CASE REPORT
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Unraveling a Rare Complication: BCG-associated Brain Abscess in Wiskott–aldrich Syndrome

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ABSTRACT

Wiskott–aldrich syndrome (WAS) is a rare X-linked primary immunodeficiency characterized by thrombocytopenia, eczema, and recurrent infections. Live vaccines, such as Bacillus Calmette–Guérin (BCG), routinely administered in tuberculosis-endemic regions, may cause severe complications in undiagnosed patients.

We report a 2-year-old boy with genetically confirmed WAS who developed a rare BCG-related brain abscess. The patient initially presented with neonatal thrombocytopenia and eczema, followed by recurrent respiratory and gastrointestinal infections. Whole exome sequencing identified a pathogenic mutation in the *WAS* gene. During pre-hematopoietic stem cell transplantation (HSCT) evaluation, brain imaging revealed a large multiloculated right parieto-occipital abscess with significant mass effect. Surgical drainage was performed, and polymerase chain reaction confirmed *Mycobacterium bovis* (BCG strain).

Antitubercular therapy was initiated. Severe thrombocytopenia complicated management and necessitated splenectomy. Although platelet counts improved and infection was partially controlled, HSCT was postponed due to active infection. The patient subsequently died following a severe COVID-19 infection.

This case highlights the diagnostic and therapeutic challenges of BCG-related brain abscess in patients with WAS and underscores the importance of early genetic diagnosis, avoidance of live vaccines, and timely definitive treatment in primary immunodeficiencies.

Keywords: Brain abscess; Mycobacterium bovis; Primary immunodeficiency diseases; Wiskott-aldrich syndrome

INTRODUCTION

Wiskott–Aldrich syndrome (WAS) is an X-linked recessive primary immunodeficiency caused by mutations in the *WAS* gene, resulting in the classical triad of thrombocytopenia, eczema, and recurrent

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infections.[1] Disease severity correlates with WAS protein expression; complete absence leads to severe thrombocytopenia, lymphopenia, and increased malignancy risk, whereas partial expression may present as X-linked thrombocytopenia with milder immune defects.[2,3] The estimated incidence is approximately 1 per 100 000 live births.[4] Due to overlapping clinical manifestations, WAS is often initially misdiagnosed as immune thrombocytopenia (ITP), leukemia, or cow's milk protein allergy.[5]

The profound immunodeficiency in WAS predisposes patients to bacterial, viral, fungal, and opportunistic infections, including complications related to the BCG vaccine (*Mycobacterium bovis*), a live-attenuated vaccine administered at birth in tuberculosis-endemic regions.[6] In undiagnosed patients, BCG vaccination may result in localized or disseminated disease, including rare manifestations such as brain abscesses, due to impaired immune cell function.[7,8] We describe a 2-year-old boy with genetically confirmed WAS who developed a BCG-associated brain abscess, highlighting the risks of routine BCG vaccination in undiagnosed primary immunodeficiencies.

CASE PRESENTATION

Patient History and Initial Presentation

A 2-year-old boy, born by cesarean delivery to nonconsanguineous parents, presented with jaundice and thrombocytopenia (platelet count, 22 000/μL) at 3 days of age, followed by eczematous skin lesions at 2 weeks. Prenatal and perinatal histories were unremarkable. A maternal uncle had died at 3 years of age with similar symptoms but without a confirmed diagnosis.

Clinical Course

During infancy, the patient experienced recurrent severe infections, including multiple episodes of pneumonia, recurrent otitis media, and chronic diarrhea requiring repeated hospitalizations. He also had frequent mucocutaneous bleeding, ecchymosis, and petechiae consistent with persistent thrombocytopenia. Mean platelet volume was reduced, supporting microthrombocytopenia.

At 7 months of age, he presented with acute respiratory distress, generalized tonic–clonic seizures, and extensive ecchymosis. Brain computed tomography (CT) revealed intracranial hemorrhage. Serologic testing revealed prior SARS-CoV-2 exposure. Immunologic evaluation showed elevated IgA (427 mg/dL) and IgE (1200 IU/mL), low IgM (14 mg/dL), and normal IgG levels. Lymphocyte subset analysis revealed reduced $CD4^+$ T cell counts with relatively preserved $CD8^+$ T cells and natural killer cells, along with decreased B-cell numbers. Functional assays demonstrated impaired T-cell proliferation.

Based on the combination of eczema, thrombocytopenia, recurrent infections, and immunologic abnormalities, WAS was suspected. Whole exome sequencing confirmed a pathogenic truncating mutation in the *WAS* gene (ChrX 48 542 731 G>A; NM_000377: exon 2: c.G192A: p.W64X rs2147262855), consistent with a severe phenotype.

Initial Management and Complications

Immunoglobulin replacement therapy and supportive care were initiated. Thrombocytopenia persisted despite platelet transfusions. Romiplostim (5 to 10 μg/kg/wk subcutaneously) and eltrombopag were added with minimal improvement in platelet counts. Intravenous immunoglobulin (IVIG) was administered at 500 mg/kg every 4 weeks. Prophylaxis with trimethoprim–sulfamethoxazole and antifungal agents was initiated. Platelet transfusions were administered during bleeding episodes.

Pre-HSCT Evaluation and Brain Abscess Discovery

At 2 years of age, during routine pre-hematopoietic stem cell transplantation (HSCT) evaluation, brain imaging was performed despite the absence of focal neurological deficits. CT revealed a right parieto-occipital multiloculated abscess measuring 4.5×5 cm with severe perilesional edema, an 8-mm midline shift, and dilation of the left lateral ventricle (Figure 1).

Given the history of neonatal BCG vaccination and underlying immunodeficiency, BCG infection was suspected, and mycobacterial testing was requested.

Polymerase chain reaction (PCR) analysis of aspirated material detected *Mycobacterium bovis* (BCG strain), confirming BCG infection. Evaluation of the liver, spleen, lymph nodes, and bone marrow showed no evidence of disseminated disease, suggesting localized infection. Broad-spectrum antibiotics were initiated pending microbiological confirmation.

Surgical Intervention and Diagnosis

The patient underwent burr hole drainage, evacuation

40 mL of purulent fluid. Initial bacterial cultures were negative. Polymerase chain reaction confirmed *Mycobacterium bovis* (BCG strain). Antitubercular therapy consisting of isoniazid, rifampicin, ethambutol, and azithromycin was initiated. Susceptibility testing confirmed sensitivity to first-line agents. Dexamethasone (1 mg/kg/d) was administered to reduce cerebral edema.

Follow-up MRI at 7 days showed minimal reduction in abscess size. At two weeks after the intial procedure, a second burr hole drainage was performed, aspirating an additional 20 mL of purulent fluid (Figure 2).

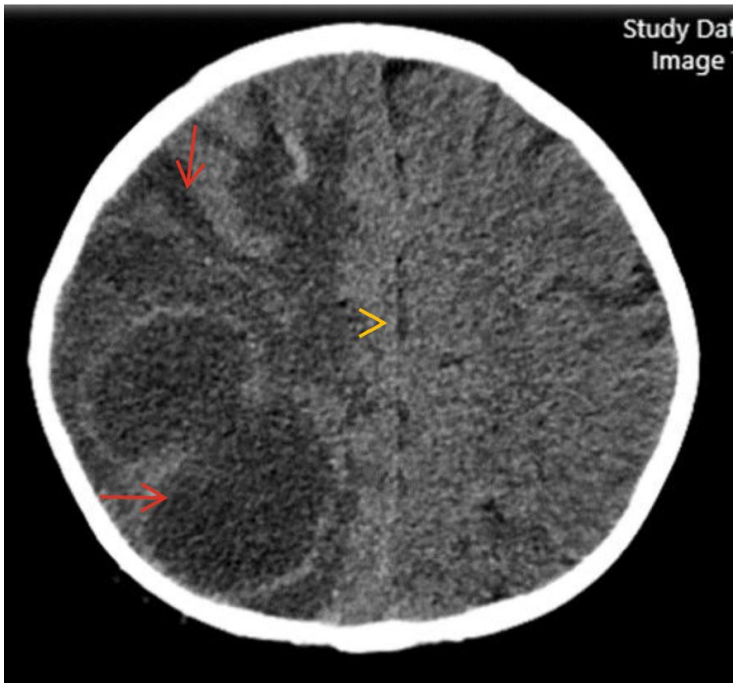

Figure 1. Brain CT scan showing a right parieto-occipital multiloculated abscess (4.5×5 cm) with severe perilesional edema (arrow), 8-mm midline shift (arrowhead), and left lateral ventricular dilation.

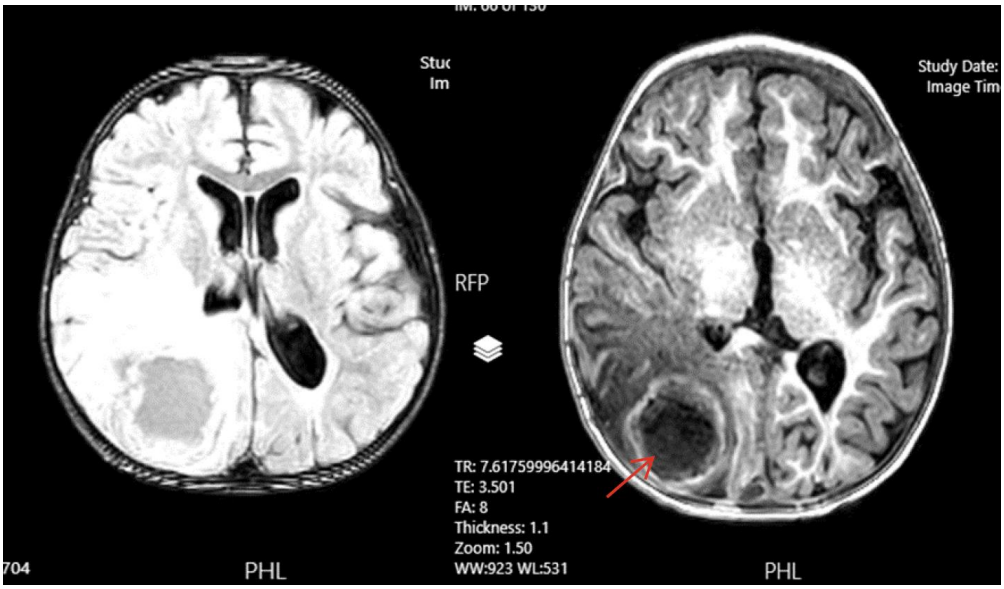

Figure 2. Brain MRI (post-second burr hole drainage, day 7) showing persistent multiloculated abscess with reduced size (arrow).

Splenectomy and Platelet Response

Open craniotomy was considered but deferred due to clinical instability and high operative risk. Because of refractory thrombocytopenia and the need for potential neurosurgical intervention, splenectomy was performed. Platelet counts improved significantly from 6000/µL to 105 000/µL preoperatively.

Despite hematologic improvement, HSCT was postponed due to the presence of an active BCG brain abscess, in accordance with international recommendations to control active infection prior to transplantation.

Ongoing Management and Outcome

The patient continued antitubercular therapy and immunomodulatory treatment. At 2.5 years of age (6 months after splenectomy), he remained clinically stable with platelet counts around 100 000/µL. Neurological examination revealed mild residual weakness without seizures, and HSCT planning was ongoing.

At 2 years and 8 months of age, the patient developed a severe COVID-19 infection and died despite supportive treatment (Figure 3).

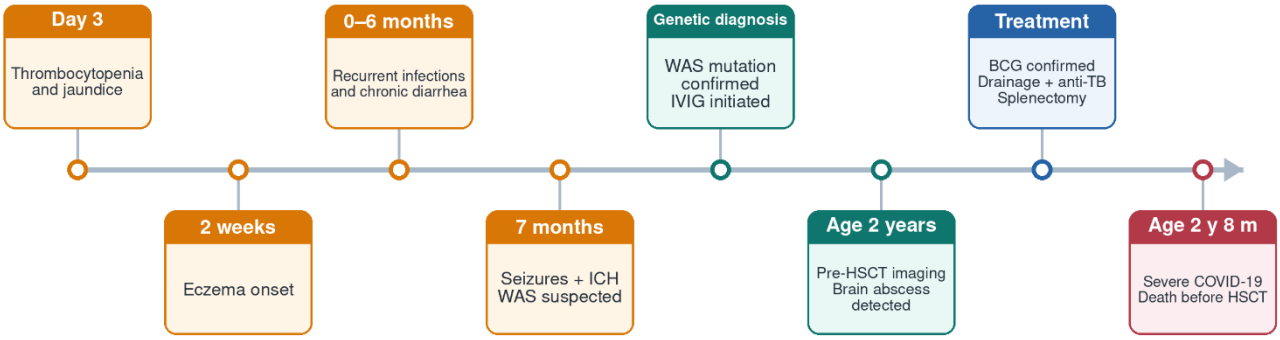

Figure 3. Clinical timeline illustrating disease progression, diagnostic milestones, therapeutic interventions, and outcome in a patient with Wiskott–Aldrich syndrome complicated by a BCG-associated brain abscess.

DISCUSSION

Wiskott–Aldrich syndrome (WAS) is a rare X-linked primary immunodeficiency characterized by combined defects in cellular and humoral immunity resulting from mutations in the *WAS* gene, which encodes the Wiskott–Aldrich syndrome protein (WASP). Dysfunction of WASP disrupts actin cytoskeleton remodeling in hematopoietic cells, impairing immune synapse formation, lymphocyte activation, migration, and phagocytic function, thereby predisposing patients to recurrent infections, immune dysregulation, and malignancy.[6–8,10,11] Clinical severity correlates with residual WASP expression, with truncating mutations typically associated with severe phenotypes, as observed in our patient.[2,12]

Infections remain a major cause of morbidity and mortality in WAS, particularly before definitive treatment with hematopoietic stem cell transplantation (HSCT).[1,6] Opportunistic infections occur due to combined T-cell dysfunction, impaired antibody responses, and abnormalities in innate immune signaling. Among these, complications related to Bacillus Calmette–Guérin (BCG) vaccination represent an important but underrecognized risk in regions where neonatal vaccination is routinely performed.[9,13] BCG is a live-attenuated strain of *Mycobacterium bovis*, and effective containment requires intact cellular immunity; therefore, patients with inborn errors of immunity are particularly vulnerable to localized or disseminated infection.

BCG-related complications are increasingly been recognized as early warning signs of primary immunodeficiencies. A large cohort study reported 197 patients with BCG complications associated with inborn errors of immunity, emphasizing the importance of considering immunodeficiency when unusual or severe post-vaccination infections occur.[9] Although disseminated BCG infection is more frequently described, central nervous system involvement and brain

abscess formation remain extremely rare manifestations. The absence of systemic symptoms in our patient contributed to diagnostic delay, highlighting the diagnostic challenge of localized BCG disease in immunocompromised hosts.

Routine neonatal BCG vaccination prior to recognition of immunodeficiency likely played a central role in the pathogenesis of the brain abscess in this case. The family history of early childhood death with similar manifestations further supports a genetic predisposition and underscores the importance of early diagnosis and genetic counseling. International recommendations advise avoiding live vaccines in patients with suspected or confirmed primary immunodeficiency and in high-risk families until immune competence isconfirmed.[14–16] In addition, screening and prevention strategies for latent tuberculosis should be considered before immunosuppression, particularly in high-risk settings.[17] Early identification through newborn screening or targeted evaluation in families with suggestive histories may prevent vaccine-related complications.

In immunocompromised patients, the differential diagnosis of brain abscess should include opportunistic fungal and bacterial pathogens, including rare Salmonella infection.[18,19] Brain abscesses in WAS are rare but clinically challenging because severe thrombocytopenia substantially increases the risk of intracranial hemorrhage and limits surgical intervention.[5,20] Neuroimaging typically demonstrates ring-enhancing lesions with surrounding edema, findings that may overlap with tuberculous or nontuberculous mycobacterial infections.[21,22] In our patient, correction of platelet counts to levels exceeding 100 000/μL was essential prior to invasive neurosurgical procedures, consistent with recommendations for minimizing perioperative bleeding risk.[23,24]

Management required a multidisciplinary approach combining antimicrobial therapy, neurosurgical drainage, and hematologic optimization. Initial broad-spectrum antibiotics reflected the diagnostic uncertainty frequently encountered in immunocompromised patients, in which polymicrobial infections must be considered until pathogen identification is achieved.[18,19] Definitive diagnosis using PCR enabled targeted antitubercular therapy, which remains the cornerstone of treatment for BCG infection.

Splenectomy was performed for refractory thrombocytopenia and the anticipated need for further neurosurgical intervention and HSCT. Although splenectomy increases susceptibility to infections, particularly encapsulated organisms, the decision was justified given the immediate bleeding risk and therapeutic limitations imposed by profound thrombocytopenia. Improvement in platelet counts following splenectomy facilitated safer clinical management and reflects previously reported hematologic benefits in selected WAS patients.

HSCT remains the only curative treatment for WAS and significantly improves long-term survival when performed early.[1,2,12] However, active infection is a major contraindication due to the risk of transplant-related mortality. In this case, persistent BCG infection delayed transplantation, illustrating a critical therapeutic dilemma frequently encountered in severe primary immunodeficiency: balancing infection control against the urgency of definitive treatment.

Another notable aspect of this case is the patient's eventual death from severe COVID-19 infection. Viral infections are well-recognized causes of severe disease in WAS due to impaired antiviral immunity, emphasizing the vulnerability of these patients even when clinically stabilized. This outcome further highlights the importance of early definitive therapy before cumulative infectious complications develop.

Overall, this case expands the clinical spectrum of BCG complications in WAS and emphasizes several key lessons: early recognition of warning signs of immunodeficiency, cautious administration of live vaccines in at-risk populations, prompt investigation of atypical infections, and timely progression toward definitive therapy. Increased awareness among pediatricians, allergists, and immunologists may facilitate earlier diagnosis and improved outcomes for patients with inborn errors of immunity.

This case of a BCG-related brain abscess in a patient with WAS highlights the severe infectious risks associated with undiagnosed immunodeficiency and routine BCG vaccination in tuberculosis-endemic regions. Despite appropriate antimicrobial therapy and supportive management, the patient died from severe COVID-19 infection before HSCT could be performed. These findings emphasize the need for early genetic diagnosis, avoidance of live vaccines, vigilant infection prevention, and timely definitive treatment to improve outcomes in combined immunodeficiencies.

STATEMENT OF ETHICS

Written informed consent was obtained from the patient's guardians for publication of this case report, including clinical details and imaging. The study was conducted in accordance with the Declaration of Helsinki.

FUNDING

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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DATA AVAILABILITY

All relevant data supporting the findings of this study are included within the article. No additional datasets were generated or analyzed.

AI ASSISTANCE DISCLOSURE

The authors used ChatGPT (OpenAI) solely to improve the language and readability of the manuscript. The authors reviewed and edited all AI-assisted content and take full responsibility for the final version of the manuscript.

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