CASE REPORT

Recurrent fever complicated by oral thrush in a case of Kawasaki disease

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Received: April 23, 2025 **Accepted:** October 29, 2025 **Online Published:** January 22, 2026
DOI: 10.5430/dcc.v11n3p7 **URL:** https://doi.org/10.5430/dcc.v11n3p7

ABSTRACT

Kawasaki disease (KD) is an acute vasculitis that commonly presents with prolonged fever and mucocutaneous involvement. The development of opportunistic infections, such as oral thrush, during immunosuppressive therapy remains a clinical challenge. This report highlights the management of recurrent fever complicated by oral thrush in a pediatric KD case. A 1-year-old girl with KD developed recurrent fever and oral thrush during prednisone tapering (2 mg/kg/day). Metagenomic NGS ruled out bacterial/viral infections, confirming IVIG-resistant KD. She achieved remission following antifungal therapy with nystatin, methylprednisolone (2 mg/kg/day), and high-dose aspirin (100 mg/kg/day), with resolution of fever and thrush by hospital day 13. This case highlights the need for prompt antifungal intervention while maintaining immunosuppression to achieve disease control. These findings are still preliminary and based on a single case.

Key Words: Kawasaki disease, Thrush, Fever, Oral

1. INTRODUCTION

Kawasaki disease (KD), first described by Dr. Tomisaku Kawasaki in 1967, is an acute systemic vasculitis and the leading cause of acquired pediatric heart disease in developed countries. Standard treatment involves intravenous immunoglobulin (IVIG, 2 g/kg) combined with high-dose aspirin (30-50 mg/kg/day), followed by low-dose aspirin (3–5 mg/kg/day) for antiplatelet therapy until coronary normalization. However, approximately 10%–20% of patients exhibit IVIG resistance, often requiring intensified immunosuppression with corticosteroids or biologics.[1]

Immunosuppressive therapy for KD carries risks of opportunistic infections, particularly fungal infections like oral thrush (candidiasis). Corticosteroid use disrupts mucosal immunity, creating opportunities for Candida overgrowth. This is exemplified in our case: a 1-year-old girl with IVIG-resistant KD developed recurrent fever and oral thrush during prednisone tapering, necessitating antifungal therapy alongside systemic corticosteroid therapy.

The patient met the American Heart Association diagnostic criteria for Kawasaki disease, with $\geq$ 5 days of fever plus four of five principal clinical features: (1) bilateral non-exudative conjunctival injection, (2) polymorphous rash (notably lower limb annular erythema), (3) oral mucosal changes (strawberry tongue and cracked lips), (4) extremity erythema with subsequent desquamation, and (5) cervical lymphadenopathy (> 1.5 cm). IVIG resistance was defined as recrudescent or persistent fever $\geq$ 36 hours after initial IVIG completion (2 g/kg), accompanied by worsening inflammatory markers (CRP 42.22-110.69 mg/L) and coronary artery dilation (left

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main coronary artery Z-score 2.9). Here, we present this pediatric case to highlight the clinical challenges of balancing immunosuppression and infection control in IVIG-resistant KD, emphasizing the need for vigilant surveillance of mucosal complications during steroid therapy.

"IVIG-resistant KD" refers to persistent or recurrent fever $\geq$ 36 hours after initial IVIG (2 g/kg), accompanied by worsening inflammation or coronary changes. "Recrudescence" denotes KD reactivation during treatment (e.g., steroid taper), while "recurrent KD" implies a new episode after full resolution."KD shock syndrome" (briefly noted in the case) is a severe variant with hypotension/vasoplegia requiring inotropic support.

2. CASE PRESENTATION

A 1-year-old female infant was admitted on February 25, 2025, for recurrent fever lasting half a day. The patient had a prior hospitalization from February 14 to 25, 2025, for IVIG-resistant KD complicated by KD shock syndrome (The patient meets KD diagnostic criteria with $\geq$ 5 days of fever plus four principal features: bilateral lower limb annular erythema, cervical lymphadenopathy, strawberry tongue, and extremity erythema/edema with non-exudative conjunctival injection). During the previous admission, she received two doses of IVIG (22.5 g each on February 17 and 19), high-dose aspirin, and intravenous methylprednisolone(methylprednisolone 4 mg = prednisone 5mg). After clinical improvement, she was discharged on oral prednisone (10 mg/day), aspirin (50 mg/day), and dipyridamole.

Upon current admission, physical examination revealed marked pharyngeal congestion, and laboratory tests showed significantly elevated high-sensitivity C-reactive protein (hs-CRP: 42.22 mg/L, normal < 5 mg/L). A preliminary diagnosis of acute pharyngitis and convalescent KD was made. Given marked pharyngeal congestion and elevated hs-CRP (42.22 mg/L), blood and throat cultures were obtained, and empirical intravenous ceftazidime was initiated for suspected bacterial superinfection. Cultures later returned negative, but antibiotics were continued pending clinical response due to high inflammatory markers. On hospital day 2, the infant developed low-grade fever and oral candidiasis (thrush). Following multidisciplinary consultation, antifungal therapy was initiated with nystatin suspension (100,000 IU/mL, 1 mL applied to oral mucosa four times daily) alongside 2% sodium bicarbonate mouthwash (5 mL swished for 30 seconds, four times daily). Bacillus licheniformis (0.5 g twice daily) was added to mitigate gut dysbiosis. Antifungal therapy was continued for 14 days until complete mucosal healing, with topical nystatin maintained for 48 hours beyond clinical resolution to prevent recurrence.

From hospital days 5 to 8, the patient exhibited persistent high fever (39.2°C) and worsening oral mucosal lesions, with extensive white plaques on the buccal mucosa and palate. Laboratory findings showed progressive inflammatory markers: CRP rose to 110.69 mg/L, platelets increased to 821 $\times$ 10^9/L(age-appropriate range 100-300 $\times$ 10^9/L), accompanied by elevated lactate dehydrogenase (810 U/L) and hypoalbuminemia (36.3 g/L, normal 35-50 g/L for age). Echocardiography revealed dilation of the left main coronary artery (Z-score 2.9). Although metagenomic next-generation sequencing (mNGS) failed to identify pathogens, the clinical presentation suggested recurrent IVIG-resistant KD.[2] The treatment regimen was adjusted accordingly: intravenous methylprednisolone (2 mg/kg/day) was restarted, and aspirin was increased to 50 mg/kg/day. With intensified antifungal therapy, the oral lesions gradually resolved. Serum cortisol was not measured, but steroid withdrawal was deemed unlikely given the absence of characteristic withdrawal symptoms and the concurrent rise in inflammatory markers and coronary changes, which were more consistent with KD recrudescence. Blood cultures and serum $beta$-D-glucan were not performed, as mNGS provided comprehensive pathogen screening and clinical suspicion for fungal dissemination was low given the localized nature of oral thrush and prompt response to topical antifungals.

By hospital days 9-12, the patient achieved afebrile status, with CRP declining to 7.06 mg/L and complete healing of oral mucosal lesions (see Figure 1). At discharge, medications included: aspirin 100 mg twice daily (20 mg/kg/day) for anticoagulation, prednisone 5 mg three times daily (planned taper over 2 weeks), calcium supplementation, and continued nystatin suspension. Follow-up was scheduled for repeat inflammatory markers and echocardiography 9 days post-discharge, with ongoing monitoring for coronary artery abnormalities.

While biologic agents (e.g., infliximab) are increasingly recommended for IVIG-resistant KD, they were not utilized in this case due to financial constraints—a critical barrier in resource-limited settings. The 2024 AHA guidelines endorse infliximab or cyclosporine as preferred escalation therapies after IVIG and steroid failure (Class IIa recommendation), particularly for patients with persistent coronary inflammation. The family declined infliximab after cost-benefit discussions, favoring corticosteroid reinitiation given its immediate availability, lower cost, and established efficacy in our center's experience. This highlights the need for broader healthcare policies to improve access to biologics for refractory KD, particularly in socioeconomic contexts where cost dictates therapeutic options.

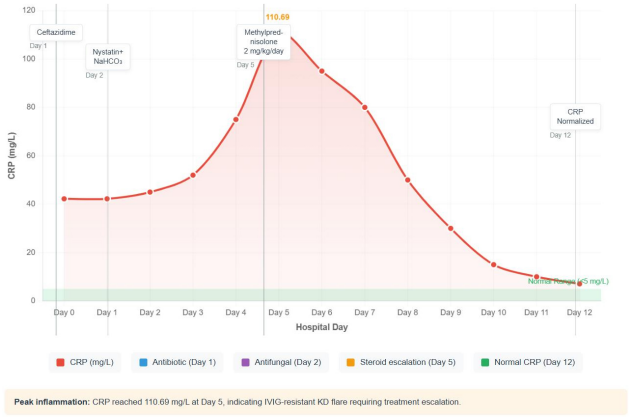

Figure 1. Temporal changes in C-reactive protein (CRP) levels during hospitalization

The patient presented with elevated CRP (42.22 mg/L) at admission, which peaked at 110.69 mg/L on Day 5 despite initial antibiotic therapy, consistent with a flare of IVIG-resistant Kawasaki disease. Antifungal therapy (initiated Day 2) and steroid escalation (Day 5) were followed by a gradual decline in CRP, normalizing to 7.06 mg/L by Day 12. Key interventions are annotated: antibiotic (Day 1), antifungal (Day 2), steroid escalation (Day 5), and CRP normalization (Day 12).

3. DISCUSSION

While oral thrush is a well-recognized complication of corticosteroid therapy, this case presents several unique aspects that enhance its clinical relevance. First, the patient had IVIG-resistant KD, a high-risk subgroup requiring aggressive immunosuppression, which increases susceptibility to opportunistic infections. The recurrent fever and oral thrush in this context highlight the challenges of balancing anti-inflammatory therapy with infection prevention. Second, the use of mNGS to exclude bacterial/viral co-infections demonstrates an advanced diagnostic approach in managing KD-related fever, distinguishing this case from conventional reports. Additionally, the multidisciplinary management strategy, incorporating rheumatology, infectious disease, and cardiology expertise, underscores the importance of collaborative care in complex pediatric cases. These findings emphasize the need for individualized corticosteroid tapering and prophylactic antifungal consideration in high-risk KD patients, offering practical insights for clinicians managing similar cases. The reason for the later recovery of glucocorticoids was that the fever was considered to be caused by IVIG-resistant KD, and the use of glucocorticoids was controlled. The reason for the sudden withdrawal of glucocorticoids is the fear of fungal infection in children, and the use of glucocorticoids will aggravate the disease. While mNGS broadens diagnostic capacity, its negative result cannot definitively exclude infection, particularly for fastidious pathogens or low microbial loads. Clinical correlation with cultures, serology, and host response remains critical.

Regarding other potential causes of fever, drug-induced fever was considered unlikely given the temporal dissociation between medication initiation (e.g., IVIG/steroids started > 72 hours before new fever onset) and absence of classic drug fever features (e.g., eosinophilia, rash). Other autoimmune diseases (e.g., systemic lupus erythematosus) were deemed less probable due to the lack of supporting clinical criteria (no malar rash, nephritis, or antinuclear antibody positivity) and the patient's prompt response to KD-directed therapy. In addition, the development of oral thrush in this patient likely reflects the convergence of multiple risk factors, including immunomodulatory effects of high-dose corticosteroids, disruption of oral microbiota from prior broad-spectrum antibiotic use, and the inherent susceptibility of young children to mucosal candidiasis due to immature local immunity.

While KD itself is not directly linked to fungal infections, the frequent use of high-dose corticosteroids (e.g., for refractory KD) can impair neutrophil and macrophage function, disrupt Th1/Th2 balance, and elevate blood glucose-creating a permissive environment for Candida overgrowth. At our center, we implement prophylactic oral hygiene measures (e.g., 2% sodium bicarbonate mouthwash) for all KD patients receiving corticosteroids, though routine antifungal prophylaxis is not administered unless additional risk factors (e.g., prolonged neutropenia, prior thrush) are present. This approach balances infection prevention with avoidance of unnecessary antimicrobial exposure.[3] This mirrors the pathophysiology of iatrogenic oral candidiasis seen in other steroid-treated pediatric populations, warranting surveillance in prolonged immunosuppression.The term "standardized protocols" should be explicitly defined to include key components such as infection screening (e.g., fungal surveillance) and corticosteroid tapering schedules to mitigate immunosuppression risks.

This single-case report of IVIG-resistant KD complicated by oral thrush underscores the delicate balance between immunosuppression and infection control. While our experience supports the need for proactive monitoring and early antifungal intervention in steroid-treated KD patients, larger prospective studies are required to validate optimal surveillance strategies. The patient's failure to respond to two IVIG courses (total 45 g) and subsequent coronary dilation (Z-score 2.9) reinforce the need for early corticosteroid intervention in refractory cases. The development of oral candidiasis during steroid tapering underscores the delicate balance between immunosuppression and infection control. The marked thrombocytosis (821×10^9/L) during disease flare demonstrates the persistent prothrombotic state in KD,

validating the safety and efficacy of dual antiplatelet therapy with high-dose aspirin (50 mg/kg/day) and dipyridamole in severe cases.[4]

The clinical course provides several key management insights for refractory KD. Disease recrudescence following initial steroid withdrawal suggests corticosteroid dependence may require more gradual tapering (4-6 weeks) rather than abrupt cessation. The successful use of methylprednisolone (2 mg/kg/day) followed by oral prednisone (5 mg tid) with sustained remission offers practical guidance for outpatient management. This case demonstrates the value of collaboration among specialists in managing complex cases. Using tools like mNGS and clinical symptoms, the team could effectively differentiate KD from opportunistic infection. This case highlights the importance of multidisciplinary collaboration, using mNGS and targeted antimicrobial therapy to manage vasculitis and infection. These findings support establishing standardized protocols for refractory KD management in tertiary centers, particularly for cases requiring balancing aggressive anti-inflammatory therapy with infection risks.

This experience highlights important unanswered questions regarding optimal corticosteroid duration, and long-term coronary outcomes in treatment of IVIG-resistant KD.[5] The case demonstrates that early corticosteroid intervention, vigilant infection monitoring, and individualized anti-inflammatory strategies can achieve disease control in complex presentations. These observations contribute to evolving treatment paradigms while emphasizing the need for prospective multicenter studies to develop evidence-based guidelines and risk stratification tools incorporating genetic and cytokine markers. The successful outcome in this high-risk case validates an aggressive yet balanced therapeutic approach guided by multidisciplinary collaboration for managing refractory KD.[6] This study is limited by the lack of long-term coronary outcome data and the potential selection bias inherent to single-center refractory KD cases, which may restrict generalizability to broader KD populations. The negative predictive value of mNGS is influenced by sequencing depth (coverage) and pathogen burden, as low microbial loads or inadequate sequencing may yield false-negative results despite active infection.

This study is limited by the lack of long-term coronary outcome data. While the patient's initial follow-up at 9 days post-discharge showed improving inflammatory markers (CRP 7.06 mg/L), echocardiographic documentation of coronary artery normalization remains pending. Given the observed left main coronary artery dilation (Z-score 2.9) during the acute phase, extended monitoring for coronary sequelae is imperative, as persistent abnormalities may require ongoing antiplatelet therapy or further intervention. We emphasize the need for standardized long-term surveillance protocols in IVIG-resistant KD cases, particularly those with transient coronary changes during acute illness.Methylprednisolone was selected over oral prednisolone due to its superior bioavailability in critically ill pediatric patients and established efficacy in IVIG-resistant KD, with 2 mg/kg/day chosen based on the AHA's recommended dosing range (1-2 mg/kg/day) for refractory disease.[1] Aspirin was escalated to 50 mg/kg/day-exceeding standard anti-inflammatory dosing (30-50 mg/kg/day)-given the patient's coronary dilation (Z-score 2.9) and extreme thrombocytosis (821×10^9/L), reflecting an intensified antiplatelet strategy for high thrombotic risk as per KD treatment guidelines.Because this report describes a single patient, causality between corticosteroid taper and thrush associated fever cannot be proven; larger case series are required.While mNGS broadens diagnostic capacity, its negative result cannot definitively exclude infection, particularly given technical limitations in sequencing depth and pathogen burden.[7,8]

ACKNOWLEDGEMENTS
We would like to extend our special thanks to the patients who participated in this study.

AUTHORS CONTRIBUTIONS
All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

FUNDING
The Hubei Pediatric Alliance Medical Research Project, No. HPAMRP202117.

CONFLICTS OF INTEREST DISCLOSURE
The authors declare no conflicts of interest.

INFORMED CONSENT
Obtained.

ETHICS APPROVAL
The journal's policies adhere to the Core Practices established by the Committee on Publication Ethics (COPE). Written informed consent was obtained from the patient's guardians for publication. Ethical approval for this case report was obtained from the institutional review board of [The First Affiliated Hospital of Yangtze University], approval number: [KY2025-013-01].

PROVENANCE AND PEER REVIEW
Not commissioned; externally double-blind peer reviewed.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

DATA SHARING STATEMENT

No additional data are available.

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