Neonatal nephrotic syndrome: all is not gloomy

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SUMMARY

Congenital nephrotic syndrome (CNS) is a rare clinical syndrome with a constellation of proteinuria, hypoalbuminaemia and oedema, presenting within 3 months of birth. We present a rare case of neonatal nephrotic syndrome with a probable sepsis induced aetiology. The neonate was referred at day of life 15 with *Klebsiella pneumonia* sepsis and anasarca. On investigation, the patient had nephrotic range proteinuria, hypoalbuminaemia, generalised anasarca and ascites. The neonate was started on broad-spectrum antibiotics and furosemide. Genetic and other secondary causes of CNS were ruled out. With supportive management and resolution of sepsis, the neonate improved. This case highlights the rare cause of sepsis-induced nephrotic syndrome (NS), which required only supportive treatment without the need for aggressive management of CNS.

BACKGROUND

Congenital nephrotic syndrome (CNS), a triad of proteinuria, hypoalbuminaemia and oedema, presenting within 3 months of birth is a rare disorder and remains frequently undiagnosed by paediatricians.[1 2] Any neonate with anasarca should be evaluated for nephrotic syndrome (NS) and confirmed in the presence of anasarca, nephrotic range proteinuria (urine protein creatinine ratio >2000 mg/g) and hypoalbuminaemia (<2.5 g/dL). These patients should be monitored for complications such as intravascular fluid dysbalance requiring aggressive monitoring and dyanamic fluid decisions, dyselectrolaemia, recurrent infections, hypertension, thromboembolic events, hypothyroidism, kidney failure and failure to thrive.[3] Failure to diagnose this condition early may lead to complications and poor prognosis. Neonatal NS (NNS) may have a genetic cause or may be secondary to causes like infections, toxins, immunological or idiopathic.[4] Non-viral sepsis is a rare cause of NNS.

CASE PRESENTATION

A male neonate born at 38 weeks of gestation with a birth weight of 3.1 kg, appropriate for gestation age, was referred to the hospital on the day of life (DOL) 15, in view of sepsis and generalised swelling. The patient was born by emergency caesarean section for fetal distress. Mother had history of gestational diabetes mellitus on dietary management. Level 2 ultrasound scan showed echogenic foci in left ventricle. She had three previous abortions at 1.5–2 months gestations, of unknown causation. Her antenatal TORCH workup was negative and antiphospholipid profile was normal. Quadruple test was low risk. She had one previous 8 years old healthy girl child and an infant death at 6 months of age due to generalised swelling over body, preceded by generalised illness. Documents were not available to collaborate the findings or to ascertain the cause.

The index case cried immediately after birth, but developed respiratory distress soon after, requiring continuous positive airway pressure (CPAP) support. Placental information was unavailable. Gradually, the neonate improved and taken on nasal oxygen by prong on DOL 4. At DOL 7, he developed sepsis with pancytopenia. Blood culture grew pan resistant *Klebsiella pneumoniae*. Neonate was treated for sepsis, meningitis, disseminated intravascular coagulation (DIC) and received multiple units of fresh frozen plasma (FFP), random donor platelets and packed red blood cell (PRBC) transfusions along with broad-spectrum antibiotics and immunoglobin. The patient also received anticonvulsant drugs for neonatal seizures. Neonate was intubated in view of worsening respiratory distress. At DOL 12, he developed anasarca for which was referred to our centre.

At admission, neonate had anasarca and ascites with a weight of 3.715 kg. He had pancytopenia with positive septic screen markers (table 1). The patient had coagulopathy with INR 2.4. Reticulocyte count was 5.8% and peripheral blood smear showed schistocytes, target cells and few spherocytes. His serum reports showed sodium 142 mmol/L, potassium 3.32 mmol/L, total calcium 8.45 mg/dL, serum proteins of 3.54 gm/dL, albumin 2.16 gm/dL, globulins 1.38 gm/dL, serum glutamic oxaloacetic transminase (SGOT) 165 IU/L, serum glutamic pyruvic transaminase (SGPT) 28 U/L, alkaline phosphatase (ALP) 77 IU/L, total bilirubin 3.52 mg/dL with direct bilirubin of 2.2 mg/dL, triglycerides 132 mg/dL, cholesterol 111 mg/dL, high density lipoprotein (HDL) 17.5 mg/dL, low density lipoprotein (LDL) 67.5 mg/dL, very low density lipoprotein (VLDL) 26 mg/dL, lactate dehydrogenase (LDH) of 294 U/L, urea 15.9 mg/dL and creatinine 0.29 mg/dL. Serum osmolarity was 290 mosm/L and urine osmolarity was 237 mosm/L. Urine examination showed urine protein creatinine ratio of 6570 mg/g with bacteria and 30–35 white blood cells (WBCs) per high-power field in microscopy. There was no gross haematuria, but 25–30 isomorphic red blood cells (RBCS) were present per high-power field. Urine culture sent twice was sterile. Cerebrospinal fluid (CSF) evaluation for meningitis was within normal limits.

Chest X-ray showed bilateral infiltrates. Ultrasonography (USG) abdomen with pelvis showed portal vein thrombosis and ascites with normal renal size and texture and normal urinary bladder. Two-dimensional (2D) echocardiography showed distended inferior vena cava (IVC), large patent ductus arteriosus (PDA) and tricuspid regurgitation with pulmonary pressure of 45–50 mm Hg. The neonate had maculopapular rash over the trunk and extremities at admission, which was suspected to be post inflammatory hyperpigmentation.

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Table 1 Relevant investigations during hospital stay

	DOL 15	DOL 17	DOL 21	DOL 22	DOL 27	DOL 31	DOL 40	DOL 47
Hb (g/L)	46.8	107	97	138.2	116			90
TLC (/cumm)	2826	8900	4500	6520	4000			7100
ANC (/cumm)	723	2000	2200	3770	1300			1900
Platelet (x10^9/L)	17.9	14	90	90	70			203
CRP (mg/L)	89				85	27	30	
Serum proteins (g/dL)	3.54		4.52					
Serum albumin (g/dL)	2.16	2.49				2.72	3.10	
Urine protein creatinine ratio (mg/g)	6570	8570	2770			2980	4060	1420
Urine routine microscopy								
WBCs	30–35	8–9		0–1	6–10	0–1	2–4	
RBCs	25–30	10–15		Nil	5–6	Nil	1–2	
Bacteria	+	Nil		Nil	Nil	Nil	Nil	

ANC, absolute neutrophil count; CRP, C reactive protein; DOL, day of life; Hb, hemoglobin; RBCs, red blood cells; TLC, total leukocyte count; WBCs, white blood cells.

A skin biopsy was done which showed features suggestive of non-specific mild dermatitis, which had spontaneous resolution.

The patient was transfused PRBC, platelet and FFP. Treated with antibiotics meropenem and colistin. Oral sildenafil was started in view of pulmonary hypertension. He was started on restricted fluid regimen with furosemide infusion in view of anasarca and excess weight gain. Urine output was 3–4 mL/kg/hour. Neonate had dyselectrolytaemia with hypokalaemia and hypomagnesaemia at admission, which were accordingly treated. Anticoagulants were considered for portal vein thrombosis, but in view of coagulopathy were deferred. Parenteral nutrition was given with amino acids of 3 gm/kg/day. The patient was haemodynamically stable and did not require inotropes throughout the hospital stay. He was started on minimal enteral nutrition, feeds were gradually graded up but had repeated episodes of feed intolerance. Blood culture sent at admission grew candida for which fluconazole was added.

In view of anasarca, hypoalbuminaemia and nephrotic range proteinuria within 1 month of life, he was diagnosed with NS. For the aetiological workup, intrauterine infection workup was sent. Syphilis, cytomegalovirus (CMV), toxoplasmosis among others were ruled out. Immune profile with anti-nuclear antibody (ANA), anti-double-stranded deoxyribonucleic acid (ds -DNA) antibodies and anticardiolipin antibodies were within normal range. Renal biopsy was planned, but not done in view of clinical improvement. With the suspected history of generalised swelling over body in the previous infant—genetic cause was suspected. Apart from previously sibling death, there was no significant family history. There was no gross dysmorphism on examination. Eye examination and head circumference were normal. Clinical exome sent revealed no pathological gene variant. In view of no other discernible cause, sepsis was attributed to be responsible for NS. To rule out complications, thyroid workup was sent, which was normal. Immunoglobin workup was planned, but not done due to logistic issues. Blood pressure was normal throughout the stay.

During the course of hospital stay, albumin, angiotensin converting enzyme (ACE) inhibitors, prostaglandin inhibitors were planned. But with improvement of septic markers, there was gradual improvement in albumin, proteinurea (table 1) and loss of oedema, so were not used. At DOL 27, neonate again deteriorated with worsening in sepsis markers, for which vancomycin was added. Though repeat cultures were sterile. Gradually, the patient improved with antibiotics and supportive management. He reached full feeds by DOL 30. In view of failure to thrive, feeds were fortified to increase calorie and proteins intake. Respiratory support was weaned and was brought to room air by DOL 41. Repeat USG abdomen at DOL 43 showed resolution of portal vein thrombosis and ascites. Repeat 2D echo at DOL 50 was normal with closure of PDA. Proteinurea, oedema, hypalbuminaemia resolved. The infant was discharged on DOL 52 with normal neurological examination.

OUTCOME AND FOLLOW-UP

The infant was followed up at regular intervals in the outpatient department (OPD). At present, 8 months of life, he is thriving well and has attained all the developmental milestones as per age. There is no repeat episode of anasarca or any generalised illness. His hearing and ophthalmology examination are normal.

DISCUSSION

CNS is a rare disorder with the clinical presentation of anasarca and the associated complications. Due to uncommon presentation and clinicians not being aware of the illness, the condition may be missed, hampering the exact estimation of the incidence. The most common cause of the CNS are the genetic defects with most common affected genes being NPHS1, NPHS2, WT1, LAMB2 and PLCE1.[5 6] Non genetic and potentially treatable causes include infections and immunological cause.

The presented case is a rare situation where NNS is caused by non-viral sepsis aetiology. Most of the cases of sepsis inducing CNS are caused by intrauterine infections such as cytomegalovirus, syphilis, toxoplasmosis, rubella, hepatitis B virus and HIV infections.[7–11] In CNS, recurrent bacterial infections as its complication are common due to loss of immunoglobin, poor nutrition status and requirement of prolonged central line.[3]

To our best knowledge, this is the first case where bacterial sepsis was the cause of NNS. In the index case, neonate had bacterial (Klebsiella) infection followed by generalised swelling indicating development of NS post sepsis, implicating bacterial sepsis as cause of NNS. Also, the patient had fungal infection and another culture negative sepsis during the course of illness as the expected complication.

In many cases of fulminant neonatal sepsis, there is generalised oedema due to capillary leak, renal failure among other causes. Therefore, in these patients, NS may be missed until and unless it is actively looked on. In the index case also, generalised oedema could be due to capillary leak because of sepsis or due to hypoproteinaemia. The exact cause cannot be delineated in our case. But to identify NS as the cause is important because of its associated complications which if not treated may lead to poor prognosis.

Treatment of NNS includes definitive management to decrease proteinuria and hypoalbuminaemia and the supportive management to treat the associated complications.[3 12 13] Definitive management includes antiproteinuria agents such as ACE inhibitors or angiotensin

type I receptor blockers, prostaglandin inhibitors, albumin infusion, nephrectomy and immunosuppression in selective cases. In our case, on treatment of primary aetiology, there was subsequent improvement in the proteinuria, hypoalbuminaemia and anasarca. Therefore, the patient did not require any antiproteinuria agents. Though at discharge, urine protein creatinine ratio was below nephrotic range, it had not normalised. This could be due to delayed recovery of glomerulus membrane.

Supportive management included dynamic fluid management and diuretics, to which the neonate responded. Treatment of associated complications depends on case-to-case basis. They may require thrombosis prophylaxis in view of higher risk of thromboembolic events due to multiple causes such as hypercoagulability due to underlying disease and risks related to treatment like central line and diuretics. In the index case, portal vein thrombosis resolved on its own as evident by USG on DOL 43. In view of increased chances of secondary infection, they may require infection prophylaxis and treatment. For failure to thrive they need aggressive nutrition management with high protein and calorie intake which was given in this case. For renal failure, dialysis may be required, though was not required in the index case.

To our knowledge, this is the first case of NNS secondary to Klebsiella sepsis. This highlights the need for detailed workup of any treatable cause of NNS, as it might lead to improved prognosis and a less aggressive management in these neonates.

Learning points

- Any neonate with sepsis may have neonatal nephrotic syndrome (NNS) as a rare complication.
- Any neonate with anasarca should be evaluated for nephrotic syndrome.
- Genetic workup along with other causes should be evaluated to know the aetiology.
- NNS with secondary causes needs to be treated for the primary cause. They may respond to supportive management without the need of albumin, renal–angiotensin–aldosterone–system antagonists, prostaglandin inhibitors, immunosuppressants or nephrectomy.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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