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Case report

An evaluation of kidney dysfunction as a common symptom of typhoid infection in an endemic country: A rare case study

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ABSTRACT

Nephrotic syndrome and encephalopathy are uncommon complications that occurred in typhoid fever. The diagnosis is based on proteinuria finding with nephrotic range value, edema, and hypoalbuminemia. In this study, a 10-year-old boy was diagnosed with encephalopathy typhoid and nephrotic syndrome. The physical examination and urinalysis were conducted with methylprednisolone 60 mg/body surface area and captopril to reduce proteinuria.

Introduction

Nephrotic syndrome is the most common glomerular disease encountered by children [1], which is characterized by edema, proteinuria, and hypoalbuminemia. It results from alterations of the perm-selectivity barrier of the glomerular capillary wall [2]. This syndrome has several etiology namely infections, genetic disorders, idiopathic, drugs, toxins, and malignancy [3]. Furthermore, typhoid fever is caused by the organism *Salmonella enterica* subspecies *enterica* serovar Typhi (*Salmonella* Typhi), a systematic infection predominantly transmitted through water or food contaminated by humans feces [4]. The fever is known to affect all body organs except the kidneys. Typhoid glomerulonephritis is a rare complication affecting 2–4% of patients in endemic areas or regions [5]. Therefore, this study aims to describe a case of nephrotic syndrome in a patient with typhoid fever without signs of glomerulonephritis.

Case study

A 10-year-old boy (Fig. 1) complained of slurred speech, along with seizures preceded by a high fever, diarrhea, and severe headache, 2 h before admission to the hospital. The complaint was also accompanied by swelling of the body that started in the eyes and spread to the face, abdomen, and leg within five days. Three weeks before hospitalization, the patient had a fever and was only given paracetamol, then, the complaint reoccurred a week later, and no treatment was received. During the illness, no complaints of respiratory or skin infection were reported. In the emergency room, a decreased consciousness was experienced with Glasgow Coma Scale (GCS) E3M5V4, blood pressure 130/100 mmHg, temperature 37.8 ℃, oxygen saturation 92% room air, capillary refill time of 2 s, as well as pulse and respiration rates of 110 and 34 times per minute, respectively.

Physical examination found periorbital edema, minimal fluid wave in the abdomen, and bilateral trunk swelling. Furthermore, the laboratory examination reported 29,910 u/L leucocyte, 3.51 mg/dL CRP, 2.77 g/dL albumin, sterile blood culture (Table 1), normal cerebral spinal fluid (Table 2), and *Salmonella* Typhi IgM reactive with a value of 4 with Tubex TF kit, equivocal, and 6–10 positive range. The chest X-ray showed bilateral infiltrate without cardiomegaly, as presented in Fig. 2. CT Scan with contrast reported no signs of bleeding, ischemic lesions, and neoplasms, as shown in Fig. 3. Furthermore, electrocardiography showed sinus rhythm and normoaxis without any chambers enlargement as described in Fig. 4.

During the treatment, the patient still suffered a slight fever (37.8℃), and urinalysis was conducted with + 1 urine protein and + 3 erythrocytes. Furthermore, the Esbach showed a urine protein of 2.184 g/24 h, as presented in Tables 3 and 4, and the ASTO examination was reactive. Albumin also decreased to 2.42 g/dL with ureum of 36 mg/dL at a range value of 15–39 mg/dL), creatinine was 0.93 mg/dL, with 89.3% GFR, and 16.7 mg/dL BUN as shown in Table 1. The patient received ceftriaxone, dexamethasone, and mannitol during the treatment.

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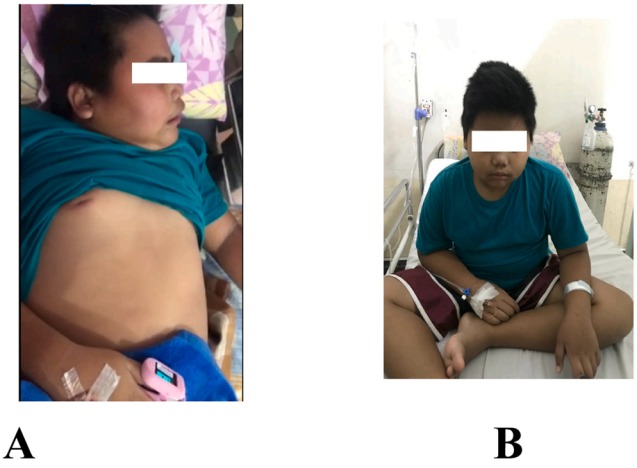

Fig. 1. The appearance of the patient. (A) The first admission in the emergency room; (B): before discharged. The patient experienced partial remission during hospitalized, with improving blood. Pressure and neurological symptoms.

Table 1
Laboratory finding.

Laboratory finding	28/7/21	30/7/21	1/8/21	3/8/21	5/8/21
Hemoglobine	12.0	11.0			13.0
Hematocryte	36.4	32.7			39.1
Erythrocyte	4.39	3.99			4.68
Leucocyte	29.910	17.280			13.830
Thrombocyte	453.000	437.000			425.000
Differential count	0/0/2/82/10/6	0/1/1/73/18/7			0/6/2/55/30/7
CRP	3.51				
Procalcitonin					0.05
ASTO				Reactive	
Ureum	53.8		36		
Creatinine	1.29		0.94		
Albumin	2.77		2.42		3.19
S Typhi IgM	4				
Blood culture		Sterile			

Table 2
Cerebral spinal fluid finding.

Cerebral spinal fluid	29/7/21
Protein total	25
Pandy	Positif
Nonne	Positif
Glucose	66 mg/dL
Colour	No colour
Clarity	A bit cloudy
Cell count	8 cell/uL
PMN	50%
MN	50%
Acid-fast bacili	Negative

The complaints improved during hospitalization, with no consciousness disorders or seizures. Based on urinalysis results, the patient was diagnosed with typhoid encephalopathy with secondary nephrotic syndrome. Therefore, methylprednisolone 60 mg/body surface area and captopril 1 mg/kg/dose were administered twice a day with the impression of secondary nephrotic syndrome related to typhoid fever. There was no previous family history of kidney disorders, swelling in the body, or previous ischemic syndrome attacks. Due to the COVID-19 pandemic, a kidney biopsy was not conducted, besides, the family did not accept the idea. Therefore, the patient was discharged with an

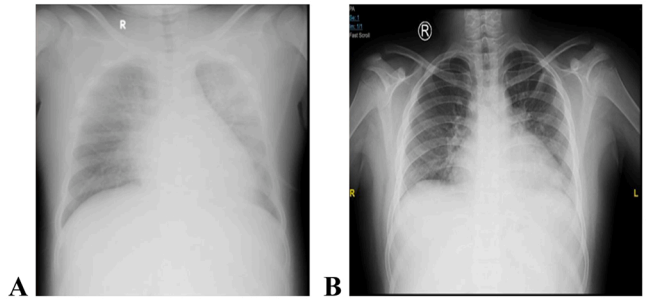

Fig. 2. Radiologic findings. Improving bilateral infiltrate on both lungs (A) first: bilateral bronchopneumonia, without heart enlargement; (B) second: improvement bronchopneumonia, without heart enlargement.

improved clinical condition and went into remission with trace urinary protein results (Table 3).

Discussion

Typhoid fever with kidney involvement is a rare condition and in previous children's study, it was manifested as acute kidney injury (AKI) and slight proteinuria [6]. Meanwhile, typhoid fever is a significant cause of mortality and morbidity in developing countries worldwide, with the highest geographic disease burden in Asia, specifically in major urban centers [7]. It is an acute systemic febrile illness caused by *Salmonella* Typhi characterized by bacterial invasion through Peyer's patches, leading to bacteremia. One of the major risk factors associated with its transmission is contaminated water [7]. The children considered in this study live in a clean and less crowded environment, but many residents have poor habits and personal hygiene, as well as polluted ditches and water sources. Children may exhibit different clinical symptoms because this organism can impact all the major body systems, leading to various complications. It may also cause a major catastrophe when this treatable disease and potential complications are ignored [8].

In this study, the patient developed neurological and renal symptoms typically described with encephalopathy typhoid in the form of seizures. Encephalopathy is a rare (4%) [9] and potentially fatal complication of typhoid fever, which is mostly found in older children and young adults [7]. Furthermore, renal involvement in typhoid fever is uncommon in 2–3% of patients, and the kidney manifestation is acute, transient, reversible glomerulonephritis with proteinuria or hematuria [10]. The physical examination found edema with hypoalbuminemia < 3 g/dL. Urinalysis revealed $+1$ proteinuria and 2.184 g proteinuria in Esbach, indicating the nephrotic range according to KDIGO 2021 [11]. The signs of glomerulonephritis are hypertension, hematuria, and ASTO reactive, while proteinuria is in nephrotic range [12].

The pathogenesis of nephrotic syndrome in typhoid fever is uncertain with several causes, including immune complex deposit and toxin-induced nephropathy, which is a direct toxin impact on podocyte [13]. Toxin-induced nephropathy is seen with *Salmonella* Typhi Vi antigen granular deposition in the mesangial area. The involvement of the immune complex is also seen with the deposition of IgA and C3 in the mesangial area [10]. Furthermore, cell-mediated immunity (CMI) and human leukocyte antigen (HLA) antigens are involved [14]. Previous studies on the plasma of acute typhoid patients showed elevations in proinflammatory cytokines interleukin-6 (IL-6), interferon-γ (IFN-γ), tumor necrosis factor-R (TNF-R), IL-1RA in acute disease [7], and the regulation of T-cell, which can damage podocytes [15]. The direct invasion of *Salmonella* Typhi is found in urine following a recent episode of typhoid fever [13]. Nephrotic syndrome patients experienced their first attack or relapse due to podocyte injury. Various environmental factors

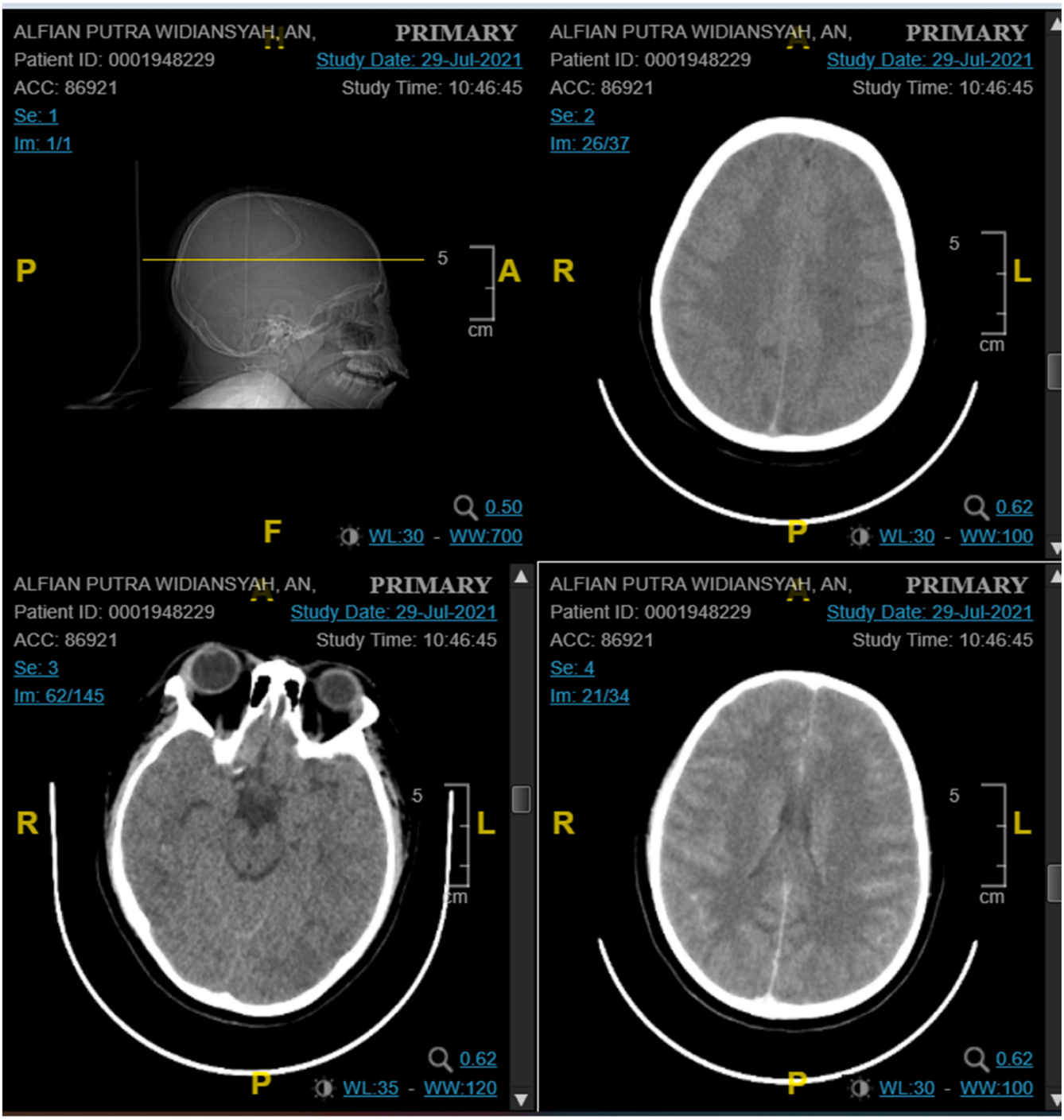

Fig. 3. CT scan findings. There were no signs of bleeding, ischemic lesions, and neoplasma.

and virus infection, which still unknown, also play a significant role in this injury [16]. According to some theories, the epigenetic factors, specifically deoxyribonucleic acid (DNA) methylation changes, influence the environmental factors [17]. The infection of this organism also plays a role in hypermethylation or hypomethylation of DNA. According to Kobayashi (2012), DNA methylation influences the recurrence of nephrotic syndrome in children [17]. Therefore, further investigation using the transcriptomic and epigenomic approaches is required to determine the DNA methylation status of infection-related nephrotic syndrome.

Conclusion

Typhoid fever can cause complications affecting all organs, including kidneys, with clinical manifestations of nephrotic syndrome, which is a rare case with an unclear mechanism.

Conflict of interest

The authors declared no conflicts of interest.

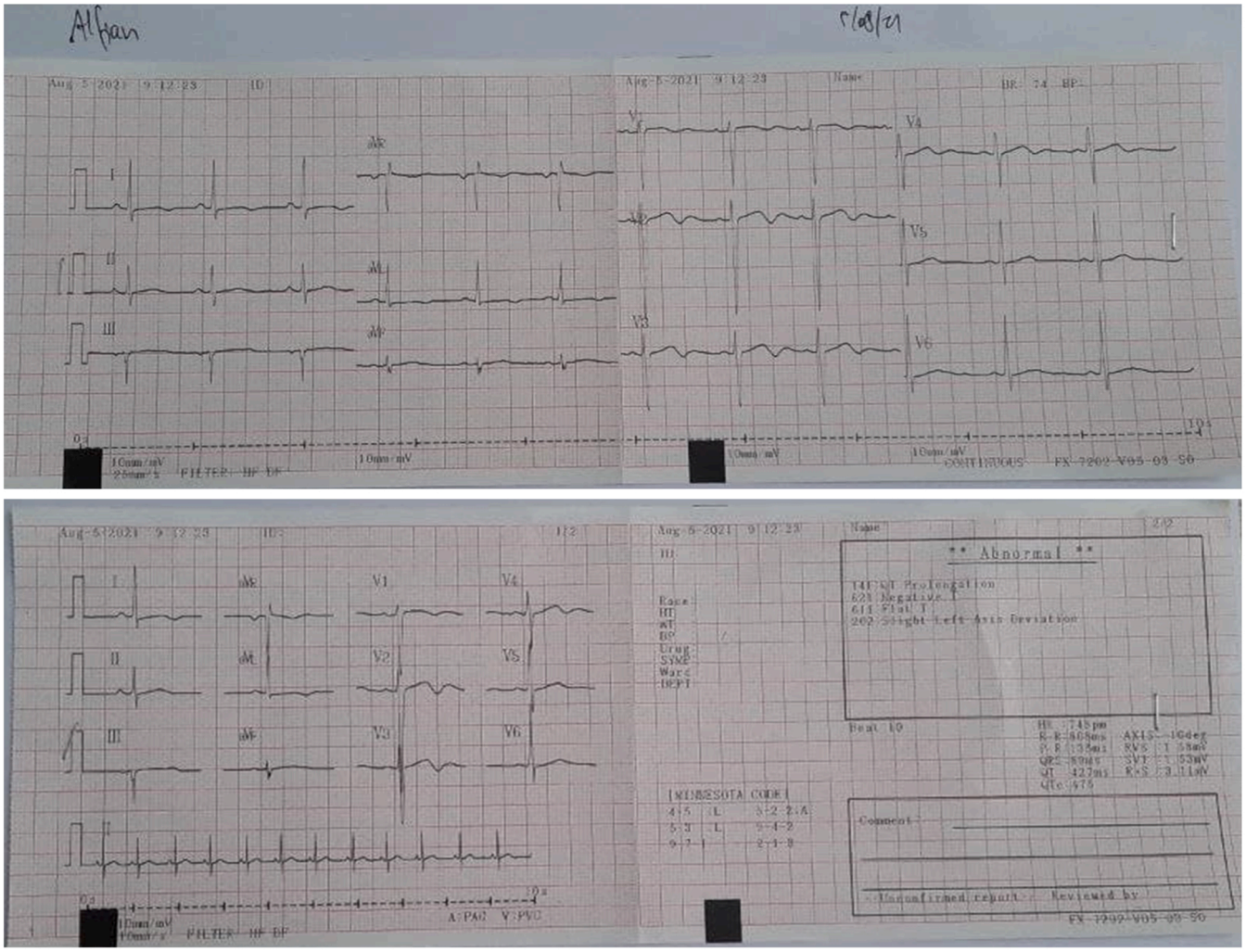

Fig. 4. Elecrocardiographic findings sinus rhythm, normoaxis, without any heart chambers enlargement.

Table 3
Urinalysis finding.

Urinalysis	31/7/21	2/8/21	5/8/21	3/9/21	12/10/21
Protein	+1	+1	+1	±	(-)
Erythrocyte	3+	2+	1+	(-)	(-)
Erythrocyte microscopic	4–6	12.4	7.1	3	3
Leucocyte	0–1	2	1	1	1
Epitel	1–3	2	1	0	0
Bacteria	Negative	Negative	Negative	Negative	Negative
Silinder	Negative	Positive	Positive	Negative	Negative
Esbach	2.184			100	

Table 4
Clinical correlation with urinalysis.

Correlation	31/7/21	2/8/21	5/8/21	3/9/21	12/10/21
Proteinuria	+1	+1	+1	±	(-)
GCS	E3M5V4	E4M5V5	E4M6V5	E4M6V5	E4M6V5
Temperature (°C)	37.8	37.6	36.8	36.6	36.7
Blood pressure (mmHg)	130/100	110/80	100/70	100/60	110/70
Pulse rate (times/minutes)	110	102	88	90	92
Saturation (%) room air	92	96	97	97	99

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Statement of ethics

This study adhered to the Declaration of Helsinki and informed consent for publication was obtained from the patient.

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Author contribution

Fiha Seratin drafted this study, while Dany Hilmanto, Ahmedz Widiasta, and Riyadi carried out critical revisions for important intellectual content and gave final approval of the version to be submitted.

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Further reading

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