Case Report

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# CMV Enteritis and Guillain-Barré Syndrome after Stem Cell Transplantation for Lymphoma

Wichean Mongkonsritragoon, M.D.[1] and Wimwipa Mongkonsritragoon, M.D.[2]

[1]Horizon Cancer Center, Department of Medicine, Bumrungrad International Hospital, Bangkok 10110, Thailand

[2]Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand

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## Abstract:

We report a 31-year-old male from Kuwait, diagnosis of advanced diffuse large B-cell lymphoma stage IV presented with extradural mass and spinal cord compression at T6 level. After T7-T8 laminectomy with 4 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) chemotherapy and high dose methotrexate (MTX) only one time then followed with 4 cycles of rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone (R-Hyper CVAD)/high dose MTX and cytarabine (Ara-C). The non-myeloablative stem cell transplantation (NMSCT) was performed because of morbid obesity (body weight 135 kg). The conditioning regimen was thiotepa, fludarabine and cyclophosphamide. The graft versus host disease (GVHD) prophylaxis was short-course methotrexate and tacrolimus. The patient developed chronic diarrhea with abdominal pain caused by CMV colitis on day 57 post-transplant and was treated with ganciclovir. Subsequently he developed Guillain-Barré syndrome manifested with progressive weakness of lower extremity which successful treatment with intravenous immunoglobulin (IVIg) 2 g/kg. The recovery of motor power was starting 2 days later. By the same period, patient developed pancytopenia from stem cell rejection. The 0.95 x $10^6$/kg of stem cell was re-infused on day 72 post-transplant and reachieved engraftment 13 days later. The motor power was recovered from grade I to grade IV and he was able to walk with walker support after 25 days treatment of IVIg

**Keywords:** Lymphoma, Stem cell transplantation, Guillain-Barré syndrome

## Introduction

The management of advanced or refractory diffuse large B-cell lymphoma (DLBCL) with CNS and bone marrow involvement should consider high dose chemotherapy with allogeneic stem cell transplantation (SCT). The cytomegalovirus (CMV) infection during immunosuppression is common. Guillain-Barré Syndrome (GBS), manifests as acute inflammatory demyelinating polyneuropathy, can be triggered by viral infections which CMV is the second most common reported pathogen

Corresponding author: Wichean Mongkonsritragoon, M.D.
Horizon Cancer Center, Department of Medicine, Bumrungrad International Hospital, Bangkok 10110, Thailand
E-mail: mwichean007@hotmail.com

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preceding GBS. The aforementioned Dutch GBS study found CMV to be present in 13% of patients.[1] The graft rejection is also possible if the patient has serious infection. We report a case of advanced DLBCL post allogeneic stem cell transplantation developed CMV enteritis with GBS and graft rejection after that.

**Case Presentation**

A 31-year-old Kuwaiti male was referred for lymphoma treatment. In March 2020, he was diagnosed with stage IV diffuse large B-cell lymphoma (DLBCL) involving scapular and T6 vertebral body with spinal cord compression from extradural mass. In Kuwait, he was treated with T7-8 laminectomy and 4 cycles of R-CHOP (rituximab, cyclophosphamide, vincristine, prednisolone) chemotherapy followed by one course of high dose methotrexate (MTX) and 2 doses of intrathecal MTX. Then, he was referred for further treatment in Thailand.

During that period, there was a pandemic spread of COVID-19 and he had to be in hospital quarantine for 14 days. The disease evaluation was done by PET/CT scan compared to the previous one in his country showed no significant change of residual left paravertebral mass adjacent to T7, 8 vertebral bodies, 1 cm in diameter, SUVmax = 2.86 (previous 1 cm SUVmax= 2.6, initially 1.8 cm thick, SUVmax= 15.9) which was determined as complete metabolic response, scoreII. Osteoblastic lesion in the T8 vertebral body showed no FDG avidity, SUVmax=3.64, same as normal vertebra; post treatment change of bone involvement (complete metabolic response) (Figure 1). The bone marrow study showed no lymphoma cell involvement.

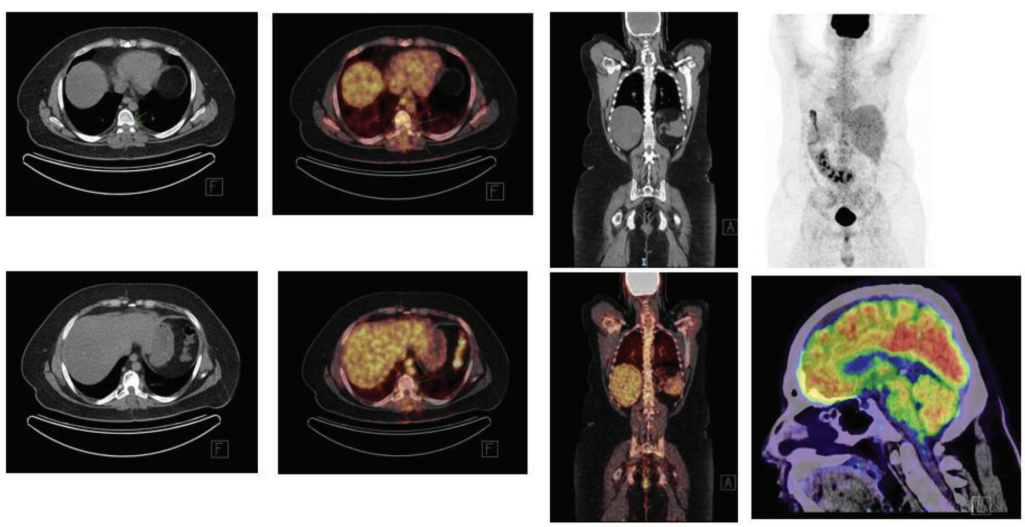

**Figure 1** PET/CT scan study on 1 September 2020 showed no significant change of residual left paravertebral mass adjacent to T7, 8 vertebral bodies, 1 cm in diameter, SUVmax = 2.86 (previous 1 cm SUVmax=2.6, initially 1.8 cm thick, SUVmax= 15.9) which was determined as complete metabolic response, score II.

By that time, we determined this case as an advanced DLBCL which was likely to involve spinal cord and had some residual paravertebral mass with SUVmax only 2.86 and determined as complete metabolic response score II after treatment from Kuwait. We decided to continue treatment with second line salvage immuno-chemotherapy followed by high dose chemotherapy with stem cell transplantation.

The salvage chemotherapy R-Hyper CVAD (rituximab/cyclophosphamide/vincrisine/doxorubicin/dexamethasone) alternating with high dose MTX and cytosine arabinoside (Ara-C) had been given for 4 cycles. The lymphoma involved bone and vertebra which was bone marrow space. The patient was morbid obesity (body weight 135 kg) and poor performance status, so we considered reduce-dose chemotherapy of non-myeloablative stem cell transplantation (NMSCT) from his sister which had matched related HLA. The conditioning regimen was thiotepa/fludarabine/cyclophosphamide (TFC) which the dose was reduced by using adjusted body weight. The PET/CT scan was evaluated on 7 Jan 2021 after NMSCT (D0=25 Jan 2021) which showed no significant change of residual left paravertebral mass adjacent to T7, 8 vertebral bodies, 0.9 cm in diameter, SUVmax =3.03 (previous 1 cm, SUVmax = 2.86, initially 1.8 cm thick, SUV max = 15.9); complete metabolic response, Score II and osteoblastic lesion in the T8 vertebral body shows no FDG avidity, SUV max = 2.24(previous SUVmax=3.64), same as normal vertebra; post treatment change of bone involvement (complete metabolic response) (Figure 2)

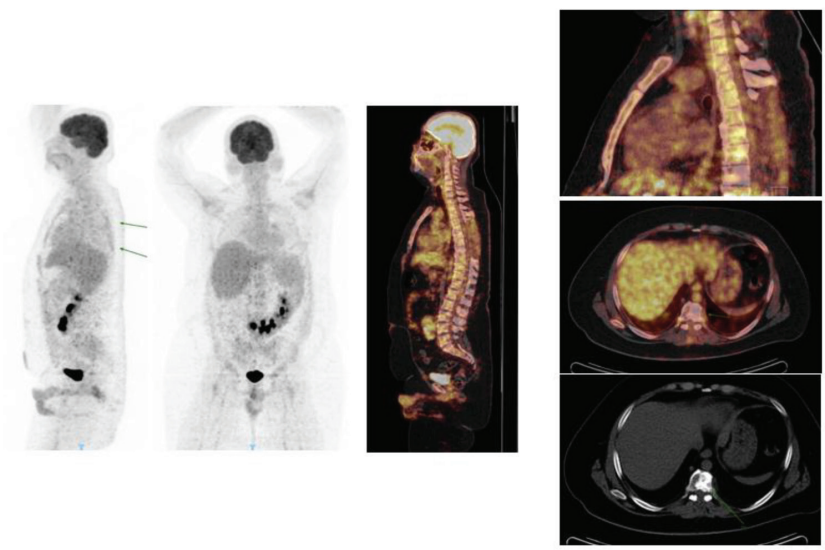

**Figure 2** PET/CT scan on 7 Jan 2021 after Hyper CVAD chemotherapy and non-myeloablative stem cell transplantation (NMSCT) showed no significant change of residual left paravertebral mass adjacent to T7, 8 vertebral bodies, 0.9 cm in diameter, SUVmax =3.03 (previous 1 cm SUVmax=2.86, initially 1.8 cm thick, SUVmax= 15.9); complete metabolic response, Score II and osteoblastic lesion in the T8 vertebral body shows no FDG avidity, SUVmax= 2.24 (previous SUVmax=3.64), same as normal vertebra; post treatment change of bone involvement (complete metabolic response)

On day 40 after NMSCT, the patient developed skin rash on his face and both ears as a manifestation of graft versus host reaction (GVHD). The tacrolimus level was 2.3 ng/mL (therapeutic range 10-20). The reaction was well controlled after increased dosage of tacrolimus with steroid combination. On day 57, the patient was admitted because of chronic diarrhea with abdominal pain. Again, the GVHD was suspected. The blood tests showed hemoglobin 14 g/dL, WBC 6.0 x $10^9$/L, platelet 97.0 x $10^9$/L, BUN 55.4 mg/dL, creatinine 2.79 mg/dL, AST 86 U/L, ALT 198 U/L, total bilirubin 1.1 mg/dL. The tacrolimus level was 25.7 ng/mL. The endoscope had been done and showed only moderate antral gastritis, gastric ulcer and duodenitis. The whole abdominal

CT-scan showed diffuse bowel wall and mural thickening of small bowel and colon with surrounding perirectal and mesenteric stranding possibly due to infectious or inflammatory process. (Figure 3).

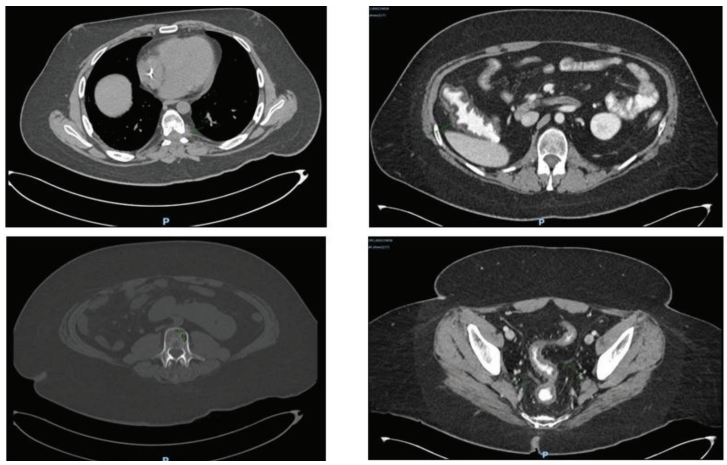

**Figure 3** The abdominal CT scan showed bowel wall thickening

The investigations of infectious cause had been done and demonstrated CMV in the stool by PCR test but the serum CMV viral load was undetected and the patient never had fever. The antiviral, ganciclovir, was started with his abdominal symptoms gradually improved. By that period, the overdose of tacrolimus was diagnosed and hold with intravenous hydration. The blood level was down and also the serum creatinine level and liver function returned to normal.

By day 68 of NMSCT, the patient developed progressive pancytopenia with hemoglobin 7.1 g/dL, WBC 2.7 x $10^9$/L, platelet 17.0 x $10^9$/L, AST 31 U/L, ALT 34 U/L, and total bilirubin 4.9 mg/dL. The pancytopenia may cause from CMV infection, ganciclovir or graft rejection. The cause of hyperbilirubinemia might be from infection or medication. The bone marrow evaluation had been done and showed severe hypocellular marrow without viral inclusion bodies or definite lymphoma involvement. The stem cell 0.95 x $10^6$ /kg was reinfused on day 72. The recovery of the blood was achieved thirteen days after (hemoglobin 10.5 g/dL, WBC 17.2 x $10^9$/L, and platelet 2.0 x $10^9$/L). By the same period (day 71), the patient developed progressive weakness of both legs. The MRI of T-spine and PET/CT scan did not show any new tumor mass or spinal cord compression. (Figure 4)

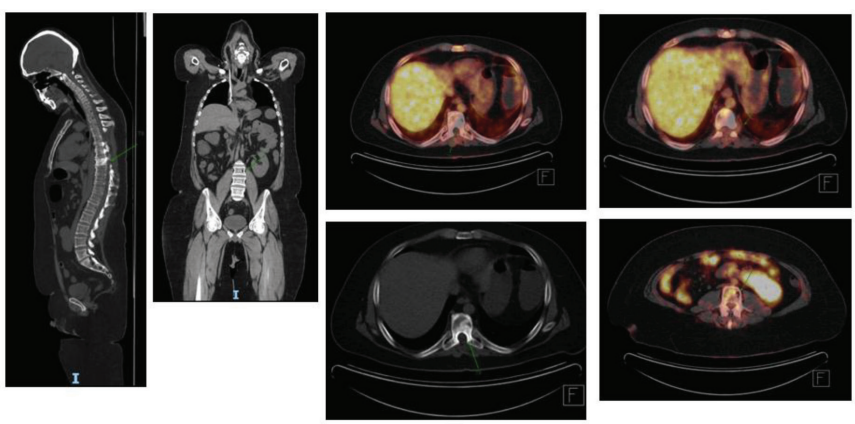

**Figure 4** PET/CT scan on 9 April 2021 showed stable small residual left paravertebral mass adjacent to T7, 8 vertebral bodies, 1 cm in diameter, SUVmax =2.74 (previous 0.9 cm SUVmax=3.03, Score 2, complete metabolic response.

The neurological examination demonstrated: awake, alert, intact cranial nerve, intact ocular movement, intact vision, cooperation and followed commands, no facial palsy, generalized weakness (upper arm grade 2/5 and hand grip grade 3-4/5), paraparesis with weakness both of legs grade 1/5 (more on proximal), no abnormal movement. Other neurological tests, bilateral flexor response of plantar reflex, impaired pinprick sensation, temperature and proprioception both feet, negative straight leg raising test and absence of all deep tendon reflexes. The conclusion was symmetrical proximal weakness of arms and legs which suspicious of acute inflammatory demyelinating polyneuropathy (AIDP e.g., Guillain-Barré syndrome). The nerve conduction study confirmed acute acquired demyelinating process. The lumbar puncture was not done because of low platelet number. The patient was treated with intravenous immunoglobulin (IVIg) 2 g/kg body weight. The motor power was gradually gained 2 days after infusion and reached more than grade 3/5 after 10 days.

**Discussion**

This patient was 31-year-old Kuwaiti man came with advanced DLBCL with spinal cord compression from paravertebral mass and vertebral bone involvement. After treatment from Kuwait with laminectomy and R-CHOP chemotherapy with high dose methotrexate, he still had residual tumor even through the SUVmax from PET/CT scan did not increase (score II). We considered to treat with second line chemotherapy followed by NMSCT. This technique was used because of vertebral bone involvement and morbid obesity. The conditioning regimen was Thiotepa-based (TFC) which the dose was reduced by using adjusted body weight. Thiotepa is a cytotoxic agent of the polyfunctional type related to nitrogen mustard. The radiomimetic action of thiotepa is believed to occur through the release of ethylenimine radicals which, like radiation, disrupt the bonds of DNA. Both thiotepa and its active metabolite, TEPA, efficiently cross the blood-brain barrier. After intravenous administration, the cerebrospinal fluid concentration achieved are nearly identical to those in plasma.2,3 The acute graft versus host disease (aGVHD) was very mild and well controlled. On day 57 of NMSCT, the patient developed sudden onset of diarrhea with abdominal pain on and off. The GVHD was ruled out because the serum tacrolimus level was high and endoscope with biopsy had been done. The CMV enteritis and colitis were diagnosed because of positive CMV in stool by PCR and abdominal CT scan. The GI symptoms were improved after ganciclovir treatment.

Unfortunately, the patient developed graft rejection which might be triggered by CMV infection or antiviral medicine. CMV infection is associated with an increased expression of MHC class II on multiple cell types. Since recognition of non self MHC antigens is the major determinant of allograft rejection, an upregulation of these molecules could contribute to graft failure.[4,5] Ganciclovir triphosphate is a competitive inhibitor of deoxyguanosine triphosphate incorporation into DNA and preferentially inhibits viral DNA polymerase more than cellular DNA polymerase.[6] This effect will be associated with bone marrow suppression, particularly leukopenia.[7] In fact, disseminated CMV per se characteristically suppresses bone marrow production, but antiviral therapy usually results in improvement of hematologic parameters. The bone marrow of the patient had been engrafted after 13 days of stem cell re-infusion. By the same period around day 68 of NMSCT, the patient developed progressive weakness of both legs and showed symmetrical proximal weakness of arms and legs which suspicious of acute inflammatory demyelinating polyneuropathy (AIDP e.g., Guillain-Barré syndrome). Infection with

*Campylobacter jejuni*, which causes diarrhea, is one of the most common risk factors for GBS. People can also develop GBS after some other infections, such as influenza virus, cytomegalovirus, Epstein-Barr virus, and Zika virus. CMV is the second most common reported pathogen preceding GBS. The aforementioned Dutch GBS study found CMV to be present in 13% of patients.[1] IVIg is a proven effective treatment for GBS (class 1 evidence). However, about 25% of patients need artificial ventilation and 20% are still unable to walk unaided after 6 months. Important clinical factors associated with poor outcome were age, presence of preceding diarrhea and the severity of disability in the early course of disease.[8] A second IVIg course should not be considered for treatment of Guillain-Barré syndrome because of a poor prognosis.[9] Fortunately, our patient had good respond after only one course of treatment.

## Conclusion

The authors report a case of advanced DLBCL post allogeneic NMSCT, developed CMV enteritis with GBS which successful treatment with ganciclovir and IVIg. The patient had graft rejection which engrafted again by reinfusion of the donor stem cell.

## Conflict of interest

The authors have declared no conflict of interest.

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