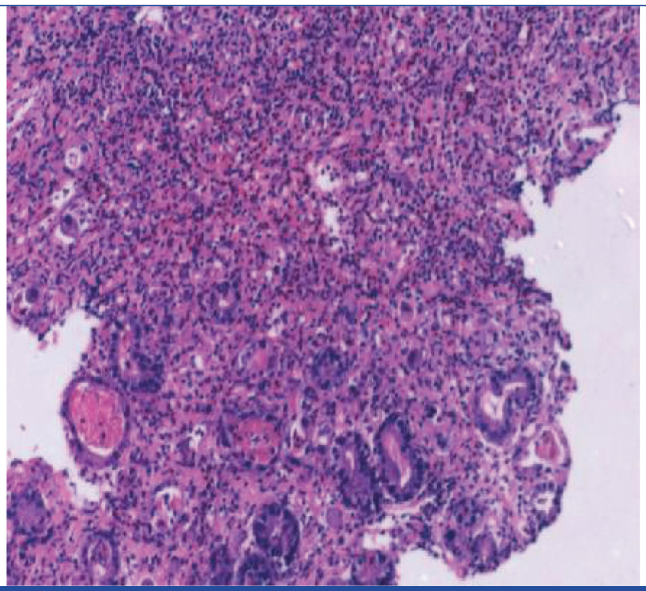
[Table/Fig-2]: MRI spine with contrast showing meningeal enhancement from T11-L1.

One month later, she presented with history of recurrent fever, headache, vomiting and burning epigastric pain for two days. Baseline investigations were normal. A diagnosis of ATT induced

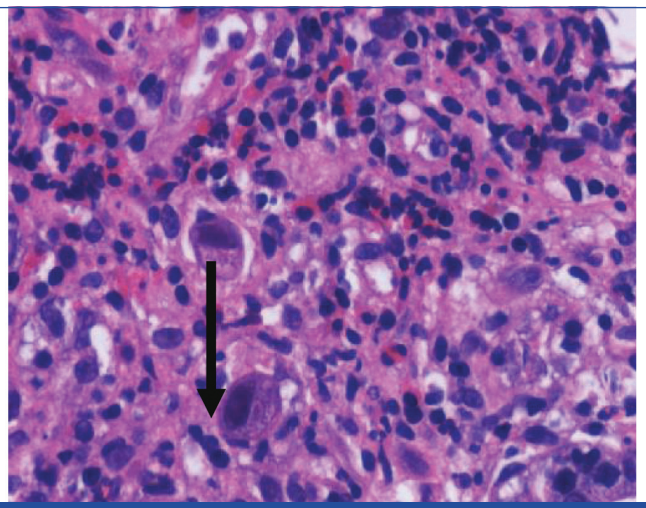
gastritis was made. She improved with symptomatic treatment with Inj.Pantaprazole 40 mg IV OD, syrup mucaine gel. Patient wanted to undergo Upper GI endoscopy later if symptoms recurred. Fundus was normal ruling out Ethambutol induced optic neuritis. Fundus examination to rule out Ethambutol induced optic neuritis in view of dull persistent headache was normal. She improved symptomatically and was discharged with the advice to continue ATT, phenytoin and a tapering dose of steroids.

The patient presented for the third time again a month later with fever for a week associated with vomiting, dysphagia and myalgia for two days duration. Her paraplegia had resolved completely. She was icteric and had upper abdominal tenderness with no evidence of organomegaly.

Total counts were 15,700 cells/cu mm with lymphocyte predominanace, total bilirubin-2.87 mg/dL, direct bilirubin-1.75 mg/dL, SGOT 81 IU/L, SGPT 109 IU/L. Ultrasound abdomen was normal. A diagnosis of drug induced hepatitis was made and she was started on liver safe regimen of ATT (Ethambutol 800 mg, Levofloxacin 750 mg, streptomycin 1g). Serum cortisol sent in view of persistant low normal BP of 90/60 -100/70 mmHg was found to be 35.19 IU/L. Upper Gastrointestinal Endoscopy for persistent dysphagia revealed oesophageal candidiasis with multiple gastric ulcers. Biopsy showed bits of grey-white soft tissue on gross examination. Microscopic examination showed fragments of gastric mucosa with areas of ulceration and features of Cytomegalovirus infection [Table/Fig-3,4].



[Table/Fig-3]: Stroma showing areas of ulceration and granulation tissue-H&E (200X).



[Table/Fig-4]: Areas of infiltration with many eosinophils and lymphocytes in the lamina propria. Many large cells showing enlarged nuclei with nuclear and cytoplasmic inclusions with a perinuclear halo suggestive of Cytomegalovirus infection. H&E (400X).

The patient was started Valgancyclovir 900 mg/day for CMV gastritis after being warned about possibility of loose stools. Patient was also found to have oral candidiasis, was started on oral Fluconazole. Repeat HIV serology was negative. Serum IgM for Cytomegalovirus was 0.29. Absolute lymphocyte count was1103 cells/microL (690-2540)-85%; T helper cell count-734 cells/microL (410-1590). T helper cells 56% (31-60%). The absolute suppressor T cell count was 351cells/microL (190-1140). T suppressor cell 27% (13-41%). The T helper/suppressor ratio was 2.09. Patient improved clinically and was discharged with the advice to continue ATT, tapering steroids, phenytoin, valgancyclovir and fluconazole.

She presented after four months of initial presentation (for the fourth time) with history of restlessness, irritability, photophobia and non-bilious vomiting. She had low grade intermittent fever and polyarthralgia. She had discontinued Valgancyclovir within a month of initiation because of persistent diarrhea. Detailed history revealed that she was consuming double the dose of phenytoin prescribed as she did not remember the doctor's instructions clearly. She had multiple hypo-pigmented maculo-papular lesions over the extensor aspect of arms, legs and peri-oral region suggestive of cutaneous manifestation of CMV infection. CNS examination showed bilateral horizontal nystagmus with gait ataxia. LFT showed total bilirubin of 3.83 mgs%, direct bilirubin of 2.29 mgs%, SGOT of 70 IU/L, SGPT of 42 IU/L. Serum phenytoin levels were 44.30.

CSF analysis was normal with Adenosine deaminase levels of 3.4 U/L and negative for cryptococcal antigen and antibodies to CMV. CSF gram stain and culture showed no abnormality. Phenytoin was stopped. Meanwhile her gastric antral biopsy done during her previous admission which was sent for quantification of CMV DNA by polymerase chain reaction revealed 45194998 copies/mL. Repeat IgM for CMV was still less than 5 IU/mL-negative. In view of very high tissue load of CMV patient was started on Ganciclovir 250 mg IV BD for 21 days and subsequently oral Valganciclovir for the next three months. Serial LFTs improved gradually and the patient was restarted on first line ATT drugs.

Outcome and Follow-Up

She presented for follow-up two weeks later. Her photophobia, ataxia and skin lesions resolved. LFT was within normal limits. She was de-escalated to oral Valgancyclovir 900 mg twice daily along with probiotics. She came for regular monthly follow-ups for the subsequent three months. She was continuing oral Valgancyclovir. She showed a steady improvement in general well-being, her appetite improved and had a remarkable gain in weight. She was advised for repeat Upper GI Endoscopy with biopsy for CMV-DNA PCR at the end of 12 weeks of Valgancyclovir to know any regression in the tissue load of the virus. The patient had undergone Upper GI Endoscopy which showed no evidence of erosions or gastritis but CMV-DNA PCR could not be done in view of logistic reasons. She is on follow-up doing well clinically and laboratory wise.

DISCUSSION

Cytomegalovirus is a Human Herpes Virus 5 (HHV 5) belonging to the beta herpes group with ds DNA. It is an opportunistic pathogenic micro-organism rarely causing disease in immunocompetent adults. While seroprevalence has been reported as 40-100% (higher percentages in developing countries), no figures are available regarding incidence of clinical presentation in the general population especially in India [1]. A search of 89 articles published over 57 years worldwide showed CMV infection in only 290 immunocompetent adults [2]. Once infected, the virus can remain latent in cells such as macrophages and B lymphocytes. Risk factors and transmission modes for the infection are well known [3].

In immunocompetent individuals it manifests as fever, headache and myalgias while in the immunocompromised host, it may produce fever, leukopenia, pneumonitis, encephalitis, retinitis, hepatitis, oesophagitis, gastritis and colitis.

The risk of clinical disease is related to the degree of immunosuppression and co-infection with other pathogens. Gastrointestinal CMV could be localised or extensive. It may present as fever, abdominal pain, nausea, vomiting, weight loss, diarrhea and malena.

Our patient had epigastric pain with vomiting and GI work up revealed CMV gastritis. Since the neurological symptoms and signs improved with empirical ATT the causative factor of the CNS symptoms was probably tuberculosis.

CMV re-activation has been postulated to occur during TB disease. On the other hand, CMV infection is associated with chronic immune activation with increased risk of tuberculosis [4,5].

The two diseases also have overlapping risk factors like poor socio-economic status, solid organ transplantation, close interpersonal contact etc., [6].

Recent retrospective studies suggest that system steroid use is a risk factor for CMV disease among certain patient population [7]. Even a low dose of steroid could be a risk factor. Use of prednisolone for four weeks at more than or equal to 8 mg per kg per day on average (i.e., cumulative dose of 23 mg per kg for 4 weeks) was seen to increase the risk of viral diseases remarkably [8]. Further studies are required to ascertain the relationship of TB disease and CMV infection and their effects of reactivation on each other [5].

Studies are also required to determine the median cumulative dose of steroids which may have an influence on host immunity in otherwise immunocompetent individuals [7].

Diagnostic modalities for CMV include serology, qualitative and quantitative Polymerase Chain Reaction (PCR), pp 65 antigenemia, culture and histopathology. The gold standard for diagnosing CMV tissue invasive disease is the identification of CMV inclusions or positive CMV specific immunohistochemistry staining on histopathology [9].

It has been recommended that HIV patients with CMV gastrointestinal disease should receive induction therapy for 2 to 6 weeks (usually IV Ganciclovir 5 mg/kg/dose every 12 hours). This should be followed with oral Valganciclovir 900 mg once daily for six months. These recommendations were followed for our case even though she did not have HIV. In view of the risk of bone marrow suppression, our patient had a CBC with differential count twice a week during induction therapy as recommended [10].

Gastric symptoms in a patient on ATT and steroids are most likely to be managed as they are due to the drugs. Unless the rare possibility of CMV disease is investigated for and treated along with tuberculosis, the outcome may be disastrous [11].

CONCLUSION

A young female with CNS tuberculous infection developed gastric symptoms. The rare possibility of co-incident CMV disease was thought of, investigated for and diagnosis was established by histopathology. Treatment of both infections simultaneously resulted in cure of the patient. This case highlights the importance of having a high degree of suspicion in diagnosing an unlikely infection in an unforeseen circumstance. It also brings to the limelight the need for clear guidelines on initiating antiviral therapy in non-transplant patients.

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