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Clinical Immunology 221 (2020) 108613

Contents lists available at ScienceDirect

Clinical Immunology

journal homepage: www.elsevier.com/locate/yclim

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

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ARTICLE INFO

Keywords:
SARS-CoV2
Kawasaki disease (KD)
Multisystem inflammatory syndrome in children (MIS-C)
Mycoplasma pneumoniae

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 phaenomenon 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 Mycoplsma pneumoniae 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

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https://doi.org/10.1016/j.clim.2020.108613
Received 6 October 2020; Received in revised form 12 October 2020; Accepted 12 October 2020
Available online 16 October 2020
1521-6616/

Table 1
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 comorbidites	7 days with: fever 40 °C, anorexia, dyspnea, rash, hypotension, conjunctivitis, oral mucositis, lynphoadenitis, induration of both hands and feet	IVIG, Ceftriaxone, Cefotaxime, Methylprednisolone, Clorochine, Enalapril, Oxygen therapy	mild interstitial pneumonia, ascites, mild left ventricular disfunction, mild mitral insufficiency	Hb 7.4 g/dl Lynphopenia 780/mm3 CRP 215 mg/dl Na 129 mmol/l D-dimers 865 ng/ml Fibrinogen 944 mg/dl Ferritin 250 μg/l Albumin 25 g/l Troponin 20 ng/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 day swith: fever 40 °C, abdominal pain, non-bloody diarrhea, vomiting, rash, oral mucositis, hypotension	IVIG, Ceftriaxone, Methylprednisolone, Idrossiclorochine,	splenomegaly, ascites	Lynphopenia 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 Albumin 35 g/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, Clorochine, Azithromycin Oxygen therapy,	interstitial pneumonia, pleural effusions, ascites	Lynphopenia 460/mm3 Platelets 60,000 CRP 104 mg/dl Na 131 mmol/l D-dimers 13,247 ng/ml Ferritin 906 μg/l Albumin 26 g/l Troponin 11 ng/l Procalcitonin 11.9 ng/ml	SARS-Co-V-2 negative, likely COVID-19 exposure from father and grandmother	IgM positive (>27 AU/ml; n.v. <10 AU/ml) and 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, Clorochine, Oxygen therapy,	mild interstitial pneumonia, laringytis, splenomegaly, wandering liver	Platelets 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, Clorochine, ASA	mild interstitial pneumonia, coronary arteries ectasia	D-dimers 387 ng/ml Pro BNP 872 ng/l	SARS-CoV-2 negative, likely 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, Clorochine, 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*)

Table 1 (*continued*)

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
		laterocervical lynphadenitis							
Patient 7 Male Caucasian	14 years, 50 Kg, BMI 17.5 Kg/m2, spinal dysgraphism, chronic renal failure, epilepsy	3 days with: fever 40 °C, severe hypotension, shock, oliguria, tachycardia, meningism, abdominal pain, vomiting	IVIG, Ceftriaxone, Amikacine, Meropenem, Methylprednisolone, Noradrenaline, Milrinone, Morphine Bisoprolol, Eparine, Sodium valproate, Oxygen therapy	severe left ventricular disfunction, pleural and pericardial effusions	Lynphopenia 880/mm3 CRP 339 mg/dl Creatinine 3.9 mg/dl Na 127 mmol/l D-dimers 10,004 ng/ml Ferritin 1980 µg/l Albumin 24 g/l Troponin 1743 ng/l Procalcitonin 8.64 ng/ml	SARS-CoV-2 negative, unknown exposure	IgM and IgG negative	Positive	Alive
Patient 8 Female Caucasian	14 years 54 Kg, BMI 20.6 Kg/m2, no comorbidities	3 days with fever 40 °C, meningism, photofobia, haedhache, nausea, oral mucositis, rash	Ampicilline/ Sulbactam	Interstitial pneumonia	CRP 12 mg/dl, Albumin 40 g/l,	SARS-CoV-2 negative, likely COVID-19 exposure from father and mother	IgM positive (12 AU/ml; n.v. <10 AU/ml) and IgG negative	Positive	Alive
Patient 9 Female Caucasian	10 years 28 kg BMI 14.9 Kg/m2 no comorbidities	3 days with fever 39,5 °C, abdominal pain, meningism, haedhache, arthralgie, oral mucositis, rash	Ceftriaxone, Clyndamicine, Azithromycin, Methylprednisolone, Noradrenaline, Milrinone, Morphine, Albumine, Furosemide, Oxygen therapy	Interstitial pneumonia pleural and pericardial effusions mild mitral insufficiency	Lynphopenia 810/mm3 CRP 340 mg/dl D-dimers 498 ng/ml Ferritin 567 µg/l Albumin 26 g/l Procalcitonin 6.84 ng/ml	SARS-CoV-2 negative, confirmed COVID 19 exposure from mother and grandfather	*IgM positive (>27 AU/ml; n.v. <10) and IgG negative	Not done	alive

BMI = Body mass index COVID-19 = Coronavirus disease 2019 CRP = C-reactive protein IVIG = human intravenous immunoglobulin, SARS-CoV-2 = severe acute respiratory syndrome Coronavirus 2, ASA = acetylsalicylic acid.
* IgM and IgG anti Mycoplasma on April 15th, were 19 and 0.13 AU/ml respectively; on April 22 increased to > 27 and 2.43 AU/ml respectively.

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 disease in children [7–9]. Although not all children with Kawasaki disease are tested for Mycoplasma infection, available data suggest a possible association. MP infection has been shown to function as an inflammatory trigger that can initiate a systemic inflammatory response, which in turn may lead to a systemic inflammatory response similar to Hemophagocytic Lymphohistiocytosis (HLH) [10,11]. The two original studies on the pediatric COVID-19-related KD did not include sierology testing for Mycoplasma [3,4]. Viral infections in children on the other hand are widely accepted as potential triggers for a cytokine storm leading to the development of Multisystem Inflammatory Syndrome in Children (MIS-C), and this has also been reported in children with COVID-19 in a minority of cases [3–5,12]. Our study would like to emphasize the importance of testing for Mycoplasma in severely ill children with KD/KSS-like disease and/or MIS-C, and underline that the dual infectious pro-inflammatory trigger, ie SARS-CoV-2 and Mycoplasma pneumoniae, may cause rapid clinic deterioration in affected children.

Key messages

Mycoplasma pneumoniae co-infection in pediatric patients with SARS-CoV-2 associated Kawasaki-like disease, may contribute to 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.

Funding

The research leading to these results has received funding from the European Community's Seventh Framework Programme FP7/2007–2013 under grant agreement no 201549 (EURO-PADnet HEALTH-F2-2008-201549) and from the Italian Ministerial Grant GR-2010-2315762. The research leading to these results also received funding from the "Fondazione C. Golgi", Brescia, Italy and the Jeffrey Modell Foundation.

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgments

We would like to thank the patients, the patients' families and the nurses for all their efforts. Several of the authors are members of the

European Reference Network for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (project identification No. 739543).

References

[1] M. Kloc, R.M. Ghobrial, E. Kuchar, S. Lewicki, J.Z. Kubiak, Development of child immunity in the context of COVID-19 pandemic, Clin. Immunol. 217 (2020 Aug), 108510, https://doi.org/10.1016/j.clim.2020.108510.

[2] C.M. Hedrich, COVID-19 - considerations for the paediatric rheumatologist, Clin. Immunol. 214 (2020 May), 108420, https://doi.org/10.1016/j.clim.2020.108420.

[3] S. Riphagen, X. Gomez, C. Gonzalez-Martinez, N. Wilkinson, P. Theocharis, Hyperinflammatory shock in children during COVID-19 pandemic, Lancet 0 (2020), https://doi.org/10.1016/S0140-6736(20)31094-1.

[4] L. Verdoni, A. Mazza, A. Gervasoni, L. Martelli, M. Ruggeri, M. Ciuffreda, E. Bonanomi, L. D'Antiga, An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study, Lancet 0 (2020), https://doi.org/10.1016/S0140-6736(20)31103-X.

[5] A. Belot, D. Antona, S. Renolleau, E. Javouhey, V. Hentgen, F. Angoulvant, C. Delacourt, X. Iriart, C. Ovaert, B. Bader-Meunier, I. Kone-Paut, D. Levy-Bruhl, SARS-CoV-2-related paediatric inflammatory multisystem syndrome, an epidemiological study, France, 1 March to 17 May 2020, Euro Surveill. 25 (22) (2020 Jun), https://doi.org/10.2807/1560-7917.ES.2020.25.22.2001010, 2001010.

[6] S. Felsenstein, C.M. Hedrich, SARS-CoV-2 infections in children and young people, Clin. Immunol. 220 (2020 Sep 6), 108588, https://doi.org/10.1016/j.clim.2020.108588.

[7] J.N. Wang, S.M. Wang, C.C. Liu, J.M. Wu, Mycoplasma pneumoniae infection associated with Kawasaki disease, Acta Paediatr. 90 (2001) 594–595.

[8] M. Ebrahim, M. Gabay, R.F. Rivas-Chacon, Evidence of acute mycoplasma infection in a patient with incomplete and atypical Kawasaki disease: a case report, Case Rep. Med. 2011 (2011), 606920.

[9] M.N. Lee, J.H. Cha, H.M. Ahn, J.H. Yoo, H.S. Kim, S. Sohn, Y.M. Hong, Mycoplasma pneumoniae infection in patients with Kawasaki disease, Korean J. Pediatr. 54 (2011) 123–127.

[10] M. Yasutomi, S. Okazaki, I. Hata, A. Tanizawa, S. Tamamura, M. Kawakita, Y. Ohshima, Cytokine profiles in mycoplasma pneumoniae infection-associated hemophagocytic lymphohistiocytosis, J. Microbiol. Immunol. Infect. 49 (5) (2016 Oct) 813–816, https://doi.org/10.1016/j.jmii.2014.11.015.

[11] A. Agnihotri, A. Ruff, L. Gotterer, A. Walker, A.H. McKenney, A. Brateanu, Adult onset still's disease associated with mycoplasma pneumoniae infection and hemophagocytic lymphohistiocytosis, Case Rep. Med. 2016 (2016), 2071815, https://doi.org/10.1155/2016/2071815.

[12] E.M. Dufort, E.H. Koumans, E.J. Chow, E.M. Rosenthal, A. Muse, J. Rowlands, M. A. Barranco, A.M. Maxted, E.S. Rosenberg, D. Easton, T. Udo, J. Kumar, W. Pulver, L. Smith, B. Hutton, D. Blog, H. Zucker, New York state and centers for disease control and prevention multisystem inflammatory syndrome in children investigation team. multisystem inflammatory syndrome in children in New York state, N. Engl. J. Med. 383 (4) (2020 Jul 23) 347–358, https://doi.org/10.1056/NEJMoa2021756.