Cytomegalovirus Retinitis in a Patient Treated with Anti–Tumor Necrosis Factor Alpha Antibody Therapy for Rheumatoid Arthritis

Georg Haerter,1 Burkhard J. Manfras, Yvonne de Jong-Hesse, Heike Wilts, Thomas Mortens, Peter Kern, and Michael Schmitt

1Division of Infectious Diseases and Clinical Immunology, Third Department of Internal Medicine, and Departments of Ophthalmology and Virology, University Hospital Ulm, Germany

Background. Anti–tumor necrosis factor α (anti–TNF-α) antibodies have been used for the treatment of chronic inflammatory diseases such as rheumatoid arthritis (RA) and psoriasis arthritis. Such antibody therapies result in a severe interference with the patient’s immune system. Increased rates of upper respiratory tract infection, reactivation of latent tuberculosis, and other systemic infectious diseases have been reported among patients receiving anti–TNF-α antibodies.

Methods. As a note of caution, we describe a 57-year-old woman who received therapy with anti–TNF-α antibodies for RA refractory to methotrexate. After almost 2 years of treatment, she developed a severe cytomegalovirus (CMV) retinitis of the right eye.

Results. Laboratory assays revealed an immune status with nearly total loss of the cellular immune response and partial reduction of the humoral immune response. Intravenous treatment with ganciclovir, followed by oral administration of valganciclovir, resulted in an ophthalmological remission. Cessation of immunosuppressive therapy led to partial immunological reconstitution in the patient. Six months after discontinuation of immunosuppressive therapy, CMV retinitis of the left eye occurred but was treated successfully with a second course of oral valganciclovir.

Conclusion. In the light of this first reported case of a serious CMV infection following therapy with anti–TNF-α antibodies, CMV infection should be considered in symptomatic patients.

Cytomegalovirus (CMV) is a β-herpes virus causing a life-long persistence after primary infection. In the immunocompetent host, primary CMV infections and viral reactivations are often clinically silent. On the other hand, in newborns and immunocompromised patients (e.g., patients with AIDS or allogeneic bone marrow transplant recipients), reactivation of CMV infection may cause severe diseases such as retinitis or pneumonia [1].

Treatment of human CMV infection consists of long-term intravenous infusions of ganciclovir, foscarnet, or cidofovir [2–3]. Recently, oral valganciclovir, a valyl ester prodrg of ganciclovir, has become available and has been administered for the induction and maintenance therapy of CMV retinitis in patients with AIDS [4]. The drug has been approved by the US Food and Drug Administration for induction therapy and prevention of CMV-associated diseases in solid organ transplant recipients [5].

Alterations of the function of the immune system, the use of immunosuppressive drugs, and comorbidity are main risk factors for infection. Thus, various infectious complications are frequent in patients with rheumatoid diseases [6]. TNF-α plays a central role in the immune response to infection and inflammation. It is characterized by various biological activities, including T and B cell activation, increased expression of class II major histocompatibility complex, and platelet activation and adhesion [7, 8]. TNF-α is a cytokine that mediates host-resistance against microorganisms, especially intracellular microbes [9]. It is believed to play a key role in the pathogenesis of rheumatoid arthritis.
CMV Retinitis and Anti–TNF-α Antibody Therapy

Figure 1. Retinal photograph of the patient’s right eye at the time of admission displaying acute cytomegalovirus retinitis, with creamy intraretinal infiltrates associated with hemorrhage and vitreous opacities.
Table 1. Hematological and immunological findings for a woman with cytomegalovirus-associated retinitis at the time of admission and at follow-up after 6, 12, and 18 months of antiviral therapy and cessation of immunosuppressive drugs.

<table>
<thead>
<tr>
<th>Immunological feature</th>
<th>Normal range</th>
<th>At admission</th>
<th>At 6 months of follow-up</th>
<th>At 12 months of follow-up</th>
<th>At 18 months of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocyte count, lymphocytes/µL</td>
<td>1500–4000</td>
<td>131</td>
<td>1265</td>
<td>2413</td>
<td>2285</td>
</tr>
<tr>
<td>B cell count, cells/µL</td>
<td>200–400</td>
<td>1</td>
<td>25</td>
<td>241</td>
<td>434</td>
</tr>
<tr>
<td>Natural killer cell count, cells/µL</td>
<td>200–400</td>
<td>5</td>
<td>721</td>
<td>1448</td>
<td>640</td>
</tr>
<tr>
<td>T cell count, cells/µL</td>
<td>1100–1700</td>
<td>121</td>
<td>443</td>
<td>579</td>
<td>937</td>
</tr>
<tr>
<td>CD4+ T cell count, cells/µL</td>
<td>700–1100</td>
<td>59</td>
<td>76</td>
<td>193</td>
<td>366</td>
</tr>
<tr>
<td>CD8+ T cell count, cells/µL</td>
<td>500–900</td>
<td>53</td>
<td>304</td>
<td>362</td>
<td>526</td>
</tr>
<tr>
<td>IgG level, g/L</td>
<td>7.00–16.00</td>
<td>4.03</td>
<td>7.53</td>
<td>11.20</td>
<td>10.30</td>
</tr>
<tr>
<td>IgA level, g/L</td>
<td>0.7–4.00</td>
<td>0.37</td>
<td>0.77</td>
<td>0.79</td>
<td>1.14</td>
</tr>
<tr>
<td>IgM level, g/L</td>
<td>0.4–2.3</td>
<td>8.07</td>
<td>6.74</td>
<td>5.11</td>
<td>4.32</td>
</tr>
</tbody>
</table>

called “ghost vessels”). CMV pp65 antigenemia was detectable again, with 11 cells positive for CMV pp65 antigen (figure 3). Induction therapy was conducted with oral valganciclovir (900 mg b.i.d.) for 3 weeks and was thereafter reduced to a daily single dose of 900 mg. After and during therapy with this dosage, CMV pp65 antigenemia has not been detected for >12 months at the time of writing (figure 3).

Initially, the cellular immune status was severely impaired, and it partially recovered during the 18 months after cessation of immunosuppressive therapy and antiviral treatment (table 1). CMV-specific CD8+ T cells, as determined by tetramer staining, were present at a very low frequency (0.91% of all CD8+ T cells) at the time of admission (figure 4). After 12 months of therapy, the CMV-specific CD8+ T cells increased in frequency (to 6.65% of total CD8+ T cells) and showed a phenotype of CD8+ CD45RO+ CD27− CD28−, consistent with differentiated memory CD8+ T cells (figure 4).

DISCUSSION

In this patient, a severe human CMV retinitis occurred after immunosuppressive therapy, including therapy with an anti-TNF-α antibody (infliximab). Five weeks after cessation of antiviral maintenance therapy with valganciclovir, CMV retinitis occurred in the contralateral eye. Initially, an extremely elevated pp65 antigen level of 2400 positive cells could be detected, indicating a severe systemic active infection. The high avidity of anti-CMV IgG antibodies and the high titer of neutralizing antibodies observed at the time of diagnosis are more likely to implicate a reactivation of CMV infection than a primary in-

Figure 2. Retinal photograph of the patient’s right eye after 5 months of therapy with ganciclovir. At this stage, the fundus is quiescent, with chorioretinal scars associated with fibrosis and peripheral vascular attenuation.
CMV Retinitis and Anti–TNF-α Antibody Therapy

Figure 3. Course of cytomegalovirus (CMV) infection as monitored by immunofluorescence assay for the number of leukocytes positive for CMV pp65 antigen per 500,000 cells counted (including both early-stage and late-stage cells). Arrows, time points of first diagnosis and relapse of CMV retinitis; gray boxes, treatment administered.

Infection. At the time of relapse, the CMV pp65 antigen level was not as elevated as it was initially (11 positive cells, compared with 2400 positive cells; figure 3). The relapse underlines the need for stringent control of the CMV antigen level and for a therapy interval of >6 months in patients with general immunosuppression.

The patient in this case had been treated with various disease-modifying antirheumatic drugs (DMARDs). Infliximab has been approved by the German health authorities for use only in combination with methotrexate and has not been approved for concomitant use with other immunosuppressive drugs. The combination of an anti–TNF-α antibody with cyclophosphamide and azathioprine may have led to severe infectious complications, as in this case. The CMV infection became apparent while the patient was receiving therapy with the combination containing the anti–TNF-α antibody but was not apparent earlier.

The patient’s CMV-specific CD8+ T cell count, as determined by staining with CMV-specific tetramers, was increasing while she recovered. This might reflect the immunological response to the virus during the CMV infection. Also, the CD8+ CD45RO+ CD27− CD28− T cells increased in number, which corresponds to a late-stage phenotype of memory CD8+ T cells [15]. The appearance of these CD27− CD28− late-stage effector cells in the clinical course in our patient after recovery might reflect virus entering the latent stage, which would be consistent with the course of CMV pp65 antigenemia. Therefore, maintenance therapy with oral valganciclovir was terminated again. At the time of writing, there is no evidence for a reactivation of CMV disease in this patient.

The Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT) demonstrated that therapy with anti–TNF-α antibodies combined with methotrexate had better efficacy than therapy with methotrexate alone in patients with RA [16]. In this trial, a significantly higher incidence of infections was reported among patients receiving therapy with anti–TNF-α antibodies: 44% of patients receiving infliximab needed to be treated with antibiotics, but only 35% of patients in the cohort who received methotrexate alone needed antibiotic therapy [17]. Certain infectious diseases showed a higher incidence in the group receiving infliximab than in the group that did not; these diseases included upper respiratory tract infection, sinusitis, and pharyngitis. The frequency of infections that required hospitalization was similar in both groups; these infections included septicemia, pneumonia, bronchitis, peritonitis, pyelonephritis, cellulitis, mycosis, and herpes simplex [16]. A series of other pathogens, including Listeria monocytogenes, causing diseases and serious bacterial infections have been reported in patients treated with infliximab [18]. These reports are summarized in table 2. The particular focus is on tuberculosis (TB), because the estimated incidence of TB in patients with RA who were treated with infliximab was calculated to be 24.4 cases per 100,000 patients, compared with the background
Figure 4. Detection of cytomegalovirus (CMV)–specific CD8+ lymphocytes by tetramer staining for a pp65-derived epitope peptide at the time of diagnosis (A) and after 12 months of antiviral therapy (B) (lymphocyte-gated and CD8+–gated). Phycoerythrin (PE)–labeled tetrameric complexes binding the HLA-A*0201–matched CMV peptide pp65 495–503 (NLVPMVATV) were purchased from ProImmune. The analysis was performed according to the manufacturer’s instructions. Allophycoerythrin (APC)–labeled CD28 antibody was purchased from BD Biosciences. Analysis was performed on a FACSCalibur flow cytometer using the MultiSET software (BD Biosciences).

incidence of TB in patients with RA of 6.2 cases per 100,000 patients [19].

Clinical benefits for patients with RA or psoriatic arthritis treated with anti–TNF-α antibodies have been demonstrated [20–22]. No significant differences have been observed in the incidence of infectious diseases in patients with RA who receive etanercept, compared with patients with RA who receive other DMARDs [21]. Infections of the upper respiratory tract were reported more often than other infectious diseases in patients with RA who received etanercept. Serious infections requiring hospitalization were rather rare and did not increase in frequency during treatment with etanercept. No reports of TB or other opportunistic infections were obtained during the trial that compared etanercept therapy with methotrexate therapy [21]. However, postmarketing surveillance revealed the occurrence of bacterial, viral, fungal, and protozoal pathogens in patients receiving etanercept therapy [23, 24].

The newest anti–TNF-α antibody is adalimumab, the first completely humanized IgG class I antibody against TNF-α. The clinical efficacy of therapy with adalimumab alone, compared with therapy with methotrexate alone, in patients with RA has been demonstrated in the Anti–Tumor Necrosis Factor Research Study Program of the Monoclonal Antibody Adalimumab (D2E7) in Rheumatoid Arthritis (ARMADA) trial [25]. The number of infections (52.2% vs. 49.4%) or serious infections (1.3% vs. 1.9%) did not differ significantly between the antibody and placebo groups, respectively.

In the case of human CMV, TNF-α can inhibit CMV production in certain cell types [26, 27], and the CMV major immediate early promoter is inhibited by TNF-α [28]. Therefore, blocking of TNF-α might act synergistically and strengthen the CMV infection. TNF-α inhibits apoptosis via activation of nuclear factor–κB, which upregulates antiapoptotic molecules [29]. In acute CMV infections, the level of TNF-α is elevated, which indicates a pivotal role for TNF-α in host immune re-

Table 2. Opportunistic infections reported in patients receiving treatment with anti–TNF-α antibodies.

<table>
<thead>
<tr>
<th>Infection</th>
<th>No. of cases</th>
<th>No. of deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycobacterium tuberculosis infection</td>
<td>277</td>
<td>0</td>
</tr>
<tr>
<td>Atypical mycobacterial infection</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Aspergillosis</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Pneumocystis jirovecii pneumonia</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Coccidiomycosis</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Listeriosis</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Cryptococcosis</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Cytomegalovirus infection*</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Systemic candidiasis</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Mucormycosis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Salmonellosis</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE. Data summarize infections observed in patients receiving infliximab [21].

* Infections were in the lungs (4 patients), eyes (1 patient), and colon (1 patient).
response to human CMV. In HIV-infected patients, impaired TNF-α production in CMV-specific T cells was associated with susceptibility to CMV infection, including CMV retinitis [30, 31]. Therefore, decreased levels of TNF-α as a result of either immunological impairment or anti–TNF-α antibody therapy may lead to higher susceptibility to CMV-related end-organ diseases.

CMV causes serious infections in patients who have undergone allogeneic stem cell transplantation. It has been shown that measurement of either CMV-specific CD4+ T cells or CD8+ T cells could help to evaluate the risk for progressive CMV infection after allogeneic stem cell transplantation [32, 33]. Impaired function of CMV-specific CD8+ T cells seems to be more important than the inability to recover sufficient absolute numbers of CMV-specific CD8+ T cells in determining susceptibility to CMV disease [34].

**RECOMMENDATIONS**

In the light of our reported case and other CMV infections observed in patients receiving therapy with anti–TNF-α antibodies, we recommend that patients receive a careful examination for end-organ manifestations of CMV infection (including an ophthalmological examination) before the initiation of therapy with anti–TNF-α antibodies. CMV pp65 antigen levels or quantification of CMV DNA from leukocytes should be assessed in symptomatic patients with clinical signs such as visual impairment, cough and dyspnea, or diarrhea, which can indicate end-organ manifestations of CMV infection.

Patients who receive anti–TNF-α antibodies and show reactivation of CMV (defined as a laboratory finding of ≥2 leukocytes positive for pp65) or the presence of clinical symptoms should receive either intravenous ganciclovir or valganciclovir as treatment. To prevent a relapse of disease, secondary prophylaxis with either oral ganciclovir or valganciclovir should be conducted for >6 months.

**Acknowledgment**

Potential conflict of interest. All authors: No conflict.

**References**


