Case Report

Superior Vena Cava Syndrome in a Child with Steroid Resistant Nephrotic Syndrome; A Case Report and Review of Literature

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Abstract: Nephrotic syndrome (NS) is one of the risk factors for thromboembolism (TE). We report here a rare case of a 6.5-year-old boy who presented with superior vena cava syndrome (SVCS) secondary to thrombosis during relapse of NS. He was diagnosed with primary steroid resistant nephrotic syndrome (SRNS) and was maintaining partial remission with triple regime immunosuppressive treatment for the last one year. He presented in the emergency department with generalized body swelling, more marked on face and neck for last one week. Initially managed as relapse of nephrotic syndrome but it was observed that his face and neck edema instead of disappearing, increased despite his pedal edema improving. This raised suspicion of neck vein thrombosis. Ultrasound doppler revealed sluggish flow in the internal jugular vein (IJV) and superior vena cava (SVC). CT angiogram further confirmed thrombosis in IJV extending to SVC. The patient was successfully treated with low molecular weight (LMW) heparin followed by maintenance anticoagulant therapy with rivaroxaban, a factor X inhibitor. Early consideration and intervention may prevent morbidity and mortality.

Keywords: Nephrotic syndrome, Thromboembolism, Superior vena cava syndrome, Rivaroxaban, Children, Morbidity and Mortality.

INTRODUCTION

Nephrotic syndrome (NS) is a common kidney problem in children characterized by hypoalbuminemia, proteinuria and generalized oedema with or without hyperlipidemia. It is a hypercoagulable state and associated with increased risk of thromboembolism (TE) [1]. The reported incidence of TE in children with NS varies from 3.6% to 8.7% in different studies [2, 3]. Certain hemostatic abnormalities have been identified in NS which contribute for TE like deficiency of antithrombin III(AT-III), protein C, S and plasminogen. Other probable risk factors are patient's genetic susceptibility, chronic inflammation and treatment related risk like use of diuretics and central venous catheterization [4]. Venous thrombosis is more common than arterial thrombosis. The most common location for TE is deep venous thrombosis (DVT) (49.3%), followed by cerebral venous sinus thrombosis or cerebral infarct (13.7%), pulmonary embolism (PE 12.3%), renal vein thrombosis (11.0%) and rarely SVC [2].

Superior vena cava (SVC) drains the head, neck upper limbs and trunk above diaphragm. In pediatric population the common etiological factors of SVCS are thrombosis, malignancies and congenital heart diseases [5].

Though the reported mortality of NS with TE in children is 8.5-10% but TE is associated with significant morbidities like delayed response to steroids, prolonging hospital stay and organ damage [3, 6].

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With the aspect of rarity of thrombosis in SVC and associated risk of grave morbidity and mortality, we share our experience of diagnosing and successfully managing a child with SRNS who presented with SVCS at time of relapse.

CASE PRESENTATION

A six and half years old boy, diagnosed with a case of SRNS, on triple regimen immunosuppressive therapy, admitted through emergency department with complaint of generalized body swelling for last 1 week.

His oedema distribution was disproportionately more over face and neck, rather than over limbs. The patient did not report neck pain, facial flushing, dysphagia, drooling and dyspnea. There were no other systemic manifestations like haemoptysis, chest pain, leg pain, headache and vomiting.

He diagnosed a case of primary SRNS at 5 years of age with features of focal segmental glomerulosclerosis (FSGS) on histology at our centre (Fig. **1**). Initially he received cyclosporin for six months (5mg/kg/day in two divided doses), but he did not achieve remission, and his spot urinary protein creatinine ratio (uPCR) was 9.6 and serum albumin was 2.3G/dl. Therefore, his immunosuppressive treatment was escalated and currently he was on triple regime; Tacrolimus 0.1mg/kg/dose twice a day, prednisolone 0.25mg/kg/on alternate day and Mycophenolate mofetil 1200mg/m2/day in two divided doses and angiotensin converting enzyme inhibitor (ACEI) -Enalapril. On this regimen he achieved partial remission, with serum albumin was >3.1 G/dl and u PCR 4.2 without clinical oedema for last 1 year (Fig. **1**).

Date	Clinical Data	Laboratory Data	Intervention
5/12/22	Generalized edema Normal BP	S. Albumin 1.6 g/dl S. Cholesterol 639 mg/dl Spot urine PCR 12.5	Diagnosis: Nephrotic syndrome Oral steroid 2mg/kg/day started
6/28/22	Severe persistent edema	S. Albumin 1.5 g/dl Spot urine PCR 15	Primary steroid resistance Counselled for kidney biopsy Alternate day steroid ACEI-Enalapril
8/5/22	Persistent mild-moderate edema	S. Albumin 2.0 g/dl Spot urine PCR 9.3	Kidney biopsy: FSGS CNI-Cyclosporin Alternate day steroid ACEI-Enalapril
3/1/23	Persistent mild-edema	S. Albumin 2.3 g/dl Spot urine PCR 9.6	Triple regimen: Mycophenolate mofetil Tacrolimus Low dose steroid Enalapril
5/8/23	No edema Partial remission	S. Albumin 3.1 g/dl Spot urine PCR 4.2	Continue Triple Regimen
1/27/24	Generalized edema Bull neck-like	S. Albumin 1.4 g/dl Spot urine PCR 7.8 Doppler US: thrombus in left IJV extending to SVC CT Angio: thrombus in left IJV extending to SVC	Enoxaparin x 5 days Rivaroxaban MMF Tacrolimus Low dose steroid
3/28/24	No edema	S. Albumin 3.0 g/dl Spot urine PCR 4.4	Rivaroxaban MMF Tacrolimus Low dose steroid
6/20/24	No edema	S. Albumin 3.1 g/dl Spot urine PCR 4.7	Rivaroxaban MMF Tacrolimus Low dose steroid
12/15/24	No edema	S. Albumin 3.0 g/dl Spot urine PCR 4.2	MMF Tacrolimus Low dose steroid

Fig. (1) Timeline of Case.

His birth history and past medical history were uneventful. He was born of non-consanguineous marriage. There was no family history of NS and thrombotic events.

On examination he was well oriented and comfortable with morbid facial and neck oedema. He was vitally stable and had no respiratory distress. He was well nourished child with weight 24kg (50th centile) and height 113cm (25thcentile). His blood pressure was 100/65 (50th centile) and he had normal peripheral pulses with good volume. He had mild ascites and pedal oedema. The rest of the systemic examination including cardiovascular, respiratory and nervous system was unremarkable.

Laboratory findings (Table **1**) during this admission revealed nephrotic range proteinuria with severe hypoalbuminemia, so we labelled it as relapse of NS and full dose prednisolone(2mg/kg/day) was prescribed. During his stay in hospital we observed that pedal edema started vanishing with improvement in ascites but unexpectedly his facial and neck swelling was increasing. Suspecting venous thrombosis, ultrasound doppler of neck veins was advised. It revealed echogenic mass in the left internal jugular vein extending to SVC. Subsequently, a CT angiography was performed (Fig. **2a-c**) which confirmed that there was complete thrombosis of left internal jugular vein extending inferiorly up to proximal SVC. There was no evidence of cerebral venous thrombosis seen on CT angiography of brain. His echocardiography was negative for the thrombus.

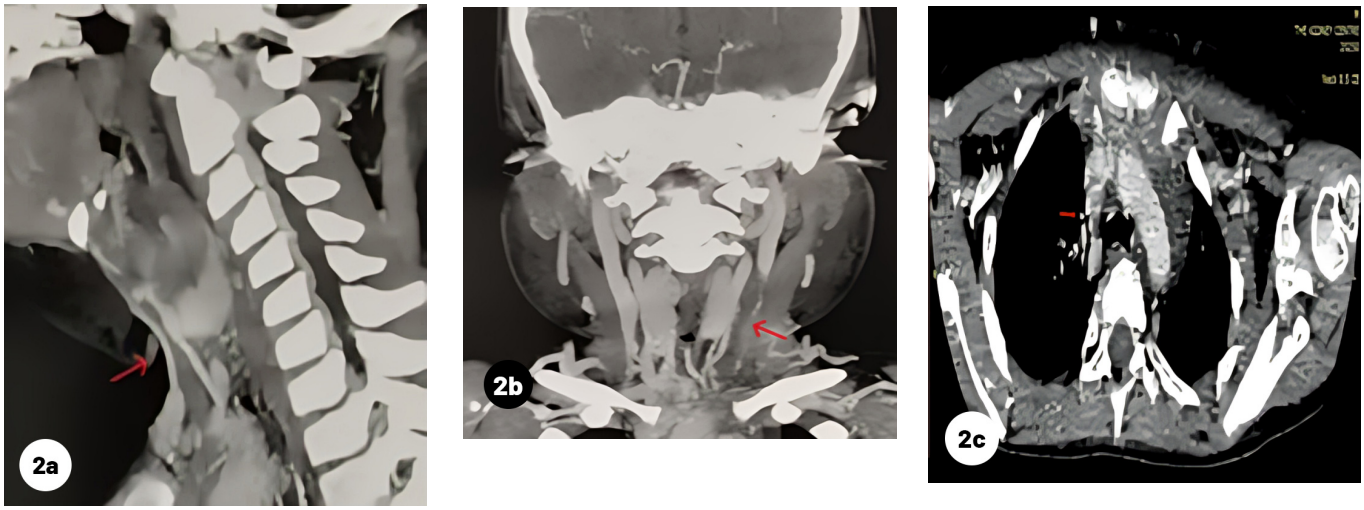

Fig. 2a: Sagittal and **Fig. 2b**: Coronal contrast enhanced CT images, showing a well-organized hypodense thrombus within the internal jugular vein on left side, resulting in near total luminal occlusion, **Fig. 2c**: Axial contrast enhanced CT image, showing organized hypo dense thrombus in SVC.

His work up to find out underlying prothrombotic factors (Table **1**) revealed raised d-dimer, a low level of AT-III and protein S, a normal level of factor V and fibrinogen, while protein C was found to be increased.

Table 1. Work up for Diagnosis of Relapse and Thrombosis in Current Admission.

Parameter	Result	Normal range
Nephrotic Relapse Workup		
Serum albumin (G/dl)	1.4	3.8-5.4
Spot urine PCR (mg/mg)	7.8	<0.2
Serum cholesterol (mg/dl)	250	>200
Complete Blood Counts		
Hemoglobin (G/dl)	11.8	11.5-15.5
White blood cells (cells/L)	13.8 x10^9	4.0-10.0 x 10^9
Platelets (cmm3)	368 x10^9	150-400 x10^9
Thrombotic Workup		
Plasma Fibrinogen(G/L)	2.57	1.5-4.5
Prothrombin Time (seconds)	9.7	11.4
Activate Prothrombin Time (seconds)	25.6	24.6
D-Dimer (mg/L FEU)	6.79	<0.5
Anti- thrombin III (%)	61	74-126
Factor V (%)	139	62-150
Protein S (%)	49	56-121
Protein C (%)	>150	70-140

He was managed with LMW heparin-enoxaparin for 5 days followed by rivaroxaban, a factor X inhibitor at dose of 1mg/kg/day in 2 divided doses instead of classical oral anticoagulant warfarin, which require frequent international normalizing ratio (INR) monitoring. His neck and face swelling started improving over 3-5 days and completely disappeared in 10 days of rivaroxaban.

As persistent proteinuria is likely the main cause of thrombotic events in our patient, we discussed with family other remaining options for control of proteinuria like rituximab, a monoclonal anti CD-20 antibody or cyclophosphamide but parents did not opt due to unaffordability and expected side effects.

Initially he called frequently in OPD once a week for 1 month then fortnightly for next 2 months to monitor efficacy and probable side effects of treatment. Fortunately, he did not develop any side effects or new thrombus. We continued oral rivaroxaban to prevent recurrence of thrombosis for six months after that we stopped it. Currently after 12 months of event, he is maintaining his baseline nephrotic status of partial remission (uPCR- 4.2 and serum albumin-3.0G/dl) on triple regimen.

DISCUSSION

Steroid resistant nephrotic syndrome is a hypercoagulable state leading to venous and arterial thromboembolism. The prevalence of TE in our nephrotic syndrome population is not studied, although one local study reported thromboembolism in hospitalized children as 5.9/10,000 hospital admissions, among them NS was contributed 2.5% of cases as etiological association in TE [7].

The current report describes SVCS in a child with SRNS. Although TE may occur anywhere in the body of a child affected with NS, to the best of our knowledge, this is a rare case of SVCS in a child with SRNS on triple regimen.

The clinical presentation of SVCS varies from trivial findings like facial swelling as in our case to life threatening airway compromise. In a recent systemic review, 142 cases of pediatric SVCS were studied and found 36% of cases of SVCS were sec-

ondary to thrombosis. Furthermore, pediatric SVCS were associated with high morbidity (30%), acute complications (55%) and mortality (18%) [5].

Persistent proteinuria along with severe hypoalbuminemia is proposed as one of the predictors of thrombosis in SRNS, so relapse of NS is highly susceptible time for thrombus formation, as in our case [2-4]. Yan *et al.* found that majority (92.7%) of the patients developed thrombosis during relapse and underwent corticosteroid and other immunosuppressant therapy [6].

Proteinuria is associated with losses of anticoagulant proteins like antithrombin III, protein C, S and plasminogen. This is alongside increased synthesis of procoagulant in the liver resulting hypercoagulopathy [3, 8]. Though in our case, AT-III and Protein S were mildly decreased while protein C rather elevated, so it is difficult to claim the sole contribution of hypercoagulable state for TE in our patient. Other risk factors in the index case are steroid resistant behavior, FSGS on histology and hypoalbuminemia as described in literature [2-4].

In a large study from China revealed thrombosis in 51.9% of the study participants with SRNS [6]. Dadgar *et al.* in the systemic review reported the similar finding of higher risk of TE in SRNS compared to steroid sensitive NS children (p-0.013). This systemic review further revealed that focal segmental glomerulosclerosis was the most common histology found (51.2%), other were MCD (14.0%), idiopathic membranous nephropathy (7.0%), membranoproliferative glomerulonephritis (2.3%) and unknown histology (25.6%) [2].

The decreased serum level of AT-III, protein C, and protein S has been reported in 29%, 18%, and 12% of patients respectively in NS experiencing TE by Tavil *et al* [9]. Consistent to our case, other studies have shown significant increase in protein C activity, suggesting its protective effect against TE [10, 11].

However, recent research work suggests that AT-III, protein C and S play only a limited role in the mechanisms underlying the acquired hyper coagulopathy of nephrotic syndrome [12, 13]. This is in line with the results of local study, revealed mean serum level of protein C (95.31+16.02), S (84.05+13.3) and AT-III (86.50+16.3) within normal range in nephrotic children [14].

Despite the significant morbidity of TE in NS, no guidelines for prophylaxis and management of TE in NS for pediatric population exist. However, for treatment of established TE in adult patients, KDIGO 2021 guidelines recommended subcutaneous low molecular weight heparin and oral warfarin with membranous nephropathy [15].

We used factor X inhibitor rivaroxaban as anti-coagulant after therapy of heparin. Rivaroxaban has several advantages, including a rapid onset of action, no need for INR monitoring and a more predictable pharmacokinetic profile. Its efficacy and safety are comparable to standard anticoagulants with low recurrence risk and reduced thrombotic burden without increased bleeding [16, 17].

The outcome of our patient was excellent with early intervention. Consistent to our results, other studies reported an outcome of 70.4% to 91.1% with early intervention [6, 18, 19].

CONCLUSION

Superior Vena Cava Syndrome secondary to thrombosis in a child with SRNS is a rare phenomenon. A high clinical suspicion and diligent examination is required to diagnose SVCS in nephrotic children. We managed SVCS successfully with rivaroxaban, an effective alternate maintenance anti-coagulant therapy. Timely intervention with anti-coagulants is a guarantee of a better outcome.

LIST OF ABBREVIATIONS

FSGS: Focal Segmental Glomerulosclerosis.

NS: Nephrotic Syndrome.

SRNS: Steroid resistant nephrotic syndrome.

SVC: Superior Vena Cava.

SVCS: Superior Vena Cava Syndrome.

TE: Thromboembolism.

AUTHORS' CONTRIBUTION

Saima Kashif: Conceptualization, Study design, Methodology, Data analysis and interpretation, Writing draft, Critical review and revision the manuscript.

Khemchand N. Moorani: Conceptualization, Methodology, Data analysis and interpretation, Writing draft, Critical review and revision the manuscript, Final approval, final proof to be published.

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CONFLICT OF INTEREST

Declared none.

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