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Rethinking kawasaki disease diagnosis: continuing the search for new biomarkers

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Abstract

This editorial provides commentary on the article titled "Kawasaki disease without changes in inflammatory biomarkers: A case report," recently published in the *World Journal of Clinical Cases*. Recent findings by Yamashita *et al*. report a Kawasaki disease (KD) case with normal biomarker levels, challenging traditional diagnostic paradigms. This editorial explores the implications of such atypical KD presentations, emphasizing the need for novel biomarkers and revised diagnostic guidelines. The case underscores the limitations of current biomarkers, the importance of clinical judgment, and the necessity for comprehensive research to identify new diagnostic tools. Emerging technologies in proteomics and genomics offer potential avenues for discovering reliable biomarkers. Revisiting clinical guidelines to incorporate flexibility for atypical presentations is crucial. Ensuring timely and accurate KD diagnosis, even without elevated traditional biomarkers, prevents severe complications. Future advancements should focus on novel biomarkers to improve patient outcomes.

INTRODUCTION

Diagnosis of Kawasaki disease (KD) has traditionally relied on clinical criteria supported by elevated inflammatory biomarkers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). KD is typically diagnosed based on clinical presentation. Classic KD is defined by the presence of at least four of the following five

major clinical features: fever, oral changes, ocular changes, rash: Polymorphous rash, and cervical lymphadenopathy[1]. However, a recent case report by Yamashita *et al.*, published in the *World Journal of Clinical Cases*, presents a case of KD with normal inflammatory biomarker levels[2]. This editorial aims to discuss the implications of these findings and the need for new inflammatory biomarkers.

Yamashita *et al.* describe a 1-year-old boy presenting with five of the six principal symptoms of KD (fever, bilateral bulbar conjunctival injection, rash, changes in the peripheral extremities, and nonsuppurative cervical lymphadenopathy) but with normal levels of CRP, ESR, and serum amyloid A[2]. Despite the atypical laboratory findings, the diagnosis was confirmed based on clinical features. The patient was treated with intravenous immunoglobulin (IVIG) and aspirin but demonstrated resistance to initial treatments, necessitating additional IVIG doses. Throughout treatment, inflammatory biomarkers remained within normal ranges, and levels of the novel biomarker leucine-rich alpha-2-glycoprotein 1 (LRG1) were not elevated. This case underscores the necessity of re-evaluating the diagnostic approach to KD, particularly in cases where traditional biomarkers fail to indicate the disease.

The diagnosis of KD has always been predominantly clinical, guided by the presence of fever lasting at least five days and at least four of the five principal features: Bilateral conjunctival injection, changes in the lips and oral cavity, polymorphous exanthema, changes in the extremities, and cervical lymphadenopathy. Laboratory tests, including elevated levels of CRP and ESR, have been auxiliary but crucial in supporting the clinical diagnosis and monitoring treatment response. The case presented by Yamashita *et al.* raises critical questions about the reliance on these biomarkers. Untreated KD has been proven to lead to serious cardiovascular complications, including coronary artery aneurysms. Thus, early and accurate diagnosis is paramount. However, as demonstrated, normal inflammatory markers do not necessarily rule out KD, posing a significant diagnostic challenge. This highlights the potential for underdiagnosis or delayed treatment in atypical cases, risking severe outcomes.

The limitations of current biomarkers require exploration of novel diagnostic tools. LRG1, as mentioned in the case report, has shown promise as a biomarker for the acute phase of KD. However, its normal levels in this patient indicate that LRG1 alone may not be sufficient as a standalone diagnostic tool. Comprehensive research is required to identify additional biomarkers or a combination thereof that can reliably diagnose KD, particularly in atypical presentations. Emerging technologies, such as proteomics and genomics, offer promising avenues for discovering new biomarkers. High-throughput screening and advanced data analytics can help identify molecular signatures specific to KD. Additionally, integrating clinical data with genetic and biomarker profiles could pave the way for more precise and personalized diagnostic criteria.

Given the findings of Yamashita *et al.*, there is a pressing need to revisit and potentially revise clinical guidelines for KD diagnosis. The American Heart Association and other leading bodies provide comprehensive guidelines for KD management, which heavily rely on clinical presentation and traditional biomarkers[3]. However, incorporating flexibility to account for cases with normal biomarker levels is essential. Clinicians should maintain a high index of suspicion for KD in patients with compatible clinical features, regardless of inflammatory marker status. Furthermore, risk stratification tools like the Kobayashi score, which predict IVIG resistance, may need re-evaluation. The reported case had a low Kobayashi score but still required intensified treatment, indicating that current risk stratification methods might not adequately capture KD presentations[4].

CONCLUSION

The case report by Yamashita *et al*. provides valuable insights into the complexity of KD diagnosis and the limitations of current biomarkers. It underscores the importance of clinical judgment and the need for novel diagnostic tools to ensure early and accurate identification of KD, especially in atypical cases[5]. Future research should focus on identifying and validating new biomarkers. Ensuring all patients with KD receive

timely and appropriate treatment is crucial for preventing long-term cardiovascular complications and improving patient outcomes.

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