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A Diagnostic Odyssey: Successfully Treated Cytomegalovirus-Induced Immunodeficiency with Tuberculosis Coinfection Presenting as Fever of Unknown Origin in a Young Male

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Abstract

Background: Fever of unknown origin (FUO) in tuberculosis-endemic regions presents a significant diagnostic challenge. This complexity is heightened when concurrent infections and immune dysregulation, such as that caused by cytomegalovirus (CMV), confound the clinical picture and mimic other immunodeficiency states. **Case Presentation:** A previously healthy 20-year-old Filipino male presented with a three-week history of intermittent fever, malaise, and left cervical lymphadenopathy. An extensive workup for common infectious, autoimmune and malignant causes was unrevealing. However, laboratory testing revealed CMV viremia (463 copies/mL) with $CD4^+$ T cell lymphopenia (332 cells/μL), despite a negative HIV evaluation. An excisional lymph node biopsy confirmed rifampicin-sensitive *Mycobacterium tuberculosis*, while bacterial culture also yielded *Enterobacter cloacae*. The patient received sequential antibacterials, then two weeks of valganciclovir—resulting in CMV clearance (undetectable viral load) and $CD4^+$ T cell recovery (661 cells/μL). A follow-up examination four months later confirmed sustained CMV clearance and normal $CD4^+$ T cell count (695 cells/μL). Anti-tuberculosis therapy, complicated by a drug-induced rash but successfully rechallenged, was completed with excellent tolerance and full clinical recovery. **Conclusion:** This case illustrates the diagnostic complexity of FUO in endemic areas, highlighting how CMV-induced immunosuppression, even in immunocompetent individuals, can mimic HIV infection and predispose to opportunistic coinfection. Careful evaluation and thorough infectious workup were pivotal in achieving diagnostic clarity and therapeutic success.

Keywords

Cytomegalovirus, *Mycobacterium tuberculosis*, Immunosuppression

1. Introduction

Fever of unknown origin (FUO) remains a challenging clinical entity, first formally defined by Petersdorf and Beeson in 1961 as fever more than 38.3˚C on several occasions, exceeding three weeks in duration, with no diagnosis established after one week of inpatient evaluation [1]. Although diagnostic modalities have since evolved, FUO continues to represent a complex clinical puzzle, with the majority of cases attributable to infections, malignancies, autoimmune conditions, or miscellaneous causes [2]. In tuberculosis-endemic regions such as the Philippines, extrapulmonary tuberculosis is a frequent culprit, with tuberculous lymphadenitis representing the most common manifestation [3]. Because its presentation is often indolent and nonspecific, differentiation from other infectious, malignant, or autoimmune conditions requires a high index of suspicion and histopathologic confirmation.

Cytomegalovirus (CMV), a ubiquitous β-herpesvirus, has traditionally been associated with opportunistic infections in immunocompromised individuals such as transplant recipients, patients on immunosuppressive therapy, and people living with HIV [4]. However, recent evidence highlights that CMV can also cause clinically significant disease in immunocompetent hosts, ranging from mononucleosis-like illness to severe organ-specific involvement [5]. Importantly, CMV has been implicated in immune dysregulation, with studies showing its capacity to suppress $CD4^+$ T cell responses via impaired antigen presentation and direct inhibition of T cell proliferation [6]. This immunomodulatory effect can mimic early HIV infection and contribute to increased susceptibility to secondary infections.

Here, we present a case of a previously healthy young adult who developed FUO, transient $CD4^+$ T cell lymphopenia, and concurrent CMV viremia, ultimately found to have tuberculous lymphadenitis. This case underscores the diagnostic complexity of FUO in endemic areas and illustrates how CMV-induced immune dysregulation may confound the evaluation of immunodeficiency in HIV-negative patients.

2. Case Presentation

A 20-year-old Filipino male college student, who had been previously well and asymptomatic, presented with a three-week history of intermittent fever, headache, and malaise. Two days prior to admission, he developed chills and a painful, non-erythematous left cervical lymphadenopathy. His symptoms persisted despite self-medication with analgesics.

The patient had no prior history of tuberculosis, immunodeficiency, diabetes mellitus, or other chronic illnesses. He reported no history of smoking, alcohol use, or recreational drug use, and denied the use of immunosuppressive medications. He denied high-risk sexual activity, having only one non-penetrative male partner. Family history was notable for diabetes mellitus and hypertension.

On physical examination, a solitary, non-erythematous, firm, mobile, and tender lymph node was palpated in the left posterior cervical region. No hepatosplenomegaly or cardiorespiratory abnormalities were appreciated. Vital signs were stable, but the patient continued to report fever and decreased physical stamina. The remainder of the systemic examination was unremarkable.

Initial laboratory evaluation showed a normal white blood cell count with lymphocytosis. Procalcitonin was normal. Serum electrolytes, transaminases, and creatinine were within normal limits. Thyroid function was normal. Screening for hepatitis viruses, dengue, chikungunya, malaria, and SARS-CoV-2 were negative. Urinalysis showed bacteriuria; however, both blood and urine cultures were sterile. Anti-dsDNA, ANA, and interferon-gamma release assay (IGRA) were non-reactive. Syphilis (RPR), cryptococcal antigen (CALAS), serum toxoplasma IgG, and EBV DNA viral load were negative. CMV DNA viral load was detected at 463 copies/mL, with a $CD4^+$ T cell count of 332 cells/μL, despite negative HIV antigen/antibody and HIV RNA viral load testing.

Chest radiograph and chest CT scan showed no pulmonary infiltrates, masses, effusion, or suspicious mediastinal lymphadenopathy. Abdominal ultrasound was unremarkable. Neck ultrasound demonstrated an enlarged left cervical (IB) lymph node measuring 1.8 × 1.5 cm. Echocardiography excluded valvular vegetations.

Given the broad differential diagnosis—including infection (bacterial, mycobacterial, viral, and fungal), hematologic malignancies, and metastatic carcinoma—histopathologic evaluation was deemed essential. Excisional biopsy of the cervical lymph node revealed chronic inflammation, with tissue Xpert showing rifampicin-sensitive *Mycobacterium tuberculosis*—confirming mycobacterial etiology and strengthening diagnostic certainty. Lymph node bacterial culture yielded *Enterobacter cloacae*. Fungal culture was negative.

The patient was initially started on ceftriaxone but developed an allergic reaction, prompting a switch to piperacillin-tazobactam. He was discharged on levofloxacin and later commenced on valganciclovir 900 mg twice daily for two weeks, after which CMV viral load became undetectable and $CD4^+$ T cell count improved to 661 cells/μL. A follow-up examination four months later confirmed sustained CMV clearance and normal $CD4^+$ T cell count (695 cells/μL).

Anti-tuberculosis therapy was subsequently initiated; however, he developed a drug-related morbilliform rash. A structured drug rechallenge allowed successful continuation of therapy, which he completed for 6 months without further adverse events. Treatment adherence was monitored via clinic follow-up and patient self-report, with overall excellent treatment tolerance (**Figure 1**).

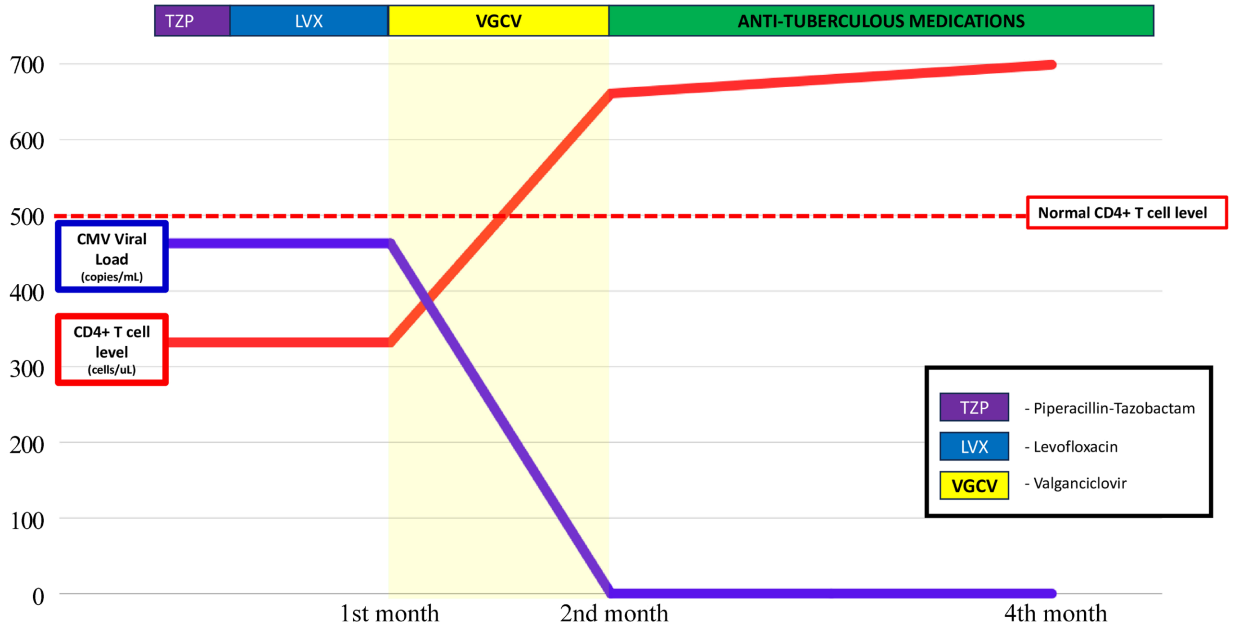

Figure 1. Timeline of antimicrobial therapy and trends of CD4⁺ T cell count and CMV viral load.

3. Discussion

The complex nature of FUO in young adults presents significant diagnostic challenges that require careful consideration of various etiological factors. One such factor is CMV viremia, which has been less frequently recognized as a cause of FUO, particularly in immunocompetent populations [2].

While CMV infection can manifest with nonspecific symptoms like fever and fatigue, its clinical presentation can mimic other infectious diseases, complicating the diagnostic process [5]. Incorporating detailed patient history and appropriate laboratory evaluations, including blood cultures and serological tests for CMV, is essential in identifying the underlying cause of FUO [2]. Given the transient nature of CD4⁺ T cell lymphopenia observed in this case, an understanding of the immunopathogenic mechanisms is critical to differentiate between opportunistic infections and reactive inflammatory processes.

This case underscores the underrecognized capacity of CMV to induce clinically significant immunosuppression even in ostensibly immunocompetent individuals. Although CMV is often regarded as a latent virus of little consequence outside immunocompromised hosts, reactivation of this viral infection has been shown to cause profound immune dysregulation [7]. In our patient, the striking decline in CD4⁺ T cell count despite negative HIV testing illustrates this phenomenon. Prior studies have demonstrated that CMV interferes with host immunity through multiple mechanisms, including downregulation of antigen presentation [8], impairment of dendritic cell function [9], and direct suppression of T cell proliferation and survival [6]. These mechanisms were implicated in the development of secondary immune deficiency in CMV infection [10]. The subsequent recovery of CD4⁺ T cell count following valganciclovir therapy strongly supports

CMV as the driver of immune dysfunction in this case (Figure 2).

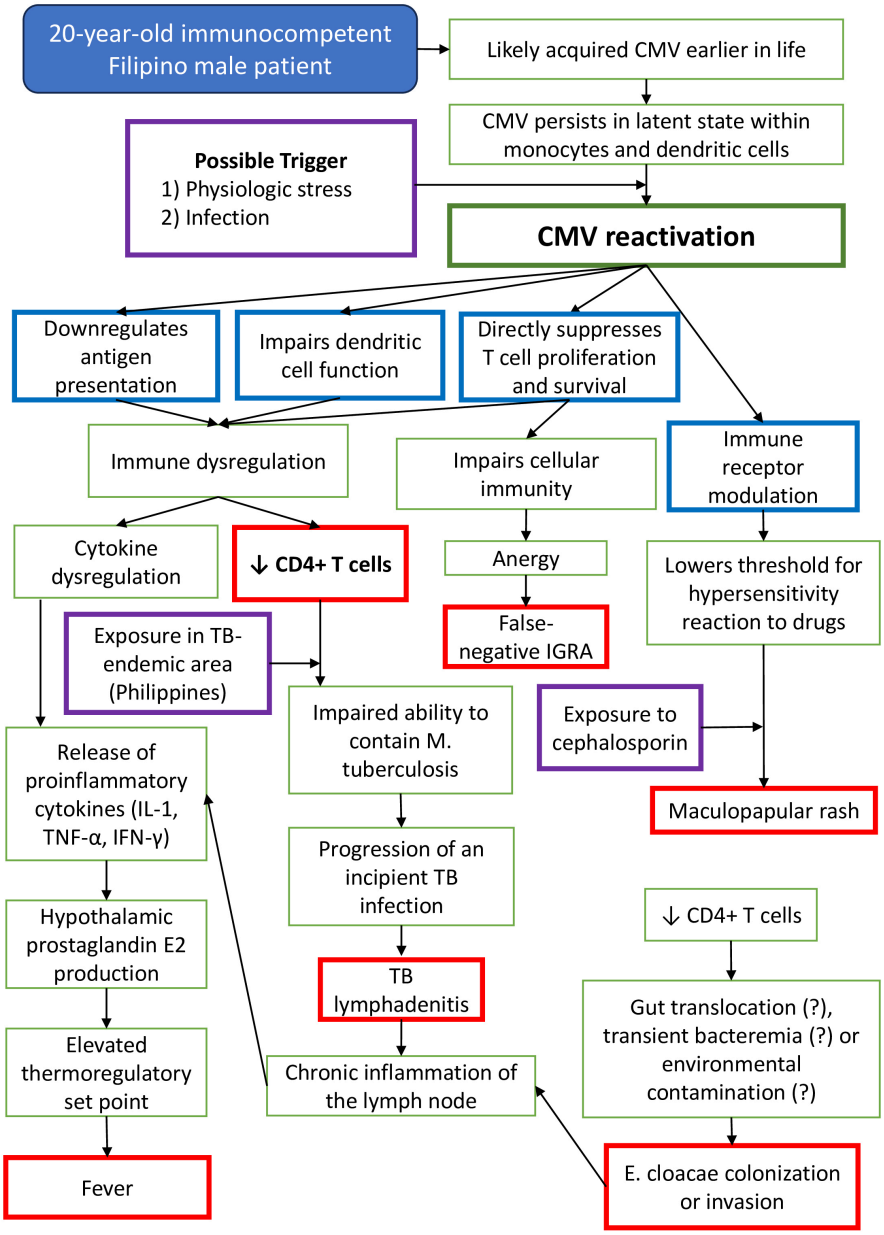

Figure 2. Concept map.

Recent research further substantiates the role of CMV in modulating immune responses among non-HIV, non-transplant individuals. In 2021, Zhang and colleagues demonstrated that CMV serostatus independently influences $CD4^+$ T cell differentiation, driving an accelerated shift toward effector-memory and terminally differentiated phenotypes even in immunocompetent adults. This skewing of the T cell pool results in reduced proliferative capacity and impaired immune surveillance, predisposing to opportunistic infections and delayed immune recovery [11]. Complementing these findings, Gadoth and colleagues, in 2024, reviewed

multiple observational studies linking CMV persistence to features of immunosenescence—including T cell exhaustion, chronic inflammatory activation, and dysregulated cytokine signaling—in otherwise healthy populations [12]. Together, these data highlight how CMV infection exerts long-term, systemic immune effects beyond classical immunocompromised contexts. In our patient, the transient $CD4^+$ T cell lymphopenia and enhanced susceptibility to *Mycobacterium tuberculosis* may thus represent a manifestation of this broader CMV-driven immune modulation.

Although the patient's CMV DNA level (463 copies/mL) was below traditional thresholds used to guide therapy in immunocompromised populations, antiviral therapy was justified given the symptomatic viremia, concurrent $CD4^+$ T cell lymphopenia, and the exclusion of other causes of immunosuppression. Recent evidence demonstrated that CMV reactivation, regardless of viral load magnitude, was independently associated with prolonged hospitalization and increased mortality in non-immunocompromised patients, while antiviral treatment was linked to improved long-term outcomes [13]. This supports early therapeutic intervention even in low-level viremia when accompanied by clinical and immunologic abnormalities. Hence, the decision to treat our patient was guided by both his symptomatic presentation and the potential for ongoing CMV-driven immune suppression.

The choice of valganciclovir 900 mg twice daily reflects the established induction dose used for treatment of CMV disease, while the two-week total duration was guided by contemporary management perspectives for non-immunocompromised patients. In 2024, Bhide and colleagues emphasized that short-course therapy (2 - 3 weeks) with valganciclovir is appropriate when there is prompt clinical improvement and virologic clearance, minimizing the risks of drug-induced cytopenia and nephrotoxicity while achieving effective viral suppression [14]. In this patient, the two-week regimen resulted in undetectable CMV DNA and normalization of $CD4^+$ T cell count, supporting adequacy of the chosen duration.

The occurrence of transient $CD4^+$ T cell lymphopenia introduces additional complexity, especially in the context of infections like tuberculosis. The immunologic perturbation caused by CMV likely created a permissive environment for tuberculous lymphadenitis to emerge. Tuberculosis is well recognized to exploit weakened cellular immunity, and suppression of $CD4^+$ T cell activity—whether from HIV or alternative causes—facilitates reactivation or primary infection [15]. In HIV-negative individuals, such an opportunistic presentation can be diagnostically misleading, delaying timely recognition and treatment. This overlap highlights how CMV reactivation can mimic the immunosuppressive phenotype of HIV infection, producing diagnostic uncertainty in cases of fever of unknown origin.

The negative IGRA result in this patient can be plausibly explained by the immunomodulatory effects of CMV infection. IGRA relies on $CD4^+$ T cells recognizing *Mycobacterium tuberculosis*—specific antigens and releasing interferon-gamma [16], but in this case the patient demonstrated transient CD4 lymphopenia

(332 cells/μL), suggesting impaired T cell function. This impaired cellular immunity may explain anergy and false-negative result of IGRA [17]. Thus, CMV-induced immunosuppression likely contributed to the discordant negative IGRA finding in this case, despite histopathologic and microbiologic confirmation of tuberculous lymphadenitis.

The additional finding of *Enterobacter cloacae* in lymph node culture further complicated interpretation, raising questions of superimposed bacterial infection versus contamination. While its role in pathogenesis remains uncertain, the presence of this bacterial isolate underscores how secondary bacterial signals can obscure the primary etiology in the setting of virus-induced immune dysfunction. The *Enterobacter cloacae* isolate was susceptible to fluoroquinolones and third-generation cephalosporins, and the patient completed a 14-day course of oral levofloxacin with resolution of local tenderness. Given its single isolation and absence of systemic bacteremia, contamination could not be ruled out, but transient bacterial lymphadenitis secondary to viral immune suppression remained plausible. Importantly, the patient's improvement with antiviral therapy, subsequent immune recovery, and eventual resolution of symptoms with anti-tuberculous therapy collectively emphasize that CMV-induced immunosuppression was the pivotal event that unmasked latent or incipient tuberculosis.

During admission, the patient was initially started on ceftriaxone but was later shifted to piperacillin-tazobactam due to the development of a cutaneous drug reaction. Although there is no direct evidence linking cytomegalovirus (CMV) infection to cephalosporin-induced hypersensitivity, viral infections such as CMV have been shown to increase susceptibility to drug-induced delayed hypersensitivity reactions through mechanisms involving immune receptor modulation and T-cell activation [18]. Viral infections can act as immunologic triggers, lowering the threshold for hypersensitivity reactions to drugs and thereby facilitating the development of manifestations such as a maculopapular rash [18]. In this context, the rash is not considered a direct cytopathic effect of CMV but rather an indirect outcome of virus-induced immune activation that predisposes the host to heightened drug reactivity.

Overall, this case highlights CMV not merely as a bystander but as an active driver of transient immunodeficiency with tangible clinical consequences. While the temporal relationship between CMV clearance and $CD4^+$ T cell recovery suggests a causal link, this association remains inferential. In tuberculosis-endemic regions, clinicians should maintain a high index of suspicion for CMV-related immune modulation when evaluating HIV-negative patients presenting with fever of unknown origin and lymphadenitis. Awareness of this interaction is crucial to prevent diagnostic delay and to ensure both viral and opportunistic processes are adequately addressed.

4. Conclusion

This case underscores the intricate interplay between CMV-induced immune per-

turbation and tuberculosis in an immunocompetent young adult presenting with FUO. It highlights the importance of maintaining a broad differential, including extrapulmonary TB and viral reactivation, even in HIV-negative patients. CMV may transiently suppress $CD4^+$ T cell level and mimic early immunodeficiency, delaying recognition of coinfections. Histopathologic confirmation and molecular diagnostics remain essential. Careful evaluation and thorough infectious workup were pivotal in achieving diagnostic clarity and therapeutic success.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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