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Neonate born with ischemic limb to a COVID-19 positive mother: management and review of literature

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Abstract

Objectives: To describe challenges in diagnosis and treatment of congenital neonatal gangrene lesions associated with history of maternal coronavirus disease 2019 (COVID-19) infection.

Case presentation: A preterm neonate was born with upper extremity necrotic lesions and a history of active maternal COVID-19 infection. The etiology of his injury was challenging to deduce, despite extensive hypercoagulability work-up and biopsy of the lesion. Management, including partial forearm salvage and hand amputation is described.

Conclusions: Neonatal gangrene has various etiologies, including compartment syndrome and intrauterine thromboembolic phenomena. Maternal COVID-19 can cause intrauterine thrombotic events and need to be considered in a differential diagnosis.

Keywords: COVID pregnancy; limb necrosis; newborn; thromboembolic phenomenon.

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Introduction

Pregnant women and their fetuses, because of necessary routine health care visits, are at increased risk for the acquisition of coronavirus disease 2019 (COVID-19). Despite this, the impact of COVID-19 on pregnancy and perinatal outcomes remains unclear. The potential of vertical transmission of COVID-19 has been suggested, but of relevant concern are complications of COVID-19 coagulopathy or impact on blood circulation [1].

Reports have suggested increased risk for miscarriage, preeclampsia, preterm birth, and stillbirth in mothers infected with COVID-19 [1, 2]. Moreover, some histopathologic examinations of placental tissue have shown fetal vascular malperfusion, vascular thrombi, and arteriopathy in COVID-19 mothers [3, 4]. A larger study has demonstrated lack of any clinically significant differences in the placentas of mothers with COVID-19 compared to matched controls [5]. These findings indicate a need for more data to determine any relationship between COVID-19 infection and increased hypercoagulability during pregnancy. Accordingly, data is needed to determine whether fetuses may be at theoretical risk for intrauterine thrombotic events or any other events induced by maternal infection with COVID-19. Thromboembolic events can be multifactorial and of unclear etiology a lot of times. Here we report a neonate born with an ischemic limb to a COVID-19 positive mother.

Case presentation

A previously healthy 25-year-old woman (gravida 1, para 0) presented at 33 weeks of gestation to the labor and delivery unit of an outside hospital for painful and irregular contractions. The mother was without fever, shortness of breath, or cough. However, a screening admission test revealed she was COVID-19 positive. Genital herpetic lesions were incidentally found on exam. Dexamethasone and ampicillin were given for preterm labor, and the mother underwent an uncomplicated caesarean section delivery. At birth, the infant was noted to have purpuric plaques and hemorrhagic bullae of the left forearm, wrist,

and hand with no spontaneous movement of the left upper extremity. Purpura and bullae soon progressed to necrotic plaques, and the newborn was transferred to our institution for further care at day 2 of life.

Upon presentation, the newborn was admitted to the neonatal intensive care unit (NICU). Empirical acyclovir, ampicillin, and gentamicin were started. Nasopharyngeal COVID-19 PCR swab was negative, but infant was found to have COVID IgG antibodies. These antibodies are understood to have been passed from the mother to the fetus *in utero*. On exam, the left arm of the patient was noted to have necrotic plaques with cyanosis and early necrosis of all digits on the left hand (Figure 1). This progressed to necrosis of the distal forearm and hand (Figure 2). No radial pulse was palpable. Cultures of the blood, urine, and as bulla were sterile at 72 h, and herpes simplex virus (HSV) polymerase chain reaction (PCR) of cerebrospinal fluid (CSF), blood and bullous fluid were non-diagnostic. For possible ischemic event, the neonate was started on unfractionated heparin.

Duplex doppler ultrasound showed no flow within the radial artery at the level of the wrist; however, no venous or arterial clot was visualized. Magnetic resonance angiography/venography (MRA/MRV) of the left upper extremity demonstrated flow in the radial and ulnar arteries up to the level of the wrist, but not beyond. MRA/MRV was also concerning for abnormal enhancement near the elbow thought to represent fasciitis vs. myositis vs. abscess. The condition of the tissues was not unlike what may occur in compartment syndrome.

As amputation of the left arm at the elbow level was initially considered, orthopedics followed closely. Wound care was started in hopes to salvage forearm tissue and minimize amputated length. Nitroglycerin 2% ointment

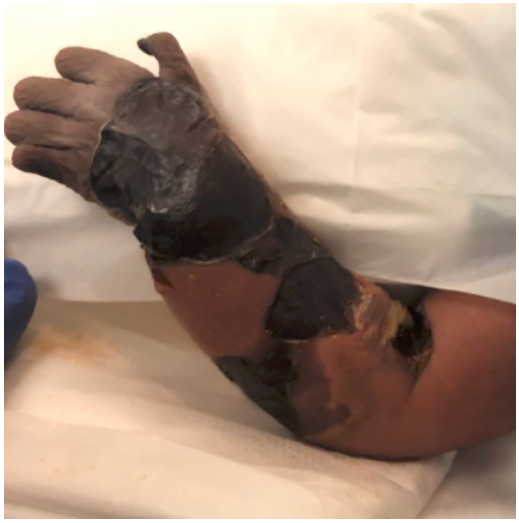

Figure 2: Progression of necrosis of the distal forearm and hand.

was started twice a day to all affected areas followed by concentrated surfactant burn and wound gel (PluroGel®, Medline, Northfield, IL) to alternate with Nitroglycerin ointment (Figure 3). Improvement was noticed as ischemic plaques of the volar forearm and patchy ischemic radial areas began to regress. Necrotic eschars started to demarginalize from healthy tissue. Nitroglycerine treatment was stopped after six days. Enzymatic debrider, Collagenase (Santyl, Smith & Nephew, Fort Worth, TX) was added to wound care regimen to help soften the eschars and facilitate sharp debridement of the dead tissue.

On hospital day 11, the first sharp debridement of the wound was done (Figure 4), followed by two more debridements on hospital days 13 and 14. A clear demarcation border between lower forearm tissues and necrosis at and below the wrist was observed. On hospital day 17, an

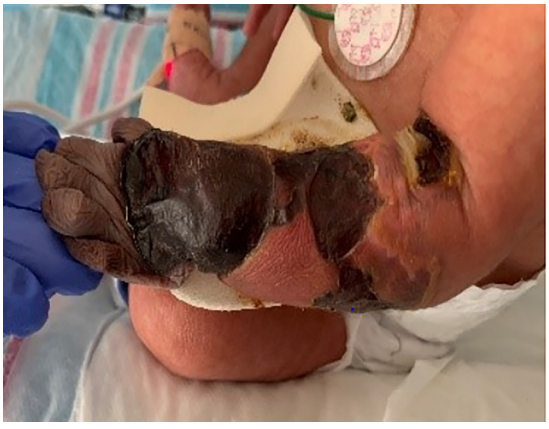

Figure 1: Necrotic plaques with cyanosis and early necrosis of all digits on the left hand.

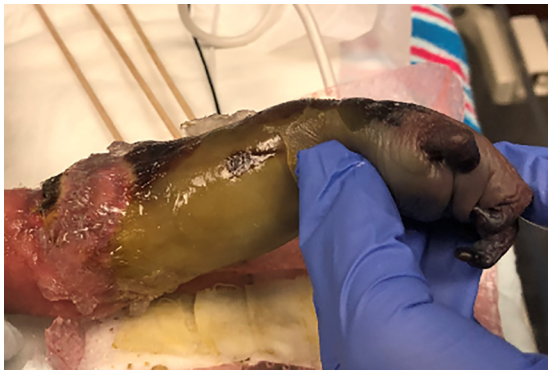

Figure 3: Concentrated surfactant burn and wound gel applied to entire affected area.
It was alternated with nitroglycerin ointment.

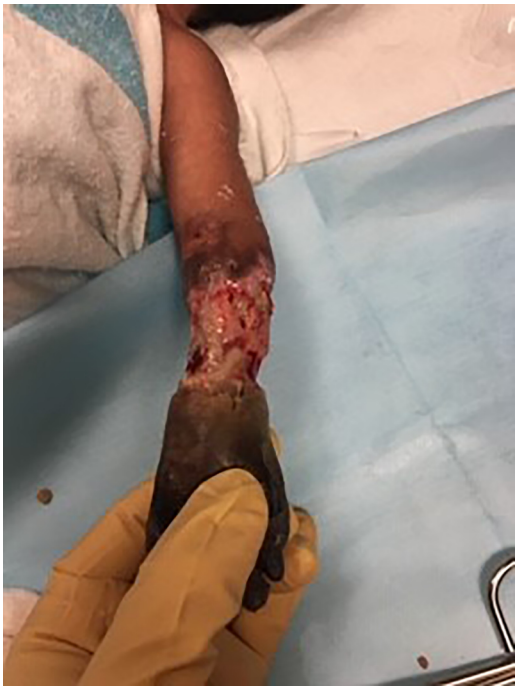

Figure 4: Necrotic forearm tissue removed.
Note healthy underlying muscles and granulation tissue. There was a clear demarcation of full-thickness necrosis starting at the proximal hand.

amputation 4 cm distal to the olecranon tip was performed at 19 days of age. Proximal forearm tissue was viable. Complex wound care with myodesis and meshed matrix wound dressing graft (Integra, Integra Lifesciences, Plainsboro, NJ) was placed, covered by petrolatum wound dressing (Xeroform, DeRoyal, Powell, TN) gauze, and Coban wrap.

Newborn experienced no post-operative complications and on day 5 after surgery (hospital day 22) patient was safely discharged to home with careful follow-up.

Work-up

A thrombophilia workup was negative for Factor V Leiden or prothrombin gene mutation. Levels of homocysteine, plasminogen activator inhibitor-1 activity, Dilute Russell's viper venom time, Factor VIII, D-dimer and lipoprotein a were normal. Antibody screening for Lupus anticoagulant, anticardiolipin, and anti-beta 2 glycoprotein were unrevealing. Protein S, protein C, antithrombin-III, were unable to be interpreted in the setting of prematurity, anticoagulation, and consumption from acute thrombus.

The placenta showed intraluminal focally layered fibrin in chorionic plate vasculature which is inconclusive of thromboembolism [6], along with patency and absence of thromboembolism in all three umbilical cord vessels. In the parenchyma evidence of fetal vascular malperfusion was lacking; there was no finding that would suggest thrombosis in the fetal vasculature. The placental weight was markedly large for gestational age, above the 97th percentile, while the newborn's weight was comparably small, at 50th percentile. The fetal: placental weight ratio is 3.8. This is small and falls below the 3rd percentile, which is 4.3. Normal range of fetal: placental weight ratios at 33 weeks' gestational age is 4.7 (10th percentile) to 7.7 (90th percentile). The baby's weight ratio is small and indicates lower than average placental efficiency in transfer of nutrients to the fetus [7]. Onset of spontaneous preterm labor in the mother also lends credence to the likelihood of reduced placental efficiency. The placenta showed a single infarct, which measured 0.5×0.3 cm, and a separate focus <0.4 cm in diameter, of chronic villitis. These lesions involve <1% of the disc volume and would not impair perfusion of the placenta (Figure 5A–D).

The amputation specimen revealed ischemic necrosis of the left hand and distal forearm without vasculitis, malformation, or tissue anatomic evidence of thromboembolism, or inflammation. A separate biopsy of viable skin showed a thin parakeratotic crust and mild acanthosis. There was subcutaneous fat necrosis, squamous metaplasia of the eccrine sweat glands, and panniculitis with neutrophils and frequent eosinophils (Figure 6A, B). No compelling evidence of vasculitis or vasculopathy was present. On this skin sample, special stains for microorganisms GMS (Gromori Methenamine Silver) and PAS (Periodic Acid Schiff base) for fungus, AFB for acid fast bacteria, and Gram for bacteria, were all negative; no organism seen. No viral cytopathic effect was identified. No inflammatory or thromboembolic etiology for the necrosis was identified. The cause remains uncertain.

Repeat IgG levels of antibodies in the baby against severe acute coronavirus 2 (SARS-CoV-2) obtained on 14 day of life and showed a decrease in titers. IgM antibody testing was not available at our institution.

Discussion

Our report of a congenital ischemic limb in a neonate born to a COVID-19 mother illustrates several aspects of COVID-19 infection in pregnancy that are not yet fully understood, including risk to the fetus. Our patient with *in utero* limb ischemia had no evident risk factors. The pregnancy course was uncomplicated including absence of oligohydramnios or amniotic bands. The mother of the patient had no prior

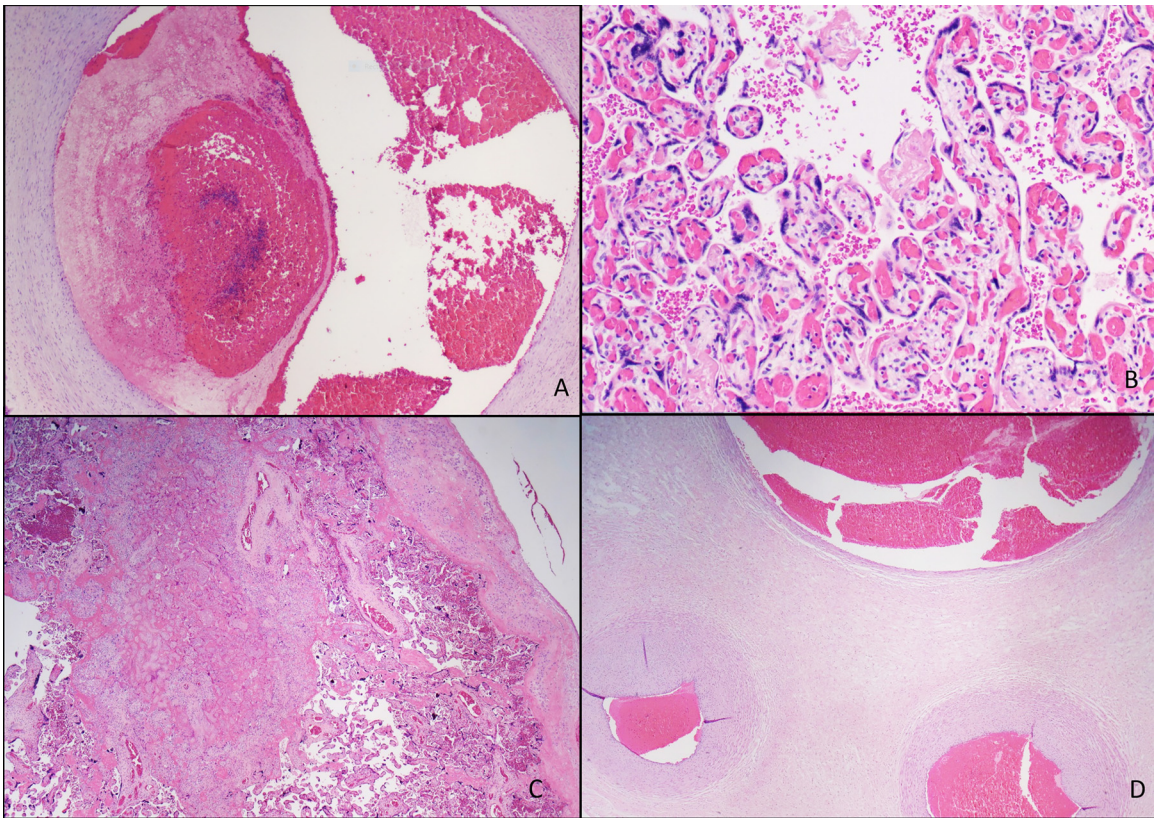

Figure 5: Umbilical vessels and chorionic plate vessels, placental parenchyma.
(A) Fibrin focally layered within lumen of chorionic plate vessel, 400× magnification. (B) Placental villi, with patent fetal vasculature and accelerated maturation, 100× magnification. (C) Placental infarct, 200× magnification. (D) Trivascular umbilical cord; absence of thrombus and absence of embolism in umbilical vessels, 200× magnification.

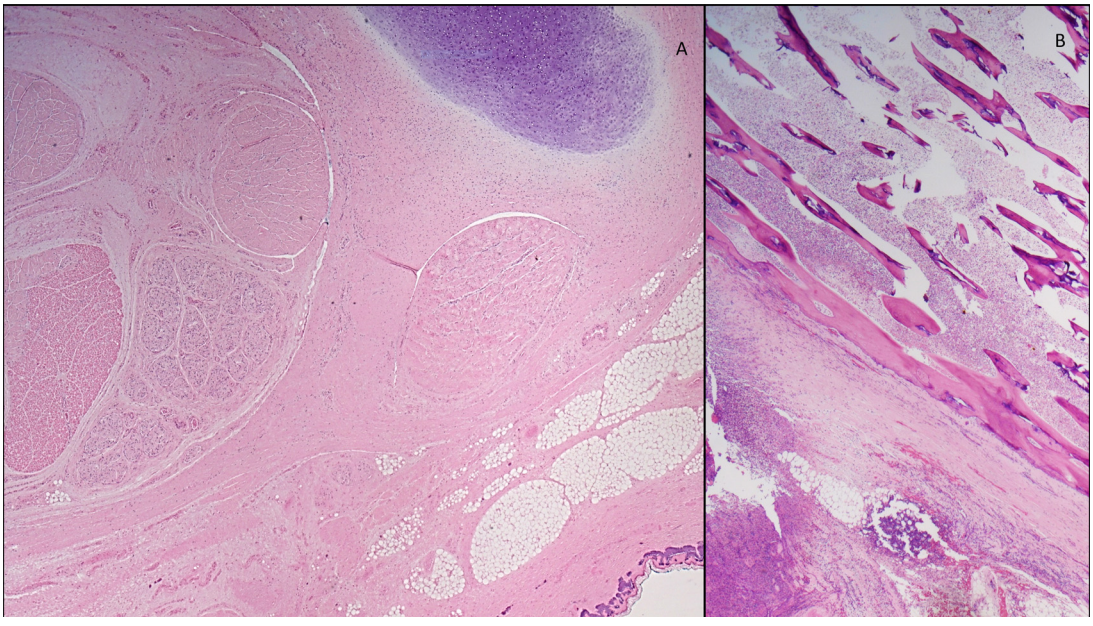

Figure 6: Forearm necrosis.
(A) Ischemic necrosis of skin, subcutaneous connective tissue, muscle, and bone; Bacterial spread into lymphatic channels, 20× magnification.
(B) Ischemic necrosis of bone and attached connective tissue, 20× magnification.

thrombotic events, no family history of thrombophilia/thrombo-embolic events, and no past miscarriages. Lastly, the hypercoagulable workup for the neonate was unremarkable. In all, our patient showed what could be sequelae of compartment syndrome or of thromboembolism. It is not clear whether her events were related to COVID-19 infection in pregnancy, but the association is not excluded. Arterial thrombosis affecting a limb in a neonate *in utero* has previously been reported, with definitive identification of the thrombus [8] and it occurred several years prior to COVID-19.

Another possibility of limb ischemia in a neonate is compartment syndrome, a rare condition of unclear etiology. This phenomenon is associated with increased pressure in fascio cutaneous compartments leading to inadequate perfusion, ischemia, and necrosis. Causes of compartment syndrome in the newborn include extrinsic (oligohydramnios, umbilical loops, or amniotic band), or intrinsic (arterial embolus or neonatal hypercoagulability) [9–11]. There is no consensus in the literature on causal relationship to the condition. Newborns can present with varying degree of ischemia with or without skeletal involvement but, interestingly, without any signs of rhabdomyolysis or renal failure, as also observed in our patient. That our patient's placenta was so extremely large might be a basis for relative oligohydramnios, reducing the effective space for movement of the arm and for flow of amniotic fluid around the arm. If the excessive volume of the placenta effectually led to restriction of fluid and movement of the arm, compression of the arm, and consequent ischemia, this would result in compartment syndrome as the etiology for ischemia. To date, COVID-19 maternal infection has not been found a risk factor for excessive placental size [5].

Some placental pathology studies related to SARS-COV-2 during pregnancy have suggested COVID-19-related tendency towards coagulopathy and possible transplacental impact on the fetus [3, 4]. In a review of 20 placentas whose mother tested positive for COVID-19, 10 showed evidence of fetal vascular malperfusion from fibrin deposition or fetal vascular thrombosis [3]. In a case control study from Chicago of 15 placentas compared against 17,500 historical controls, a statistically significant increase in intervillous thrombi was demonstrated among COVID-19 patients [4]. Conversely, a retrospective control study in New York of 50 placentas from COVID-19 mothers compared to 50 control placentas from patients without COVID-19 showed no statistically significant differences [5]. In our patient, placental pathology was significant for excessive size for gestational age, intravascular fibrin, and infarct – signs of lower than average efficiency. Our case showcases the significant clinical implication this may have. Of note, the mother of our patient is similar to the patients in these case series, none had any identified thrombophilia and most had only mild to absent COVID-19 disease course.

Conclusions

To the best of knowledge, we report the first *in utero* neonatal perfusion complication taking place in the setting of maternal COVID-19 infection. Our case raises important concerns for neonatal morbidity from COVID-19 infection in mother, even with an asymptomatic clinical course. Moreover, our case highlights the perplexing and largely unknown pathophysiology of COVID-19 impact on vascular circulation. While studies have suggested COVID-19 coagulopathy as a secondary outcome of severe illness, it is not clear what impact this may have on the pregnant state or on fetuses *in utero*. Various mechanisms of adverse outcomes may be involved, including viral mediated endothelial dysfunction, antiphospholipid syndrome, and unique properties of the virus itself [12]. Pregnant patients and their providers should be aware of the need for caution and continue social distancing, hand hygiene, and other preventive methods to limit the spread and acquisition of COVID-19.

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Informed consent: Informed consent was obtained from all individuals included in this study.
Ethical approval: Research involving human subjects complied with all relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration (as revised in 2013).

References

1. Di Mascio D, Khalil A, Saccone G, Rizzo G, Buca D, Liberati M, et al. Outcome of coronavirus spectrum infections (SARS, MERS, COVID 1-19) during pregnancy: a systematic review and meta-analysis. Am J Obstet Gynecol MFM 2020;2:100107.
2. Khalil A, von Dadelszen P, Draycott T, Ugwumadu A, O'Brien P, Magee L. Change in the Incidence of Stillbirth and Preterm Delivery During the COVID-19 Pandemic. JAMA. 2020. https://doi.org/10.1001/jama.2020.12746.
3. Baergen RN, Heller DS. Placental pathology in Covid-19 positive mothers: preliminary findings. Pediatr Dev Pathol 2020;23:177–80.

4. Shanes ED, Mithal LB, Otero S, Azad HA, Miller ES, Goldstein JA. Placental pathology in COVID-19. Am J Clin Pathol 2020;154: 23–32.
5. Gulersen M, Prasannan L, Tam HT, Metz CN, Rochelson B, Meirowitz N, et al. Histopathological evaluation of placentas after diagnosis of maternal SARS-CoV-2 infection. Am J Obstet Gynecol MFM 2020:100211. https://doi.org/10.1016/j.ajogmf.2020.100211.
6. Mulvey JJ, Magro CM, Ma LX, Nuovo GJ, Baergen RN. Analysis of complement deposition and viral RNA in placentas of COVID-19 patients. Ann Diagn Pathol 2020;46:151530.
7. Hayward CE, Lean S, Sibley CP, Jones RL, Wareing M, Greenwood SL, et al. Placental adaptation: what can we learn from birthweight: placental weight ratio? Front Physiol 2016;7:28.
8. Szvetko A, Hurrion E, Dunn A, Fasihullah S, Withers S. Axillary artery thrombosis in a neonate in utero: a case report. Case Rep Pediatr 2014;2014:417147.
9. Mehta S, Agarwal J. Neonatal compartment syndrome. Eplasty 2015;15:ic57.
10. Agrawal H, Dokania G, Wu SY. Neonatal Volkmann ischemic contracture: case report and review of literature. AJP Rep 2014;4: e77–80.
11. Ragland R, Moukoko D, Ezaki M, Carter PR, Mills J. Forearm compartment syndrome in the newborn: report of 24 cases. J Hand Surg Am 2005;30:997–1003.
12. Rico-Mesa JS, Rosas D, Ahmadian-Tehrani A, White A, Anderson AS, Chilton R. The role of anticoagulation in COVID-19-induced hypercoagulability. Curr Cardiol Rep 2020;22:53.