Cytomegalovirus Reactivation in Patients with Solid Malignancies: A Case Series and Literature Review

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Abstract

Cytomegalovirus (CMV) is a double-stranded DNA virus that belongs to Herpesviridae family. Primary CMV is mostly asymptomatic; however, it has the ability to reactivate in immune-compromised patients. CMV reactivation is a well-known complication in transplant patients; however, its clinical significance in non-transplant patients remains unclear. We report five cases of CMV reactivation and disease in patients with solid malignancies, three of which had CMV reactivation, one had probable CMV pneumonia, and the last had CMV reactivation with gastrointestinal (GI) involvement. The diagnosis was based on the detection of CMV replication in respective tissue samples (bronchoalveolar lavage (BAL), urine and colonic tissue, and blood. Our case series highlights the fact that CMV may reactivates in patients with advanced cancer with a possibility to cause tissue invasive disease. Thus, CMV disease should be considered in patients with solid malignancies in those presenting with compatible clinical presentation.

Keywords: Cytomegalovirus;Solid Malignancies;Immune-Suppression;CMV Dnaemia;CMV Disease.

Introduction

Cytomegalovirus (CMV) is a double-stranded DNA virus that belongs to the β Herpesviridae subfamily.[1] Since its discovery in 1965, CMV infection became one of the most common herpes viruses affecting at least 50% of the global population in United States and reaching 100% in the developing countries.[2] Primary CMV infection is mostly asymptomatic in immune-competent patients. In immunocompromised patients, CMV reactivates leading to CMV disease. CMV disease is sub-categorized into CMV syndrome, symptomatic CMV DNAemia or tissue invasive CMV disease that requires pathological detection of CMV on tissue in a symptomatic patient.[3] While CMV reactivation and disease is commonly observed in transplant recipients, it is less frequently reported in individuals with solid malignancies. Herein we reported five cases of advanced solid malignancies presented with CMV reactivation.

Case Reports

In the current case series, we report five cases of CMV reactivation in patients with advanced solid malignancies. Table 1 summarizes the demographics, clinical and laboratory findings, management and outcomes.

Table 1: A summary of clinical demographics, laboratory findings, antiviral therapy and outcomes of patients presented for CMV reactivation.

Patients	Age/Sex	Comorbidities	Tumor type	Stage of the tumor	Oncology treatment	Site of CMV reactivation	CMV DNA levels (IU/ml)	Antiviral therapy	Outcome
Case 1	63-F	CKD/DM type II/HTN/ Hypothyroidism	RCC	IV	NA	Plasma	68,000 IU/ml	Ganciclovir 2.5 mg/kg/dose every 12 hours then Valganciclovir 900 twice po daily for three weeks	Recovered
Case 2	82-F	DM/HTN	Ovarian cancer	IV	Gemcitabine & Carboplatin	Plasma	112,300 IU/ml	Valganciclovir 450 mg every 48 hours for 4 weeks	Death
Case 3	61-M	HTN/DM/DL	Anorectal Squamous carcinoma	IV	Carboplatin % Paclitaxel	Plasma	24,540 IU/ml	Ganciclovir 2.5 mg/kg/dose every 24 hours	Death
Case 4	30-M	NA	Adenoid cystic adenocarcinoma	IV	Carboplatin and Doxorubicin	Lung/plasma	Plasma: 12,220 IU/ml BAL: 5,580 IU/ml	Ganciclovir 5 mg/kg every 12 hours IV	Death
Case 5	67-M	DM/ Hypothyroidism	Breast cancer	IV	Pembrolizumab-Nab-paclitaxel	Gastrointestinal tract	Colon tissue: 3,267 IU/ml	Valganciclovir 900 mg po every 12 hours for two weeks	Recovered

DM: Diabetes mellitus; HTN: hypertension; NA: not available; DL: dyslipidemia; CKD: chronic kidney disease; po: per os. Figure 1

Case one

A 63-year-old woman with a history of renal cell carcinoma (RCC) was referred to the nephrology team on November 2022 for proteinuria (uPCR 161mg/mmol, uACR 121mg/mmol) and serum creatinine of 99 umol/L. The laboratory work-up for proteinuria revealed normal complement 3 and complement 4 (C3, C4) levels. Her antineutrophil antibody (ANA), perinuclear and cytoplasmic antineutrophil cytoplasmic antibodies (pANCA and cANCA) were negative. The patient was kept on valsartan 80 mg daily. On December 2022, she was admitted to the hospital for contrast-induced nephropathy. The patient's electrolyte imbalances were corrected with IV hydration and bicarbonate infusion. However, urinary studies showed significant deterioration in proteinuria with uACR at 383mg/mmol and uPCR at 530mg/mmol. After a few days of conservative therapy without improvement in renal function, and given her worsening proteinuria, additional etiologies for acute kidney injury (AKI) were sought. The CMV PCR was requested and turned out to be highly positive with 68000IU/mL.

Case two

An 82-year-old woman who is known to have stage IV high-grade serous ovarian carcinoma was followed by the nephrology team for nephrotic-range proteinuria (uACR of 670mg/mmol and uPCR of 765mg/mmol) that was detected after four cycles of gemcitabine (800mg/m^2) and carboplatin. Her laboratory tests showed a white blood cell

(Wbc) count of 4,750 cells/mm3 with 75% neutrophils and 12% lymphocytes. Her Hb level was 7.7 mg/dL, platelet count was 458,000/uL, and creatinine level was 125umol/L. The differential diagnosis for nephrotic range proteinuria was wide and included: membranous nephropathy, vascular endothelial growth factor inhibitor (VEGFI) induced nephropathy, gemcitabine-induced nephropathy and systemic disease-related nephropathy. A work-up to exclude secondary causes of nephropathy was done, including ANA profile, C-ANCA, P-ANCA, and anti-glomerular basement membrane. All the work-up was negative. C3 and C4 values were normal. Gemcitabine was held, and the patient was consequently started on a sodium-glucose cotransporter-2 (SGLT2) inhibitor for proteinuria (dapagliflozin 10mg OD). She was also started on oral prednisolone 40 mg once daily. The patient was followed up over two months when her uACR increased again from 182 to 250mg/mmol. For that, further investigations were requested. Laboratory findings showed normal white cell count, creatinine level and electrolytes level. CMV PCR was done, and the result showed a measurement of 112,300 IU/mL.

Case three

A 61-year-old man with a history of metastatic anorectal squamous cell carcinoma (SCC) was hospitalized for neurological impairment, respiratory distress and hypotension. Due to his severely low GCS, the patient was intubated and mechanically ventilated with supportive care, including vasopressors. The laboratory work-up showed anemia with a hemoglobin level of 7.8 g/dl, severe thrombocytopenia (platelets: 49,000/uL), schistocytes on blood film and AKI (247umol/L, baseline: 70-80umol/L) all of which points toward the diagnosis of thrombotic thrombocytopenic purpura (TTP). Based on these laboratory findings, the patient was started on high-dose steroids (methylprednisolone 1g once daily) for three days, followed by Rituximab (dosed at 375mg/m2). He was also started on empirical IV piperacillin-tazobactam and IV vancomycin due to the suspicion of sepsis/aspiration pneumonia. Moreover, his Epstein-Barr virus (EBV) and CMV PCR were both positive (109,500IU/mL and 24,540IU/mL, respectively). He was started on ganciclovir at a renally adjusted dose of 2.5mg/kg/dose every 24 hours. Unfortunately, the patient continued to deteriorate despite appropriate antiviral and antimicrobial therapy. He suffered a cardiac arrest and passed away despite CPR attempts.

Case four

A 30-year-old man with a history of adenoid cystic adenocarcinoma of the right lacrimal gland presented with type I respiratory failure and pneumonitis on the computed tomography (CT) scan chest (figure 1). The patient underwent a bronchoscopy procedure, and thorough investigations were carried out, including bronchoalveolar lavage (BAL) for bacterial culture, Galactomannan (GM), respiratory panel, and molecular testing for COVID-19, PCP, CMV, and Mycobacterium tuberculosis. All except CMV PCR returned negative. Plasma and bronchoalveolar lavage tested positive for CMV reactivation (12,220 IU/ml and 5,580 IU/ml, respectively). The cytology was negative for malignancy. The patient was started on ganciclovir 5 mg/kg/day IV twice daily. Unfortunately, the patient continued to deteriorate despite appropriate antiviral therapy. He eventually developed severe respiratory failure that resulted in death.

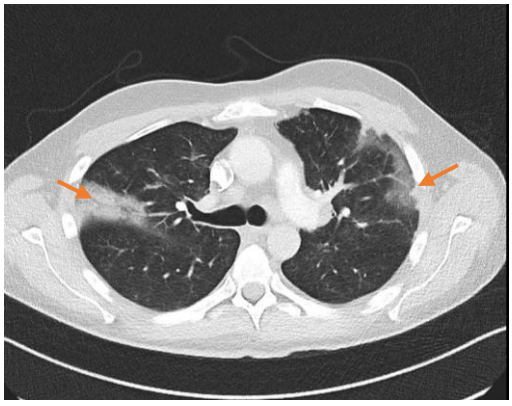

Figure 1: Bilateral peripheral patchy glass opacities and consolidation in upper lung distribution(arrows).

Case five

A 67-year-old woman with breast cancer presented with hematochezia, diarrhea, and signs of colitis on the abdomen pelvic CT scan (figure 2). The colonoscopic evaluation showed diffuse mucosal edema, erythema, erosions, and scattered superficial mucosal ulcerations. After ruling out infectious pathologies with negative stool culture and

Clostridiodes difficile (C. diff) studies, the patient was started on IV prednisolone at 1mg/kg/day for presumed Pembrolizumab-induced colitis. Despite clinical improvement, the colonic tissue mucosa under microscopic exam showed ulceration and acute and chronic inflammation of the lamina propria with granulation tissue formation. Moreover, tissue necrosis, neutrophilic abscesses formation, and small vessel vasculitis were observed (figure 3). The immune histochemistry stain was positive for CMV (figure 4). The molecular testing of CMV on the colonic tissue was also positive and showed a CMV viral load of 3,267IU/mL. The patient was thus started on oral valganciclovir 900mg every 12 hours for two weeks. The patient was followed up over two months without any recurrence of her symptoms.

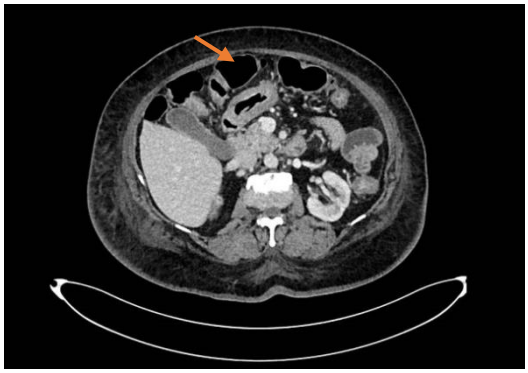

Figure 2: CT scan abdomen-pelvis showing diffuse thickening of the colonic wall (arrow).

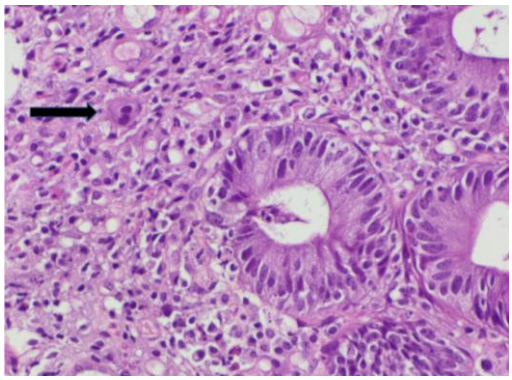

Figure 3: H & E (40x) showing neutrophilic abscess in the background with few enlarged cells exhibiting intranuclear inclusions (arrow)

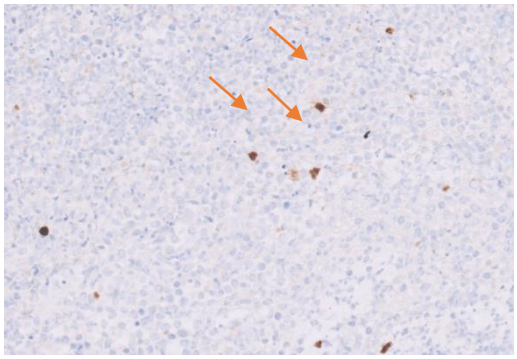

Figure 4: Immunoreactivity with CMV immunostain (arrows).

Discussion

CMV, the fifth member of the human herpes-viridae family, is one of the largest viruses known to cause clinical disease. Primary CMV infection is usually asymptomatic but may cause non-specific symptoms of fever, myalgias, lymphadenopathy and lymphocytosis.[4] CMV infection is a lifelong infection where the virus establishes latency in the progenitor cells, fibroblasts, endothelial cells, and macrophages.[5] This is of no importance when dealing with immune-competent patients. However, in immunocompromised patients, latent CMV infection can progress into symptomatic CMV disease, causing a broad spectrum of clinical syndromes. CMV is one of the major complications in post-solid organ and hematopoietic stem cell transplantation. In addition to the direct consequences of CMV

disease, it has several indirect effects, including an increased risk of fungal and bacterial infections, acute and chronic graft rejection and coronary vasculopathy.[6]

CMV reactivation and disease occur in other patient cohorts, including oncological non-transplant patients; however, limited data is reported. Wang et al. showed in their retrospective analysis that 70% of oncological patients who were studied for CMV reactivation had solid malignancies.[7] In a different study, Schlick et al. stated that 17 out of the 107 oncological patients with CMV reactivation had solid malignancies, eight of which were diagnosed with symptomatic CMV disease.[8] The frequency of CMV pulmonary invasive disease was retrospectively studied by Jorge Mera et al., who analyzed the lung autopsies in non-transplant patients over 26 years.[9] Out of the 10,441 autopsies reviewed, 20 cases had confirmed CMV pneumonia, and 6 of them had a background of solid malignancies.[9] In a more recently published retrospective study, Torres et al. showed that the incidence of GI-CMV disease was 6 per 100,000 patients with solid neoplasms compared to 102 per 100,000 patients with hematological malignancies.[10] Thus, although CMV disease is more common in transplant patients; however, it should be considered in non-transplant patients. The risk factors for CMV reactivation/disease are profound lymphopenia post-chemotherapy, advanced metastatic disease, steroid therapy, and recent chemotherapy.[7-10] All patients reported in this review had advanced malignancy, four of which were on chemotherapy and steroids. Two out of five patients had lymphopenia. The reported all-cause mortality rate of CMV reactivation in solid tumors ranges between 42% to 60%.[11]

CMV reactivation can progress to either CMV syndrome with fever, leucopenia and fatigue or tissue-invasive disease with various clinical syndromes like pneumonitis or colitis, and in rare cases, adrenalitis, nephritis, hepatitis, or carditis.[6] CMV nephritis presents with a spectrum of renal manifestations, including interstitial nephritis, glomerulonephritis, and to a lesser extent, focal segmental glomerular sclerosis (FSGS) and membranoproliferative glomerulonephritis.[12]

The diagnosis of CMV disease relies on the detection of CMV in the blood if dealing with CMV syndrome or the detection of CMV cytopathic changes or positive immunohistochemistry stains in clinically symptomatic patients.[13,14] CMV inclusions affect endothelial cells, macrophages and mesenchymal cells. Cells affected by CMV are usually larger in size (25-35 micrometres), with a larger ovoid or pleomorphic nucleus with basophilic intranuclear inclusions surrounded by a halo. These cells stain positive for CMV immunohistochemical stain. CMV DNAemia may or may not be present in CMV tissue invasive disease; however, high CMV viral loads are a prognostic factor for the development and severity of CMV disease.[13] In our report, we identified five cases of CMV reactivation, with one patient having CMV pneumonitis. The diagnosis was based on the presence of a compatible clinical picture, a positive CMV PCR in both blood and BAL, as well as radiological evidence of pneumonitis. The last patient had immune-related colitis caused by ICPI and was treated with steroids. The patient improved clinically; however, she was found to have a high CMV viral load on the colonic biopsy with positive pathological findings for CMV reactivation. This includes positive macroscopic findings and CMV immunostaining.

The use of CMV PCR in fluids to diagnose CMV tissue invasive disease is still debatable. This is mainly because there are no standardized methods and clear cut-offs to distinguish between tissue invasion and viral shedding.[3,6] However, data on the role of high CMV viral load in BAL in diagnosing CMV pneumonia is currently evolving. Lodding et al. reported that a cut-off of 5,500IU/mL was associated with 91% sensitivity and 75% specificity.[3] Moreover, a negative CMV DNA in the BAL fluid had a negative predictive value of almost 100%.[3] Based on these results, Per Ljungman et al. updated the definition of CMV pneumonia to include the role of CMV viral load in BAL fluid in the diagnosis.[3]

The role of CMV PCR is still unclear in other CMV invasive tissue diseases such as CMV nephritis, where the guidelines still recommend against depending on CMV DNA level in urine to prove diagnosis.[3]

The guidelines of the management of CMV disease are primarily based on data from transplant patients.[13] Based on the available guidelines, CMV disease should be treated with either IV ganciclovir at 5mg/kg every 12 hours or oral valganciclovir at 900 mg every 12 hours.[13-15] In cases of intolerance or evidence of CMV resistance, foscarnet or mirabilis can be considered.[13,16] Induction therapy of two weeks with weekly monitoring of CMV DNA levels in the blood is recommended. Antiviral treatment should be continued for at least two weeks with clinical resolution of symptoms and eradication of CMV DNAemia.[13,15] In our case series, three out of five patients received at least two weeks of antiviral therapy; two of which had a negative CMV PCR as a follow-up before stopping the antiviral. The decision to treat was based on the high levels of CMV DNAemia in patients with CMV reactivation, positive CMV in both BAL and plasma in the patient with CMV presumed pneumonitis and pathological findings of CMV reactivation (positive CMV immunostaining and CMV inclusion bodies) in the patient with immune-related colitis.

Conclusion

As a conclusion, CMV reactivation do occur in patients with advanced solid malignancies and rarely it can progress into CMV disease. The risk factors include lymphopenia, steroids and advanced disease. The decision to investigate for CMV disease should be based on clinical, laboratory, and radiological findings after ruling out more common differentials. More studies are needed to shed the light on the role of CMV reactivation, indications for treatment and duration of therapy.

Disclosure

No conflict of interest and no funding sources. Informed consent was taken from the patients.

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