LETTER TO THE EDITORS

Cardiac affection associated to severe Multisystem Inflammatory Syndrome in Children (MIS-C) in a 6-year-old girl with a single coronary artery

Jochen Pfeifer1 · Peter Fries2 · Lorenz Thurner3 · Hashim Abdul-Khaliq1

Received: 29 April 2022 / Accepted: 28 June 2022 / Published online: 29 July 2022 © The Author(s) 2022

Sirs:

A 6-year-old former healthy girl was admitted to hospital 4 weeks after asymptomatic SARS-CoV2 infection. She presented in a poor general condition with fever for 5 days, diarrhea, emesis, rash, and hepatosplenomegaly. Laboratory examination showed hyponatremia, elevated inflammatory parameters, thrombopenia, and increasing cardiac parameters in terms of elevation of troponin T and pro-brain natriuretic peptide (NT-pro-BNP) as well as anemia and leucopenia (the Table 1 shows the laboratory findings in the course of the therapy). Serological examination revealed SARS-CoV2-antibodies (both IgG and IgA).

Because both severe infection and Kawasaki disease (KD) initially were possible differential diagnoses, an antibiotic treatment was started, as well as high-dose ASS (30 mg/kg/d) and intravenous immunoglobulin (IVIG, 2 g/kg) were administered.
administered. After developing a shock symptomatic and polyserositis, the child was transferred to pediatric ICU. Pleural and peritoneal draining as well as inotropic and diuretic therapy were necessary. Non-invasive ventilation had to be performed.

Echocardiography initially showed mitral regurgitation and decreased systolic function of the left ventricle (EF < 50%). Furthermore, there was a single coronary artery deriving from the right aortic sinus as an incidental finding. During daily echocardiographic controls, the ostial coronary diameter increased from 2.5 up to 6 mm within the first 3 days (Fig. 1). ECG showed non-specific abnormal repolarization in terms of flattened T waves.

After exclusion of viral or bacterial infection, Multisystem Inflammatory Syndrome in Children (MIS-C) was the hypothesized diagnosis according to the CDC and WHO definitions [1]. In a refractory state, the girl was then treated by administration of intravenous pulse methylprednisolone (30 mg/kg/d for 5 days, followed by prednisolone 2 mg/kg/d with gradual tapering) whereupon crucial improvement occurred with regressing clinical symptoms and defervescence within the next days. The echocardiographic findings including systolic function and coronary diameter (Fig. 1) as well as the blood parameters improved and nearly normalized. Interestingly, the cardiac markers gradually decreased and reached normal levels within 6 months (Table 1).

| Laboratory analysis          | Reference value | Day 1 | Day 3 | Day 6 | Day 13 | Follow up after 6 months |
|------------------------------|-----------------|-------|-------|-------|--------|--------------------------|
| Hemoglobin                   | 10.8–15.6 g/dl  | 8.5   | 8.4   | 7.7   | 13.8   | 10.8                     |
| Leucocytes                   | 4800–12,000/µl  | 3400  | 24,900| 13,200| 14,700 | 5000                     |
| Platelets                    | 186,000–488,000/µl | 100,000| 120,000| 150,000| 778,000| 282,000                 |
| Sodium (Na⁺)                 | 135–145 mmol/l  | 129   | 141   | 139   | 137    | 141                      |
| Potassium (K⁺)               | 3.4–5.1 mmol/l  | 3.4   | 3.8   | 4.6   | 5.3    | 4.4                      |
| Creatinine                   | 0.4–0.6 mg/dl   | 0.6   | 0.9   | 0.7   | 0.4    | 0.6                      |
| AST                          | 10–40 U/l       | 35    | 27    | 10    | 35     | 33                       |
| ALT                          | 5–25 U/l        | 17    | 14    | 7     | 40     | 20                       |
| Troponin T                   | <14 pg/ml       | <3    | 45    | 32    | 19     | <3                       |
| NT-pro-BNP                   | <190 pg/ml      | 2069  | 28,667| 52,003| 493    | 163                      |
| Albumine                     | 38–54 mg/l      | 26    | 45    | 51    | na     | na                       |
| Ferrite                      | 7–84 ng/ml      | 421   | 459   | na    | na     | na                       |
| CrP                          | <5 mg/l         | 184   | 182   | 13.8  | 1.5    | <0.6                     |
| Procalcitonin                | <0.05 ng/ml     | 6.3   | 63.2  | 4.6   | na     | na                       |
| D-Dimer                      | <0.5 mg/ml      | 3.7   | 4.0   | 2.0   | na     | na                       |

AST aspartate aminotransferase, ALT alanine aminotransferase, NT-pro-BNP N-terminal pro-brain natriuretic peptide, CrP C-reactive protein

Fig. 1 A transthoracic echocardiographic image at day 3: aortic root (AO) with a single coronary artery arising from the right aortic sinus; diameter 6 mm at ostium and 4 mm distally (white arrows). B transthoracic echocardiographic image at follow-up: diameters now decreased to 3 mm both at ostium and distally (white arrows). C computed tomography image: aortic root (AO) with a single coronary artery arising from the right aortic sinus and a left coronary trunk with retroaortic course (black arrows)
Discharge from hospital was possible at day 16 with oral anticongestive medication and ASS.

Cardiac computed tomography confirmed the single coronary artery arising from the right coronary sinus. The branching left coronary artery showed a retroaortic course (Fig. 1). According to the Lipton classification, this represents a type RII-P single coronary artery [2]. There were no signs of acute myocarditis in cardiac magnetic resonance tomography.

MIS-C is a rare complication following SARS-CoV-2 infection, usually occurring after an interval of 2–6 weeks [1]. The clinical manifestations may be similar to those of KD including affection of coronary arteries in 6–24% [3, 4]; in KD coronary localized single or multiple aneurysms occur in about 25%. Macrophage activation syndrome, toxic shock syndrome, sepsis, and other inflammatory or infectious diseases are differential diagnoses to be considered [5]. To date, the pathogenesis of MIS-C is only partially understood; the role of autoantibodies and cytokine mediated inflammation is discussed in several studies [6, 7]. Recently, we reported on neutralizing autoantibodies against the interleukin 1-receptor antagonist (IL-1Ra-Ab) in MIS-C [8] which as well had been detected in the initial samples of this patient. They may possibly play a key role in the MIS-C associated hyperinflammation, including affection of small systemic and coronary vessels.

In cases of severe MIS-C, administration of methylprednisolone and IVIG is recommended [1]. In refractory states, anakinra (a recombinant interleukin 1-receptor antagonist) may be considered [1].

An isolated single coronary artery is a very rare congenital variant with an incidence of about 0.024–0.066% [9]. There are neither standard values nor z scores for diameters of single coronary arteries available. However, the rapid dynamic changes of the arterial diameter during the clinical course was suggestive for pathological ectasia of the main coronary vessel. Notably, the coronary artery was longitudinally enlarged; neither circumscribed saccular or regional aneurysms (as typical for KD) nor myocardial ischemia did occur. Another difference is the prompt return to normal coronary diameter as KD associated aneurysms >/= 6 mm use to diminish within several months or years [10, 11]. Patients with giant aneurysms (> 8 mm) are at highest risk for cardiac events. These different manifestations may be caused by different immunological inflammatory pathogenesis of both diseases [8].

Strict cardiac evaluation and clinical surveillance are necessary in patients suffering from MIS-C. In ultra-rare cases of combined congenital and acquired coronary affections, the risk for myocardial ischemia is incalculable.

Funding Open Access funding enabled and organized by Projekt DEAL.

Declarations

Conflict of interest None.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References

1. Henderson LA, Canna SW, Friedman KG, Greerlik M, Lapidus SK, Bassiri H, Behrens EM, Ferris A, Kernan KF, Schulert GS, Seo P, Son M, Tremoulet AH, Yeung RSM, Mudano AS, Turner AS, Karp DR, Mehta J (2021) American college of rheumatology clinical guidance for multisystem inflammatory syndrome in children associated with SARS-CoV-2 and hyperinflammation in pediatric COVID-19: version 2. Arthritis Rheumatol 73(4):e13–e29. https://doi.org/10.1002/art.41616
2. Aldana-Sepulveda N, Restrepo CS, Kimura-Hayama E (2013) Single coronary artery: spectrum of imaging findings with multidetector CT J Cardiovasc. Comput Tomogr 7(6):391–399. https://doi.org/10.1016/j.jcct.2013.11.009
3. Sperotto F, Friedman KG, Son M, VanderPluym CJ, Newburger JW, Dionne A (2021) Cardiac manifestations in SARS-CoV-2-associated multisystem inflammatory syndrome in children: a comprehensive review and proposed clinical approach. Eur J Pediatr 180:307–322. https://doi.org/10.1007/s00431-020-03766-6
4. Zhang QY, Xu BW, Du JB (2021) Similarities and differences between multiple inflammatory syndrome in children associated with COVID-19 and Kawasaki disease: clinical presentations, diagnosis, and treatment. World J Pediatr 17(4):335–340. https://doi.org/10.1007/s12519-021-00435-y
5. McArdle AJ, Vito O, Patel H, Seaby EG, Shah P, Wilson C, Broderick C, Nijman R, Tremoulet AH, Munblit D, Ulloa-Gutierrez R, Carter MJ, De T, Hoggart C, Whittaker E, Herberg JA, Kafourou M, Cunnington AJ, Levin M, BATS Consortium (2021) Treatment of multisystem inflammatory syndrome in children. N Engl J Med 385(1):11–22. https://doi.org/10.1056/NEJMoa2102968
6. Gruber CN, Patel RS, Trachtmann R, Lepow L, Amanat F, Crummer F, Wilson KM, Onel K, Geanon D, Tuballes K, Patel M, Mouskas K, O’Donnell T, Merritt E, Simons NW, Barcressat V, Del Valles DM, Udendasm S, Kang G, Gangadharan S, Ofori-Amango G, Laserson U, Rahman A, Kim-Schulze S, Charney AW, Gnajtac S, Gelb BD, Merad M, Bogunovic D (2020) Mapping systemic inflammation and antibody responses in multisystem inflammatory syndrome in children (MIS-C). Cell 183(4):982-995.e14. https://doi.org/10.1016/j.cell.2020.09.034
7. Consiglio CR, Cotugno N, Sardh F, Pou C, Amodio D, Rodriguez L, Tan Z, Zicari S, Ruggiero A, Pascucci GR, Santilli V, Campbell T, Bryceson Y, Eriksson D, Wang J, Marchesi A, Lakshmikanth T, Campana A, Villani A, Rossi P, CACTUS Study Team, Landegren N, Palma P, Brodin P (2020) The immunology of multisystem inflammatory syndrome in children with COVID-19. Cell 183(4):968-981.e7. https://doi.org/10.1016/j.cell.2020.09.016

8. Pfeifer J, Thurner B, Kessel C, Fadle N, Kheiroddin P, Regitz E, Hoffmann MC, Kos IA, Preuss KD, Fischer Y, Roemer K, Lohse S, Heyne K, Detemple MC, Fedlmeier M, Juenger H, Sauer H, Meyer S, Rohrer T, Wittkowski H, Becker SL, Masjosthusmann K, Bals R, Gerling S, Smola S, Bewarer M, Birk E, Keren A, Böhm M, Jakob A, Abdul-Khalil H, Anton J, Kabesch M, Pino-Ramirez RM, Foell D, Thurner L (2022) Autoantibodies against interleukin-1 receptor antagonist in multisystem inflammatory syndrome in children: a multicentre, retrospective, cohort study. Lancet Rheumatol 4(5):e329–e337. https://doi.org/10.1016/S2665-9913(22)00064-9

9. Desmet W, Vanhaecke J, Vrolix M, Van de Werf F, Piessens J, Willems J, de Geest H (1992) Isolated single coronary artery: a review of 50,000 consecutive coronary angiographies. Eur Heart J 13(12):1637–1640. https://doi.org/10.1093/oxfordjournals.eurheartj.a060117

10. Tsuda E, Hashimoto S (2021) Changes in coronary aneurysm diameters after acute Kawasaki disease from infancy to adolescence. Pediatr Cardiol 42(8):1749–1756. https://doi.org/10.1007/s00246-021-02659-1

11. Tsuda E, Hashimoto S (2021) Time course of coronary artery aneurysms in Kawasaki disease. J Pediatr 230:133-139.e2. https://doi.org/10.1016/j.jpeds.2020.12.004