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CASE REPORT

Recurrent Talaromyces Marneffei Infection Revealing X-Linked Hyper IgM Syndrome in an HIV-Negative Infant: A Diagnostic and Therapeutic Challenge

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Abstract: *Talaromyces marneffei* (TM), a temperature-dependent dimorphic fungus and opportunistic pathogen, poses a significant threat to immunocompromised individuals, particularly in Southeast Asian regions such as China and India. This case report details an 8-month-old HIV negative Chinese infant with recurrent cough and fever, who was diagnosed with TM infection through blood culture and metagenomic next-generation sequencing (mNGS). Additionally, whole exome sequencing identified a point mutation (c.346+1G>T) in the child's CD40LG gene, primary immunodeficiency calized to chromosome position chrX:135736590, leading to X-linked Hyper IgM Syndrome (XHIGM). The patient was managed with intravenous immunoglobulin (IVIG) and a 12-day course of amphotericin B and itraconazole, which led to significant clinical improvement and discharge on a quarterly IVIG regimen. However, he required readmission for recurrent TM pneumonia at 9 and 40 months post-discharge. This case highlights the diagnostic challenge and management complexity of TM infection in the context of primary immunodeficiency.

Keywords: Talaromyces marneffei, X-linked hyper IgM syndrome, immunocompromised individuals, mNGS, primary immunodeficiency

Introduction

Talaromyces marneffei is a thermally dimorphic fungus endemic to northeastern India, Southeast Asia, and southern China, where its prevalence surpasses 10% in some areas.[1] This pathogen poses a substantial threat to immunocompromised individuals, particularly those with HIV or congenital immunodeficiency, being implicated in up to 15% of HIV-associated hospitalizations within endemic zones. The disease demonstrates a high mortality rate of 30%.[2] Ubiquitous in nature, this fungus can cause pulmonary infection in humans following spore inhalation, with potential for subsequent hematogenous dissemination to various organs. The resulting clinical presentation commonly includes cutaneous lesions and fungal pneumonia. *TM* undergoes a growth condition-mediated morphological shift, growing as mycelium at 25°C and transforming into yeast form at 37°C or in the host milieu. This morphological change allows for intracellular proliferation within macrophages, leading to localized or disseminated infections. X-linked Hyper IgM Syndrome (XHIGM) is a rare primary immunodeficiency disorder caused by mutations in the CD40LG gene on the X chromosome, characterized by reduced or absent serum IgG and IgA levels, in contrast to normal or elevated IgM levels.[3]

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Table 1 Lymphocyte Subset Analysis Results

Lymphocyte Subset	Percentage (%)/Reference Range	Absolute Count ($\times 10^9$/L)/Reference Range
Total T Lymphocytes	58.57 (49.10–83.60)	5.92 (0.60–2.99)
CD4+ T Cells	50.6 (28.20–62.80)	5.12 (0.44–2.52)
CD8+ T Cells	6.8 (10.20–40.10)	0.69 (0.12–1.31)
NK Cells	4.23 (7.00–40.00)	0.43 (0.15–1.10)
B Cells	36.7 (6.48–16.64)	3.71 (0.11–0.70)
CD4/CD8 Ratio	7.36 (0.70–2.80)	

Case Presentation

We report an 8-month-old male infant who presented with a 6-day history of fever and cough. The fever failed to respond to self-administered ibuprofen, and the illness course was notable for the absence of convulsions, vomiting, diarrhea, skin rash, or arthralgia. Physical examination revealed tonsillar hypertrophy (grade I), enlarged left postauricular and axillary lymph nodes, along with increased breath sounds with rhonchi in both lung fields. Notably, the patient had developed a skin ulcer with purulent discharge at the BCG vaccination site at one month of age, with persistent axillary lymphadenopathy documented since that time. Laboratory tests revealed a white blood cell count of 21.5×10^9/L ($5.00–12.00\times10^9$/L), lymphocyte count of 10.11×10^9/L ($1.55–4.80\times10^9$/L), C-reactive protein level of 62.38mg/L (0.00–5.00mg/L), IgG level of 0.49g/L (2.32–14.11g/L), IgA level of 0.07g/L (0.00–0.83g/L), and IgM level of 0.94g/L (0.00–1.45g/L), serum free kappa light chain 0.42g/L (1.38–3.75g/L), serum free Lamda light chain 0.35g/L (0.93–2.42g/L), the (1,3)-β-D-glucan assay was 28.90 pg/mL (0–100.5 pg/mL), and the HIV antibody test was negative. The results of the lymphocyte subset analysis of the patient are detailed in Table 1. The etiological diagnosis was initially established by metagenomic next-generation sequencing (mNGS), which detected *Talaromyces marneffei*. This finding was subsequently confirmed by a blood culture that yielded *TM* after 4 days of incubation (Figure 1).

Upon hospitalization for pulmonary infection and fever, the infant received a seven-day empirical course of imipenem/cilastatin (120mg, q6h), which yielded a suboptimal clinical response. Following the detection of *TM* via mNGS, targeted antifungal therapy with itraconazole and amphotericin B was promptly initiated. Concurrently, intravenous immunoglobulin (IVIG) at 500 mg/kg was administered to address a documented significant deficiency in immunoglobulin G. Given the patient's HIV-negative status, a primary immunodeficiency was suspected. Whole-exome sequencing (WGS) performed on the patient and parents (Figure 2) identified a heterozygous mutation c.346 +1G>T in the CD40LG gene of the infant, located at chromosome X: 135736590, with pedigree validation confirming the maternal origin of the variant.

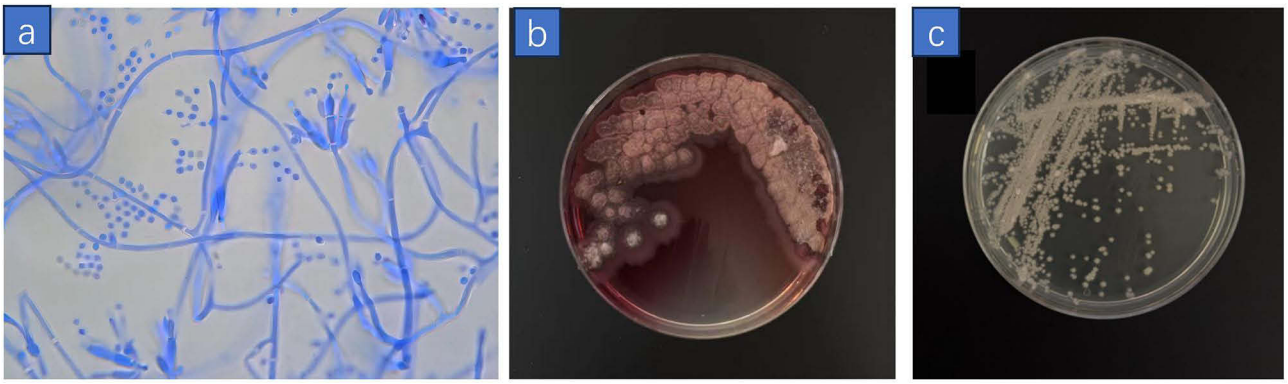

Figure 1 Microscopic morphology of the isolate from the patient's blood culture. (**a**) Blood culture smear stained with Giemsa method under 1000× oil immersion. (**b**) The colony morphology was observed after 7 days of incubation at 28°C on Sabouraud agar after a positive blood culture. (**c**) Post-positive blood culture, fungal colony morphology was noted after 7 days' incubation at 37°C on Sabouraud dextrose agar.

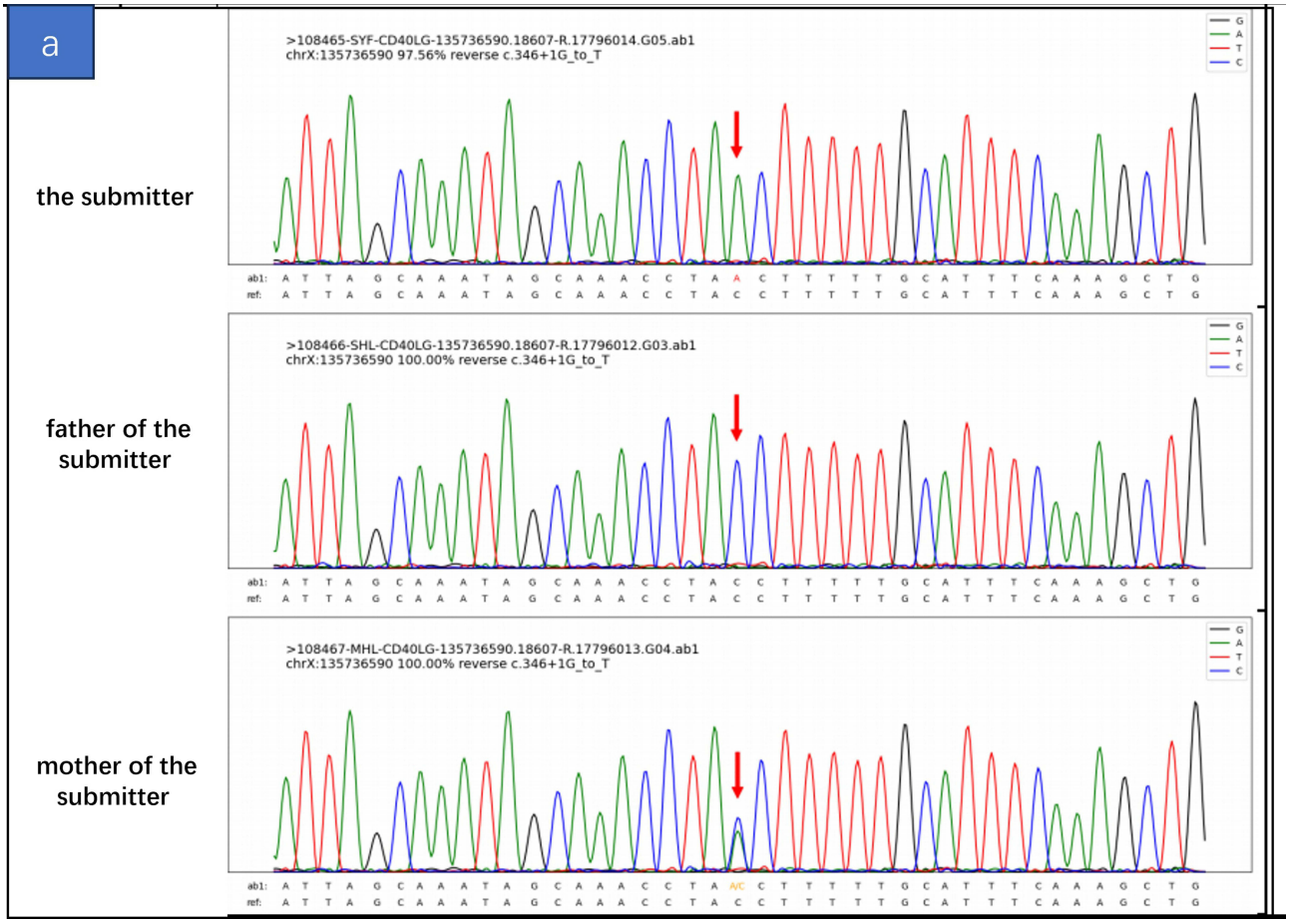

Figure 2 Genetic findings from whole-exome sequencing of the patient's family. Whole-exome sequencing revealed the hemizygous splice-site variant c.346+1G>T in the CD40LG gene of the patient (the C→A change indicated by the arrow in the reverse trace corresponds to G→T on the forward strand), located at chrX:135736590. The sequence chromatogram showed a mutant allele burden of ~97.56% in the child. The mother was heterozygous (100% mutant reads), whereas the father was wild-type, indicating maternal origin of the mutation.

Figure 3a shows a computed tomography (CT) scan obtained during the patient's initial hospitalization for pulmonary *TM* infection, demonstrating scattered patchy opacities in both lungs and consolidation in the left upper lobe. The trachea and main bronchi were patent, with no enlarged lymph nodes observed in the bilateral hila or mediastinum. The heart and great vessels appeared normal, accompanied by a small right-sided pleural effusion. Bone scintigraphy revealed no evidence of bone destruction. Figure 3b and c present follow-up CT scans acquired 9 months and 40 months later, respectively, during recurrent fungal pneumonia episodes, revealing a similar pattern of scattered patchy opacities in both lungs.

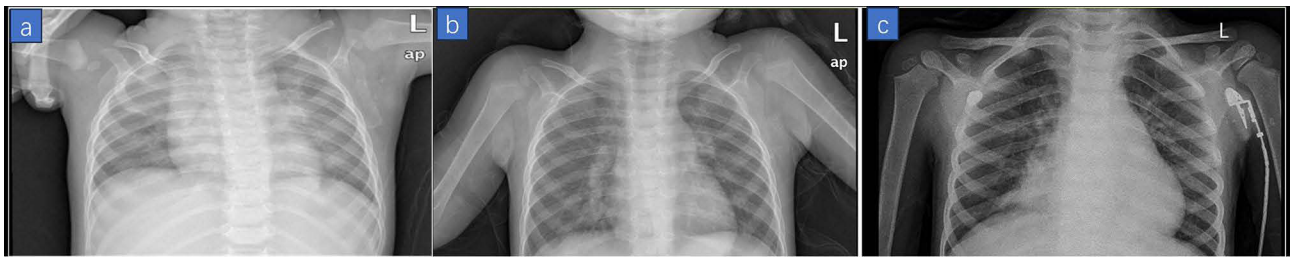

Figure 3 Chest computed tomography (CT) scans of the patient. (**a**) Scan obtained during the initial hospital admission. (**b** and **c**) Scans acquired during episodes of recurrent pulmonary infection at 9 months and 40 months, respectively.

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Result

Following initial management with intravenous immunoglobulin (IVIG), itraconazole, and amphotericin B, the patient's symptoms resolved, leading to hospital discharge. However, the patient experienced recurrent *TM* infections at 9 and 40 months post-discharge, prompting readmission on both occasions. Each relapse was successfully managed with a 6-day course of the original antifungal regimen combined with IVIG, which resulted in clinical improvement and subsequent discharge. To prevent further recurrences, the long-term management plan included oral fluconazole (75 mg twice weekly) and monthly IVIG (500 mg/kg) for immunoglobulin G support and antifungal prophylaxis, in addition to scheduled follow-up assessments. Hematopoietic stem cell transplantation was recommended as a curative strategy but was declined by the family due to financial constraints and difficulties in finding a suitable donor.

Discussion

Talaromyces marneffei is a thermally dimorphic fungus that transitions from a mycelial form in the environment to a yeast form in the host. This phase transition is closely associated with its virulence and immune evasion mechanisms, leading to persistent infections in immunocompromised individuals.[4] In the present case, the infant developed a localized ulceration, purulent discharge, and persistent axillary lymphadenopathy (BCGitis) following neonatal Bacille Calmette-Guérin (BCG) vaccination. This abnormal reaction is strongly associated with primary immunodeficiencies such as X-linked Hyper-IgM Syndrome (XHIGM) and serves as an important clinical indicator of severe T-cell functional deficiency.[5]

In recent years, the incidence of *TM* infection in HIV-negative individuals has shown an increasing trend.[6] The clinical manifestations are complex and non-specific, resulting in high rates of misdiagnosis, prolonged infection, disseminated disease, recurrence, and mortality. In terms of diagnosis, conventional fungal culture is time-consuming, whereas mNGS offers rapid, highly sensitive, and unbiased pathogen detection. For immunocompromised hosts presenting with fever of unknown origin or pneumonia, mNGS enables comprehensive pathogen screening and provides critical evidence for early etiological diagnosis and targeted antimicrobial therapy, significantly improving the detection of challenging pathogens in severe infections.[7,8]

The diagnosis of X-linked Hyper-IgM Syndrome requires integration of clinical presentation, immunophenotyping, family history, and molecular genetic evidence. Characteristic immunological features include significantly reduced serum IgG levels, normal or elevated IgA and IgM,[9] and abnormal T-cell subset ratios. Mutations in the CD40LG gene constitute the primary genetic basis of XHIGM, leading to impaired CD40-CD40L co-stimulatory signaling, which affects CD4+ T-cell function and B-cell class-switch recombination.[10] While most cases are associated with decreased CD4+ T-cell counts.[5,11] The patient in this case paradoxically exhibited an elevated CD4/CD8 ratio alongside reduced NK cell counts. Furthermore, significantly low serum levels of IgG, kappa, and lambda light chains were observed, collectively exacerbating his susceptibility to opportunistic infections.

To eradicate the intracellular pathogen *TM*, antifungal agents with excellent cell membrane penetration, such as amphotericin B and itraconazole, are required.[12] This case highlights a central clinical dilemma in management: whether to pursue long-term antifungal prophylaxis or curative hematopoietic stem cell transplantation (HSCT). Although prophylaxis can reduce recurrence frequency, it fails to correct the underlying immunodeficiency and carries risks of drug toxicity, interactions, and resistance. Notably, this patient experienced recurrent pulmonary infections at 9 and 40 months after discharge despite receiving standardized antifungal prophylaxis and immunoglobulin replacement. While suboptimal adherence in infancy or inadequate tissue drug levels cannot be ruled out, the recurrence strongly suggests that for XHIGM patients, IVIG combined with antifungal prophylaxis may be insufficient for long-term infection control, making definitive immune reconstitution via HSCT a potential necessity for sustained remission. However, HSCT itself entails significant risks, including transplant-related morbidity and mortality. A long-term US cohort study of 176 patients with X-linked Hyper-IgM Syndrome found no significant difference in overall survival between those who underwent HSCT and those who did not during the study period (1964–2013), although HSCT survivors reported a marginally better quality of life.[13] The equivocal long-term survival benefit of HSCT reported in some cohorts, combined with the significant hurdles of donor availability and economic burden, creates a complex decision-making landscape for clinicians and families.

This report also identifies key avenues for future research. Firstly, prospective, multi-center registries for rare IEIs like XHIGM are needed to better define the natural history of *TM* infection in this population and to establish evidence-based guidelines for the duration of primary antifungal treatment and the optimal strategy for long-term prophylaxis. Secondly, further studies are warranted to investigate the apparent discrepancy between our patient's immunophenotype (elevated CD4/CD8 ratio) and the classic presentation of XHIGM. Exploring the functional consequences of specific CD40LG mutations on T-cell homeostasis and cytokine profiles could provide novel insights into the genotype-phenotype correlations in this disease. Finally, comparative cost-effectiveness analyses of lifelong prophylaxis versus early HSCT in different socioeconomic settings are crucial to inform healthcare policy and guide resource allocation for these complex patients.

Conclusion

For HIV-negative infants with recurrent or disseminated infections, this case emphasizes the importance of considering *TM* and initiating early evaluation for primary immunodeficiency. Underlying conditions such as XHIGM can be occult drivers of disease severity, and delayed recognition of TM may lead to fatal dissemination. The rapid (48-hour) identification of a pathogenic CD40LG variant by WGS in this case was pivotal, establishing the diagnosis and guiding timely, targeted management. Compared to conventional stepwise diagnostics, technologies like mNGS markedly reduce time to diagnosis, limit unnecessary broad-spectrum antibiotic exposure, decrease hospital stay, and lower healthcare expenditures.

Ethics Approval and Informed Consent

All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Guangdong Provincial People's Hospital (approval ID: KY2025-993-01). Details of the case report have been anonymized, and written informed consent for the publication of clinical data and images was obtained from the patient's parents. The case details can be published without further institutional approval.

Consent for Publication

A written consent form for publication was provided by the parents of the child. They agreed to publish the child's personal or clinical details along with images in this study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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