Osteomyelitis and Thrombosis in a Newborn with Group A Streptococcus Infection

Georgios Mitsiakos, Dimitra Gialamprinou, Christos Tsakalidis, Evgenia Babatseva, Maria Lithoxopoulou, Elisavet Diamanti
2nd Neonatal Department and Neonatal Intensive Care Unit, Aristotle University of Thessaloniki, "Papageorgiou" General Hospital of Thessaloniki, Thessaloniki, Greece

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Abstract: Neonatal osteomyelitis (OM), although exceptionally rare, has been linked to detrimental sequel, as diagnosis in the early stages is challenging and any delay in treatment can lead to disturbance in skeletal growth. In pediatric OM the most commonly grown bacteria is *Staphylococcus aureus* followed by *group A Streptococcus* (GAS). Notwithstanding, sepsis-induced coagulopathy is a well-known entity in children and adults, still sepsis-associated thrombosis is sparsely observed. we present a case of a newborn with GAS associated OM and thrombosis. A term neonate on the 11th day of life was referred to our NICU due to right (R) lower limb edema, cyanosis and core temperature up to 39 °C. Late onset sepsis was suspected and started on vancomycin and amikacin. A colour Doppler scan showed thrombosis of the R common femoral vein. The neonate started on iv unfractionated heparin. Ampicillin was added given positive for GAS blood culture. An MRI on the 5th day of admission, showed evidence of thrombosis resolution. On the 14th day of admission, a bone Tc99 scan showed evidence of OM of R femur. Antibiotic treatment switched to amoxicillin per os. The management was restricted to anticoagulant therapy with low molecular weight heparin for 3 months and antibiotic therapy for 6 months without surgery intervention and the patient recovered and discharged at 42 days of age. Early diagnosis and treatment of neonatal osteomyelitis can prevent bone destruction. Sepsis-associated thrombosis is barely observed during osteomyelitis, yet it should be considered as an emerged case requiring prompt treatment.

Mailing Address: Assoc. Prof. Georgios Mitsiakos, MD., PhD., 2nd Neonatal Department and Neonatal Intensive Care Unit, Aristotle University of Thessaloniki, "Papageorgiou" General Hospital of Thessaloniki, Ring Road, Nea Efkarpia, PC 56403, Thessaloniki, Greece; Phone: +30 231 332 33 54; e-mail: mitsiakos@auth.gr

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Introduction

The prevalence of osteomyelitis (OM) in neonates ranges from 1–3 cases for every 1,000 hospitalized subjects (Frederiksen et al., 1993). From a pathophysiological aspect, the presence of transphyseal vessels crossing the growth plate makes possible the spread of infection from metaphysis to epiphysis. Osteomyelitis in neonates is challenging to diagnose in early stages and, although not frequent, can potentially lead to joint destruction and growth failure. The most common cause of OM is *Staphylococcus aureus* followed by maternal vaginal pathogens (Ilharreborde, 2015). In neonates very few cases of OM attributed to *group A Streptococcus* (GAS) have been described (Berberian et al., 2010). The invasive type of GAS infection is linked to the M-protein mediated activation of the clotting cascade (Ben Nasr et al., 1995). Vascular thrombosis as purpura fulminans is a well-recognized clinical feature of coagulopathy dysregulation provoked by generalized GAS infection (González-Abad and Alonso Sanz, 2020).

Regarding coagulopathy in the neonatal period, hemostasis following developmental age-related maturation pattern is widely stressed for thromboembolic events (Andrew, 1995). Thromboembolism in hospitalized neonates ranges from 2.4 to 6.8 events per 1,000 admissions (van Elteren et al., 2011). Particularly, venous thrombosis represents 50% of thromboembolic events, and deep venous thrombosis mostly comes as a complication of central line insertion while neonatal thrombosis is strongly correlated with sepsis (Monagle et al., 2012).

However, neonatal OM from GAS combined with deep vein thrombosis as a sequel of GAS-associated invasive disease has not been reported so far. We report a case of neonatal OM in parallel with thrombosis of the affected limb caused by GAS in a term female newborn.

Case report

A female neonate on the 11th day of life was referred to our NICU (Neonatal Intensive Care Unit) from a secondary hospital facility due to right (R) lower limb edema, cyanosis and core temperature up to 39 °C. A 2-day course of agitation and reduced oral intake had preceded the referral. Reduced spontaneous movement of the right (R) lower limb and pain in diaper changes were also reported. No clinical signs of upper respiratory tract infection were noted. This was a term neonate delivered from a multigravida 24-years-old mother at 40 weeks postmenstrual age with caesarean section due to breech position of the baby. Birth weight was 3,760 g and somatometric features were within normal range.

During admission, physical examination revealed paleness, mottled skin and irritability, rectal temperature of 39 °C. She weighed 3,850 g. Clinical evidence of right lower limb swelling combined with erythematous appearance of skin which was painful on palpation with markedly reduced spontaneous movements of femur, raised the suspicion of deep vein thrombosis (Figure 1A). She was hemodynamic stable without need for cardiovascular or respiratory support. Laboratory

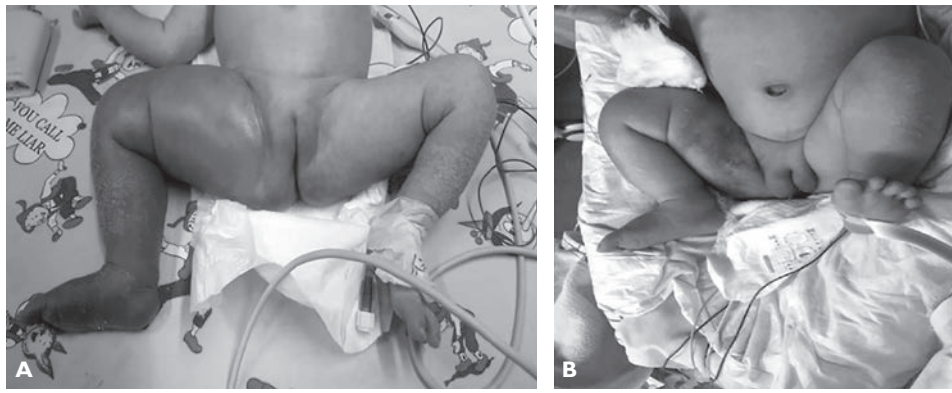

Figure 1A – Swelling and discoloration of right lower limb indicative of thrombosis on admission (at 11th day of life); 1B – remission of right lower limb swelling after 48 h of heparin treatment.

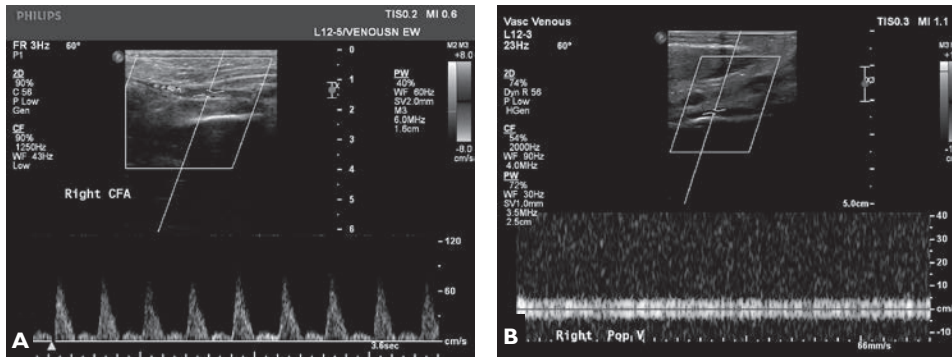

Figure 2A and B – Colour Doppler ultrasound scan of right leg showed thrombosis of right common femoral vein (CFV) with unobstructed arterial flow on admission.

examination showed a hemoglobin of 12.5 g/dl, thrombocytes were 146×10^9/l, leukocytes were 5.88×10^9/l with an absolute neutrophil count of 2.96×10^9/l and C-reactive protein was 21.8 mg/dl. Urine sediment and cerebrospinal fluid analyses were negative for pathogens isolation. Screening for coagulation disorders was unremarkable. Sepsis screen was obtained, a late onset sepsis was suspected and was commenced on vancomycin and amikacin as well as sedation with fentanyl. Brain ultrasound including Doppler scan was performed, without evidence of hemorrhage or infarction. Joint vascular and radiology team also performed a colour Doppler scan of R leg that showed thrombosis of R common femoral vein (CFV) with unobstructed arterial flow (Figure 2A and B). The neonate was immensely started, as per our NICU protocol, on iv unfractionated heparin with a loading dose of 75 mg/kg and maintenance dose of 28 mg/kg/hour for 4 hours. The

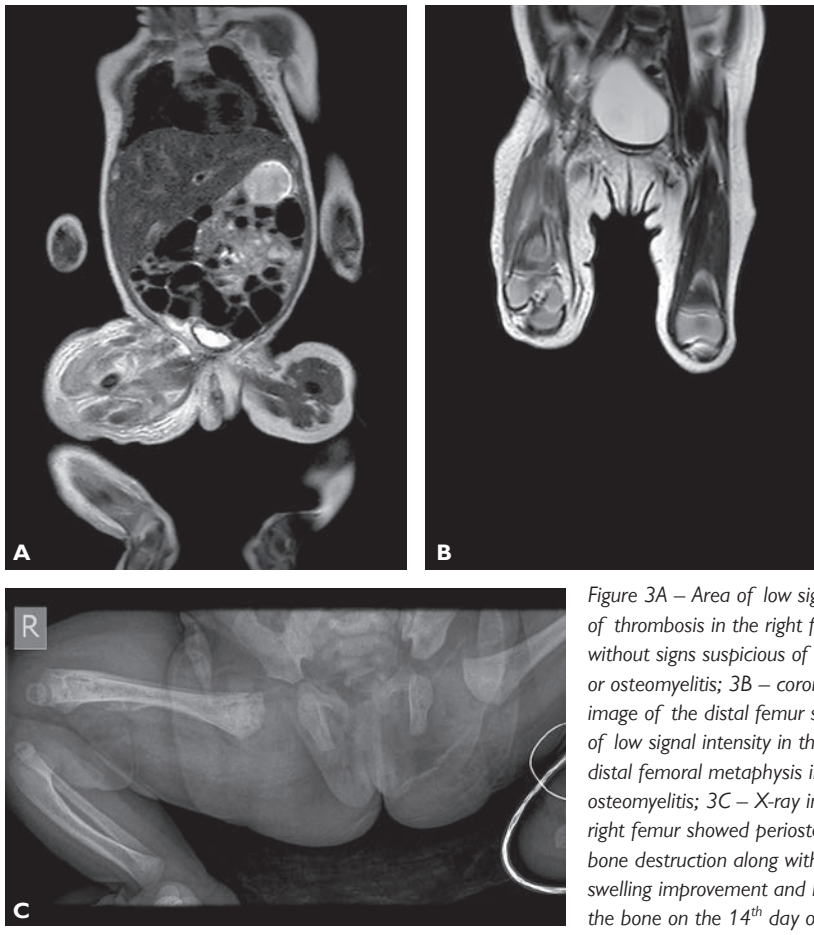

Figure 3A – Area of low signal in the site of thrombosis in the right femoral lumen, without signs suspicious of bone malignancy or osteomyelitis; 3B – coronal T1-weighted image of the distal femur shows an area of low signal intensity in the right medial distal femoral metaphysis indicative of osteomyelitis; 3C – X-ray imaging of the right femur showed periosteal reaction and bone destruction along with deep soft tissue swelling improvement and lytic changes in the bone on the 14th day of admission.

efficacy of heparin was evaluated with activated partial thromboplastin time (APTT), international normalized ratio (INR), anti-Xa in the end of the aforementioned course of intravenous heparin. The switch to low molecular weight heparin (LMWH) enoxaparin (150 mg/kg/dose subcutaneously) was guided by conventional laboratory scan. Antibiotic treatment was adjusted to ampicillin, vancomycin, amikacin given positive for *Streptococcus pyogenes* (*group A*) blood culture at the admission sample. On the 3rd day of admission, 48 hours post heparin infusion, there was noted clinical improvement in terms of edema reduction and decrease in R leg discoloration as well as lessening in pain (Figure 1B). The colour Doppler ultrasound showed reduction of the thrombus and blood flow improvement. An MRI (magnetic resonance imaging) R lower limb was performed on the 5th day of admission, showing evidence of gradual improvement in the site of thrombosis, without signs suspicious of bone malignancy (Figure 3A). On the 14th day of

admission, due to localized pain in the proximal part of R femur, a bone Tc99 scan was performed, which showed evidence of osteomyelitis of R femur. Similar findings indicative of osteomyelitis were detected on MRI (Figure 3B). Simultaneously, an X-ray imaging of the femur revealed periosteal reaction, bone destruction and soft tissue improvement while there were no pathological findings on X-ray at disease onset (Figure 3C). Orthopedic consultation was performed, and antibiotic treatment switched to amoxicillin per os after a 4-weeks intravenous course. The overall antibiotic treatment lasted for a 6 week course.

Evaluation of the family for *Streptococcus* colonization or infection was performed and nasal, rectal and vaginal samples were obtained. *Streptococcus pyogenes* was not confirmed in the isolates.

The management restricted to anticoagulant therapy with LMWH for 3 months (1-month therapeutic dose and 2-months prophylactic dose) and antibiotic therapy alone without surgery intervention and the patient recovered and discharged at 42 days of age. There were no profound complications and no recurrence for both bone damages or impaired movement and thrombosis with a mean follow up period of 12 and 6 months respectively. Labouring for the evaluation of coagulation disturbances remained consistently negative for a time period of 6 months.

Discussion

In our patient GAS was isolated in blood culture, although this specific pathogen has been only described in very few cases of neonatal OM, with good response to 4-weeks intravenous vancomycin, ampicillin and amikacin and 2-weeks oral amoxicillin treatment (Frederiksen et al., 1993; Berberian et al., 2010; Ilharreborde, 2015). In our case, late onset sepsis was initially considered as the cause of the patient's clinical presentation, thus the neonate was initially started on vancomycin and amikacin. The most frequently isolated pathogen in neonates diagnosed with OM is *methicillin-resistant Staphylococcus aureus* (MRSA) followed by *Streptococcus group B* and gram-negative pathogens as part of maternal flora and breach delivery has been strongly proposed as risk factor which predisposes subjects for osteomyelitis in the neonatal period (Sarlangue et al., 2007). Based on the above, Castellazzi et al. (2016) recently suggested that, when neonatal OM is suspected, empirical antibiotic treatment with antistaphylococcal penicillin or vancomycin combined with amikacin should be opted as first choice. There is wide discussion in the management of pediatric OM, with some researchers suggesting a short-term intravenous treatment switched thereafter to oral agents in non-complicated cases, for an overall course of 3–6 weeks (Dartnell et al., 2012). However, the safety and efficacy of this approach in neonates has not been proven yet (Castellazzi et al., 2016). Our patient was initially treated as late-onset sepsis although she should have been treated for a community acquired infection. The antibiotic scheme with vancomycin and amikacin was driven by the improvement of inflammatory markers within 48 hours from the start of the above regimens.

Typically changes in X-ray may be present approximately 7–10 days after the disease onset while MRI imaging may play a role in the diagnosis in early stages (Blickman et al., 2004). Bone ultrasound (u/s) is a promising diagnostic tool in specialists with experience. The mean time of diagnosis is reported at 12–14 days after disease onset (Zhan et al., 2019). Our patient's diagnosis was set at 14 day of disease progress by bone Tc99 scan and confirmed by MRI and X-ray findings.

Group A Streptococcus has been reported as the second more frequent bacterial cause of OM in children. The invasive form of GAS-associated infection causes coagulation disorders mostly linked to plasminogen and kininogen activation, for this reason is also associated with episodes of vascular thrombosis (Ben Nasr et al., 1995). Soluble M-protein and its serotypes by using immunoregulatory properties activate equally the tissue factor, contact system and platelets (Shannon et al., 2007). This protein mediated activation of clotting factors and cells results in a stable fibrin structure which entraps bacteria and eliminates infection spread. GAS as a major immunomodulator leads to dysregulation of the coagulation system enhancing its invasive nature and presenting as purpura fulminans (González-Abad and Alonso Sanz, 2020). Sepsis-induced coagulopathy and immunothrombosis in the context of bacteria spread elimination is a well-established knowledge in both children and adults but scarcely investigated in neonates. Aberrations in the activation of coagulation cascade may lead in disturbances like disseminated intravascular coagulation with thrombosis or bleeding. Limited cases of thrombosis during osteomyelitis have been reported in the neonatal period. Moreover, it is a unique report of the deep vein thrombosis manifestation in GAS-associated neonatal osteomyelitis.

Neonatal venous thrombosis mostly is observed in hospitalized neonates while signs and symptoms are linked with thrombosis location. Premature infants are more prone to venous thrombosis accounted for 71% of the overall incidence. The underlying sickness and intensive care unit handlings are responsible for differences in timing thrombosis occurrence between term and preterm neonates (Saracco et al., 2016). In a German registry thrombosis was more commonly detected at 11^{th} or 12^{th} day of life than at birth mainly for premature neonates (Nowak-Göttl et al., 1997). Similarly, in our patient the diagnosis was placed on 12^{th} day of life. Moreover, the presence of thrombosis at the admission was misleading for the final diagnosis. Ultrasonography is the most common imaging modality widely used to diagnose venous thrombosis (Male et al., 2003). An ultrasonography and a confirmatory MRI scan were performed to our patient.

There is a paucity of data regarding evidence based on clinical trials in treatment of neonatal thrombosis which is largely based on consensus guidelines. According to American College of Chest Physicians' guidelines treatment include unfractionated heparin and low molecular weight heparin and the administered doses are much higher to reach therapeutic targets compared to older children regarding the developmental hemostasis in neonates (Andrew, 1995; van Elteren et al., 2011;

Monagle et al., 2012). Duration of treatment varies from 3 months for thrombosis related to underlying disease to 6 months for idiopathic thrombosis (Monagle et al., 2012). Recent literature has introduced a new generation anticoagulant, rivaroxaban, for neonatal venous thrombosis. Its use is considered to secure non-recurrence of thrombosis, thrombus elimination and reduction of bleeding risk compared to standard heparin and vitamin K antagonists (Male et al., 2020). In our patient therapeutic levels of LMWH achieved with enhanced doses under monitoring with aPTT and anti-Xa levels. By simultaneously monitoring the maximum of safety and efficacy of heparin administration was achieved.

Conclusion

It follows that although osteomyelitis in neonates is rare it should be considered along with reduction in limb movement. Early diagnosis and treatment can prevent bone destruction and impairment of bone growth. *Group A Streptococcus*-associated osteomyelitis is equally rare and a potential risk factor for deep venous thrombosis development which in turn could be life threatening without prompt treatment.

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