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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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

| 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      | Consistently| Consistently   | Consistently   | Common              |
| Macrohematuria      | Very rare   | Fairly common| Less common   | Less common   | Less common         |
| Conjunctivitis      | Common      | Common     | Consistently   | Consistently   | 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
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Conflict of interest

The authors declare that the research was conducted in the
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