Correspondence on: 'Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking Kawasaki disease (Kawa-COVID-19): a multicentre cohort' by Pouletty *et al*

We read with interest the article by Pouletty *et al*,[1] in which the authors describe a multicentre compilation of patients with Kawasaki disease (KD) in France, associated with the detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Other colleagues in Europe and USA have recently reported similar experiences.[2–5]

We report a prospective case series of paediatric patients that fulfilled clinical diagnostic criteria of KD during the SARS-CoV-2 pandemic in a paediatric referral centre in Barcelona, Spain. KD was defined according to the 2017 criteria of the American Heart Association.[6] Assessment of SARS-CoV-2 infection was made by means of quantitative real-time PCR assay (GeneFinder COVID-19 Plus, Elitech; Puteaux, France) in nasopharyngeal samples; stools were tested in patients with diarrhoea. SARS-CoV-2 IgG qualitative determination (SARS-CoV-2 IgG chemiluminescent microparticle immunoassay; Abbot, Chicago, Illinois) was performed during admission. Statistical analyses were performed using SPSS V.25 (IBM). Informed consent was obtained from parents or legal guardians, as was informed assent in patients aged >12 years.

From March 23 to May 14, twelve previously healthy patients with KD were admitted to our institution (table 1). The yearly number of patients with KD diagnosed in our centre is around 10–12. Prior to diagnosis, several patients reported gastrointestinal symptoms (10/12, 83.3%; vomiting, diarrhoea and abdominal pain) and neurological symptoms (5/12, 41.6%; irritability, headache, decreased consciousness and febrile seizures). Only patient 10 was referred with respiratory symptoms (cough) and had an abnormal chest X-ray showing pneumonia at presentation. Lymphopenia and thrombocytopenia were observed at diagnosis in eight and five patients, respectively. Inflammatory markers (C-reactive protein, ferritin, erythrocyte sedimentation rate and procalcitonin) were elevated in most patients, as were N-terminal pro-brain natriuretic peptide levels (median (range): 2930 (178–7994) ng/L).[7]

At or during admission, 6/12 (50%) patients showed microbiological and/or serological evidence of SARS-CoV-2 infection. As compared with children in whom SARS-CoV-2 infection was not demonstrated, the former had statistically significant lower platelet counts, and higher levels of inflammatory markers (C-reactive protein, procalcitonin and ferritin) and N-terminal pro-brain natriuretic peptide at diagnosis (table 2).

Ultrasound or clinical signs of cardiac involvement were noted at admission only in patient 8 (left and right coronary aneurysm, +4.7 and +4.8 Z-score). Coronary aneurysms were observed later in two further patients: on day 14 in patient 1 (left coronary aneurysm, 4.2 Z-score) and on day 12 in patient 10 (left coronary aneurysm, +3.6 Z-score). Patient 10 was a toddler who

Table 1 Clinical and laboratory features of 12 patients with Kawasaki disease who presented during the SARS-CoV-2 pandemic

Patient No	1	2	3	4	5	6	7	8	9	10	11	12
	Complete KD							Incomplete KD				
Age, ethnicity	Infant, Latin	Infant, Caucasian	Infant, Caucasian	Toddler, Caucasian	Toddler, Caucasian	Toddler, Caucasian	Child, Caucasian	Infant, Asian	Toddler, Caucasian	Toddler, Black	Adolescent, Caucasian	Adolescent, Caucasian
Symptoms prior to diagnosis												
Duration (days)	6	4	5	5	7	5	4	7	7	4	7	7
Respiratory	No	No	No	No	Yes	No	No	No	No	Yes	No	No
Gastrointestinal	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Neurological	No	Yes	No	Yes	No	No	Yes	Yes	No	Yes	No	No
KD signs at diagnosis												
Conjunctivitis	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
Erythema mouth/pharynx	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No
Polymorphous rash	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Lymphadenopathy	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes
Erythema of the palms/soles	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Contact with SARS-CoV-2 case	No	No	No	No	No	No	No	No	No	Yes	No	Yes
SARS-CoV-2 RT-PCR in respiratory sample/stools	NEG/ND	NEG/POS	NEG/NEG	NEG/NEG	NEG/ND	NEG/NEG	NEG/NEG	NEG/NEG	NEG/ND	POS/ND	POS/ND	POS/ND
SARS-CoV-2 IgG	NEG	POS	NEG	NEG	NEG	POS	POS	NEG	NEG	POS	POS	POS
CRP (normal <15 mg/L)	184	73	46	42	33	165	173	128	133	229	276	241
PCT (normal <0.5 ng/mL)	0.08	3.1	0.11	0.21	0.14	6.75	6.7	0.51	0.07	4.65	3.97	2.11
Ferritin (normal <120 ng/mL)	114	358	66	450	96	67	604	219	142	563	>2000	1424
ESR (normal <15 mm/hour)	83	14	43	2	23	63	9	2	46	19	39	76
NT pro-BNP (normal <200 ng/L)	1416	647	178	291	457	7994	4510	3628	344	4840	2930	5500
Platelet count (normal 150–400×10^9/L)	449	129	373	129	509	296	149	249	456	170	117	76
Lymphopenia	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
Treatment	IVIG followed by IVIG+mPDN	IVIG+mPDN	IVIG	IVIG	IVIG	IVIG	IVIG+mPDN	IVIG+mPDN	IVIG followed by IVIG+mPDN	IVIG	mPDN	None
Length of stay (days)	5	6	5	2	3	4	8	12	8	10	3	6

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IVIG, intravenous immunoglobulin; KD, Kawasaki disease; mPDN, methylprednisolone; ND, not done; NEG, negative; NT pro-BNP, N-terminal pro-brain natriuretic peptide; PCT, procalcitonin; POS, positive; RT-PCR, real-time PCR; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 2 Differences between patients with Kawasaki disease with and without SARS-CoV-2 infection

	Positive SARS-CoV-2 infection RT-PCR or serology (n=6)	Negative SARS-CoV-2 infection RT-PCR or serology (n=6)	P value
Female sex	3 (50.0)	3 (50.0)	1
Age (years)	5.3 (2.5–11.2)	2.1 (1.2–3.1)	0.078
Complete Kawasaki disease	3 (50.0)	4 (66.7)	0.55
Symptoms prior to diagnosis			
Respiratory	1 (16.7)	1 (16.7)	1
Gastrointestinal	6 (100)	4 (66.7)	0.45
Neurological	3 (50.0)	2 (33.3)	0.5
Development of aneurysms	1 (16.7)	2 (33.3)	0.5
Lab values at admission			
C-reactive protein (mg/L)	180 (119–252)	87 (40–146)	0.029
Procalcitonin (ng/mL)	4.65 (3.53–6.72)	0.12 (0.08–0.28)	0.02
Ferritin (ng/mL)	563 (212–1302)	127 (89–277)	0.065
ESR (mm/hour)	14 (7–41)	33 (2–55)	0.12
NT pro-BNP (ng/L)	4510 (1788–6417)	400 (263–1969)	0.015
Platelet counts (x10^9/L)	149 (114–233)	408 (219–469)	0.016
Lymphopenia	5 (83.3)	3 (50.0)	0.54

Data are expressed with n (%) or with medians and IQRs.
ESR, erythrocyte sedimentation rate; NT pro-BNP, N-terminal pro-brain natriuretic peptide; RT-PCR, real-time PCR; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

developed decreased consciousness, hypotension and clinical signs of hypoperfusion consistent with KD shock syndrome on day 3 of fever. Transfer to the paediatric intensive care unit was required and vasoactive support (for 48 hours) and non-invasive mechanical ventilation (for 3 days) were implemented, together with intravenous immunoglobulins (IVIG), methylprednisolone, hydroxychloroquine and azithromycin.

All patients were treated within 10 days of symptoms onset; only patient 12, with a self-limited incomplete KD, did not receive any immunomodulatory treatment. Median (range) duration of admission was 4 (2–12) days and all patients were discharged without incidents. Follow-up is ongoing in all cases.

We describe a higher than expected incidence of KD within a very short time frame (7 weeks) in Catalonia, compared with a historical series,[8] with half of the cases being associated with SARS-CoV-2 infection, in line with the experience of other authors.[2–5] Surprisingly, SARS-CoV-2-related KD cases were not reported in China, where the pandemic began and where the incidence of KD (40.9–55.1 per 100 000 children <5 years) is higher than in European countries.[9]

KD seems to be caused by a complex interaction between genetic and immunity factors, triggered by infections.[6 10] Several pathogens have been found to be involved in the pathogenesis of KD, including coronaviruses.[11] As compared with 'classical' KD, SARS-CoV-2-related KD cases differ in several clinical characteristics: patients are older[2–5]; present more often with respiratory, gastrointestinal or neurological symptoms[3]; and develop a more severe disease in terms of cardiovascular involvement.[3–5] The incidence of coronary aneurysms in KD treated with IVIG ranges from 4% to 6%,[12] as compared with 25% in our series. Also, higher rates of leucopenia, lymphopenia and thrombocytopenia, as well as increased inflammation, have been reported.[1 3–5] Interestingly, in our series, significant differences in these lab values were observed between patients with and those without confirmed SARS-CoV-2 infection. While preliminary, these differences point at an association between SARS-CoV-2 infection and the pathogenesis of KD, beyond the temporal sequence.

Given the lack of evidence-based treatments for COVID-19, we treated the patients in our series according to available KD treatment guidelines,[6] mainly IVIG (n=10) and steroids (n=6). Outcomes were good in all cases. We did not need to use other immunomodulatory drugs, such as anakinra or infliximab, as other authors have reported doing.[2–5]

Our study is limited by low numbers, the short follow-up period and its observational design. Nevertheless, our series is in line with recent observational data that describe an association between SARS-CoV-2 infection and a paediatric inflammatory multisystem syndrome that shares a number of clinical and analytical features with KD in children. Further studies are needed to confirm the more pronounced inflammatory response we observed in those cases in which a SARS-CoV-2 infection was demonstrated.

Rosa Pino,[1] Ana Carolina Izurieta,[1] María Ríos-Barnés,[2] Sílvia Ricart,[1,3] Mariona F De Sevilla,[1,4] Laura Monfort,[1] Cristian Launes,[1,4] Iván Cano,[1] Laura Lecina,[1] Judith Sánchez Manubens,[5,6] Juan Manuel Mosquera,[5] Iolanda Jordan,[4,7] Joan Sánchez de Toledo,[8,9] Manuel Monsonís,[10] Cristina Esteva,[4,11] Carmen Muñoz-Almagro,[4,11] Victòria Fumadó,[2,3] Clàudia Fortuny,[2,4] Juan José Garcia Garcia,[2,4] Antoni Noguera-Julian ,[2,4] Jordi Anton,[3,5] On behalf of the Kids Corona Project

[1]Hospital Medicine Unit, Pediatrics Department, Hospital Sant Joan de Déu, Barcelona, Spain
[2]Infectious Diseases and Systemic Inflammatory Response in Pediatrics, Infectious Diseases Unit, Hospital Sant Joan de Déu, Barcelona, Spain
[3]Faculty of Medicine, Universitat de Barcelona, Barcelona, Spain
[4]CIBERESP, Madrid, Spain
[5]Pediatric Rheumatology Unit, Hospital Sant Joan de Déu, Barcelona, Spain
[6]Pediatric Rheumatology, Consorcio Corporación Sanitaria Parc Taulí, Sabadell, Barcelona, Spain
[7]Pediatric Intensive Care Department, Hospital Sant Joan de Déu, Barcelona, Spain
[8]Pediatric Cardiology Department, Hospital Sant Joan de Déu, Barcelona, Spain
[9]Department of Critical Care Medicine, Children's Hospital of Pittsburgh of University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA
[10]Department of Microbiology, Hospital Sant Joan de Déu, Barcelona, Spain
[11]Department of Molecular Microbiology, Hospital Sant Joan de Déu, Barcelona, Spain

Correspondence to Professor Antoni Noguera-Julian, Hospital Sant Joan de Déu, Passeig Sant Joan de Déu 2, 08950 Esplugues, Barcelona, Spain; ton@sjdhospitalbarcelona.org

Contributors RP, IJ, VF, CF, JJGG, ANJ and JA designed the study. RP, ACI, MRB, SR, MFDS, LM, CL, IC, LL, JSM, JMM, JSdT and VF collected the clinical data. MM, CE and CMA supervised the microbiological studies. RP, ANJ and JA analysed the data and wrote the paper. All authors have reviewed and approved the version submitted for publication.

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ORCID iD
Antoni Noguera-Julian http://orcid.org/0000-0001-7485-0583

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