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AIMS AND SCOPE

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SYSTEMATIC REVIEWS

Pulmonary cytomegalovirus infection: A case report and systematic review

Awotar Kanika, Jonathan Soldera

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Abstract

BACKGROUND

Cytomegalovirus (CMV) is a common virus that can cause the first infection in childhood or adolescence and reactivate later in life due to immunosuppression. CMV pneumonia is a rare illness in immunocompetent patients but is one of the most significant opportunistic infections in immunocompromised patients.

AIM

To report a case and review published cases of pulmonary CMV infection in both immunocompromised and immunocompetent patients.

METHODS

We conducted a systematic search on the MEDLINE (PubMed) database, without date or language restrictions, to identify relevant studies using Medical Subject Headings and Health Science Descriptors. We manually searched the reference lists of the included studies. Simple descriptive analysis was used to summarize the results.

RESULTS

Our search identified 445 references, and after screening, 43 studies reporting 45 cases were included in the final analysis, with 29 (64%) patients being immunocompromised and 16 (36%) being immunocompetent. Fever (82%) and dyspnea (75%) were the most common clinical findings. Thoracic computed tomography showed bilateral ground-glass opacities, a relevant differential diagnosis for severe acute respiratory syndrome coronavirus 2 infection. The majority of patients (85%) received antiviral therapy, and 89% of patients recovered, while 9% of patients died.

CONCLUSION

CMV pneumonia should be considered as a differential diagnosis for coronavirus disease 2019 pneumonia, especially in immunocompromised patients. Clinicians should be aware of the clinical presentation, management, and outcomes of CMV

pneumonia to guide appropriate treatment decisions.

Key Words: Cytomegalovirus; Immunocompromised; Immunocompetent; Severe acute respiratory syndrome coronavirus 2; Coronavirus disease 2019; Ganciclovir

Core Tip: The paper reports a case of disseminated cytomegalovirus (CMV) infection in an immunocompetent patient who presented with cough, dyspnea, high-grade fever, and jaundice. The patient was diagnosed with CMV pneumonia after developing sepsis and being admitted to the intensive care unit. The study conducted a systematic search on the MEDLINE database to identify published cases of pulmonary CMV infection in both immunocompromised and immunocompetent patients. The search identified 43 studies reporting 45 cases, with 29 (64%) patients being immunocompromised and 16 (36%) being immunocompetent. Fever and dyspnea were the most common clinical findings, and thoracic computed tomography showed bilateral ground-glass opacities. The majority of patients received antiviral therapy, and 89% of patients recovered, while 9% of patients died. The study highlights that CMV pneumonia should be considered as a differential diagnosis for coronavirus disease 2019 pneumonia, especially in immunocompromised patients, and clinicians should be aware of the clinical presentation, management, and outcomes of CMV pneumonia to guide appropriate treatment decisions.

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INTRODUCTION

Cytomegalovirus (CMV) is a DNA virus that belongs to the herpesviridae family and shares similarities with other herpes viruses. In immunocompetent adults, CMV infection is usually asymptomatic and causes mild mononucleosis-like syndrome, typically in childhood or adolescence. However, CMV can cause severe disease and pneumonia in immunocompetent individuals, albeit rarely[1,2]. CMV infection may lead to severe viral pneumonitis in immunocompromised patients, such as those with autoimmune deficiency syndrome (AIDS), allogeneic bone marrow transplantation recipients, or those on immunosuppressive drugs or high-dose steroids. The incidence of CMV infection is approximately 25%-30% in recipients of hematopoietic stem cell transplantation[3]. The gastrointestinal tract and central nervous system are the most frequent sites of severe CMV infection. CMV was one of the three most common causes of severe viral community-acquired pneumonia (CAP), along with influenza and adenovirus. However, this has changed with the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 2020[4]. The pulmonary manifestations of CMV infection may vary from a dry cough to severe interstitial pneumonia, with patients presenting with diffuse pulmonary infiltrates resembling a ground glass appearance. The diagnosis of CMV pneumonia is based on radiological patterns and serology (CMV IgM antibody) or polymerase chain reaction (PCR)[4]. In 1968, the first case of CMV CAP was reported by Carlstorm and colleagues in their case series of CMV infection in immunocompetent hosts[5]. CMV CAP in immunocompetent hosts presents as prolonged fever and interstitial infiltrates on chest X-ray that resolved slowly over 6 wk. Patients with CMV CAP present with relative lymphopenia, atypical lymphocytes, and mildly elevated serum transaminases. Primary CMV infection persists for life and is generally acquired through close physical contact involving direct inoculation with infected cells or body fluids. The spread of viral infection is through coughing, direct contact with body fluids such as blood, urine, feces, semen, vaginal fluid, and breast milk, or *via* mucous membranes, including the mouth or genitals. CMV infection following transplantation can be acquired if the transmission is from the organ from a CMV-seropositive donor. Mothers infected with CMV during pregnancy may transmit this infection to their newborn baby, leading to congenital CMV. CMV infection is one of the leading causes of miscarriage[1,6]. Babies with congenital CMV sometimes may be healthy for months or years after birth but may have late occurring signs such as hearing loss, and develop vision problems and developmental delay. Latent CMV can reactivate and replicate rapidly when the immune system is suppressed. It can lead to high levels of CMV viremia, and infection of multiple organ systems can cause severe illness such as retinitis, colitis, hepatitis, pneumonia, or encephalitis. Fatal CMV pneumonia is more common in patients who have received marrow transplants than those who received transplant of solid organs like the lung, heart, liver, or kidney[7,8]. CMV accentuates the sepsis-induced immunologic effects, leading to an increase in the risk for secondary

infections. CMV infection in critically ill patients is associated with prolonged ventilator support, nosocomial infections, prolonged hospital/intensive care unit (ICU) stay, and increased mortality rates [9].

As the coronavirus disease 2019 (COVID-19) pandemic continues and becomes an endemic, it is crucial to recognize that not all clinical and radiological presentations are solely attributable to COVID-19[10]. Therefore, diagnostic differentiation is essential, and ground-glass opacities (GGOs) must be evaluated in conjunction with other imaging findings, laboratory tests, and clinical features to reach a definitive diagnosis. CMV pneumonia can be diagnosed by detecting the virus in serum and/or respiratory samples such as bronchoalveolar lavage (BAL) or tracheal aspiration[10]. Quantitative real-time PCR (qRT-PCR) can be utilized to measure viral loads in blood and BAL fluid[11]. Lung biopsy histopathology is considered the gold standard for diagnosing pulmonary CMV infections, with the presence of CMV inclusion bodies (owl's eye) in biopsy specimens being confirmatory of lung infection [12]. However, the diagnostic yield of lung biopsy for diagnosing lung CMV infections can vary as inclusions may not always be visualized. Immunohistochemical (IHC) staining for CMV in cytological specimens of bronchial washing fluid can also detect CMV[13,14].

The first-line treatment for CMV disease is intravenous ganciclovir and its prodrug, oral valganciclovir, which inhibits viral deoxyribonucleic acid (DNA) polymerase, thereby interfering with DNA elongation. Mild disease in immunosuppressed patients may be treated with oral valganciclovir, whereas severe illness requires initial treatment with intravenous ganciclovir or foscarnet at full doses (adjusted for renal function)[15]. Treatment at full doses should be continued until symptom resolution and blood antigenemia (or DNAemia) clears. Adjuvant treatment with intravenous immunoglobulin or CMV hyper-immunoglobulin is recommended in immunocompromised patients and may be used in cases of severe CMV disease and hypogammaglobinemia[12].

This study aimed to report a case of disseminated CMV in an immunocompetent patient, and systematically review published cases of pulmonary CMV infection in both immunocompromised and immunocompetent patients.

Case report

Chief complaints: A 32-year-old man presented with a cough, dyspnea, high-grade fever, and jaundice.

History of present illness: The patient had no significant medical history and was not taking any medication. Physical examination revealed a temperature of 39.5°C, tachypnea, icteric sclera, and hepatosplenomegaly. He had no skin rash or lymphadenopathy. The initial blood tests showed pancytopenia, elevated liver enzymes, elevated bilirubin, and hypoalbuminemia. CT of the thorax showed GGOs, while CT of the face showed sinusitis, raising suspicion of an infectious etiology.

History of past illness: The patient had no significant past medical history.

Personal and family history: No significant personal or family history was reported.

Physical examination: The patient presented with a temperature of 39.5°C, tachypnea, icteric sclera, and hepatosplenomegaly. He had no skin rash or lymphadenopathy.

Laboratory examinations: Complete blood count revealed a platelet count of 87000/mm^3, hemoglobin level of 8.2 g/dL, and leukocyte count of 4830/mm^3. Liver function tests showed alkaline phosphatase of 1174 U/L, gamma-glutamyl transferase of 804 U/L, aspartate aminotransferase of 403 U/L, total bilirubin of 17.2 mg/dL, albumin of 1.7 g/dL, and international normalized ratio of 1.11. Autoimmune antibody testing for fluorescence antinuclear antibody was negative. COVID-19 antigen swab test was negative.

Imaging examinations: After a liver biopsy, the patient's results were suggestive of drug-induced liver injury, and subsequent immunochemistry testing returned negative results for CMV. Magnetic resonance imaging (MRI) of the abdomen showed a liver with enlarged dimensions, regular contours, and heterogeneous signal intensity, with predominance of hyper signal in the T2-weighted sequences, suggestive of an inflammatory process (hepatitis), and splenomegaly and pancreatic edema suggestive of pancreatitis. CT of the thorax showed GGOs (Figure 1), while CT of the face showed sinusitis.

Final diagnosis: The patient's clinical condition worsened, and he developed hypotension and sepsis, requiring admission to the ICU. Broad-spectrum antibiotics were started, and he was investigated for possible Wegener's granulomatosis. However, auto-antibodies were negative and his final diagnosis was disseminated CMV infection, confirmed by the high viral load of 325192.5 copies/mL.

Treatment: The patient was started on ganciclovir therapy.

Outcome and follow-up: After 6 wk of treatment, the patient recovered completely from his symptoms, achieving a sustained undetectable viral load.

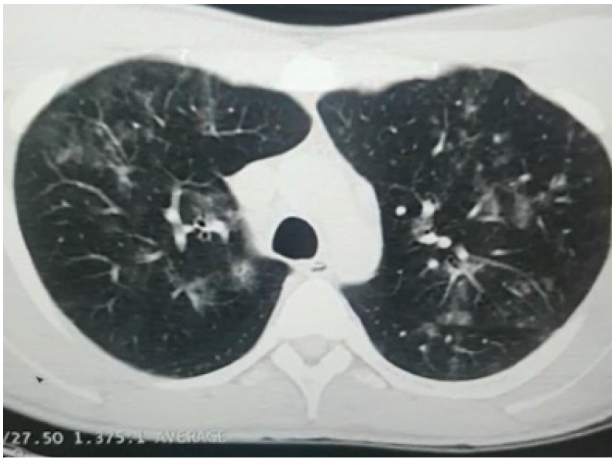

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Figure 1 Computed tomography of the thorax showing ground glass opacities.

MATERIALS AND METHODS

This study followed the recommendations outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[16].

Data sources

The electronic database MEDLINE (PubMed) was searched using the terms described in the Supplementary material. The searches were conducted in September and October 2022, with no date of publication restrictions and language restricted to English. References of included studies were screened for relevant records, and the reference lists of the retrieved studies were submitted to a manual search.

Inclusion and exclusion criteria

Case report or case series studies were eligible for selection. If there was more than one study published using the same case, the most recent study was selected for analysis. Studies published only as abstracts were also included, as long as the data available made data collection possible. Studies written in languages other than English were excluded. Studies having other co-existing causes of pneumonia were excluded from our study, for example, superimposed bacterial, parasitic, or fungal infections in existing CMV pneumonia, and other lung pathologies.

Study selection and data extraction

Titles were screened initially to select the cases of pulmonary complications of CMV infection and filter out non-relevant studies. Then, abstracts of chosen studies were read to select potentially relevant papers. The third step was the analysis of the full-length papers, and those which were not case reports of pulmonary CMV were filtered out. Data was extracted on the characteristics of the subjects and the outcomes measured from each eligible study. A table of extracted data on eligible studies was made in order to measure and identify patterns.

RESULTS

Using the search strategy, a total of 435 references were retrieved. After reviewing titles, 232 studies were found to be relevant for our topic and 203 studies were excluded. By analyzing abstracts, 172 studies were found to be potential relevant papers for our topic and therefore 60 studies were excluded. After reading and analyzing full length papers, 43 studies with 45 case reports of pulmonary CMV infection were included. The data of 45 case reports was extracted and prepared in Table 1 to measure and identify the patterns to get the results to reach a conclusion. Figure 2 shows the PRISMA search strategy. Every study included was a case report.

The baseline features are described in Table 2 and Table 3 for the 45 patients who were included for data extraction. All patients were diagnosed with CMV pneumonia. The majority of patients were males (58%) and in the age group of 16-45 years (55.6%). The most common symptoms reported were fever (82%), dyspnea (76%), and cough (53%). Respiratory distress was observed in 58% of the patients. Almost two-thirds of the patients (64%) were immunocompromised. Radiographic findings were reported in 71% of the patients by chest X-ray and 69% by CT. Blood/serum was the most commonly used method for serology testing (89%), and bronchoalveolar fluid was used in 45% of the cases.

Table 1 Summary of systematically reviewed clinical cases of cytomegalovirus pneumonia

Ref.	Age	Sex	Clinical findings	Immune status	Radiographic findings	Serology	Immunohistochemistry & biopsy	Treatment	Out-come
Luís *et al*[22], 2021	42	M	Fever, headache, odynophagia, bilateral otalgia	Immunocompetent	CXR – B/L infiltrates; Thoracic CT – B/L GGO	Blood – CMV PCR positive; BAL fluid – CMV PCR positive		Ganciclovir and valganciclovir	Recovery
Balakrishnan *et al* [23], 2022	41	M	Fever, cough, weight loss	Immunocompromised; chronic glomerulo- nephritis, IgA nephropathy; on immunosup-pressive drugs	CXR – B/L infiltrates; Thoracic CT – B/L GGO, patchy consolidation, nodular opacities	Blood – CMV PCR positive; BAL fluid – CMV PCR positive		Valganciclovir	Recovery
Basinger *et al*[24], 2022	70	M	Rapid decline in general condition, resp. distress	Immunocompromised; a history of allogenic hematopoietic stem cell transplant	Rapidly progressive bilateral pulmonary nodules	Not done	Post mortem cytopatholog. Change, consistent with CMV infection, confirmed by IHC	Not initiated	Died
Gonçalves *et al* [2], 2018	29	M	Fever, headache, malaise, cough, thoracic pleuritic pain	Immunocompetent	Thoracic CT showed bilateral infiltrates	Blood – positive for CMV IgG and IgM; BAL – CMV PCR was positive		Ganciclovir and valganciclovir	Recovery
Wong *et al*[25], 2022	37	M	Fever, cough, dyspnea	Immunocompromised; X-linked agammaglobulinemia is a hereditary immune disorder		CMV positive		Antiviral and immune globulin therapy	Recovery
Gangemi *et al* [26], 2021	72	M	Non-healing buccal ulcer, fever, acute hypoxic respiratory failure, worsening odynophagia, weight loss	Immunocomromised; oropharyngeal Ca in remission	Chest X-ray – patchy opacities of B/L lung fields; Thoracic CT – bilateral upper and lower lobe consolidations, B/L pleural effusions	Positive for both CMV IgG and IgM		Ganciclovir and valganciclovir	Recovery
Patil *et al*[27], 2020	23	F	Worsening dyspnea, high grade fever, dry cough	Immunocompetent	Chest X-ray – mild bilateral interstitial infiltrates with small bilateral pleural effusions; CT chest - worsening of bilateral interstitial infiltrates	BAL CMV PCR and blood CMV PCR positive		Ganciclovir and valganciclovir	Recovery
Alyssa *et al*[28], 2017	63	F	Fever, hypotension, dyspnoea on exertion, hypoxemia, weakness	Immunocompromised; diagnosis of dermatomyositis - history of prolonged use of glucocorticoids and treatment with rituximab	CT chest - bilateral GGOs in a mosaic distribution and consolidations of B/L lower lobes	CMV DNA PCR quantitation in whole blood was positive and shell-vial culture for CMV positive		Ganciclovir and valganciclovir	Recovery
Fragkiadakis *et al* [29], 2018	36	F	Fever, respiratory distress	Immunocompromised; undergone multiple transfusions, and splenectomy was done for homozygous β-thalassemia	CT chest demonstrated pneumonitis	Serology and molecular blood testing reports – CMV infection and viremia		Ganciclovir	Recovery
Waqas *et al*[30], 2019	36	M	Fever, cough, malaise	Immunocompetent	CXR – B/L infiltrates	Diagnosed with CMV infection		Ganciclovir	Recovery
Xie *et al*[31], 2021	22	M	Fever, progressive dyspnea,	Immunocompromised; newly	Chest CT – extensive GGOs of	CMV quantitative PCR		Ganciclovir	Recovery

			dry cough	diagnosed HIV infection	bilateral lungs with multiple cavity lesions in the left upper lung	positive			
Al-Eyadhy *et al* [32], 2017	12	M	Tachycardia, tachypnea, fever, severe ARDS with multi-organ failure	Immunocompetent; CMV infection associated morbidity and mortality among immune-competent children	CXR and chest CT – ARDS features	CMV PCR positive in blood	HPE of lung biopsy CMV positive	Ganciclovir	Recovery
Reesi *et al*[33], 2014	3	M	Fever, dyspnea	Immunocompromised; acute lymphoblastic leukaemia on chemotherapy	CXR - pulmonary infiltrates; CT chest - diffuse GGOs of B/L lung fields, few pleural-based nodules	BAL CMV PCR was positive; CMV IgG and IgM positive		Ganciclovir and valganciclovir	Recovery
Cunha *et al*[34], 2008	64	M	"Flu-like illness", fever, myalgias, progressive dyspnoea, and required mechanical ventilation	Immunocompetent; slowly improved over 14 d and was eventually extubated	Chest X-ray showed B/L interstitial markings that rapidly progressed over 24 h	Initially IgG, IgM and CMV PCR negative; 10 d later, IgG, IgM, and CMV PCR were positive	BAL cytology was negative for viral inclusions	Did not receive CMV antiviral therapy	Recovery
Demirkol *et al* [35], 2018	2	M	Respiratory distress, fever, multiple organ dysfunction secondary to sepsis	Immunocompetent; developed necrotizing pneumonia	Thoracic CT – features of necrotising pneumonia	Serological tests indicated that the patient had CMV reactivation	Excised lung tissue, features of CMV infection	Ganciclovir	Recovery
Margery *et al*[36], 2009	43	F	Fever, dyspnoea	Immunocompetent	Thoracic CT – diffuse GGOs	Anti-CMV IgM and PCR detection of viral DNA in serum		Not treated	Recovery
Bansal *et al*[37], 2012	45	F	Nausea and vomiting. CMV infection can present with only atypical symptoms in liver transplant patients	Immunocompromised; liver transplant due to anti- tubercular drug induced acute liver failure	CXR showed B/L infiltrates	Testing of CMV viral load showed a viral load of 9640 copies/mL		Ganciclovir	Recovery
Sunnetcioglu *et al* [38], 2016	24	M	Cough, fever dyspnoea, haemoptysis, shortness of breath, and was intubated	Immunocompromised; on immunesuppressive therapy for polyarteritis nodosa	Chest X-ray showed right-sided opacity in the middle and lower lung zones Thoracic CT showed B/L alveolar opacity	Positive test for serum CMV IgM antibodies		NA	NA
Liatsos *et al*[39], 2017	40	F	Acutely ill with fever, dry cough, and mild shortness of breath	Immunocompromised; β-thalassemia major with splenectomy, regularly transfused with packed and leukocyte-depleted red blood cells	Thoracic CT - B/L interstitial lung infiltrates and small nodules marked toward the lower lobes, with a few ground-glass areas and bilateral pulmonary effusions	Positive RT-PCR for CMV in both blood and BAL		Ganciclovir and valganciclovir	Recovery
Wickramasinghe *et al*[40], 2022	32	M	Headache, fever, cough, and shortness of breath. The patient was in respiratory distress, shifted to ICU and electively intubated	Immunocompromised; Tuberculosis meningitis	Chest X-ray showed left-sided consolidation. CT chest revealed lower lobe (left more than right) consolidation and nodules	Positive CMV IgM and negative IgG, suggesting acute infection		Antitubercular drugs and ganciclovir	Recovery
Barclay *et al*[41], 2011	38	F	Fever and non-specific symptoms & increasingly hypoxaemic	Immunocompetent	Thoracic HRCT showed diffuse multilobular ground glass appearance with	CMV IgM antibody was positive and CMV PCR was positive		Valganciclovir	Recovery

					peripheral nodular opacities				
Coussement *et al* [42], 2016	64	F	Fever, cough, dyspnea, hypoxemia	Immunocompromised; bilateral lung transplant for chronic obstructive pulmonary disease	Thoracic CT demonstrated bilateral infiltrates; abdominal CT showed peri-colic infiltration compatible with a recurrence of diverticulitis	CMV VL observed both in blood and BAL samples; a diagnosis of CMV pneumonitis using BAL sample; a macrophage characteristic of CMV viral infection	Resected colon revealed HPE CMV colitis, viral inclusions, and positive immunohistochemistry	Ganciclovir	Recovery
Kanhere *et al*[43], 2014	3 1/2	M	Fever, respiratory distress, hepatosplenomegaly	Immunocompromised; hemophagocytic lymphohistiocytosis		CMV IgM serology was reactive in both infant and mother		Ganciclovir	Recovery
Suresh *et al*[44], 2013	7/12	M	Cough, dyspnoea, respiratory distress, progressive increase in oxygen requirement	Immunocompetent	Chest XR -prominent bronchovascular markings	CMV IgM serology was positive and CMV PCR based on BAL was also positive		Ganciclovir and valganciclovir	Recovery
Suresh *et al*[44], 2013, Case 2	3/12	F	Cough, dyspnoea, respiratory distress, progressive increase in oxygen requirement	Immunocompetent	CXR normal	CMV IgM blood was raised; BAL positive for CMV PCR		Ganciclovir and valganciclovir	Recovery
Yu *et al*[45], 2017	64	M	Acute respiratory failure with renal failure	Immunocompromised; diabetic; severe CMV pneumonia with slow resolution or persistent viremia on treatment	Chest X-ray -predominately right lung infiltrates; chest CT showed multiple consolidative patches with air bronchograms	Positive CMV PCR in blood and BAL	Lung biopsy was done. Inclusion bodies, positive for CMV IHC	Ganciclovir and valganciclovir	Died
Tollitt *et al*[46], 2016	71	F	Hemoptysis	Immunocompromised; antineutrophil cytoplasmic antibody-associated vasculitis; on therapy with cyclophosphamide, steroids, and plasma exchange	Pulmonary CMV disease mimics pulmonary disease associated with vasculitis on CXR	BAL demonstrated positivity for CMV DNA and serum CMV PCR positive		Ganciclovir and valganciclovir	Recovery
Vetter *et al*[47], 2010	70	F	Fever, nausea, dyspnea	Immunocompromised; immunosuppressive therapy with methotrexate and prednisone for large-vessel vasculitis	Chest X-ray showed no interstitial pneumonitis; chest and abdominal CT showed no signs of inflammation	CMV IgG and IgM antibodies positive; CMV PCR positive in BAL fluid		Ganciclovir	Recovery
Snape *et al*[48], 2011	28	F	Fever, cough tender sinuses, frontal headache	Immunecompetent	CXR showed consolidation of the middle and right upper lobe; Pulmonary CT angiography revealed no pulmonary embolus and patchy consolidation of B/L lungs	Positivity for CMV IgM		Valganciclovir	Recovery
Karakelides *et al* [49], 2003	47	M	Cough, hemoptysis, weight loss	Immunocompetent	CXR and chest CECT showed a 3.5-cm cavitary mass, upper lobe of left lung and mild left mediastinal and hilar adenopathy	Transbronchial biopsy - CMV inclusions	Wedge excision of left upper lung mass; HPE -nuclear & cytoplasmic inclusions of CMV	NR	Recovery

Shimada *et al*[50], 2004	27	F	Fever	Immunocompromised; on immunosuppressive treatment for viral-associated hemophagocytic syndrome	CXR and chest HRCT – diffuse small pulmonary nodules	CMV DNA PCR was positive on bronchoalveolar lavage cells; immunoassay pp65 CMV antigen positive	Lung biopsy inclusion-bearing cells for CMV	Gancyclovir	Recovery
Simsir *et al*[51], 2001	43	M	Malaise, fever, pleuritic chest pain, epigastric pain, diarrhea, nausea, vomiting	Immunocompromised; underwent renal transplant secondary to diabetic nephropathy	CXR showed a nodule in the upper lobe of the right lung; chest CT revealed bilateral smaller pulmonary nodules	CMV antigen test was positive, with negative CMV IgG	CMV was established by fine-needle aspiration biopsy of the lung nodule	Gancyclovir	Recovery
Abbey *et al*[52], 2014	51	M	Fever, dry, cough, dyspnoea, general malaise	Immunocompromised; Crohn's disease on azathioprine; also had mild pancreatic insufficiency and bile salt malabsorption	CXR showed bilateral infiltrates in middle and lower zones; chest CT showed B/L small pleural effusions and B/L basal lung consolidation	CMV IgM positive, acute CMV infection		Ganciclovir and valganciclovir	Recovery
Belin *et al*[53], 2003	47	F	Shortness of breath, fever, stomatitis, genital ulcerations, burning sensations	Immunocompromised; severe rheumatoid arthritis, on prednisolone, methotrexate, and cyclosporine	CXR showed interstitial infiltrates in both lung bases	BAL showed CMV mRNA		Ganciclovir	Recovery
Kaşifoğlu *et al* [54], 2006	21	F	Polyarthralgias, fatigue, fever, muscle weakness, non-productive cough, dyspnea	Immunocompromised; dermatomyo-sitis, treated with azathioprine, prednisolone, and cyclosporine	Chest XR showed bilateral interstitial infiltration; chest HRCT - bilaterally ill-defined multifocal GGOs	Positivity for anti-CMV, IgM, and anti-CMV IgG antibodies and presence of CMV DNA by PCR		Ganciclovir	Recovery
Chen *et al*[55], 2010	5	M	Fever, cough, dyspnea, hypoxemia, ARDS	Immunocompetent; the patient developed ventilator-associated pneumonia, and died of burkhoderia sepsis	Chest XR – multiple parenchymal consolidations; chest XR disclosed "white lung" during the second week	Positive PCR; bronchoal-veolar and seroconversion of CMV IgM and IgG		NR	Died
Tambe *et al*[56], 2019	32	F	Fever, dyspnea, generalized rash, weakness	Immunocompromised; stage IV, classical Hodgkin's lymphoma, treated with chemotherapy	Chest CT revealed bilateral pulmonary infiltrates and bilateral pleural effusion	CMV was detected on BAL culture; serum quantitative CMV PCR was positive		Ganciclovir and valganciclovir	Recovery
Boussouar *et al* [57], 2018	47	F	Dry cough, chest pain and fever	Immunocompromised; orthotopic heart transplant and immunosup-pressive treatment was initiated with corticosteroids, cyclosporine, and mycophenolate	Chest XR - alveolar opacities with upper lobe predom-inance; chest CT revealed consolidation in the right upper lobe associated with septal thickening and multiple nodules	Blood CMV PCR, which has been undetectable	Lung biopsy showed nuclear inclusions suggestive of CMV infection; IHC showed nuclear positivity for CMV	Ganciclovir and valganciclovir	Recovery
Haddad *et al*[58], 1984	18	M	Fever, chills, non-productive cough, severe hypoxia requiring intubation	Immunocompromised; sickle cell thalassemia	Chest XR suggested early pulmonary edema and cardiomegaly	On postmortem culture of lung parenchyma, CMV grew in 5 d		NR	Died
Katagiri *et al*[59], 2008	35	F	Deterioration of lupus nephritis and received treatment with a high dose of steroid and cyclosporine	Immunocompromised; SLE with increased risk of opportunistic infection	Chest X-ray showed bilateral pleural effusion; chest CT revealed a cavitary lesion in the right middle lobe of the lung	Positive for CMV; antigenemia		Ganciclovir	Recovery

Ayyappan *et al* [60], 2006	72	M	Fever, productive cough, worsening breathlessness and tenderness in epigastrium	Immunocompromised; rheumatoid arthritis-related interstitial lung disease, on corticosteroids and cyclophosphamide	Chest XR showed bilateral consolidation; chest CT revealed cavitating masses in the right upper lobe & lingula and diffuse interstitial fibrosis	PCR assay of BAL fluid was positive for CMV	Gastric biopsy - intracytoplasmic viral inclusions consistent with CMV gastritis; transbronchial lung biopsy showed intracytoplasmic viral inclusion	Gancyclovir	Recovery
Manian *et al*[61], 1993	32	F	Fever, non-productive cough, worsening oxygenation	Immunocompetent	Chest X ray - bilateral interstitial infiltrates	Enzyme immune-assay showed that CMV IgG and CMV IgM were positive		Ganciclovir	Recovery
McCormack *et al* [62], 1998	31	M	Fever, abdominal pain, jaundice, cough, palpitations, shortness of breath with atrial fibrillation	Immunocompetent	Chest radiograph showed bilateral interstitial pulmonary infiltrates	EIA for antibodies to CMV showed a strong reaction to IgM and a weak reaction to IgG	A urine culture yielded CMV; a cytopathic effect was observed and con-firmed by immunofluorescence	Ganciclovir	Recovery
Najjar *et al*[63], 2004, Case 1	34	F	Fever	Immunocompromised; SLE with renal failure on haemodialysis	Chest XR - bilateral infiltrates; chest CT - bilateral peripheral parenchymal infiltrates and a cavitating mass in right lower lobe	A CMV antigenaemia assay was positive and CMV isolation in blood	Histological findings included numerous intranuclear and intracytoplasmic CMV inclusions confirmed by IHC	IV ganciclovir and IV IgG	Recovery
Najjar *et al*[63], 2004, Case 2	33	M	Fever, dyspnoea, worsening renal function	Immunocompromised; SLE, class IV lupus, nephritis treated with chronic steroid therapy, azathioprine, and cyclophosphamide	Chest CT revealed a right upper lobe thick-walled cavitary lesion	Serology revealed raised CMV IgM & IgG	HPE - evidence of focal interstitial fibrosis, accumulation of intraalveolar macrophages, and CMV with intracytoplasmic and nuclear inclusions in the lining alveolar cells	Gancyclovir	Recovery
Kanika *et al*	32	M	Fever, dyspneia, hypotension, jaundice	Immunocompetent	MRI showed hepatitis and pancreatitis; CT showed GGO	Serum PCR with a high viral load	Liver biopsy suggestive of drug induced liver injury and immunochemistry negative for CMV	Ganciclovir	Recorvery

B/L: Bilateral; GGOs: Ground glass opacities; CT: Computed tomography; ARDS: Acute respiratory distress syndrome; SLE: Systemic lupus erythematosus; IgG: Immunoglobulin G; IgM: Immunoglobulin M; HRCT: High resolution CT; IHC: Immunohistochemistry; BAL: Bronchoalveolar lavage; HPE: Histopathological examination; EIA: Enzyme immune assay; PCR: Polymerase chain reaction.

Immunohistochemistry (IHC) was reported in 24% of the cases, and biopsy-histopathology was performed in 27% of the patients. The treatment was reported in 84% of the cases, with a high recovery rate of 89%. Unfortunately, the mortality rate was 9%, with four patients reported to have died.

DISCUSSION

This paper analyzed 45 cases of CMV-induced pneumonia. Patients were divided into two main categories: Immunocompetent and immunocompromised. Twenty-nine (64%) patients were immunocompromised, and 16 (36%) were immunocompetent and developed CMV pneumonia. This suggests that CMV infection prevalence is higher in immunocompromised patients[2]. The reported case highlights the importance of considering CMV infection in patients who present with fever, respiratory symptoms, and abnormal liver function tests. Although CMV infection is more common in immunocompromised patients, this case demonstrates that it can also occur in immunocompetent individuals. It

Table 2 Baseline features of 45 patients with cytomegalovirus pneumonia

Variable	Patients, *n* = 45 (100%)
Age group	
0–15 yr	7 (15.6)
16–45 yr	25 (55.6)
46–75 yr	13 (28.8)
Sex	
Male	26 (58)
Female	19 (42)
Symptoms	
Fever	37 (82)
Cough	24 (53)
Dyspnoea	34 (76)
Resp. distress	26 (58)
Immune status	
Immunocompetent	16 (36)
Immunocompromised	29 (64)
Radiograhic findings	
Chest X-ray	32 (71)
Thoracic CT	31 (69)
Serology	
Blood/serum	40 (89)
Bronchoalveolar fluid (BAL)	18 (45)
Specific tests	
Immunohistochemistry	11 (24)
Biopsy - histopathology	12 (27)
Treatment	38 (84)
Recovery	40 (89)
Died	4 (9)

Table 3 Summary of data collected

	Immunocompetent	Immunocompromised
Total	16	29
Fever	13	24
Cough	11	13
Dyspnoea	12	22
Respiratory distress	10	16
Treatment	12	26
Recovered	15 (94%)	25 (86%)

is important to note that CMV is a common cause of pneumonia, particularly in immunocompromised patients, and should be considered in the differential diagnosis of patients with respiratory symptoms who do not respond to standard treatment. Early diagnosis and treatment are essential in improving patient outcomes, especially in severe cases. Therefore, clinicians should be aware of the clinical features

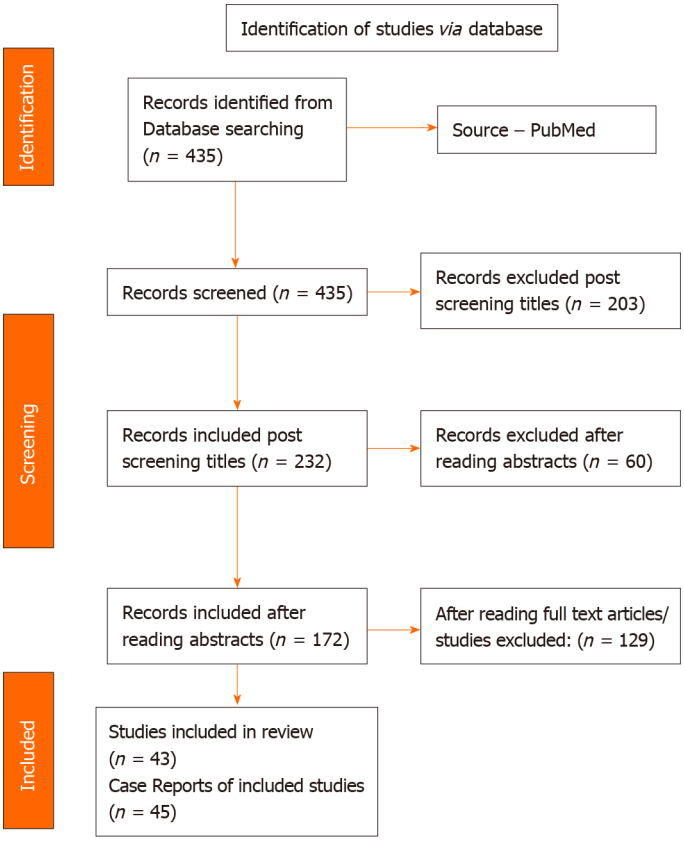

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Figure 2 PRISMA search strategy for systematic review.

and radiological findings of CMV pneumonia to enable early diagnosis and appropriate management [17-20].

The differential diagnosis of this case includes severe COVID-19 infection, which shares some clinical features with CMV pneumonia, such as cough, dyspnea, and fever. However, some features of the case, such as jaundice, hepatosplenomegaly, and pancytopenia, are not typically seen in severe COVID-19 cases. Additionally, GGOs on CT imaging can be seen in both CMV pneumonia and COVID-19. Therefore, it is important to consider other infectious and non-infectious etiologies in patients with respiratory symptoms and abnormal liver function tests.

A systematic review was performed a total of 45 patients, of which 26 (58%) were male and 19 (42%) were female. Infection was more prevalent in males, with 11 immunocompetent and 15 immunocompromised male patients and 5 immunocompetent and 14 immunocompromised female patients. This suggests that CMV infection is more prevalent in immunosuppressed patients in both males and females. Immunocompromised states are an important host-associated risk factor to get CMV infection [2].

Regarding age, 25 patients were adults (13 males and 12 females), indicating that the adult population is more prone to developing pulmonary CMV infection. As it is estimated that more than half of the adult population are infected with CMV in the United States, and 80% of the adult population have this infection by the age of 40 years, the prevalence of CMV-induced pneumonia may increase with age[1]. The clinical findings of most patients were fever (82%), dyspnea (75%), cough (53%), and respiratory distress (53%) in both immunocompetent and immunocompromised patients. These findings are consistent with previous studies on CMV pneumonia[4].

Regarding radiological findings, 32 patients were submitted to a chest X-ray mostly showing bilateral diffuse pulmonary infiltrates. CT of the thorax was done in 31 patients, and the main finding was bilateral GGOs. In some patients, there were small bilateral pulmonary nodules, confluent consolidations, and bronchiectasis. In case of atypical radiological findings other than bilateral infiltrates and GGOs, further investigation, such as blood and BAL serology, lung biopsy histopathological examination (HPE), and IHC, should be considered to rule out CMV pneumonia[7].

Blood serology was done in 40 (89%) patients, and IgM and IgG were positive for CMV. Other tests, such as BAL fluid serology, lung biopsy histopathology, and IHC, were done to confirm the diagnosis in some patients. IgM CMV positive in blood represents acute CMV infection, and antiviral treatment was given to the patients with a successful outcome[2,5].

A study by Basinger *et al*[24] demonstrated that immunocompromised states, particularly those with a history of allogenic hematopoietic stem cell transplant, can result in rapidly deteriorating conditions and respiratory status post-CMV infection. Radiologically, patients may present with rapidly progressive bilateral pulmonary nodules approximately 2 mo after receiving a bone marrow transplant. This patient died shortly after admission, and the diagnosis was made on post-mortem microscopic examination of the pulmonary nodules that demonstrated viral cytopathologic changes consistent with CMV infection, confirmed by IHC. It is essential to note that the radiographic presentation is not always GGOs, and rapidly enlarging pulmonary nodules in an immunosuppressed patient are highly suggestive of an infectious process. Therefore, careful histologic examination for viral cytopathologic changes is essential[3].

Regarding treatment, 38 (85%) patients received antiviral therapy, and 2 patients recovered without receiving antiviral treatment. In total, 89% of patients recovered, indicating that the prognosis of CMV pneumonia is good if diagnosed early and treated in time, in both immunocompetent and immunocompromised patients[2]. A study by Al-Eyadhy *et al*[32] in 2017 presented the case of a 12-year-old immunocompetent patient who was admitted with severe ARDS and developed multi-organ failure, which is an important differential diagnosis from severe acute respiratory syndrome coronavirus 2 infection. Due to the correct diagnosis and treatment of CMV infection in time, the patient recovered. Another study by Coussement *et al*[42] in 2016 showed that a 63-year-old immunocompromised patient who did a bilateral lung transplant for chronic obstructive pulmonary disease admitted with severe CMV infection and due to timely diagnosis and antiviral treatment, the patient recovered well.

In immunocompetent patients, the recovery rate was 94%, while in immunocompromised patients, it was 86%. The study showed that there were four deaths, three of which were among immunocompromised patients. This suggests that immunocompromised patients may develop more severe CMV illness that deteriorates quickly, sometimes making it challenging to make a timely diagnosis. Therefore, it is crucial to consider CMV infection as one of the important differentials in immunocompromised patients[1,4].

The final result of this analysis showed that 89% of total patients recovered, indicating that the prognosis of CMV pneumonia is good if patients are diagnosed early and treated promptly, even for immunocompromised patients[1,4].

To reach a definitive diagnosis, clinical findings must be correlated with imaging tests and laboratory tests. Polymerase chain reaction (PCR) is the most sensitive method of detecting CMV, and qRT-PCR can be used to quantify viral loads in blood and BAL fluid. BAL CMV-PCR is considered the most accepted approach for viral isolation in the lungs due to its high sensitivity. Lung biopsy histopathology is considered the gold standard for the diagnosis of pulmonary CMV infections, and the presence of CMV inclusions in the HPE report is confirmatory of lung infection. Additionally, CMV can be detected by IHC staining for CMV in cytologic specimens of bronchial lavage fluid[1,2].

In critically ill patients, CMV infection is associated with prolonged mechanical ventilation, nosocomial infections, prolonged hospital and ICU stay, and increased mortality. The first-line treatment for CMV disease is intravenous ganciclovir and its prodrug, oral valganciclovir. Mild disease in immunosuppressed patients may be treated with oral valganciclovir, while severe illness is treated with IV ganciclovir or foscarnet at full doses (adjusted for renal function), followed by valganciclovir. Treatment at full doses should be continued until the resolution of symptoms and blood antigenemia (or DNAemia) is cleared. The prognosis of CMV pneumonia is good if patients are diagnosed and treated at an early stage[1,2,4]. This systematic review aimed to understand the pattern, presentations, clinical course, and outcome of patients with COVID-19 and CMV coinfection and analyzed data from 34 reports with 59 patients. The results showed that middle-aged and elderly patients with comorbidities were more susceptible to coinfection, and CMV colitis was the most common manifestation of end-organ involvement. The findings of this study may assist in detecting and treating patients with unusual clinical courses or severe, prolonged, or unexplained deterioration of end-organ function[64].

CONCLUSION

In conclusion, CMV pneumonia is a serious complication in both immunocompromised and immunocompetent patients, with a higher morbidity and mortality rate in the former group. The diagnosis of CMV pneumonia can be challenging as it may present with nonspecific clinical and radiological features similar to COVID-19 pneumonia. Therefore, it is crucial to consider CMV infection as a differential diagnosis in immunocompromised patients with respiratory symptoms. Early diagnosis and treatment with antiviral therapy can lead to a good prognosis, while delayed diagnosis and treatment can lead to a more severe illness and potentially fatal outcomes. Clinicians should have a high index of suspicion for CMV pneumonia in immunocompromised patients and perform appropriate diagnostic tests, such as PCR and histopathological examination. Further research is needed to better understand the pathogenesis, risk factors, and optimal management of CMV pneumonia.

ARTICLE HIGHLIGHTS

Research background

Cytomegalovirus (CMV) is a DNA virus that can cause severe disease in immunocompromised patients and is common in recipients of hematopoietic stem cell transplantation. CMV is acquired through direct contact with infected cells or body fluids, and transmission can occur from a CMV-seropositive donor organ. Congenital CMV, transmitted from infected mothers to their newborns, is a leading cause of miscarriage. CMV is one of the three most common causes of severe viral community-acquired pneumonia, but this has changed with the emergence of severe acute respiratory syndrome coronavirus 2 in 2020.

Research motivation

During the COVID-19 pandemic, it is important to differentiate clinical and radiological presentations from other diseases. Ground-glass opacities (GGOs) require evaluation along with other tests to reach a diagnosis. To diagnose CMV pneumonia, the virus can be detected in serum or respiratory samples, and quantitative real-time PCR can measure viral loads in blood and BAL fluid. Lung biopsy histopathology is the gold standard for diagnosing pulmonary CMV infections. However, the diagnostic yield of lung biopsy varies, and the study of CMV pneumonia in immunocompetent patients with GGOs remains limited.

Research objectives

This study aimed to report a case of CMV pneumonia in an immunocompetent patient with GGOs on chest CT, to review the literature on the clinical, radiological, and laboratory features of CMV pneumonia in immunocompetent hosts, and to discuss the diagnostic workup and management of CMV pneumonia.

Research methods

This study followed PRISMA guidelines to identify case reports and case series studies on pulmonary complications of CMV infection. The selection criteria included studies that reported only CMV pneumonia without other co-existing causes of pneumonia. Data extraction involved identifying the characteristics of the subjects and the outcomes measured. The patient case report presented in the article was included in the study as it met the inclusion criteria, and the patient received ganciclovir therapy resulting in complete recovery from symptoms and sustained undetectable viral load after 6 wk of treatment.

Research results

The study found 45 case reports of pulmonary CMV infection after analyzing 435 references. The majority of the patients were males (58%) in the age group of 16-45 years (55.6%). Common symptoms included fever, dyspnea, and cough, with respiratory distress observed in 58% of the cases. Most patients (64%) were immunocompromised. Radiographic findings were reported in 71% of the patients, and blood/serum was the most commonly used method for diagnosis. Treatment was reported in 84% of the cases, with a high recovery rate of 89%, but the mortality rate was 9%. Early diagnosis and prompt treatment are crucial to improve outcomes and reduce mortality rates, especially in immunocompromised individuals.

Research conclusions

The study analyzed 45 cases of CMV-induced pneumonia and found that it can occur in both immunocompetent and immunocompromised patients, with clinical findings of fever, dyspnea, cough, and respiratory distress. Radiological findings showed bilateral diffuse pulmonary infiltrates and bilateral GGOs. Blood serology was positive for CMV, and antiviral treatment was given with a successful outcome. The recovery rate was high, but four deaths were reported, with three among immunocompromised patients.

Research perspectives

Future studies can investigate the prevalence of CMV pneumonia in different age groups and genders, and the possible link between CMV and COVID-19. The effectiveness of antiviral therapy in preventing severe CMV illness and the optimal duration of treatment can be evaluated. Pathophysiology and immunology of CMV pneumonia in immunocompromised patients need further research.

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