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CYTOMEGALOVIRUS INFECTION IN AN IMMUNOCOMPETENT HOST PRESENTING AS HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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ABSTRACT

Cytomegalovirus (CMV) is a human herpes virus with a worldwide seroprevalence of 60-100%, mainly known to cause severe life-threatening disease in immunocompromised patients. In immunocompetent hosts (IMCh), CMV causes a self-limiting mononucleosis-like infection, and severe pictures are less recognized.

We report a case of a previously healthy 62-year-old woman evaluated in the Internal Medicine outpatient clinic for 3 weeks of progressive fatigue, generalised inflammatory arthralgias, hypogastric discomfort and daily persistent fever. On first examination, paleness and hepatomegaly were noted. Further evaluation showed the presence of haemolytic anaemia; lymphocytosis and monocytosis; thrombocytosis; elevated C-reactive protein; hypertriglyceridemia and hyperferritinaemia; peripheral blood immunophenotyping with a 44% population of T cells and diminished CD4/CD8 ratio. Hemophagocytic lymphohistiocytosis (HLH) was suspected, with an Hscore of 190 points, giving a 70-80% probability. CMV serology was positive for acute infection (IgM positive/IgG negative), with a viral load of 4470 IU/ml. CMV primary infection was admitted, complicated with haemolytic anaemia, cholestatic hepatitis and possible HLH. Despite the laboratory frame exuberance, the patient remained stable and was discussed with Infectious Diseases, deciding not to initiate antiviral therapy. Over the next month, the fever, anaemia and hepatitis resolved, and the white blood cell count normalized. After two months, the CMV viral load was negative, and seroconversion was documented.

Primary CMV infection is unusual in older patients. Additionally, in IMCh infection is usually mild, and severe infections are rare. In such cases, the use of antiviral therapy is not well established, and risk/benefit must be considered in a personalised approach. Altogether, the clinical and laboratory presentation of this case reinforces the need for high clinical suspicion.

KEYWORDS

Cytomegalovirus, immunocompetent host, haemolytic anaemia, cholestatic hepatitis, hemophagocytic lymphohistiocytosis

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LEARNING POINTS

- Cytomegalovirus can have serious, and life-threatening manifestations in immunocompetent hosts and its incidence may be higher than previously thought.
- Despite its seroprevalence ranging near 100% in the global population, primary infection in the elderly immunocompetent hosts is uncommon, but not impossible.
- Antiviral treatment is not well established in non-life-threatening disease in immunocompetent hosts, and a personal and individual approach must be considered with risk/benefit consideration.

INTRODUCTION

Cytomegalovirus (CMV), a member of the herpesvirus family, also known as human herpesvirus 5 (HHV-5), has a worldwide seroprevalence ranging from 45-100%[1,2], with most of the population being infected during childhood[3]. The virus can be found in all kinds of secretions, such as oropharyngeal, cervical, and vaginal, breast milk, tears, urine, and blood[3]. Infection occurs after contact with contaminated fluid and, although the cellular receptor for CMV entry into cells has not been yet identified, the virus proliferates mainly in the salivary glands, kidney, and leukocytes[3]. The primary infection is usually asymptomatic or causes a mild self-limiting mononucleosis-like syndrome in immunocompetent hosts (IMCh) and is followed by a lifelong latency within peripheral monocytes and myeloid progenitor cells[1,2]. Virus reactivation is a common feature in immunocompromised patients, such as patients with adult immunodeficiency syndrome (AIDS), use of immunosuppressive therapies (namely transplant recipients), or use of aggressive chemotherapy regimens[3]. Clinical syndromes encountered in these patients include encephalitis, pneumonitis, hepatitis, uveitis, retinitis, and colitis[2,3]. In IMCh, serious infections are less well recognised and have received little attention. In a systematic review of CMV infection in IMCh, by Rafailidis et al[2], 89 studies regarding 290 patients were included, and the authors suggested that life-threatening infections are not as rare as previously thought, with manifestations affecting almost any organ system. In this review, the gastrointestinal tract was the primary site of involvement (91 patients), with gastroenteritis, duodenitis, ileitis, colitis and proctitis being the main recognised clinical pictures. The central nervous system was the second most frequently involved system (56 patients), with manifestations such as myelitis, encephalitis, and meningitis. Haematological abnormalities were found in 25 patients, namely thrombocytopenia, haemolytic anaemia, disseminated intravascular coagulation, myelodysplastic changes, and pancytopenia. Less frequent manifestations include thrombosis (namely deep vein thrombosis and pulmonary embolism), eye disease (retinitis, uveitis) and pulmonary disease (pneumonitis).

Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening disorder, characterised by hyperimmune activation and multiorgan failure. It can be secondary to several stimuli, namely viral infections such as CMV[4]. CMV associated HLH (CMV-HLH) is poorly characterised, although in a review by Ramos-Casals et al., CMV appears to be the second most prevalent viral trigger for HLH, with an incidence of 9% of total HLH cases[5]. The exact role of viral infection in the development of HLH is controversial, firstly because patients usually have several infections, each of which may contribute to the immune dysregulation and the primary role of CMV infection may be secondary, and secondly because many immunocompromised patients are subject to CMV reactivation, which in turn increases the chance for opportunistic infections leading to HLH[4]. Seroconversion is the most reliable evidence of primary infection (but not for CMV reactivation)[3,4]. In a review of CMV-HLH cases performed by Chevalier et al., 12 IMCh were diagnosed with CMV-HLH, which manifested mainly as pneumonitis[4]. In other review, Bonnecaze et al. described five cases of CMV-HLH in IMCh[6]. It seems severe, life-threatening CMV infections, although rare, are probably much more frequent than previously thought. The mainstay treatment in such cases are antivirals together with immunosuppressive agents such as corticosteroids[4-6]. There are few studies of severe CMV infections specifically in IMCh, which is thought to have an estimated incidence of 1-5%[7,8]. As for mortality, no generalised data exists in the literature. Rafailidis et al.[2], estimated a 6.2% mortality in IMCh with CMV induced colitis, although in other cohorts the estimated mortality is as high as 30%[9]. Immunologically, CMV induces a cytotoxic cellular response, with proliferation of CD8+ T lymphocytes and natural killer cells (NK cells), essential for recognition and lysis of infected cells. The serum rise in cellular immunity is correlated with viral clearance and resolution of symptoms[3]. Regarding treatment, in immunocompromised hosts antiviral treatment with ganciclovir or valganciclovir is generally accepted. However, in IMCh few studies have appropriately evaluated antiviral use in severe disease[1]. Therefore, no guidelines have been published and treatment use in IMCh depends upon clinical evaluation as risk/benefit ratio.

CASE DESCRIPTION

A 62-year-old woman with no relevant medical history, was evaluated in the Internal Medicine outpatient clinic for a 3-week history of fatigue, generalised inflammatory arthralgias, hypogastric discomfort and daily persistent fever (maximum 39.9°C). Prior to symptom development, the patient had recent contact with sick children (respiratory infections) and stayed in a rural area.

Parameters	Reference range	14/04/23	17/07/23	24/04/23	28/04/23	08/05/23	30/06/23
Haemoglobin (g/dl)	13-16	**11.7**	**10.6**	**10.7**	**11.4**	12.6	12.7
Leukocyte (×10^9/l)	4-11	**17.6**	**16.7**	**14.7**	**15.4**	9.8	8.1
Neutrophils (×10^9/l)	1.9-7.5	7.22	5.34	3.54	4.4	3.91	3.66
Lymphocytes (×10^9/l)	1-4.8	**8.98**	**10.02**	**10.38**	**9.83**	**5.02**	3.86
Platelets (×10^9/l)	150-450	**462**	**488**	**466**	389	385	253
Erythrocyte sedimentation rate (mm/h)	<20	15	**28**	-	-	**40**	19
C-reactive protein (mg/dl)	< 0.5	**4.95**	**3.92**	**0.7**	**0.61**	0.26	**0.62**
Creatinine (mg/dl)	0.7-1.2	0.58	0.71	0.77	0.76	0.73	0.92
Alanine aminotransferase (U/l)	<33	**48**	**40**	20	15	14	19
Aspartate aminotransferase (U/l)	<32	**50**	**47**	26	22	16	16
Gama glutamyl transferase (U/l)	<60	**617**	**565**	**268**	**211**	**127**	**118**
Alkaline phosphatase (U/l)	40-130	**302**	**296**	-	-	**111**	125
Total bilirubin (mg/dl)	<1.2	**3.16**	**1.9**	0.43	-	0.41	0.23
Direct bilirubin (mg/dl)	<0.2	**0.84**	**0.54**	**0.23**	-	0.13	0.09
Lactate dehydrogenase (U/l)	100-250	**961**	**916**	**588**	**499**	**303**	197
Haptoglobin (mg/dl)	30-200	**<10**	**<10**	-	-	112	-
Ferritin (ng/ml)	30-400	-	**2392**	**776**	-	-	71
Triglycerides (mg/dl)	<150	-	**428**	-	-	**350**	-

Table 1. Blood work evolution during evaluation.

On initial examination her vital signs were all normal, she was haemodynamically stable, heart and respiratory rates were normal, and exhibited paleness and hepatomegaly, without any other relevant findings. The National Early Warning Score (NEWS) upon first observation was 0. Initial blood work *(Table 1)* showed the presence of haemolytic anaemia (haemoglobin 10g/dl); lymphocytosis (10000/µl) and monocytosis (1340/µl); thrombocytosis (400000/µl); elevated C-reactive protein; hypertriglyceridemia and hyperferritinemia; elevated alkaline phosphatase, gamma-glutamyl transferase and total bilirubin, including conjugated and unconjugated fractions; and a peripheral blood immunophenotyping with a 44% population of T cells with diminished CD4/CD8 ratio. Hemophagocytic lymphohistiocytosis (HLH) was suspected, with an Hscore of 190 points, giving a 70-80% probability. Further work-up showed: negative blood cultures for aerobes and anaerobes; negative real-time polymerase chain reaction (RT-PCR) for respiratory viruses (SARS-CoV-2, influenza A and respiratory syncytial virus); increased serum total IgM; negative interferon-gamma release assay (IGRA). Serologic tests for zoonoses were negative for acute infection, as was serology for Epstein-Barr infection. CMV serology showed positive IgM with negative IgG, suggestive of acute infection. The CMV serum viral load was 4470 IU/ml. Primary CMV infection, complicated by haemolytic anaemia, cholestatic hepatitis and possible HLH, was diagnosed. Despite the laboratory results, the patient remained haemodynamically stable, with no symptom evolution of symptoms in addition to the presenting symptoms and was evaluated by an ophthalmologist without findings suggestive of retinitis. Causes of immunocompromise were ruled out, namely the patient was not under any suppressive medication, no diagnostic criteria for diabetes were noted, and the patient was human immunodeficiency virus (HIV)-negative. Given all these factors, after discussion with the Infectious Disease team it was decided not to initiate antiviral therapy with valganciclovir nor corticosteroid therapy, unless worsening. Over the course of the next month and upon weekly re-evaluation in our output patient clinic, fever resolved, together with resolution of anaemia and hepatitis, and normalisation of leukocyte count *(Table 1)*. Two months after initial presentation, CMV viral load was negative, and seroconversion (with negative IgM and positive IgG) was documented.

DISCUSSION

The case presented stands out for two main reasons. Firstly, we not only present a true epidemiological link between the patient's clinical picture and probable previous exposure to sick school-aged children with upper respiratory tract infection, but we also present a case of CMV primary infection late in life, unusual given the high seroprevalence of the virus, ranging up to 100%, and probable exposure during childhood. This fact is supported by the seroconversion seen with a negative IgG and positive IgM on the first evaluation, followed months later by a positive IgG and negative IgM. This phenomenon excludes viral reactivation other than primary infection, since in that scenario IgG remained positive with IgM either positive or negative. Although we cannot exclude a scenario in which the patient acquired contact and immunity to the virus earlier in life, with loss of immunity over time and a new primary infection with subsequent exposure, since CMV infection is usual life-long, loss of immunity is rare. Therefore, the most probable option is primary infection in the 6th decade of life, *per se* a rare and uncommon occurrence.

Secondly, the case expressed a severe manifestation of CMV infection in IMCh, once again an uncommon feature. Secondary causes for immunodeficiency were searched for and ruled out, namely diabetes, immunosuppressive therapy, autoimmunity diseases, and neoplastic disease. In spite of the apparent clinical stability, the patient had haemolytic anaemia, cholestatic hepatitis and a suspected HLH. As for the haemolytic anaemia, a haematological manifestation in IMCh is *per se* a rarity. As described by Rafailidis et al.[2], only 25 out of 290 patients reviewed presented with any kind of haematological manifestation (incidence of 8.6%) and the true incidence of haemolytic anaemia is unknown. Cholestatic hepatitis is somewhat more common and elevations in gamma-glutamyl transferase and bilirubin are particularly frequent in mononucleosis-like primary infection. As for HLH, the patient had an Hscore of 190 points (probability of 70-80%), fulfilling 4 (cytopenia + fever + hyperferritinaemia + hypertriglyceridemia) out of 8 criteria according to HLH-2004 diagnostic criteria[10], not allowing for the definitive diagnosis of this entity. Given the clinical stability, with the patient always haemodynamically stable, fever resolving over time, and no worsening of the blood test results, further diagnostic tests, such as bone marrow evaluation or soluble CD25 dosing, which could have completed the full criteria for HLH diagnosis, were not performed. The relationship between CMV and HLH is well established, with an estimated incidence of 9%[5], however, contrary to most reviews on this topic[4-6] in which pneumonitis is the primary form of manifestation, our case is particularly interesting because of the absence of involvement of the most frequently affected sites, such as the lungs and gastrointestinal tract. The patient denied symptoms such as diarrhoea, abdominal pain, nausea, vomiting, dyspnoea, fatigue, or cough, and was always eupnoeic on room air, without need for oxygen supplementation and without relevant findings on pulmonary auscultation or chest X-ray. Once again, the uncommonness of the case is highlighted, since not only we are in the presence of primary CMV infection contracted late in life, with suspected HLH, but in addition, involvement of the most commonly affected organs is lacking and there are particularly striking haematological manifestations.

Additionally, a note must be made regarding the peripheral blood immunophenotyping, initially done in search of haematological neoplasms before it was known that the patient had primary CMV infection. However, there is a predominance of a T lymphocyte population, with a diminished CD4/CD8 ratio, suggesting an increase of CD8 cells. Retrospectively, these findings are in accordance with immune system adaptations to CMV infection, with an emphasis on cellular immunity as the major motor of cellular immunity.

Finally, in the case presented no specific antiviral therapy was used, as a result of multiple case discussions with the Infectious Diseases team and the absence of guidelines regarding treatment of CMV infection in IMCh. It is generally accepted that serious life-threatening infection, either in immunocompetent or immunocompromised hosts must be treated with valganciclovir or ganciclovir. However, CMV infections that are not life-threatening in IMCh are a grey area, with clinical evaluation as the cornerstone for treatment decisions. Since the patient remained stable, with no immunosuppression diagnosed, and no major organ involvement other than the haematological manifestations, which were stable and did not worsen, it was decided that no antiviral nor corticosteroid therapy was required. As stated, this decision took into account the Infectious Diseases team expertise and highlights the need for an individualised approach and risk/benefit consideration. In the case presented, if we had observed a clinical deterioration, with signs and symptoms of organ failure related either to the viral infection or the dysregulated activation of the immune system seen in HLH, high dose corticosteroid therapy for the latter, together with valganciclovir for the former, (which could be assumed to be the trigger for HLH) would have been adequate therapy.

In conclusion, severe manifestations of CMV infection can be observed in IMCh, differential diagnosis is extensive, the use of antiviral therapy is not well established, and risk/benefit must be considered in a personalised approach. This case highlights the diagnosis of primary CMV infection in an elderly patient, with particularly interesting laboratory features, rarely described in the literature.

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