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CASE REPORT

Neonatal severe COVID-19 infection complicated by Staphilococcus aureus could be misinterpreted as MIS-C?: case report and review of literature

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SUMMARY

At 23 days of life a neonate presented to the emergency room with crying and decreased oral intake. His parents were positive to SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), but he turned out negative. After one week he was admitted to NICU (neonatal intensive care unit) for respiratory failure, and nasopharyngeal swab (PCR test: polymerase chain reaction test) was positive for SARS-CoV-2. On examination the child had fever, tachy-dyspnea, reduced oxygen saturation, tachycardia, abdominal distension and tenderness, irritability and hypertonia. Blood exam showed respiratory acidosis, lymphocytopenia, hypoalbuminemia and coagulopathy; CRP (C reactive protein), procalcitonin, D-dimer, ferritin and NT-proBNP (N-terminal prohormone of brain natriuretic peptide) were elevated. Chest X-ray revealed bilateral interstitial infiltration and abdomen ultrasound a thin fluid effusion; echocardiography was normal. SARS-CoV-2 PCR tests on CSF (cerebrospinal fluid) and stool were also positive. He was started on non-invasive intermittent positive pressure respiratory ventilation, treated with antibiotic therapy, methylprednisolone, intravenous immunoglobulins, and antiplatelet therapy. Rapid clinical improvement was seen with remission of fever after eight days. The child complicated with bacterial super-infection presenting as pleural empyema.

As presented in our case, it is not always easy to differentiate between severe forms of COVID-19 and MIS-C. Due to the rarity of these presentations in neonates, multicentric collaboration is needed to identify the specific characteristics of the two forms, better define diagnostic criteria, and treatment options.

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INTRODUCTION

SARS-CoV-2 usually causes a less severe form of COVID-19 in children compared to adults. Nevertheless, a minority of children may have significant respiratory symptoms and could develop a hyperinflammatory response (Henderson LA *et al*., 2021). Severe disease indicators, including oxygen requirement, invasive/non-invasive mechanical ventilation, vasopressors, renal dialysis, cardiopulmonary resuscitation and death, have been used to define severe COVID-19 (Hobbs CV *et al*., 2022). A clinical syndrome similar to Kawasaki Disease has been described in children with a history of exposure to SARS-CoV-2 and named multisystem inflammatory syndrome in children (MIS-C) (Henderson LA *et al*., 2021). The incidence of MIS-C in patients younger than 21 years old is 2 per 100,000 (Dufort EM *et al*., 2021) Recent case series of MIS-C have been described in neonates born to mothers positive to SARS-CoV2 during pregnancy (Costa S *et al*., 2021) (Viraraghavan Vadakkencherry Ramaswamy *et al*., 2023). We present a case of a neonate with severe COVID-19 that could fulfil the diagnostic criteria for MIS-C, and discuss the case after the review of available literature on severe forms of COVID-19 and MIS-C in neonates and infants.

Key words:
Neonatal COVID-19, MIS-C, S. aureus.

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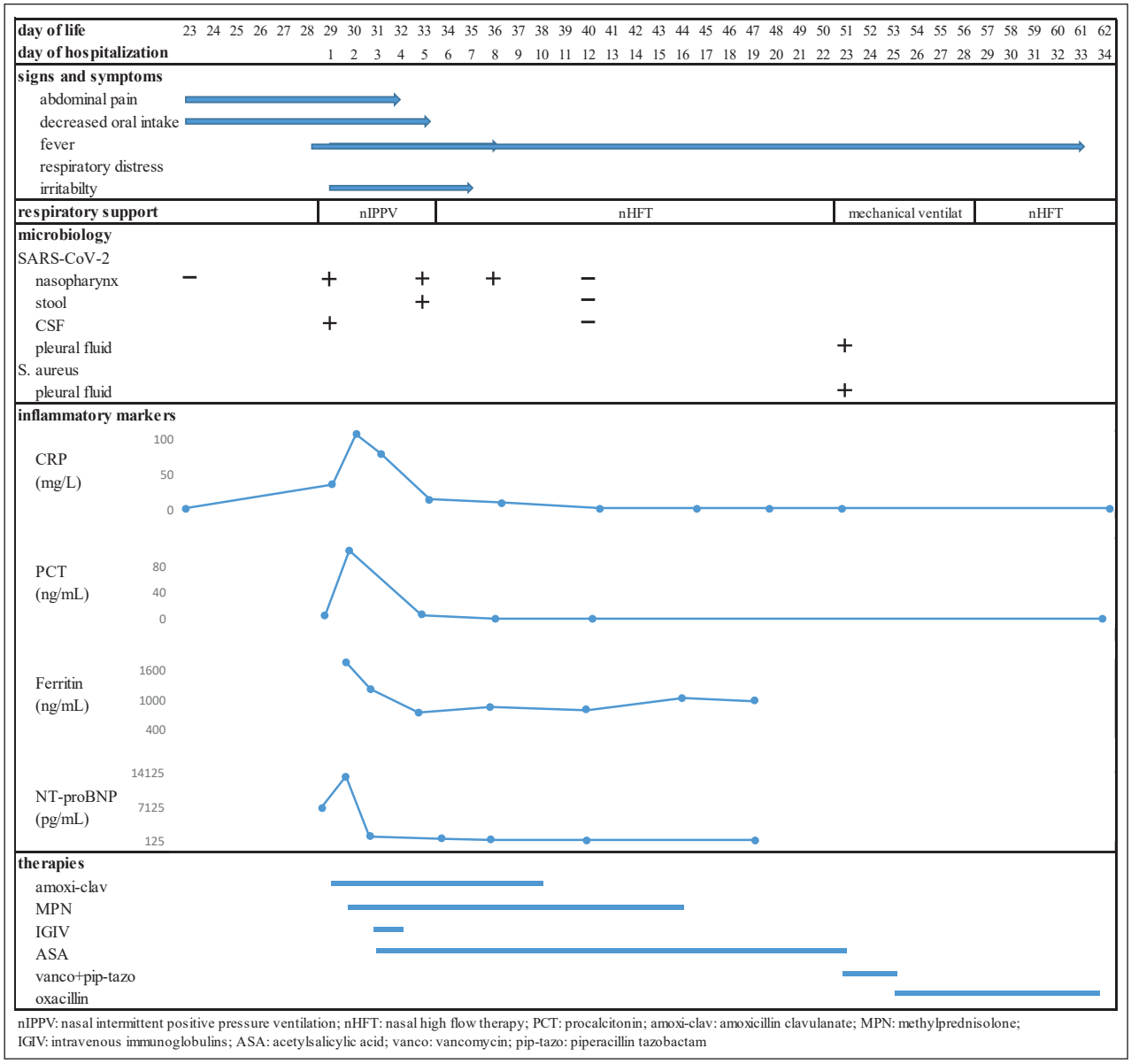
CASE PRESENTATION

A 2780 g male baby was delivered via spontaneous vertex delivery at term in a state hospital after normal gestation. The baby was discharged without any problem on postnatal Day 2. At 23 days of life, he presented to the emergency room of a peripheral hospital with a brief history of irritability and decreased oral intake. Past medical history as well as

family history were uneventful. His mother was not vaccinated for SARS-CoV-2 and the maternal nasopharyngeal swab at delivery was negative for SARS-CoV-2.

On admission his parents were discovered with a positive third generation SARS-CoV-2 antigen test on nasopharyngeal swab; on the contrary, the baby's test was negative. Routine blood tests (complete blood count and CRP) were unremarkable and after brief observation the child was discharged. One week later he returned and was admitted at our department for respiratory failure. On admission polymerase chain reaction test for SARS-CoV-2 was positive on nasopharyngeal swab. Physical examination revealed fever, respiratory distress (respiratory rate of 66/min) with bilateral rales, tachycardia (heart rate of 180/min), and abdominal tenderness on palpation. His oxygen saturation was 88-89% in room air and blood gas analysis showed respiratory acidosis (pH 7.13, pCO_2 78 mmHg, pO_2 32,4 mmHg, HCO_3- 25.5 mmol/l, BE -5 mmol/l). The neurological examination showed irritability, axial hypertonia and opisthotonos. Complete blood count [WBC (white blood cells) 4900/mL, hemoglobin 10.4 g/L, hematocrit 36.2% and platelet counted 163,000/mmc] and biochemical parameters (liver and renal function tests) were all in normal ranges except for a modest leukopenia and anemia. CRP was 108 mg/L (reference range: 0-5), procalcitonin 104 ng/mL (reference range < 0.5), ESR (erythrocyte sedimentation rate) 17 mm/h (reference range: <35), ferritin 1759 ng/mL (reference range: <400), albuminemia 19 g/L (refer-



nIPPV: nasal intermittent positive pressure ventilation; nHFT: nasal high flow therapy; PCT: procalcitonin; amoxi-clav: amoxicillin clavulanate; MPN: methylprednisolone; IGIV: intravenous immunoglobulins; ASA: acetylsalicylic acid; vanco: vancomycin; pip-tazo: piperacillin tazobactam

Figure 1 - *Clinical history, microbiology, laboratory findings and therapies.*

ence range 27-48), NT-proBNP: 7080 pg/mL (reference range: <125), troponin I 38 pg/mL (reference range: <14), prothrombin time INR 0,98, activated partial thromboplastin time 1.33, fibrinogen 381 mg/dL (reference range: 200-450), antithrombin III 44% (reference range: 75-125), D-Dimer 1606 ng/mL (reference range <500 ng/ml) (*Figure 1*). Cerebral ultrasound and EEG were normal. Chest X-ray revealed bilateral interstitial infiltration. Abdomen ultrasound showed a thin fluid effusion in the perihepatic and perisplenic areas (4 mm) and in the pelvic cavity (7 mm). Echocardiography was normal. Nasopharyngeal swab was negative for other viral and atypical agents of pneumonia (adenovirus, bordetella pertussis/parapertussis, chlamydia pneumonia, mycoplasma pneumonia, metapneumovirus, rhinovirus, influenza virus A/B, parainfluenza, respiratory syncytial virus and cytomegalovirus). Blood, urine and cerebrospinal fluid (CSF) cultures for bacterial infection were negative. SARS-CoV-2 PCR tests on CSF and stool were positive. On admission non-invasive intermittent positive pressure respiratory ventilation was initiated together with antibiotic therapy with amoxicillin clavulanate while waiting for microbiological results. On the second day of hospitalization methylprednisolone (2 mg/kg/die) was started for worsening respiratory distress, and was continued, with progressive tapering, for a total of 15 days. Suspecting a multisystem inflammatory syndrome intravenous immunoglobulins (1 g/kg) were given on the third and fourth day of hospitalization and antiplatelet therapy with acetylsalicylic acid was started. Clinical improvement was seen beginning from the fifth day when ventilation was weaned to high flow nasal therapy.

Complete remission of the fever was seen on day eight. Blood tests showed improvement; in particular, CRP and procalcitonin levels showed prompt decrease with negativization after seven days from admission. SARS-CoV-2 PCR tests on nasopharyngeal swab, CSF and stool became negative on the 11th day of hospitalization.

On the 20th day of hospitalization, the patient showed new respiratory difficulty with clinical worsening. Chest X-ray revealed right interstitial infiltration and corpuscular pleural effusion consistent with empyema. Thoracoscopic cleaning was then performed. Methicillin-sensitive S. aureus was isolated on pleural fluid culture and antibiotic therapy with oxacillin was started for 10 days. SARS-CoV-2 PCR test on pleural effusion was positive.

DISCUSSION

Since April 2020, several studies in the UK, New York, Italy and France have described clusters of children, temporally associated with SARS-CoV-2 infection, presenting with manifestations similar to Kawasaki disease (Hobbs CV *et al.*, 2022; Riphagen S *et al.*, 2020; Toubiana J *et al.*, 2022). This new clinical entity was later named MIS-C, and the CDC (United States Centers for Disease Control and Prevention) and the WHO (World Health Organization) have established specific criteria for its diagnosis. (HAN, 2019) (WHO, 2020) (*Table 1*). MIS-C more commonly affects children and adolescents (>7 years of age) (Gottlieb M *et al.*, 2021; S. Diggikar *et al.*, 2022) but cases have also been reported in children younger than 12 months (Orlanski-Meyer E *et al.*, 2020; Saha S *et al.*, 2021). Furthermore, some authors have warned the neonatal community of the possibility of MIS-C in neonates born to mothers with COVID-19, labelled as multisystem inflammatory syndrome - MIS-N (L.A. Shaiba *et al.*, 2022). The authors hypothesize that the multisystem inflammation in MIS-N is secondary to COVID-19 in the mother with passive transmission of antibodies (Pawar R *et al.*, 2021). Our case could be interpreted as a multisystem inflammatory syndrome in a neonate secondary to postnatal SARS-CoV-2 infection, with the limit of the short time passing between the first SARS-CoV-2 exposure and the onset of symptoms (usually two to six weeks vs one week in our case). The etiopathogenesis of MIS-C in neonates is still debatable; furthermore, the exact mechanism of MIS-C in children is still unclear, but is likely due to immune dysregulation following SARS-CoV-2 exposure (Pawar R *et al.*, 2021; Sristi Upadhyay *et al.*, 2023). The neonatal immune system

Table 1 - *WHO and CDC case definition of MIS-C.*

*WHO**		*CDC***	
1.	Age less than 19 years	1.	Age less than 21 years
2.	Fever for more than 3 days	2a.	Fever lasting more than 24 hours
3.	Clinical signs of multisystem involvement	2b.	Severe illness requiring hospitalization with two or more organ systems involved
4.	Elevated markers of inflammation	2c.	Laboratory evidence of inflammation
5.	No other obvious microbial cause of inflammation	3.	No alternative plausible diagnoses
6.	Evidence of SARS-CoV-2 infection or contact with patients with COVID-19	4.	Recent or current SARS-CoV-2 infection or exposure to SARS-CoV-2 within the 4 weeks prior
*All six criteria must be met		**All four criteria must be met	

is immature and may not produce sufficient SARS-CoV-2 antibodies (More K *et al*., 2022). Our case poses a diagnostic and therapeutic dilemma between a severe form of coronavirus disease with multisystemic involvement in a neonate and a case of MIS-C secondary to postnatal SARS-CoV-2 infection. In fact, our patient fulfills the diagnostic criteria for MIS-C for both the CDC and the WHO, but the time elapsed between the first SARS-CoV-2 exposure and the onset of symptoms is shorter than expected (usually two to six weeks vs one week in our case). In addition, children with MIS-C are more likely to have severe cardiovascular or mucocutaneous involvement and extreme inflammation than those with severe COVID-19 (Feldstein LR *et al*., 2021). Our patient had no mucocutaneous manifestation and only biochemical signs of cardiovascular involvement. Although it is questionable whether our case could be classified as MIS-C in a neonate, it can certainly be classified as an acute severe form of COVID-19 due to the severity of pneumonia that required non-invasive ventilation and the multiorgan involvement. Children with a complex medical history tend to have a more severe form of the disease, but also healthy infants, less 1 year of age, most likely develop severe illness from SARS-CoV-2 infection (Alsohime F *et al*., 2020; Cook J *et al*., 2020). In a case series of 38 infants ≤90 days old nearly 10% had severe or critical presentation, suggesting that infants of that age may have more severe disease than what has been reported in older children (Shaiba LA *et al*., 2019). Furthermore, an active surveillance study from the UK confirmed a higher rate of severe COVID-19 in neonates, 42% of their cases, probably overestimated in view of the prematurity of 24% of the babies in the series (Gale C *et al*., 2021). A systematic review of 17 articles and meta-analysis of 10 concluded that neonate and premature infants had a high risk of severe COVID-19 (Choi JH *et al*., 2022).

The aim of differentiating between severe acute form of COVID-19 and MIS-C is not only speculative but can have therapeutic and prognostic implications. Peculiar to our case report is also the presence of SARS-CoV-2 in several specimens. To our knowledge, this is the first documented case of positivity of SARS-CoV-2 PCR test on CSF. Cases reported in the literature in which CSF was analyzed to detect SARS-CoV-2 found negative results (Toubiana J *et al*., 2020; Gottlieb M *et al*., 2021; Bakhle A *et al*., 2022; Agrawal G *et al*., 2021). In addition, our patient presented with a very rare complication of SARS-CoV-2 pneumonia, i.e., pleural empyema. Among children a single case was described in a 12-year-old boy (Abbasi R *et al*., 2021). The positivity of SARS-CoV-2 PCR test on the pleural exudate is also exceptional.

In summary, we present a neonatal case of acute severe COVID-19 disease with multisystem inflammatory syndrome and positive SARS-CoV-2 PCR tests on nasopharyngeal swab, stool, cerebrospinal fluid and pleural effusion. Severe forms of COVID-19 and MIS-C are rare in neonates and infants, and it is not always easy to differentiate between the two entities. Multicentric collaboration is needed to identify the specific characteristics of the two forms and to better define diagnostic criteria and treatment options.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report.

Author Contribution

Giovanna Stringari, Laura Nai Fovino and Aldo Naselli conceived of the paper, participated in its design and coordination, and helped draft the manuscript. Michela Capogna helped draft the manuscript. All authors read and improved the final manuscript.

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