Cytomegalovirus-Associated Nephrotic Syndrome in a Patient with Myasthenia Gravis Treated with Azathioprine: A Case Report

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Conflict of interest: None declared

Patient: Female, 68-year-old
Final Diagnosis: Nephrotic syndrome
Symptoms: Edema • fever • oliguria • proteinuria
Medication: —
Clinical Procedure: —
Specialty: Nephrology

Objective: Rare coexistence of disease or pathology
Background: Patients taking azathioprine (AZA) are very susceptible to development of cytomegalovirus (CMV) infection. The symptoms of CMV infection are varied. In some rare cases, CMV infection can even result in nephrotic syndrome.

Case Report: Here, we present a rare case of nephrotic syndrome associated with CMV infection, induced by azathioprine intake. The patient, diagnosed with myasthenia gravis, was initially treated with azathioprine for 2 years. Then, the patient was admitted to the hospital due to nephrotic syndrome and acute kidney injury. Minimal change disease with acute tubular necrosis were diagnosed through biopsy. After an initial good response to hemodialysis and steroids, the patient developed severe pneumonia and oral ulcers. Further anti-CMV IHC staining of kidney tissues showed positive cells in tubules, indicating nephrotic syndrome secondary to CMV infection.

Conclusions: This case reminded us that CMV may be an under-recognized cause of nephrotic syndrome. Patients treated with azathioprine are very susceptible to developing CMV infection. During the diagnosis of nephrotic syndrome, we should always take CMV infection into consideration, especially in patients with on azathioprine.

Keywords: Acute Kidney Injury • Azathioprine • Case Reports • Glycoprotein H, Cytomegalovirus • Nephrotic Syndrome

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**Background**

Cytomegalovirus (CMV) is a double-stranded DNA virus belonging to the herpesvirus family. It usually causes subclinical diseases with asymptomatic syndromes or mild infection with spontaneous cure in immunocompetent adults [1]. However, it can cause severe infections in AIDS patients, solid-organ transplant patients, and hematopoietic stem-cell transplant recipients, resulting in uncontrolled viral replication [2]. CMV infection may also occur in other immune-compromised patients, mostly patients on immunosuppressive treatment. The symptoms can be varied, including fever, diarrhea, pneumonia, hepatitis, and encephalitis. A systematic meta-analysis of case reports and reviews found that severe CMV infection most common involve the gastrointestinal tract, followed by the central nervous system, and then hematological abnormalities [3]. In some rare cases, azathioprine leads to immunosuppression and is associated with CMV infection. Here, we present a case report of a patient with secondary nephrotic syndrome and acute tubular necrosis due to CMV infection, subsequent to azathioprine treatment.

**Case Report**

A 68-year-old woman was admitted to the hospital because of a 1-week history of edema and oliguria. Two years before admission, she was diagnosed with myasthenia gravis and was subsequently taking azathioprine 100 mg/day. She has also been diagnosed with breast cancer 10 years ago and had a mastectomy. Other medical history included hypertension for 10 years.

Laboratory test results are shown in Table 1. Hypoalbuminemia, hyperlipidemia, proteinuria, and edema met the diagnostic criteria for nephrotic syndrome. Furthermore, the elevated serum creatinine met criteria for AKI diagnosis. Light microscopy and immunofluorescence of kidney biopsies suggested minor glomerular abnormalities and acute tubular necrosis. Electronic microscopy indicated extensive foot process effacement of podocytes (Figure 1). After ruling out the possible secondary causes, the patient received hemodialysis and also started intravenous administration of methylprednisolone 40 mg per day. After edema was alleviated and serum creatinine levels returned to normal, the patient was treated with prednisone at an initial dose of 1 mg/kg per day orally and discharged home.

However, 2 weeks later, the patient was re-admitted for fever, dyspnea, and large oral ulcers (Figure 2). Laboratory test results are shown in Table 1. Computed tomography (CT) of the chest revealed viral pneumonia (Figure 3). We suspected the patient had viral infections. A further viral work-up came back negative for Epstein-Barr virus, Coxsackie virus, and rubella virus antibodies. However, CMV-IgG and IgM antibodies were positive (CMV-IgG 500.00 IU/mL, range 0.00-1.0 IU/mL; CMV-IgM 5.25 IU/mL, range 0.00-0.70 IU/mL). The serum CMV PCR test result was also positive (CMV viral load 5236 copies/mL).

To identify whether a patient was infected with CMV before or after the initiation of prednisone, immunohistochemical (IHC) staining is regarded as the criterion standard of CMV diagnosis [4,5], so we performed anti-CMV IHC staining on the patient’s renal tissue (CMV 8B1.2, 1G5.2, and 2D4.2, Cell Marque, USA). The IHC staining of renal tissues showed positive staining of cells in tubules compared to the negative control (Figure 4). These results strongly confirmed our suspicion that the patient was initially infected with cytomegalovirus only after initiation of azathioprine treatment. The nephrotic syndrome was secondary to CMV infection.

Given the probable causal relationship between the patient’s medications and the development of CMV pneumonia, azathioprine was discontinued, and prednisone was quickly reduced to 10 mg/day. Induction therapy with ganciclovir was administered intravenously at a dose of 5 mg/kg twice a day.

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**Table 1. Laboratory results of the patient on admissions.**

|                      | First time admission | Second time admission |
|----------------------|---------------------|-----------------------|
| **Blood**            |                     |                       |
| Nitrogen of urea (mmol/L) | 21.49              | 14.94                 |
| Creatinine (μmol/L)  | 466.0               | 109.9                 |
| Uric acid (μmol/L)   | 559.0               | 224                   |
| WBC (×10⁹/L)         | 5.5                 | 3.2                   |
| Lymphocyte (%)       | 11.1                | 4.0                   |
| Neutrophil (%)       | 81.5                | 91.3                  |
| Albumin (g/L)        | 24.4                | 32.9                  |
| CRP (mg/L)           | 4.7                 | 35.87                 |
| AKP (U/L)            | 344                 | 347                   |
| γ-GT (U/L)           | 146                 | 696                   |
| ALT (U/L)            | 32                  | 36                    |
| AST (U/L)            | 14                  | 45                    |
| TG (mmol/L)          | 2.90                | 1.85                  |
| TCh (mmol/L)         | 7.40                | 5.21                  |
| **Urine**            |                     |                       |
| 24 hours proteinuria (g/24 h) | 3.65              | 0.85                  |
| Urine volume (ml)    | 500                 | 1800                  |

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However, after 1 week of treatment, the patient required intubation and was transferred to the Intensive Care Unit (ICU). Her condition was complicated by acute respiratory distress syndrome and bacterial pneumonia, and she died of respiratory failure after transfer to the ICU.

Figure 1. Electron microscopy of kidney tissue. Electron microscopy shows diffuse effacement of foot processes of podocytes, with normal mesangial cellularity and matrix, and normal thickness of the glomerular basement membrane.

Figure 2. Cytomegalovirus-induced lingual ulcers.

Figure 3. CT scan of the chest obtained at the second admission. CT scans of the chest at the second admission, show bilateral patchy areas of ground-glass opacity with crazy paving appearance and bilateral pleural effusion.

Figure 4. Immunohistochemical staining of CMV in (A) renal tubules of the patient compared with (B) control tissue from the kidney of a normal person shows CMV positivity in the tubules of the patients.
Discussion

Cytomegalovirus is a unique virus, and primary exposure to CMV can occur at an early age. It is rare for immunocompetent individuals to manifest signs of CMV infections. Adult-onset infection mainly occurs due to primary infection, reinfection, or activation of a latent infection. Azathioprine is a prodrug converted in the liver to 6-mercaptopurine, and, via further metabolic steps, is converted to the biologically active metabolite 6-thioguanine nucleotide (6-TGN) [6]. Purine synthesis is inhibited, and the proliferation of T and B lymphocytes are prevented as well [7]. As a result, immunosuppression is induced by azathioprine. Thus, patients with long-term azathioprine intake are more susceptible to developing CMV infections in the late stage.

It has been widely reported that patients with inflammatory bowel disease who are receiving azathioprine treatment are susceptible to CMV infection [8-11]. A systemic review of CMV pneumonia in patients with inflammatory bowel disease found that thiopurines carry a disproportionately higher risk of viral infection reactivation, particularly CMV [12].

Furthermore, CMV infection can present in various ways. Besides CMV pneumonitis, several case reports showed that immunosuppressive therapy might have a role in development of CMV retinitis [13,14], as well as thrombocytopenia [15], myalgia [16], arthralgia [17,18], hepatitis [19], pericarditis [20], or gastrointestinal [8,10] and neurological disorders [19,21], and even oral ulcers [22,23]. In some rare cases, CMV infection also presents as nephrotic syndrome. It was reported [24] that a 5-month-old infant in whom genetic mutations were diagnosed with CMV infection. Antiviral treatment leads to a complete remission of the nephrotic syndrome. Moreover, CMV infection can cause FSGS, especially collapsing FSGS, both in immune-competent patients [25-27] and in renal transplant recipients [28-30]. A prevalence of 1.2% for CMV nephritis in kidney transplant patients was also reported, mainly characterized by tubule-interstitial nephritis [31]. In the diagnosis of the present patient, we could not rule out the possibilities of FSGS, owing to low numbers of glomeruli in the biopsy (only 5 glomeruli were counted in the renal tissue). This may also explain why we did not observe anti-CMV-positive staining in the 5 glomeruli in the renal tissue.

Regarding this patient’s treatment, without considering CMV infection-induced nephrotic syndrome at the beginning, we directly added steroids to azathioprine, which further suppressed the immune system and exacerbated the CMV infection. Thus, in the late stage of the disease, the patient manifested CMV pneumonia and oral ulcers. We withdrew immune-suppression drugs immediately and initiated intravenous ganciclovir treatment. However, the patient’s condition deteriorated, and she eventually died of respiratory failure. Although intravenous ganciclovir has long been regarded as the criterion standard for treating severe CMV infection, the antiviral treatment in our patient seemed to be ineffective. Studies have demonstrated that mutations in CMV UL97, which encode viral kinase, are associated with ganciclovir resistance [32]. Mutations in UL54, which encodes for CMV DNA polymerase, confer resistance (or cross-resistance) to ganciclovir, cidofovir, and/or foscarnet [33]. New drugs and vaccines are being developed to treat mutated CMV.

From a clinical perspective, it is essential to keep in mind that, in some instances, apparently nephrotic syndrome represents a lesion arising secondary to an extraglomerular disease process. Thus, patients should be thoroughly evaluated for potential underlying diseases, particularly neoplasia and drug exposure, when atypical features are present (such as weight loss, anorexia, lymphadenopathy, or acute renal failure) [34]. Routine screening of CMV serology before initiating treatment should be highly recommended for patients with nephrotic syndrome, especially those receiving azathioprine treatment.

Conclusions

This case report should serve as a reminder of a rare but potentially life-threatening condition that can occur in patients who receive immunosuppressive treatment, especially thiopurines. Early diagnosis is crucial owing to the condition’s high mortality rate, and the failure to appropriately diagnose and treat these patients promptly can lead to significant morbidity and mortality.

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