

Cytomegalovirus Disease in Patients with Common Variable Immunodeficiency: Three Case Reports

Pavlina Kralickova^a Eva Mala^a Doris Vokurkova^a Irena Krcmova^a
Lenka Pliskova^b Vlasta Stepanova^c Vladimir Bartos^d Vladimir Koblizek^d
Ilja Tacheci^e Jan Bures^e Jan Brozik^f Jiri Litzman^{g, h, i}

^aInstitute of Clinical Immunology and Allergy, ^bDepartment of Biochemistry and Diagnostics, ^cInstitute of Clinical Microbiology, ^dDepartment of Lung Diseases, ^eGastroenterology and Hepatology, ^{2nd} Department of Internal Medicine, and ^fDepartment of Roentgenology, University Hospital Hradec Kralove, Faculty of Medicine, Charles University in Prague, Hradec Kralove, ^gDepartment of Clinical Immunology and Allergology, Faculty of Medicine, ^hSt. Anne's University Hospital, and ⁱCentral European Institute of Technology, Masaryk University, Brno, Czech Republic

Established Facts

- Common variable immunodeficiency (CVID) is the most common clinically relevant primary immunodeficiency and shows enormous heterogeneity in clinical presentation. However, opportunistic infections are not a typical manifestation in these patients.

Novel Insights

- The frequency of cytomegalovirus (CMV) disease in CVID may be higher than previously described.
- Frequently, the clinical manifestation of CMV disease in CVID is an end-organ disease, indicating that the detection of CMV DNA in the blood could be inconclusive, whereas the direct detection of CMV from bronchoalveolar lavage, stool or tissue samples is a beneficial laboratory diagnostic approach.
- In our experience, the probability of opportunistic infections in CVID patients increases with secondary comorbidities.

Key Words

Common variable immunodeficiency · Cytomegalovirus · Mycobacteriosis · Opportunistic infection · Pneumonitis · Enteritis

Abstract

Common variable immunodeficiency (CVID) is the most frequent clinically relevant primary immunodeficiency and shows enormous heterogeneity in clinical presentation. De-

spite clinical immunodeficiency, opportunistic infections are not a typical manifestation of CVID. A retrospective study of 32 patients followed up for 335 patient-years was performed to determine the frequency of cytomegalovirus (CMV) disease. Symptomatic CMV infection was documented in 3 CVID patients. Patients No. 1 and 2 suffered from CMV pneumonia, with complications due to atypical mycobacteriosis in patient No. 1. Patient No. 3 suffered from CMV enteritis. A history of cancer and chronic hepatitis C infection (patient No. 1), immunosuppressive therapy for interstitial lung disease (pa-

tient No. 2) and serious enteropathy complicated with malnutrition (patient No. 3) may have contributed to the complications despite only mild abnormalities in T-cell subpopulations. The direct detection of CMV in bronchoalveolar lavage, stool or tissue samples was the most beneficial diagnostic laboratory method, whereas the detection of CMV DNA in blood did not produce positive results. Adequate treatment of CMV disease led to significant clinical improvement in all 3 patients. The frequency of CMV disease appears to be higher than previously described. In our experience, the probability of opportunistic infections in CVID patients increases with secondary comorbidities and their management. © 2013 S. Karger AG, Basel

Introduction

Common variable immunodeficiency (CVID) is the most frequent clinically relevant humoral primary immunodeficiency and shows enormous heterogeneity in clinical presentation [1]. Recurrent bacterial infections predominate in CVID, and non-infectious manifestations of immune dysregulation, including autoimmune diseases, granuloma formation, interstitial lung inflammation or enteropathy, as well as malignant tumours are also frequent [2–5].

Cytomegalovirus (CMV) is a member of the human herpes virus family. CMV infections in the general population are common and cause no or mild clinical symptoms. Indeed, 10–20% of children are infected with CMV before puberty, and seroprevalence increases to 40–100% in adults [6, 7].

The occurrence of symptomatic CMV disease (CMV infection leading to tissue damage and clinical symptoms) is almost exclusively restricted to immunocompromised patients with impaired cellular immunity, including individuals with late HIV-1 disease [8], persons with immunosuppressive treatment, mainly after bone marrow or solid organ transplantation [9, 10], patients with inflammatory bowel disease [11], interstitial lung disease [12] and connective tissue autoimmune diseases [13, 14], and also cancer patients [15].

The most common clinical presentation of symptomatic CMV disease includes fever, arthralgia, myalgia and myelosuppression (altogether termed ‘CMV syndrome’), though it may also present with evidence of end-organ involvement, such as diarrhoea and abdominal pain (gastrointestinal disease), cough and hypoxia (pneumonia), blurred vision or floaters (CMV retinitis), and confusion (CMV encephalitis) [16].

The diagnosis of CMV disease may be difficult, and various routine laboratory tests are generally used, including the detection of specific anti-CMV antibodies in serum, direct CMV cultivation in tissue culture, histopathological detection of viral deposits, determination of the quantity of polymorphonuclear cells containing internal matrix CMV protein pp65, and real-time polymerase chain reaction (RT-PCR) of viral DNA, with the latter typically being regarded as the ‘gold standard’ [11, 16–18]. Nonetheless, the ultimate confirmation of CMV disease is based on clinical symptoms and paraclinical observations which, in addition to laboratory tests, include endoscopy or imaging methods.

Here, we report the frequency of CMV disease in a retrospective study of 32 patients with a well-established diagnosis of CVID [19] followed up at a tertiary referral clinical immunology centre for 335 patient-years. Symptomatic CMV infection (CMV syndrome and end-organ disease), defined according to standard, previously published criteria [20], was documented in 3 patients.

Case Report 1

The first patient, a female, suffered from recurrent respiratory infections (otitis media, sinusitis and pneumonia) approximately from the age of 14 years. When she was 28 years old, pernicious anaemia, vitiligo and splenomegaly were diagnosed. Hepatitis C virus (HCV) infection of an unknown transmission route was incidentally diagnosed when she was 40 years old. Interferon- α therapy was repetitively administered, with only a transient decline in HCV replication activity. CVID was diagnosed at the age of 42 years based on immunoglobulin (Ig) G 1.68 g/l, IgA 0.07 g/l and IgM 0.16 g/l in association with a poor response to tetanus and non-conjugated pneumococcal polysaccharide vaccination and the absence of isohaemagglutinins (blood group 0). Other defined causes of hypogammaglobulinaemia were excluded by past history, ultrasonography, lung high-resolution computed tomography (HRCT), urinalysis, full blood count, and routine serum biochemical analysis [19]. The flow cytometric analysis is shown in table 1. The lymphocyte proliferation response to polyclonal mitogens (pokeweed mitogen, ConA) was normal. Intravenous Ig (IVIG) replacement was initiated at a dose of 330 mg/kg/4 weeks. Gastric adenocarcinoma was diagnosed at the age of 44 years, and she successfully underwent total gastrectomy without the necessity of any adjuvant therapy.

At age 51 years, she was admitted for dyspnoea and fever lasting for 2 weeks and not responding to antibiotic treatment. Non-productive cough, chest pain and night sweats had worsened over the last several weeks prior to admission. HRCT showed bilateral ground-glass opacities and infiltrates in the lower lobes and multiple bronchiectasis. CMV DNA was detected using PCR from a bronchoalveolar lavage (BAL) sample, and the CMV was isolated in the BAL sample. Treatment with ganciclovir (1.0 g/day for 10 days) led to clinical recovery, with the ground-glass opacities and infiltrates completely resolved.

Table 1. Absolute number of leukocytes, thrombocytes and T-lymphocyte subpopulations in patients with CMV disease at the time of CVID diagnosis and at the time of CMV disease flare

	Patient No. 1		Patient No. 2				Patient No. 3		CVID patients ¹
	Dg. CVID	CMV disease	Dg. CVID	CMV disease			Dg. CVID	CMV disease	
Leukocytes, $\times 10^9/l$ (4.0–9.0)	5.8	5.3	5.5	6.9	3.8	3.1	3.8	1.8	6.3 [3.8–11.6]
Lymphocytes, $\times 10^9/l$ (1.0–4.0)	1.8	1.8	1.1	1.3	0.3	0.6	0.6	0.2	1.6 [0.7–3.3]
CD3+ T cells, $\times 10^9/l$ (0.7–2.1)	1.4	1.4	0.95	1.1	0.3	0.5	0.4	0.2	1.2 [0.5–2.9]
CD4+ T cells, $\times 10^9/l$ (0.5–1.4)	0.7	0.7	0.58	0.5	0.1	0.1	0.2	0.1	0.5 [0.3–1.4]
CD8+ T cells, $\times 10^9/l$ (0.3–1.0)	0.6	0.6	0.37	0.6	0.1	0.3	0.1	0.1	0.6 [0.2–1.5]
CD19+ B cells, $\times 10^9/l$ (0.13–0.33)	0.36	0.15	0.03	0.01	0	0	0.07	0.01	0.15 [0.01–0.55]
CD4+CD45RA+/CD4+, %	21	NA	7.1	NA	NA	5	13	15	24 [2–53]
CD4+CD45RO+/CD4+, %	68	NA	91	NA	NA	96	80	70	75 [44–98]
Thrombocytes, $\times 10^{12/l}$ (149–409)	135	97	115	126	57	61	221	58	NA

The reference range for the healthy population is given in parentheses. Dg. CVID = CVID diagnosis; NA = not applicable.

¹ CVID patients: median [5–95th percentile] in 47 adult CVID patients without known CMV infection.

Tonsillar carcinoma was diagnosed 6 months after this recovery; a complete remission was achieved by extended tonsillectomy with adjuvant radiotherapy. Despite adequate Ig replacement treatment with antibiotic prophylaxis, recurrent respiratory tract infections resulted in chronic respiratory insufficiency. Chronic HCV progressed to cirrhosis. The patient died due to hepatic failure in the course of a respiratory infection at the age of 57 years.

Case Report 2

This female patient suffered from recurrent respiratory tract infections, including two episodes of pneumonia from her early 30s. CVID was diagnosed at the age of 40 years: IgG 3.4 g/l, IgA 0.6 g/l, and IgM 0.36 g/l, with no response to tetanus and non-conjugated pneumococcal polysaccharide vaccines. The anti-B isohaemagglutinin titre was 2 (reference range >8), and defined causes of hypogammaglobulinaemia according to PAGID/ESID [19] were excluded. The flow cytometric analysis is shown in table 1. No abnormalities in the proliferation response of lymphocytes to phytohaemagglutinin or ConA stimulation were observed. Regular intravenous Ig replacement at a dose of 200 mg/kg monthly was initiated. The IgA level decreased to 0.07 g/l and IgM to 0.04 g/l during the subsequent 10 years. She had a history of post-exertional dyspnoea, non-productive cough and splenomegaly at the time of diagnosis. Lung biopsy, HRCT and BAL revealed lymphocytic interstitial lung disease. Intermittent oral methylprednisolone treatment at doses of up to 48 mg/day, depending on the activity of the lung disease, led to clinical improvement, with the amelioration of interstitial lung abnormalities.

At the age of 53 years, the dyspnoea accompanied by non-productive cough progressed. The patient suffered from myalgia, arthralgia, weight loss, and fatigue. HRCT showed the progression of multiple bilateral infiltrates. The clinical symptoms and HRCT changes, together with the positivity of CMV DNA PCR in BAL and the isolation of CMV virus in BAL, confirmed the diagnosis of

CMV pneumonia. Ganciclovir therapy (1.0 g/day for 10 days) led to clinical recovery, and the HRCT abnormalities partially regressed. The patient was treated with methylprednisolone (dose 8 mg/day) between 53 and 56 years of age, and her clinical status was stable.

At age 56 years, the patient was admitted for fever, weight loss, progressive fatigue, intermittent diarrhoea, post-exertional dyspnoea, and chest pain. CMV DNA PCR in BAL showed 374×10^3 copies/ml, whereas 10^3 copies/ml was detected in serum. HRCT showed new multiple ground-glass opacities, interstitial infiltrates and mediastinal lymphadenopathy, all indicating a reactivation of CMV disease. Ganciclovir therapy (1.0 g/day) for 14 days with subsequent valganciclovir (900 mg/day) administration for 28 days dramatically improved her clinical state; the HRCT abnormalities significantly regressed. Diarrhoea with the progression of signs of malnutrition recurred in 3 months. Colon biopsy did not show the presence of CMV DNA, but a coeliac disease-like enteropathy was diagnosed. Enteral nutrition was initiated, with improvement in her nutrition state.

Nine months later, the patient suffered from fatigue, dyspnoea, cough, and pain in the lower extremities. A third recurrence of CMV pneumonitis was confirmed (CMV DNA PCR, 1.58×10^4 CMV DNA copies/ml in BAL; progression of interstitial changes on HRCT). At that time, her CD4+ cells had decreased to $0.080 \times 10^9/l$ (table 1). *Mycobacterium avium intracellulare* was simultaneously cultivated from sputum and BAL samples. IVIG replacement was increased to 800 mg/kg/month, and ganciclovir (1.0 g/day) for 21 days, together with anti-mycobacterial treatment with clarithromycin, rifampicin and ethambutol, led to a good clinical outcome accompanied by an increase in the number of CD4+ T cells ($0.32 \times 10^9/l$).

A vigorous recurrence of CMV disease occurred 6 months later. After only several hours of ongoing fever and intensive dry cough, the patient was hospitalized for respiratory insufficiency and emerging septic shock with multiorgan failure. A significant number ($1.9 \times 10^5/ml$) of CMV DNA copies in BAL was docu-

mented, though serum showed only 2.56×10^2 CMV DNA copies/ml. An X-ray scan showed the progression of interstitial lung changes and newly developed pleural effusion. The immediate therapy with ganciclovir resulted in a prompt decline in inflammation markers and the improvement in vital functions, with complete restitution in 2 months.

A severe attack of autoimmune haemolytic anaemia at the age of 61 years was treated with high-dose corticosteroids. The patient died at age 62 years of a severe pneumonia of *Klebsiella pneumoniae* origin.

Case Report 3

The third patient, a female, was treated from the age of 24 years for megaloblastic anaemia connected with antral gastritis. Her first incidence of pneumonia was documented at the age of 31 years. She was diagnosed with CVID at the age of 33 years: IgG 3.41 g/l, IgA <0.08 g/l and IgM <0.08 g/l. The serum anti-A isohaemagglutinin titre was 2 (reference range >16), and causes of secondary hypogammaglobulinaemia [19] were excluded. IVIG treatment (400 mg/kg for 3–4 weeks) was initiated. Despite this treatment, the patient suffered from recurrent bronchitis and also two episodes of pneumonia by the age of 45 years. At the time of diagnosis, she was also suffering from a mild chronic diarrhoea; colonoscopy did not indicate any abnormalities, though histopathology revealed mild chronic colitis. The chronic diarrhoea slowly progressed, accompanied by a loss in body weight. Refractory coeliac disease (Marsh histopathology classification stage 3c) was suspected at the age of 41 years; however, therapy with a gluten-free diet in combination with mesalazine 3 g daily and budesonide 9 mg daily was ineffective. Colitis with ulcerative lesions and pararectal fistula developed at the age of 45 years. Immunosuppressive therapy with prednisolone (0.5–1.0 g/kg/day) and azathioprine 50 mg daily was initiated with transient effects.

At age 46 years, the patient was hospitalized because of malnutrition, intensive diarrhoea and perirectal ulcer for parenteral nutrition support to prepare for sigmoidostomy. An endoscopy picture of antral gastritis with multiple hyperplastic polyps (histologically mixed inflammatory infiltrates) and severe mucosal atrophy involving the entire small bowel was presented. Colonoscopy revealed the worsening of atypical ulcerative pseudomembranous colitis. CMV was immunohistochemically positive, and CMV DNA PCR from biopsy and stool samples confirmed significant CMV positivity. However, the number of CMV copies in the serum was not significantly increased (4.2×10^2 /ml). A diagnosis of CMV gastrointestinal disease in the background of pre-existing CVID-associated changes was made. Therapy with ganciclovir 1 g daily for 14 days led to the disappearance of CMV from the colon biopsy material, with a significant decrease in stool frequency, allowing the interruption of parenteral nutrition.

Discussion

Opportunistic infections do not appear to be markedly increased in CVID patients. Indeed, the cumulative incidence is reported between 5.4 and 9.2% and includes

Pneumocystis jiroveci, serious herpes zoster, *Mycobacterium* spp., *Aspergillus* spp., *Toxoplasma gondii*, and *Candida* spp. as the most common pathogens [5, 21, 22]. In contrast, data regarding the incidence of CMV infections in CVID patients are scarce, with predominantly only case reports being published. Our search of the English literature published between 1966 and 2012 (PubMed database) yielded only 15 cases of CMV disease described in detail in CVID, with 9 cases affecting the gastrointestinal tract [22–30], 2 cases of retinitis [22, 31] and a single case each of pneumonia [32], pleuritis [33] and lymphadenitis [34]. In addition to this, the study of Cunningham-Rundles and Bodian [21] reported only 1 CMV colitis in 248 patients, and the study of Resnick et al. [5] from the same centre showed 2/473 patients with CMV. The French Determination of Epidemiology of Fibromyalgia study revealed 2 cases of retinitis and 1 case of colitis in 313 CVID patients [22]. Kainulainen et al. [33] detected latent or chronic viral or bacterial infections in BAL samples from 14 CVID patients and observed positive CMV cultivation in 1 clinically asymptomatic patient; the patient, however, died of disseminated CMV disease 6 months later.

The incidence of CMV disease in our cohort was higher (3/32) than in other studies. CMV affected the lungs in 2 of the 3 patients; however, as mentioned, only 1 case report of CMV pneumonia and 1 case of pleuritis in CVID patients have been reported thus far. In contrast, CMV colitis predominated in previously reported cases. In 6/13 patients, immunosuppression or malignancy was reported as an enhancing risk factor for a possible secondary defect in cell-mediated immunity facilitating CMV onset [26, 29, 30, 32–34]. In addition to primary hypogammaglobulinaemia, other complications leading to secondary immunodeficiency were also present in all patients with CMV disease described herein. The first patient had a history of cancer and chronic HCV infection, and her lungs displayed multiple bronchiectasis and focal fibrosis. The second patient had a history of lymphocytic interstitial lung disease and coeliac disease-like enteropathy, with the necessity of long-term corticosteroid immunosuppressive therapy. The third woman suffered from malnutrition due to severe enteropathy managed with combined immunosuppressive treatment. T cells play an important role in the protection against CMV infection [35]. In HIV disease, a decrease in CD4+ cells $<200 \times 10^6$ /l is considered to be an important risk factor for the occurrence of opportunistic infection [36], and the probability of CMV disease increases with further CD4+ cell count decline, with $<100 \times 10^6$ /l representing a high risk for CMV disease in HIV-positive individuals [37]. However,

as observed in table 1, a decrease in CD4+ cells $<200 \times 10^6/l$ was detected only in patients No. 2 and 3 at the time of CMV flare, whereas the number of CD4+ T lymphocytes in patient No. 1 was not decreased at that time, though a T-lymphocyte decrease was observed in patient No. 1 approximately 10 years before CMV colitis was diagnosed.

Although RT-PCR is a very useful laboratory test with a high sensitivity [38], it is still necessary to clinically determine the appropriate threshold levels for a diagnosis of CMV disease. Previously published data and recommendations have involved a broad range of biological samples from different categories of patients (mainly recipients of bone marrow transplantation or recipients of solid organs) [39–42]. Moreover, CMV monitoring in the peripheral blood may not be beneficial in patients with end-organ limited disease [43–46], as documented also in our case reports. In such a situation, it was difficult to achieve a consensus for the ideal cutoff point for the diagnosis of active CMV disease specifically in our CVID

patients. Therefore, the final diagnosis of CMV disease had to be made in accord with clinical and paraclinical investigations.

Our observations show that CMV disease in CVID patients is most likely underdiagnosed. Indeed, it may be difficult to make this diagnosis, particularly in patients with extensive lung abnormalities or enteropathy, and the clinical symptoms may be obscure, non-specific or misleading. However, CMV infection may aggravate the course of seemingly refractory CVID complicated by enteropathy or interstitial lung disease. The early diagnosis with intensive treatment leads to good clinical outcomes in most cases.

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