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Mycoplasma infection may complicate the clinical course of SARS-CoV-2 associated Kawasaki-like disease in children

Alessandro Plebani a,*, Antonella Meini a, Marco Cattalini a, Vassilios Lougaris a, Antonella Bugatti b, Francesca Caccuri b, Arnaldo Caruso b

a Pediatrics Clinic, Department of Clinical and Experimental Sciences, University of Brescia-ASST Spedali Civili of Brescia, Brescia, Italy
b Institute of Microbiology and Virology, Department of Molecular and Translational Medicine, University of Brescia-ASST Spedali Civili of Brescia, Brescia, Italy

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To The Editor,

The current COVID-19 pandemic has created a global health emergency involving mainly adult patients with severe clinical course and unfortunately exitus, while pediatric patients with SARS-CoV-2 presented originally mainly mild clinical symptoms [1,2]. Recently, two separate groups reported on a novel SARS-CoV-2 associated phena- menon affecting previously asymptomatic children presenting as a hyperinflammatory syndrome with multiorgan involvement resembling Kawasaki disease (KD) and/or Kawasaki shock syndrome (KSS) [3,4]. Upon the first description of this SARS-CoV-2 related manifestation in children, follow-up studies suggested that this Multisystem Inflammatory Syndrome in Children (MIS-C) related to SARS-COV-2 infection may present a continuum of clinical findings, ranging from Kawasaki-like disease to myocarditis [5,6].

We identified nine previously healthy children (six males and three females) with a mean age of 8.9 years (range 13 months-14 years), eight of caucasian and one of african origin, admitted to the Pediatric Clinic of University of Brescia-ASST Spedali Civili, with Kawasaki/KSS-like disease. This incidence was 5-fold superior to what we observed in the 2015–2019 period. Eight children had known family exposure to SARS-CoV-2. Nasopharyngeal swabs were negative in all patients, while IgG antibodies against SARS-CoV-2, were detected by Western Blot in seven out the eight children tested. Demographics, clinical and imaging findings, treatment and outcome for this cohort of nine children are shown in Table 1.

Clinical symptoms were similar for all patients and included unrelenting fever, skin rash, oral mucositis, conjunctivitis, and peripheral edema. Gastrointestinal symptoms (such as diarrhea, vomiting, abdominal pain), and severe dyspnea were present in four and two patients respectively. Seven out of nine patients developed a vasoplegic shock refractory to volume resuscitation with three patients requiring vasopressors for haemodynamic support. Development of ascitic effusions occurred in three patients whereas pericardial and pleural effusions in two.

Laboratory evidence of inflammation included elevated concentrations of C-reactive protein, procalcitonin, ferritin, and D-dimer. Hypoalbuminemia and hyponatremia were present in eight out of nine patients. No pathological organisms were isolated from biological specimens.

Four out of these nine children (Pts 1,3,8,9) showed a remarkable increase of IgM serum levels against Mycoplasma pneumoniae (MP) suggestive of a primary infection. A single patient (Pt.9) was tested twice and showed a progressive increase of the IgM titers during a 7 day-period (Table 1). These four patients presented a more severe clinical course of the disease with rapid deterioration in terms of vasoplegic shock and general clinical conditions. Of note, their mean age was 9.0 years, an age group typically affected by Mycoplasma infection. For all patients, antibody testing both for SARS-CoV-2 and Mycoplasma infection was performed on the same blood sample drawn within ten days from the symptoms’ onset.

Our data confirm previous reports on the existence of a syndrome...
Demographics, clinical findings, imaging findings, treatment and outcome.

| Patients | Age, Weight, BMI, Comorbidity | Clinical presentation at hospital admission | Pharmacological treatment | Imaging results | Altered Laboratory results | Microbiology results | IgG and IgM anti Mycoplasma | IgG anti-SARS-CoV-2 | outcome |
|----------|------------------------------|-------------------------------------------|---------------------------|----------------|---------------------------|----------------------|------------------------|----------------------|---------|
| Patient 1 Male Caucasian | 3 years, 15 Kg, BMI 15 Kg/m2, no comorbidities | 7 days with fever 40 °C, anorexia, dyspnea, rash, hypotension, conjunctivitis, oral mucositis, lymphoedema, induration of both hands and feet | IVIG, Ceftriaxone, Methylprednisolone, Chlorochine, Enalapril, Oxygen therapy | mild interstitial pneumonia, asciitis, mild left ventricular dysfunction, mild mitral insufficiency | Hb 7.4 g/dl Lymphopenia 780/mm3 CRP 215 mg/dl Na 129 mmol/l D-dimers 965 ng/ml Fibrinogen 944 mg/dl Ferritin 250 µg/l Albumin 25 g/l Procalcitonin 21.3 ng/ml | SARS-CoV-2 negative, confirmed COVID-19 exposure from father, mother and grandfather | IgM positive (18 AU/ml; n. v. < 10 AU/ml); IgG negative | Positive Alive |
| Patient 2 Male Caucasian | 11 years, 39 Kg, BMI 16 Kg/m2, no comorbidities | 3 days with fever 40 °C, abdominal pain, non-bloody diarrhea, vomiting, rash, oral mucositis, hypotension | IVIG, Ceftriaxone, Methylprednisolone, Idrossiclorochine, | splenomegaly, ascites | Lymphopenia 620/mm3 CRP 22 mg/dl Na 134 mmol/l AST 63 U/l ALT 74 U/l LDH 318 U/l D-dimers 2367 ng/ml Ferritin 536 µg/l | SARS-CoV-2 negative, likely COVID-19 exposure from mother and father | IgM and IgG negative | Positive Alive |
| Patient 3 Male Caucasian | 10 years, 23 Kg, BMI 13.6 Kg/m2, no comorbidities | 7 days with fever 40 °C, anorexia, vomiting, hypotension, conjunctivitis, chest pain, scrotal painful, erythema | IVIG (2 doses), Ceftriaxone, Methylprednisolone, Azyhromycin, Oxygen therapy, | interstitial pneumonia, pleural effusions, ascites | Lymphopenia 460/mm3 Platelets 60,000 CRP 104 mg/dl Na 131 mmol/l D-dimers 13,247 ng/ml Ferritin 906 µg/l Albumin 35 g/l Procalcitonin 11.9 ng/ml | SARS-CoV-2 negative, likely COVID-19 exposure from father and grandmother | IgM positive (<27 AU/ml; n.v. < 10 AU/ml); IgG negative | Positive Alive |
| Patient 4 Male Caucasian | 16 months, 11 Kg, no comorbidities | 3 days with fever 40 °C, dyspnea, cough, rash, conjunctivitis, oral mucositis | IVIG, Ceftriaxone, Methylprednisolone, Chlorochine, Oxygen therapy, | mild interstitial pneumonia, laryngitis, splenomegaly, wandering liver | Lymphopenia 1,305,000 on the 14th day since the beginning of the fever CRP 231 mg/dl Na 134 mmol/l D-dimers 1211 ng/ml Ferritin 140 µg/l Albumin 34 g/l | SARS-CoV-2 negative, confirmed COVID-19 exposure from cohabiting relatives | IgM and IgG negative | Negative Alive |
| Patient 5 Male Caucasian | 13 months, 10 Kg, no comorbidities | 15 days with low-grade fever 37.8 °C, rhinitis, rash, conjunctivitis, oral mucositis, desquamation of the finger and the toes | IVIG, Chlorochine, ASA | mild interstitial pneumonia, coronary arteries ectasia | Lymphopenia 610/mm3 Na 134 mmol/l Albumin 33 g/l NT-proBNP 245 ng/l | SARS-CoV-2 negative, confirmed COVID-19 exposure from father, mother and grandmother | IgM and IgG negative | Positive Alive |
| Patient 6 Female African | 5 years, 16 Kg, BMI 14 Kg/m2, no comorbidities | 3 days with fever 39 °C, rash, oral mucositis, conjunctivitis, cheilitis, | IVIG, Chlorochine, ASA | | Neutropenia 610/mm3 Na 134 mmol/l Albumin 33 g/l NT-proBNP 245 ng/l | SARS-CoV-2 negative, confirmed COVID-19 exposure from father | IgM negative and IgG positive (21.3 AU/ml; n.v. < 10 AU/ml) | Positive Alive |

(continued on next page)
with hyperinflammation, similar to KD/KSS and Multisystem Inflammatory Syndrome in Children (MIS-C) linked to the SARS-CoV-2 pandemic. This study suggests for the first time that, upon the SARS-CoV-2 infection, the clinical course of these children may deteriorate rapidly by the co-occurrence of Mycoplasma pneumonia infection. MP infection has been reported as potentially related to the onset of Kawasaki-like disease, four of which were co-infected with Mycoplasma pneumoniae; of note, the latter presented a more severe clinical course.

**Capsule summary**

We report on nine pediatric patients with SARS-CoV-2 associated Kawasaki-like disease, four of which were co-infected with Mycoplasma pneumoniae; of note, the latter presented a more severe clinical course.

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**Declaration of Competing Interest**

The authors declare no conflict of interest.

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