Clinical features of cytomegalic disease in immunocompetent subjects: a 1990-2000 survey
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All cases of Cytomegalovirus-related disease in previously healthy immunocompetent subjects admitted to the University Hospital of Catania between 1990 and 2000 were reviewed. Eighty-one immunocompetent subjects were discharged with a diagnosis of acute cytomegalic disease. Nevertheless, only in 26 cases was the diagnosis confirmed by the determination of the specific immunoglobulin M, viremia or antigenemia. Fifteen subjects presented with a mononucleosis-like syndrome.

Eleven subjects had a more severe form of the disease with organ involvement: 3 hepatitis, 3 interstitial pneumonia, 2 aseptic meningitis, 2 ulcerative colitis and 1 peripheral vasculitis. All patients recovered. Two out of 11 severe cases were treated with ganciclovir and 7 with steroids; the remainder received only supportive treatment. Large-scale surveys are required to assess the real impact of Cytomegalovirus disease in immunocompetent subjects and to elaborate guidelines for the management of severe cases.

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Key words: Cytomegalovirus; Immunocompetent; Severe disease.

Introduction

Cytomegalovirus (CMV) infection has a worldwide prevalence varying between 40 and 100%1. Major cellular targets of primary CMV infection are the pharynx and intestinal epithelial cells, liver cells, macrophages and blood mononuclear cells. Following primary infection the virus can establish a lifelong persistence. Immune responses against CMV mainly depend on cell-mediated mechanisms such as CD4+-secreted interferon-gamma and CD8+ effector cells. Nevertheless, CMV-specific T-cell responses do not seem to be able to control viral replication but only to attenuate the clinical manifestations of viral infection2. Recently, Gamadia et al.2 showed that in asymptomatic CMV-infected individuals, the CMV-specific CD4+-T-cell response preceded the CMV-specific CD8+ T-cell responses, whereas in symptomatic cases the CMV-specific effector CD4+ T-cell response was delayed.

Cases with multiorgan involvement are usually seen in severely immunocompromised patients such as those undergoing organ transplantation, antitumor chemotherapy or in subjects with human immunodeficiency virus (HIV) infection3,4. Primary CMV infection in immunocompetent subjects is mostly asymptomatic, but 10% of new infections are characterized by a self-limiting mononucleosis-like disease5. A literature survey by Eddleston et al.6 has also reported the possibility of severe organ involvement during CMV infection among immunocompetent subjects.

In this study we retrospectively reviewed all symptomatic cases of CMV infection in previously healthy immunocompetent subjects admitted to the Department of Infectious Diseases of the University of Catania over a 10-year period with the purpose of reporting the clinical features and outcome.

Methods

The study was undertaken in January 2001 and was restricted to all adult patients admitted between January 1990 and December 2000 to the Department of Infectious Diseases of the University of Catania. Clinical registers were retrospectively reviewed and all clinical records referring to cases discharged with a diagnosis of acute cytomegalic disease were analyzed in detail. The clinical, virological, biochemical and histological data were collected.

The study included those cases in which the diagnosis of acute CMV infection was confirmed by at least one of the following: specific immunoglobulin M titer (determined by complement fixation or ELISA); viremia (determined by hybridization assays and/or the polymerase chain reaction); positive pp65 antigenemia (assessed by immunofluorescence); histological evidence of cytomegalic inclusions in biopsy specimens; immunohistochemical detection of CMV antigens in tissue sections or bronchoalveolar lavage specimens.
In order to ensure that only immunocompetent cases were selected for revision, we excluded: anti-HIV-1 positive patients; subjects affected by immunosuppressive diseases such as hematological or lymphoproliferative disorders, cancer and diabetes; subjects on steroids or other immunosuppressive drugs; subjects over the age of 65 years and subjects who had been diagnosed with an acute or chronic infectious disease within 6 months prior to hospital admission. Subjects were also excluded when evidence was found of a CD4+ cell count < 300/mm³, of a weak in vivo delayed-type skin reaction to recall antigens (candida, mumps, tetanus, toxoid, purified protein derivative) or of low levels of serum immunoglobulins.

**Results**

Between 1990 and 2000, 81 previously healthy immunocompetent subjects were discharged from our Department with a diagnosis of acute cytomegalic disease. Nevertheless, in only 26 cases was the diagnosis confirmed by at least one of the parameters required for inclusion in the study.

Fourteen subjects were male and 12 female; the mean age was 30 ± 11 years. All patients were admitted to the hospital with prolonged (> 2 weeks) fever. The mean duration of fever was 19 ± 10 days.

Fifteen subjects presented with a typical mononucleosis-like syndrome characterized by sore throat, cervical lymphadenomegaly, spleen enlargement, leukocytosis with atypical mononuclear cells in the peripheral blood film, and a negative serology for Epstein-Barr virus (immunoglobulin M antiviral capsid antigens and/or Monospot test). In all the mononucleosis-like cases the disease ran a self-limiting course and symptoms usually resolved within 2 weeks of hospital admission.

Eleven out of 26 subjects had a more severe clinical picture with organ involvement. These subjects did not differ from those with a self-limiting mononucleosis-like disease in terms of sex, age, race, serum immunoglobulin levels and CD4+ and CD8+ T-cell count.

Three out of 11 patients with severe disease had acute hepatitis. None of the patients were positive for other hepatitis virus serology (hepatitis B surface antigen, anti-hepatitis C virus, anti-hepatitis A virus immunoglobulin M). None reported the assumption of hepatotoxic drugs or alcohol abuse. Serum non-organ-specific autoantibodies were negative in all cases. All subjects reported loss of appetite, nausea, dark urine, pale stools and jaundice. The mean alanine aminotransferase (ALT) level was 1810 ± 348 U/L; the mean bilirubin level was 15 ± 4 mg/dL and the mean alkaline phosphatase 518 ± 133 U/L. Two cases had a rapid self-limiting course with ALT normalization within 3 weeks of hospital admission. The remaining case presented with features of sub-fulminant hepatitis such as drowsiness, confusion, a reduction in serum albumin and coagulation disorders. Treatment with neomycin, lactulose, steroids, ranitidine and fresh frozen plasma was commenced. During the next 24 hours the subject went into a grade IV hepatic coma. In the following days, he improved rapidly with decreasing jaundice and increasing consciousness. Seven days later, he presented with a normal prothrombin activity and a consistent decrease in the ALT (656 U/L) and bilirubin levels (8 mg/dL). Complete health was recovered 30 days after the onset of liver failure.

Three patients presented with severe lung involvement with a dry cough and tachypnea. Physical examination revealed bilateral pulmonary crepitations. Lung X-ray showed bilateral hyperinflation and interstitial infiltrates in the mid and lower zones. In 2 out of 3 cases, arterial blood gas analysis revealed severe hypoxemia (< 50 mmHg). Serology for Legionella, Mycoplasma, Chlamydia and Coxiella was negative as was the search for acid-fast bacilli in the sputum and bronchoalveolar lavage specimens. CMV disease was diagnosed in all 3 cases by detection of CMV-antigens in the bronchoalveolar lavage specimens. Having diagnosed acute cytomegalic infection, the 2 cases with severe hypoxemia were treated with steroids, oxygen and ganciclovir at a dose of 5 mg/kg daily for 3 days, whereas only steroids were given in the other case. All patients showed a favorable course with the improvement of symptoms within 10 days of hospital admission.

Two subjects were admitted to hospital because of abdominal cramps and bloody diarrhea. Physical examination showed abdominal tenderness and meteorism in both cases. Stool microscopy and cultures did not reveal any pathogenic bacteria or parasites. Protocolonoscopy showed multiple narrow shaped bloody ulcers scattered from the rectum to the cecum in one case and restricted to the rectum in the other. Biopsies taken from around the edges of the ulcers showed typical cytomegalic inclusion bodies. A short course of steroids resulted in clinical improvement within 7-11 days of the beginning of treatment.

Two further patients presented with neurological manifestations. One subject had headache and vomiting. Physical examination revealed cervical stiffness. A cranial computed tomography scan was negative for focal lesions whereas lumbar puncture showed a high opening pressure, cerebral serum fluid hypoglycorrhachia and lymphocytic pleocytosis. The second case presented with irritability,
headache and meningeal signs. Cranial computed tomography scan showed meningeal enhancement together with abnormal attenuation and swelling of the left temporal lobe with initial narrowing of the ipsilateral ventricle. Lumbar puncture was therefore deferred. In the latter case, seizures appeared during the course of the disease requiring prompt anticonvulsant therapy. Both cases benefited from the administration of mannitol and steroids. One patient recovered without any permanent consequences whereas the other showed mild residual right hand paresis and psychiatric disorders.

One patient presented with nausea, severe pain in the upper abdomen, purpura and small-size necrotic nodules on the legs and feet. Physical examination revealed that there were no bowel movements. An abdominal computed tomography scan revealed multiple splenic infarctions and was suggestive of occlusive arteritis of the splenic artery. Urgent splenectomy was performed together with a biopsy of the cutaneous lesions and revealed inflammatory vasculitis with perivascular lymphoplasmacellular granulomas. Antinuclear and antiphospholipid antibodies were negative. The course of the disease was favorable with the spontaneous resolution of the skin lesions.

Table I summarizes the epidemiological and clinical features of those cases with a severe clinical presentation.

Discussion

Our 1990-2000 retrospective survey identified 26 cases of symptomatic CMV-related diseases among immunocompetent patients; 58% of them presented with typical self-limiting mononucleosis-like symptoms. This is compatible with the data reported by Coll et al.7 in a large series of immunocompetent patients with CMV-related disease. In 11 patients the course of the disease was complicated and severe. Eddleston et al., reviewing the worldwide literature between 1966 and 1996, identified 34 cases of severe CMV infection in immunocompetent subjects. The number of cases of severe CMV disease in immunocompetent subjects is, however, probably much higher than that derivable from a literature review, this being due to a number of reasons such as misdiagnosis, lack of notification and lack of literature reports.

We identified 3 cases of CMV-related hepatitis. In one case the disease progressed to liver failure. Liver cells are a major target of infection by CMV and asymptomatic liver enlargement with mild ALT elevation may be a frequent feature during CMV infection in immunocompetent patients7. Acute CMV granulomatous hepatitis with severely symptomatic clinical progression and extremely high ALT levels has been described in previously healthy adults elsewhere8. Recently, Miguelez et al.9 reported a case of sub-fulminant CMV hepatitis in an apparently immunocompetent pregnant woman.

In our survey, 3 patients had severe interstitial pneumonitis with hypoxemia. Interstitial pneumonia is the most common organ-involving disease caused by CMV in immunocompetent subjects10-12. Cough, dyspnea and chest pain are usually the main symptoms reported10. Our patients recovered without any permanent consequences: steroids were administered in 1 case whereas in the 2

### Table I. Features of 11 cases of severe cytomegalic disease.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Clinical presentation</th>
<th>Organ involvement</th>
<th>Duration of disease (days)</th>
<th>Methods of diagnosis</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>M</td>
<td>Dark urine</td>
<td>Liver</td>
<td>22</td>
<td>Serology</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>F</td>
<td>Diarrhea</td>
<td>Intestine</td>
<td>18</td>
<td>HI, serology</td>
<td>Steroids</td>
</tr>
<tr>
<td>3</td>
<td>42</td>
<td>M</td>
<td>Hypoxemia</td>
<td>Lung</td>
<td>18</td>
<td>IH*</td>
<td>Steroids, ganciclovir</td>
</tr>
<tr>
<td>4</td>
<td>28</td>
<td>M</td>
<td>Cough</td>
<td>Lung</td>
<td>16</td>
<td>IH*</td>
<td>Steroids</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>F</td>
<td>Dark urine</td>
<td>Liver</td>
<td>25</td>
<td>Serology</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>20</td>
<td>M</td>
<td>Vomit</td>
<td>Brain</td>
<td>22</td>
<td>PCR†</td>
<td>Steroids</td>
</tr>
<tr>
<td>7</td>
<td>18</td>
<td>F</td>
<td>Diarrhea</td>
<td>Intestine</td>
<td>20</td>
<td>HI, serology</td>
<td>Steroids</td>
</tr>
<tr>
<td>8</td>
<td>35</td>
<td>M</td>
<td>Confusion</td>
<td>Liver</td>
<td>41</td>
<td>Serology</td>
<td>Steroids</td>
</tr>
<tr>
<td>9</td>
<td>20</td>
<td>M</td>
<td>Headache</td>
<td>Brain</td>
<td>42</td>
<td>PCR†, in situ hybridization†</td>
<td>Steroids</td>
</tr>
<tr>
<td>10</td>
<td>40</td>
<td>F</td>
<td>Hypoxemia</td>
<td>Lung</td>
<td>8</td>
<td>IH*</td>
<td>Steroids, ganciclovir</td>
</tr>
<tr>
<td>11</td>
<td>22</td>
<td>M</td>
<td>Abdominal pain, purpura</td>
<td>Small arteries spleen</td>
<td>26</td>
<td>IH*, HI*, serology</td>
<td>Surgery</td>
</tr>
</tbody>
</table>

HI = histological evidence of typical cytomegalic inclusion bodies in the tissue samples; IH = immunohistochemistry; PCR = polymerase chain reaction. † performed on bronchoalveolar lavage specimen; † performed on the cerebrospinal fluid or cerebrospinal fluid cells; † performed on the spleen.
cases with a more severe hypoxemia, the patients fully recovered following therapy with parenteral ganciclovir and steroids. The latter have been reported to be beneficial in cases of severe hypoxemia. With regard to antiviral treatment, Pellegrini et al. reported 2 cases of CMV pneumonia in immunocompetent subjects who were successfully treated with parenteral ganciclovir.

Two of our patients presented with neurological abnormalities caused by an acute meningoencephalitis. Meningoencephalitis is not a rare complication of CMV infection even in immunocompetent individuals: by means of polymerase chain reaction, Salamano et al. found CMV-DNA in the cerebrospinal fluid of a young immunocompetent male who developed prolonged fever and encephalitis; Devetag et al. reported cases of CMV meningoencephalitis with paroxysmal symptoms in previously healthy immunocompetent patients. These data indicate that CMV replication may occur in the cerebrospinal fluid of immunocompetent individuals during CMV infection. In contrast with the findings of Eddleston et al., who reported a better prognosis in CMV-associated neurological disease than in cases presenting with extra-neurological manifestations, one of our patients developed permanent neurological disorders.

Two cases presented with severe ulcerative colitis. Colitis by CMV consists of an inflammation of the large bowel which leads to deep mucous and submucous ulcers. CMV may have a direct cytopathic effect on the bowel mucosa. Alternatively, it may trigger an immunological mechanism responsible for the mucosal damage. Three cases of CMV-related colitis were recently reported in immunocompetent subjects and in one of these cases the progression of the disease was fulminant. The role of steroids or other immunosuppressive agents in CMV-related colitis is debatable. Our favorable experience is contradicted by data from other authors who reported the exacerbation of the disease under steroids. Apart from the large bowel, other tracts of the gastrointestinal mucosa may be invaded and damaged by CMV in immunocompetent patients.

We observed a single case of CMV-related vasculitis with both cutaneous and visceral involvement. Different mechanisms, such as circulating immune complexes, cryoglobulinemia and/or the direct infection of the endothelial cells, have been claimed to play a pathogenetic role in CMV-related vasculitis. In addition, CMV has been reported to contribute to the pathogenesis of the vascular complications of some autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus. CMV vasculitis has previously been described in different organs such as the retina, the brain, the spinal cord, the liver, coronaries and the small bowel.

CMV disease in immunocompetent patients is usually characterized by a relative well-being and paucity of findings. Our data confirm that, apart from the typical mononucleosis-like syndrome, a severe evolution of the disease should also be borne in mind in immunocompetent subjects with an acute CMV infection. In contrast with the data from the literature, all of our cases but one recovered without permanent consequences.

In our clinical case revision 55 out of 81 (67%) immunocompetent cases with suspected CMV-related disease were not diagnosed specifically. This could be due firstly to the fact that symptomatic CMV infection is not thought to be typical in immunocompetent subjects; secondly, it could be related to the lack of an adequate sensitivity of the specific diagnostic methods. In fact, in immunocompetent patients serology, histology and pp65 antigenemia are burdened by a certain number of false-negative results and the more sensitive determination of the viremia by means of the polymerase chain reaction is not readily available in all hospital settings.

Nevertheless, the possibility that a case of fever of unknown origin could be related to acute CMV infection should be borne in mind. Evidence of thrombocytopenia, lymphocytosis and/or a mild elevation of the hepatic enzymes may aid the diagnosis. TAGA et al. recently found the CD8+ lymphocyte count to be helpful in distinguishing CMV- from Epstein-Barr virus-related mononucleosis. Anti-CMV specific immunoglobulins M should be searched for as a first-step exam. In case of organ involvement, histology with immunohistochemical and virological assays are advisable.

Therapeutic approaches to CMV disease in immunocompetent subjects vary greatly and are often performed arbitrarily. In fact, some authors suggest restricting treatment to symptomatic drugs whereas others propose the use of antiviral drugs such as ganciclovir, foscarnet and cidofovir. To conclude, there are sporadic reports on the efficacy of steroids especially in cases of severe thrombocytopenia, severe lung involvement with hypoxemia and meningeval or brain disease.

Our experience and data in the literature suggest that further large-scale and multicenter surveys are required both to assess the real impact of CMV disease in immunocompetent subjects and to formulate more correct guidelines for the management of severe cases.
Riassunto
Sono state rivisitate le cartelle cliniche di tutti i casi diagnosticati come infezione da Cytomegalovirus in soggetti immunocompetenti presso l’Unità di Malattie Infettive di Catania nel periodo fra il 1990 e il 2000. In tutto 81 soggetti sono stati dimessi con diagnosi di infezione acuta da Cytomegalovirus, ma solamente in 26 la diagnosi era stata confermata dalla determinazione di anticorpi immunoglobulina M specifici, di antigeni viral e/o di viremia plasmatica. Quindici individui hanno presentato una sindrome simile-mononucleosica; 11 soggetti hanno presentato localizzazioni d’organo severe: epatite in 3 casi, polmonite in 3 casi, meningite in 2 casi, colite ulcerosa in 2 casi, vasculite periferica in 1 caso. Tutti i pazienti tranne uno sono guariti senza reliquati. Fra gli 11 casi a severa presentazione 2 sono stati trattati con ganciclovir e 7 con steroidi; i rimanenti hanno ricevuto esclusivamente terapia di supporto. Ulteriori studi dovrebbero essere effettuati per comprendere l’impatto della malattia citomegalica nei soggetti immunocompetenti e per formulare linee guida per il trattamento dei casi con grave compromissione d’organo.

Parole chiave: Cytomegalovirus; Immunocompetente; Malattia grave.

References

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