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Commentary: Hematuria as an early sign of multisystem inflammatory syndrome in children: A case report of a boy with multiple comorbidities and a review of the literature

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A commentary on
Hematuria as an early sign of multisystem inflammatory syndrome in children: A case report of a boy with multiple comorbidities and a review of the literature

By Generalić A, Davidović M, Kos I, Vrljičak K, Lamot L. *Front Pediatr.* (2021) 9:760070. doi: 10.3389/fped.2021.760070

Introduction

Recently, we encountered an article that describes hematuria as the early onset of multisystem inflammatory syndrome in children (MIS-C) (1). Upon further analysis, we found some inconsistencies in the commented article, which we outlined in the following article.

Subsections relevant to the subject

Cardiac involvement:

- Chromosome 8p23.1 deletion has been associated with severe and life-threatening congenital heart disease (CHD), requiring complex cardiac procedures and follow-ups (2). Pro-BNP levels in children with some CHD can remain elevated even after corrective surgeries (3). The type of CHD should have been presented with prior

follow-ups, surgical corrections, and pro-BNP levels. Pro-BNP in CHD is primarily a marker of left ventricular systolic function, but very high levels are also an independent marker of inflammation (4–6). As increased pro-BNP is one of the markers of MIS-C cardiac inflammation and/or ventricular dysfunction, it should have trended until normalization and not presented as a single value like in the article (7).

- Common observed ECG abnormalities in MIS-C involve prolonged ECG intervals (PR, QRS complex, and QT segment), low QRS amplitude, T-wave abnormalities, or first-, second, or third-degree atrioventricular (AV) blocks (8, 9). Nodal (junctional) rhythms are uncommon in MIS-C (6.3%) and can be adequately interpreted only with a complete ECG presentation. Apart from AV blocks, they can also be a side effect of potential medications used in children with CHD (e.g., β-blockers, digitalis) or correction surgery for CHD (10, 11). As the ECG report before the MIS-C episode has not been presented and the described ECG report in the article is incomplete, we can only speculate on its interpretation. For instance, second- or third-degree AV block can show with normal troponin and elevated pro-BNP, just like the described case (9).
- Telemetry ECG monitoring is also recommended in patients with MIS-C with conduction delays or ectopy, which is not presented or approached in this case report (7).
- The statement that "normal values of Troponin I and creatine kinase (CK) ruled out myocarditis" is false. Troponin I and troponin T are neither specific nor sensitive markers of myocarditis (for instance, only 35% of patients with suspected viral myocarditis have elevated troponin I) (12, 13). CK used by authors is not as accurate as creatine kinase myocardial band (CK-MB) for suspected myocarditis. Cardiovascular MRI should have been at least considered, even though direct tissue examination remains the diagnostic reference standard. The indirect statement in the article that thrombocyte levels can rule out Kawasaki disease at "day 7" is also misleading, as thrombocytosis in Kawasaki disease is often seen in the second or third week of illness (1, 14).

Nephrology involvement:

- It is well known that red blood cell (RBC) morphology helps differentiate glomerular from nonglomerular hematuria. The percentage of acanthocytes >5% in urine would be beneficial, which was not done in the article (15).
- Although abnormal urinalysis was underreported in MIS-C, hematuria was scarcely found at its onset. In reported cases, it was only associated with severe acute kidney injury (AKI) or other underlying conditions (thrombotic microangiopathy (TMA), renal infarcts). No authors report spontaneous remission without treatment, which contradicts the case presented and the relevant articles (16–20). The article indirectly suggests that the hematuria was of short duration.
- Some aspects of the case report suggest a possible underlying nephrological disease as comorbidity. It is known that acute Sars-Cov-2 infection may trigger an underlying disease to manifest clinically (17, 21). IgA nephropathy manifests with periodic macrohematuria with spontaneous remission. Since we do not have a kidney biopsy, such a possibility remains unresolved.
- If the nasopharyngeal swabs are PCR-negative, Sars-Cov-2 samples could be taken from stool and urine samples. New studies isolated Sars-Cov-2 spike S1 protein from urine in 25% of patients with severe COVID-19 disease (22, 23).

Therapy:

- Despite apparent myocardial dysfunction, the patient was treated with a single 2 g/kg intravenous immune globulin (IVIG) infusion. Infusion of large volumes of IVIG (40 ml/kg) increases oncotic pressure, which may cause a liquid shift and volume overload in MIS-C patients who are already at risk due to potential capillary leak syndrome (24, 25). To cite "In patients with heart failure immunoglobulins should be administered over at least 16 h or, alternatively, the total dose should be split in two

TABLE 1 Common (and uncommon) differential diagnostic possibilities in case report presentation.

Symptom	MIS-C	Adenovirus	Coxsackievirus	Parvovirus B19	*Bartonella henselae*
Fever	Consistently	Consistently	Consistently	Consistently	Less common
Maculopapular rash	Common	Common	Consistently	Consistently	Common
GI symptoms	Common	Less common	Common	Uncommon	Common
Macrohematuria	Very rare	Fairly common	Less common	Less common	Less common
Conjunctivitis	Common	Common	Common	Common	Less common
Pleural effusion	Common	Less common	Less common	Less common	Rare
Myocardial involvement	Common	Less common	Less common	Less common	Less common
Proteinuria	Uncommon	Uncommon	Less common	Less common	Less common

MIS-C, multisystem inflammatory syndrome in children; GI, gastrointestinal.

infusions 12 h apart" (26). In patients with cardiac involvement, glucocorticoids (1–2 mg/kg/day) should be "administered upfront in case of heart involvement" in conjunction with IVIG (divided/slowed infusion or with diuretics) to avoid heart overload rather than any drug alone (26, 27). Low-dose aspirin (3–5 mg/kg) is recommended in MIS-C patients with Kawasaki disease features, which is something the authors neglected or omitted from their presentation (28).

Final remarks:

1. The authors forgot or neglected to add common viral pathogens to their differential diagnosis, which can mimic or complicate MIS-C diagnosis. Pathogens that commonly include fever, exanthems, conjunctivitis, cardiomyopathy, and hematuria/hemorrhagic cystitis are adenoviruses, *Bartonella henselae*, and rarely parvovirus B19 and enteroviruses. Adenovirus can cause self-limiting hemorrhagic cystitis and myocarditis with an immediate response to IVIG therapy. Enteroviruses and Parvovirus B19 can cause glomerulonephritis, albeit rarely. Even though the symptoms match, ceftriaxone is commonly used to treat *Bartonella henselae* myocarditis (**Table 1**). Some authors have correctly asked the question: "Are we losing awareness of other infections due to the fear of coronavirus disease-2019 and MIS-C"? (29, 30)
2. Instead, Nino (22) in Table 1 should be Niño-Taravilla (22).

Discussion and conclusions

The authors perhaps hastily concluded that hematuria is an early sign of MIS-C, especially in a patient with no apparent acute kidney injury (normal creatinine level). Nor is this the first published case of MIS-C-related hematuria at the time of the article's release (16, 31). Therefore, the content of the article does not correspond with the title of the article.

It is, however, a case with no apparent kidney injury but spontaneous remission of hematuria, which necessitates further diagnostic investigation. According to the presented symptoms and the clinical course of the disease, adenovirus infection appears to be the most likely cause. Subsequently, the authors should have considered the possibility of an underlying nephrological disease or bacterial/viral co-infection —with or without MIS-C.

Author contributions

All authors wrote and critically revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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