Case Report

Reactivation of Latent Tuberculosis in a Patient with COVID-19 and Epstein-Barr Virus Coinfection: A Case Report

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Reactivation of Latent Tuberculosis in a Patient with COVID-19 and Epstein-Barr Virus Coinfection: A Case Report

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Abstract: We describe the case of a 24-year-old woman who developed a swelling under her collarbone, along with fever, swollen lymph nodes, tiredness, and weight loss. These symptoms started about three months after she had a moderate COVID-19 infection. Blood tests showed a high white blood cell count, with more neutrophils and fewer lymphocytes, as well as high levels of inflammation markers. Serological and molecular diagnostics confirmed Epstein-Barr virus (EBV) reactivation.. Despite receiving antiviral and supportive treatment, her condition worsened. Advanced imaging showed that her lymph nodes remained swollen and started to break down. Doctors ruled out other possible causes, such as bacterial infections, blood cancers, autoimmune diseases, and cancer spread. A needle biopsy, combined with a special genetic test (PCR), confirmed the presence of *Mycobacterium tuberculosis*, the bacteria that cause tuberculosis. She started a standard tuberculosis treatment, which led to major improvement within two months. Her swollen lymph nodes shrank, and her inflammation markers returned to normal. This case shows how COVID-19-related immune system changes, EBV reactivation, and tuberculosis infection can be connected. It highlights the need for careful monitoring of patients with long-lasting swollen lymph nodes, especially those with weakened immune systems.

Keywords: COVID-19; Epstein-Barr virus; Mycobacterium tuberculosis; lymphopenia; lymphadenopathy; scrofuloderma

1. Introduction

Tuberculous lymphadenitis (scrofuloderma) is the most common form of extrapulmonary tuberculosis, presenting as chronic lymphadenopathy that can mimic a wide range of infectious, autoimmune, and neoplastic diseases [1,2]. The diagnostic challenge is further compounded by overlapping clinical manifestations with systemic illnesses, particularly viral infections such as COVID-19 and Epstein-Barr virus (EBV) [3–5]. Both viruses can cause prolonged lymphadenopathy, immune dysfunction, and lymphopenia, complicating the determination of the underlying etiology [6,7].

EBV is a well-known trigger of lymphoproliferative disorders and can cause infectious mononucleosis, characterized by generalized lymphadenopathy, hepatosplenomegaly, and immune disturbances [8,9]. At the same time, COVID-19, beyond its respiratory manifestations, has been

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associated with persistent immune alterations, including lymphocyte depletion, which may increase susceptibility to secondary bacterial and mycobacterial infections [10–13].

Given the epidemiological significance of tuberculosis and the growing role of viral infections in immune system modulation, maintaining a high level of clinical suspicion is crucial when evaluating patients with persistent lymphadenopathy [14,15]. In this context, timely differential diagnosis between tuberculous lymphadenitis, viral infections, and other systemic diseases is essential for appropriate treatment and improved patient outcomes [16,17].

2. Case Description

2.1. Clinical Manifestations and Disease Course

A 24-year-old female presented with an acutely developed subclavicular mass that had appeared two days prior to consultation. The lesion was raised above the skin surface, exhibited a bluish discoloration, and was associated with mild tenderness (**Figure 1**). In addition to the mass, the patient reported persistent low-grade fever, generalized lymphadenopathy, fatigue, rapid fatigability, reduced work capacity, unintentional weight loss, and excessive night sweating, which had been ongoing for the past three months.

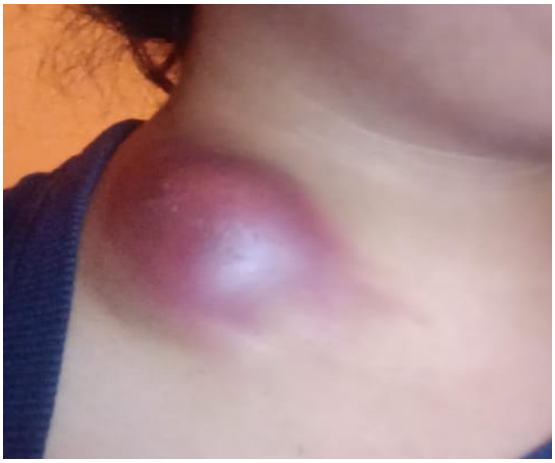

Figure 1. Acute Subcutaneous Inflammatory Mass in the Neck Region.

The patient had a documented history of COVID-19 three months prior, classified as a moderate-severity case with significant respiratory involvement, including acute respiratory distress syndrome and pneumonia without respiratory failure, confirmed by PCR testing. The results of the conducted complete blood count show an increase in the level of leukocytes, particularly neutrophils, and a decrease in the level of lymphocytes. Elevated levels of ESR, C-reactive protein, procalcitonin, D-dimer, and ferritin are also observed (**Table 1**). She received a treatment regimen consisting of Paxlovid (nirmatrelvir 300 mg + ritonavir 100 mg twice daily for five days), azithromycin (500 mg daily for three days), and dexamethasone (6 mg daily for ten days), which initially led to clinical improvement. However, after completing the therapy, the patient developed lymphadenopathy, which was accompanied by generalized weakness, rapid fatigability, and low-grade fever.

A comprehensive differential diagnosis was conducted to exclude infectious causes, including viral hepatitis (HBV, HCV), HIV, cytomegalovirus (CMV), and EBV. Serological and molecular testing for most infections returned negative results, except for EBV, which was confirmed through the detection of IgM and IgG to EBV VCA, EBV DNA via PCR, and elevated IgG to EBV EA, indicating active viral replication and reactivation.

Based on the diagnosis, the patient was prescribed antiviral therapy with acyclovir (400 mg five times daily for ten days) and symptomatic treatment, including paracetamol (500–1000 mg every 6–8 hours as needed) or ibuprofen (200–400 mg every 6–8 hours as needed) to manage fever, general

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malaise, and discomfort associated with lymphadenopathy. Although there was some improvement in the patient's condition, signs of lymphadenopathy remained present.

Table 1. Dynamics of Laboratory Parameters in the Patien.

Parameter	Normal Range	Before Diagnosis	After Initial Treatment	Worsening Symptoms	After Tuberculosis Treatment
Hemoglobin (g/L)	120–160	118	110	102	115
Erythrocytes (×10⁹/L)	3.8–5.2	3.7	3.5	3.2	3.6
Hematocrit (%)	36–46	35	33	31	34
Leukocytes (×10⁹/L)	4.0–9.0	9.8	11.2	12.5	10.3
Neutrophils (%)	40–75	78	82	85	76
Lymphocytes (%)	20–45	15	12	9	14
Monocytes (%)	2–10	2	1.6	1.5	1.8
Eosinophils (%)	1–6	0.5	0.5	0.2	0.8
Basophils (%)	0–1	0.5	0.3	0.2	0.4
ESR (mm/h)	< 20	25	32	40	28
C-reactive protein (mg/L)	< 5	12	18	24	10
Procalcitonin (ng/mL)	< 0.5	0.8	1.2	1.5	0.6
D-dimer (μg/mL)	< 0.5	1.5	2.3	2.8	1.1
Ferritin (ng/mL)	30–400	450	500	550	470

Approximately one month after completing treatment, symptoms of lymphadenopathy persisted, primarily affecting the cervical and supraclavicular regions bilaterally. The enlarged lymph nodes were firm, non-tender, and mobile, with some forming clusters. Additionally, the patient reported a sensation of pressure in the affected areas, though without significant pain.

The results of the complete blood count showed continued inflammation and some deterioration in the patient's condition. Hemoglobin and erythrocyte levels decreased, indicating worsening anemia, while hematocrit also dropped. Leukocytes remained elevated, with a higher proportion of neutrophils, suggesting ongoing inflammation. Lymphocytes decreased further, reflecting immune system alterations. Monocytes and eosinophils were slightly reduced, and basophils remained low. ESR and C-reactive protein increased, indicating active inflammation. Procalcitonin and D-dimer levels rose, suggesting possible bacterial infection or coagulation issues, while ferritin continued to rise, aligning with the inflammatory process (**Table 1**).

The ultrasound revealed bilateral, enlarged, hypoechoic lymph nodes, increased peripheral vascularity, and clustered distribution in the cervical and supraclavicular regions, without significant cystic changes or abscess formation.

The immunogram results show a decrease in CD4+ T lymphocytes, CD8+ T lymphocytes, B lymphocytes, and NK cells. Complement C4 was below the normal range, while C3 remained within normal levels. IgG and IgM levels were at the lower end of the normal range, and IgA was also reduced. IgE level was normal (**Table 2**).

Due to persistent symptoms, the patient underwent repeat testing, including for viral hepatitis (HBV, HCV), HIV, CMV, and EBV. The results confirmed the absence of any new infectious agents. However, they revealed elevated levels of IgG antibodies to EBV VCA and EBV EA. The IgM to EBV VCA remained low, suggesting the absence of an acute phase of the infection. Additionally, the levels of IgG to EBV VCA were elevated, but the negative PCR result for EBV DNA indicates the absence of ongoing viral replication, suggesting a latent or reactivated infection in a chronic state. Furthermore, a high titer of IgG antibodies to SARS-CoV-2 was detected, indicating a past infection and a sustained immune response to the virus.

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Table 2. Immunological Profile Changes in the Patient.

Pameter	Normal Range	After Initial Treatment	Worsening Symptoms	After Tuberculosis Treatment
CD4+ T lymphocytes (%)	30–60	25	20	30
CD8+ T lymphocytes (%)	15–35	14	12	18
B lymphocytes (%)	5–20	3	2	5
NK cells (%)	5–15	4	4	6
Complement C4 (mg/dL)	18–40	10	8	15
Complement C3 (mg/dL)	90–180	110	100	130
Immunoglobulin G (IgG, Serum) (g/L)	7–16	7.0	6.8	7.8
Immunoglobulin M (IgM, Serum) (g/L)	0.4–2.3	0.6	0.8	0.7
Immunoglobulin A (IgA, Serum) (g/L)	0.7–4.0	1.1	0.9	1.3
Immunoglobulin E (IgE, Total, Serum) (IU/mL)	<100	80	78	73

The patient was prescribed non-steroidal anti-inflammatory drugs to alleviate symptoms, including fever reduction, general discomfort, and pain relief. Paracetamol was administered at a dose of 500–1000 mg every 6–8 hours as needed, while ibuprofen was given at a dose of 200–400 mg every 6–8 hours as needed.

The patient experienced a slight improvement following the administration of nonsteroidal anti-inflammatory drugs; however, lymphadenopathy symptoms persisted. Approximately one month after NSAID use and nearly three months post-COVID-19 infection, her condition worsened, characterized by pronounced weakness, excessive sweating, and decreased functional capacity. Additionally, a supraclavicular mass emerged, leading her to seek medical evaluation.

The results of the complete blood count and biochemical markers showed a decrease in hemoglobin, erythrocytes, and hematocrit levels. Leukocyte count, particularly neutrophils, was elevated, while lymphocyte percentage decreased. ESR, C-reactive protein, procalcitonin, and ferritin levels were elevated (**Table 1**).

The results of the immunogram showed a decrease in CD4+ T lymphocytes, CD8+ T lymphocytes, and B lymphocytes, while NK cells remained low. Complement C4 and C3 levels were further reduced. IgG level remained low, while IgM slightly increased. IgA level decreased, and IgE level was normal (**Table 2**).

The performed computed tomography (CT) revealed a subcutaneous fluid collection in the left supraclavicular region, external to the sternocleidomastoid muscle. The lesion was irregular in shape, encapsulated (capsule thickness 2–4 mm), and exhibited active contrast enhancement, measuring 49 × 28.7 × 35.5 mm. The surrounding tissues showed moderate infiltration with hypervascular supraclavicular lymph nodes. Enlarged left supraclavicular and lower jugular lymph nodes (up to 12 mm in short axis) were observed with poorly defined contours. Chest CT revealed enlarged paratracheal (level 4R, up to 30 mm) and subcarinal (level 7, up to 15.8 mm) lymph nodes, showing heterogeneous contrast enhancement with necrotic areas and indistinct margins. No lung infiltrates, pleural effusion, or mediastinal masses were detected. Abdominal and pelvic CT showed no free fluid, no pathological lymphadenopathy, and no significant organ abnormalities. The liver, spleen, pancreas, adrenal glands, kidneys, gastrointestinal tract, and major vessels were unremarkable. The uterus and ovaries appeared normal. No destructive bone changes were noted (**Figure 2**).

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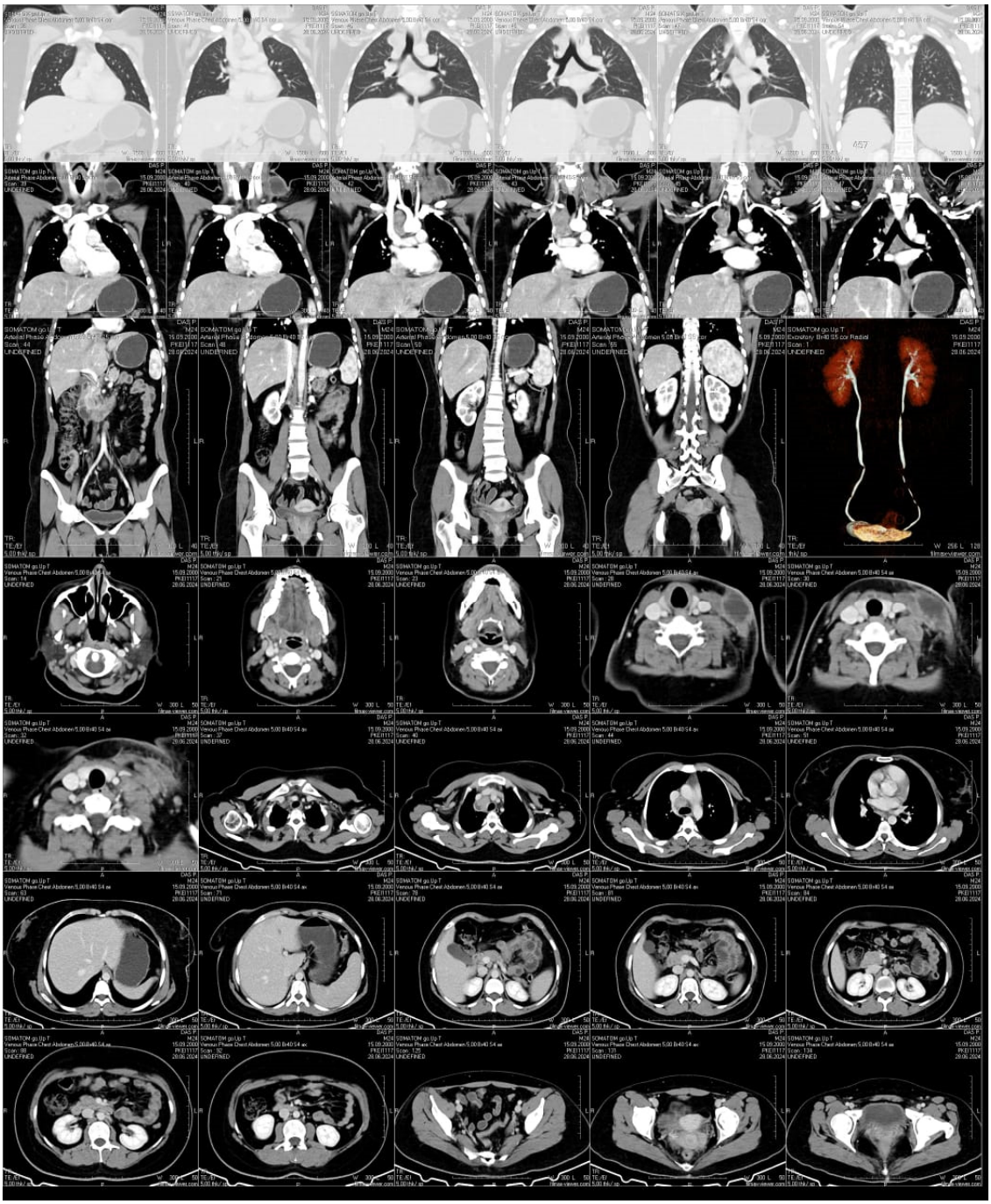

Figure 2. Contrast-Enhanced CT Scan.

A differential diagnosis was conducted to distinguish between several potential conditions, including bacterial infections (such as MRSA-associated carbuncle), hematologic malignancies (Hodgkin's lymphoma, non-Hodgkin's lymphoma, multiple myeloma), hemophagocytic lymphohistiocytosis (HLH), viral infections (HIV, Epstein-Barr virus, cytomegalovirus, and viral hepatitis), autoimmune diseases (such as sarcoidosis and systemic lupus erythematosus), and metastatic malignancies.

Bacterial infections were ruled out based on negative wound cultures, Gram staining, and ultrasound findings that showed no abscess formation. Hematologic malignancies were excluded as PET-CT revealed hypermetabolic supraclavicular and cervical lymph nodes without mediastinal involvement, lymph node biopsy showed no Reed-Sternberg cells (CD30-, CD15-) or clonal plasma cells, and serum electrophoresis detected no monoclonal (M) protein.

HLH was considered unlikely due to only mildly elevated ferritin levels, non-significant soluble CD25 (sIL-2R), normal fibrinogen levels, and the absence of NK-cell dysfunction, as assessed by the

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CD107a degranulation assay. Additionally, lactate dehydrogenase (LDH) levels were not markedly elevated, further reducing the likelihood of HLH.

Viral infections, including HIV, HBV, HCV, and CMV, were ruled out with negative serological and molecular tests. Autoimmune diseases were excluded based on normal angiotensin-converting enzyme (ACE) levels, negative antinuclear antibodies (ANA), and the absence of other systemic inflammatory markers. Metastatic malignancy was ruled out due to negative cytology for malignant cells in lymph node biopsy and PET-CT findings showing no evidence of a primary tumor.

The diagnosis of tuberculous lymphadenitis (scrofuloderma) was confirmed by multiple tests, including fine-needle aspiration cytology (FNAC), which showed granulomatous inflammation with caseous necrosis, and PCR confirmation of *M. tuberculosis* DNA. Additional supportive findings included a strongly positive interferon-gamma release assay (IGRA), elevated adenosine deaminase (ADA) levels in lymph node aspirate, and a positive tuberculin skin test (TST). Chest X-ray and computed tomography (CT) of the thorax showed no evidence of active pulmonary tuberculosis, confirming an extrapulmonary form.

Given the confirmed diagnosis, a standard first-line antituberculosis regimen was initiated. The treatment included an intensive phase of two months, consisting of isoniazid (300 mg once daily), rifampicin (600 mg once daily), pyrazinamide (1500 mg once daily), and ethambutol (1200 mg once daily). To prevent isoniazid-induced peripheral neuropathy, pyridoxine (25–50 mg daily) was added. Following the intensive phase, a continuation phase of isoniazid (300 mg once daily) and rifampicin (600 mg once daily) for at least four additional months was prescribed.

After two months of antituberculosis therapy, the patient underwent a follow-up examination to assess treatment response. Clinically, there was a significant improvement: fatigue, sweating, and lymph node tenderness decreased, and the supraclavicular mass had reduced in size. A repeat CT scan of the neck and chest showed a decrease in lymph node size and resolution of necrotic changes, with no new lesions detected. Laboratory tests, including complete blood count (**Table 1**), liver function tests (ALT, AST, bilirubin), and inflammatory markers (**Table 1**), and immunogram (**Table 2**) showed normalization and improvement. Microbiological reassessment, including PCR and culture of lymph node aspirate, revealed no further mycobacterial growth, indicating a positive response to therapy. The patient continued with the continuation phase of treatment (isoniazid and rifampicin) with ongoing monitoring (**Figure 3**).

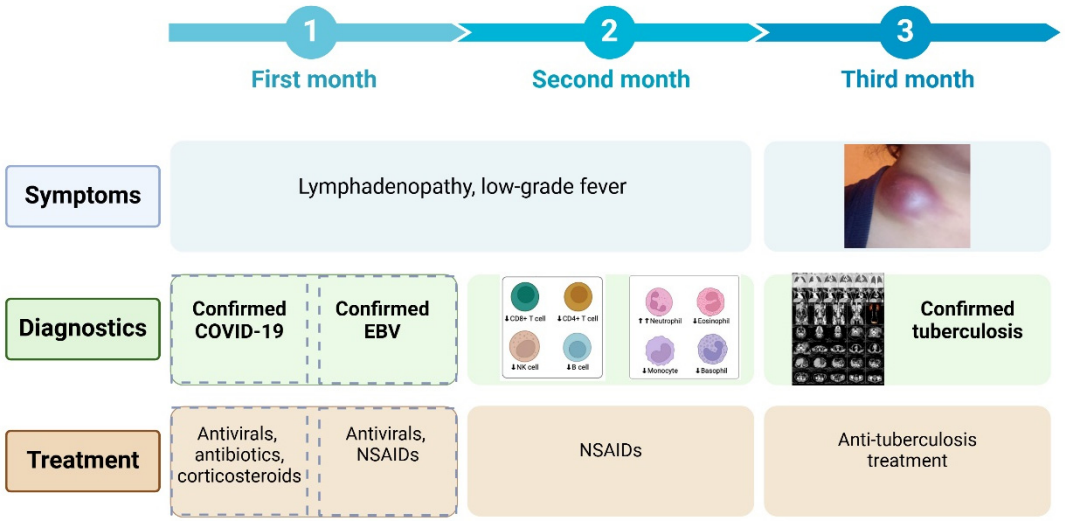

Figure 3. Timeline of symptom progression, diagnostics, and treatment over three months.

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3. Discussion

The co-infection of SARS-CoV-2 and EBV represents a significant immunological challenge, particularly in the context of lymphopenia and its broader implications for immune function (**Figure 4**) [18,19].

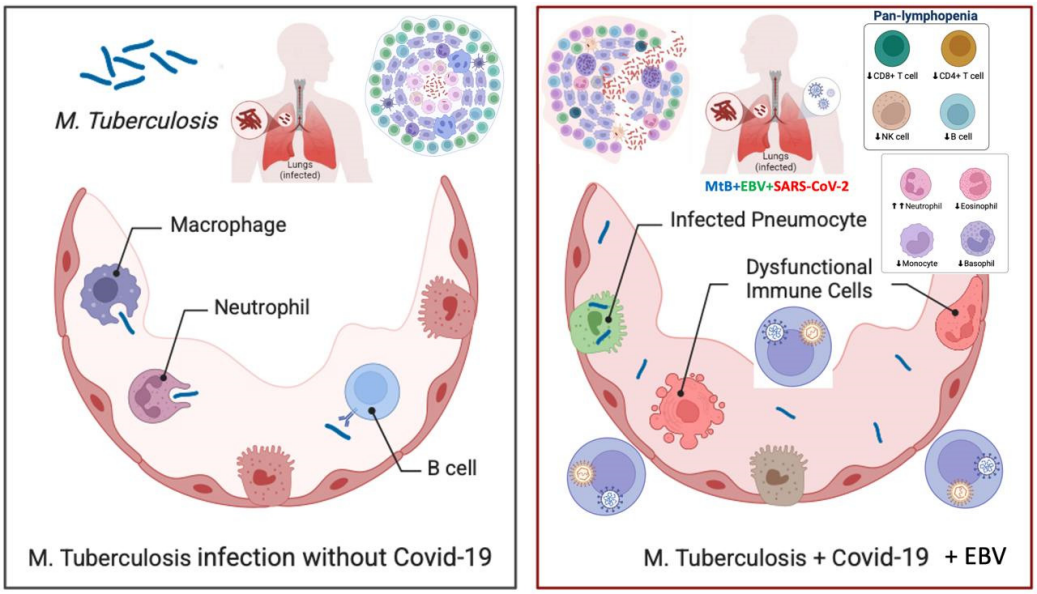

Figure 4. The Impact of SARS-CoV-2 and Epstein-Barr Virus (EBV) Co-Infection on Tuberculosis Progression. The figure compares tuberculosis infection in the absence (left) and presence (right) of SARS-CoV-2 and EBV co-infection. The left panel illustrates an effective immune response against Mycobacterium tuberculosis (M. tuberculosis), where macrophages, neutrophils, and B cells help control the infection. In contrast, the right panel shows how co-infection with SARS-CoV-2 and EBV leads to immune dysfunction, including infected pneumocytes, dysregulated immune cells, and pan-lymphopenia (reduced CD4+ T cells, CD8+ T cells, NK cells, and B cells). This weakened immune defense increases the risk of tuberculosis reactivation and progression, underscoring the need for close monitoring and early intervention in affected patients.

Lymphopenia, characterized by a decreased lymphocyte count, is a well-documented consequence of both SARS-CoV-2 and EBV infections [20–22]. This reduction in lymphocyte levels, particularly CD4+ and CD8+ T cells, can compromise the host's ability to mount an effective immune response, increasing susceptibility to secondary infections and reactivation of latent pathogens, including Mycobacterium tuberculosis [23–25]. It is crucial to consider the genetic predisposition of patients, as host genetic factors can influence immune resilience, susceptibility to infections, the reactivation of latent pathogens such as Mycobacterium tuberculosis, the severity of COVID-19, and the efficacy of antiviral therapy [26–28].

SARS-CoV-2 infection has been associated with a profound alteration of the immune system, including excessive inflammatory responses and cytokine dysregulation [29,30]. Severe COVID-19 cases often present with cytokine storm syndromes, where elevated levels of pro-inflammatory cytokines, such as IL-6, TNF-α, and IFN-γ, contribute to systemic inflammation and immune exhaustion [31–33]. Meanwhile, EBV, a herpesvirus with lifelong persistence in the host, is known to establish latency in B cells and periodically reactivate under conditions of immune suppression [34–36]. The interplay between these two viruses may create an immunosuppressive environment that not only prolongs lymphopenia but also diminishes immune surveillance, thereby increasing the likelihood of opportunistic infections [37,38].

Latent tuberculosis (LTB) remains a global health concern, with an estimated one-quarter of the world's population harboring dormant Mycobacterium tuberculosis [39–41]. Under normal immune conditions, latent TB remains controlled by T cell-mediated immunity [42,43]. However, the immune dysregulation caused by SARS-CoV-2 and EBV co-infection may disrupt this balance, reducing the

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ability of the host to contain latent infections and increasing the risk of reactivation [44–46]. Reports have documented cases of tuberculosis emerging after severe COVID-19, supporting the hypothesis that viral infections may act as triggers for TB reactivation [47,48].

Furthermore, the depletion of CD4+ T cells—critical in the defense against tuberculosis—weakens granuloma formation, a key mechanism in TB containment [49,50]. The combined effect of SARS-CoV-2 and EBV on immune homeostasis may accelerate granuloma breakdown, leading to active TB disease [45,51]. This phenomenon highlights the importance of TB screening in patients with prolonged viral illnesses, particularly in endemic regions where LTB is prevalent [52,53].

Given the overlapping clinical manifestations of SARS-CoV-2, EBV, and tuberculosis, early differentiation among these conditions is crucial [54,55]. Patients presenting with prolonged fever, lymphadenopathy, and respiratory symptoms may require extensive workups, including serological, molecular, and microbiological testing, to accurately identify the underlying pathology [56–58]. The potential for co-infections complicates the clinical picture, often delaying appropriate treatment [59–61]. In patients with comorbidities, this challenge is even more pronounced, as underlying conditions may further impair immune responses and influence disease progression [62,63]. Identifying pharmacological agents that can mitigate the impact of co-infections and modulate host immunity remains a critical area of research [64–67].

The administration of immunosuppressive therapies, such as corticosteroids or biologics used to manage severe COVID-19 or post-viral inflammatory syndromes, may further exacerbate TB reactivation risk [47,68]. Clinicians should carefully evaluate immunosuppressive treatment strategies in patients with a history of TB exposure, particularly those with prolonged lymphopenia [69,70]. Additionally, the impact of gut microbiota on immune homeostasis and susceptibility to infections should be considered, as dysbiosis may further modulate the risk of TB reactivation, impaired antiviral responses, and the severity of COVID-19 [71–73]. Furthermore, the presence of comorbidities, such as diabetes mellitus, can exacerbate disease severity, prolong recovery, and complicate the management of both TB and COVID-19 [74–76].

The observed interactions between SARS-CoV-2, EBV, and TB suggest a need for further investigation into the long-term immune consequences of viral co-infections [44,77]. Longitudinal studies assessing immune recovery post-COVID-19, along with TB incidence among previously infected individuals, could provide valuable insights into disease pathogenesis and prevention strategies [78,79].

From a public health perspective, screening for latent TB in individuals recovering from severe viral infections may be warranted, particularly in high-risk populations [80,81]. Enhanced surveillance and early intervention strategies, including preventive TB therapy in selected cases, could help mitigate the impact of viral co-infections on TB reactivation [82–84].

The interplay between SARS-CoV-2, EBV, and tuberculosis presents a complex clinical and immunological challenge [55,85]. Understanding the mechanisms by which viral co-infections contribute to immune suppression and TB reactivation is essential for improving patient management and reducing the burden of post-viral complications [86–88]. Further research is needed to develop targeted approaches for monitoring and treating individuals at risk of TB reactivation in the context of viral-induced immunosuppression.

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