Paediatrica Indonesiana

p-ISSN 0030-9311; e-ISSN 2338-476X; Vol.60, No.4(2020). p.223-5; doi: http://dx.doi.org/10.14238/pi60.4.2020.223-5

Case Report

Case report on Fanconi syndrome in Wilms tumor

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Fanconi syndrome is a group of clinical manifestations including aminoaciduria, proteinuria, glycosuria, hypophosphatemia, and metabolic acidosis. It may occur after exposure to certain drugs. The most common causes are antiepileptic, antiviral, antibiotic, and antineoplastic drugs.[1] The two most common causes in the antineoplastic regimen are cisplatin and ifosfamide. Ifosfamide, a derivative of cyclophosphamide, has been used to treat pediatric solid tumors.[2] Its high efficacy in numerous studies has led to its long-term administration for pediatric malignancies, including Wilms tumor. Along with other treatment modalities, ifosfamide considerably improved the survival rate (90%) of Wilms tumor while only a few cases resulted in Fanconi syndrome.[1,3,4]

Here we illustrate a case of presumed drug induced Fanconi syndrome in a Wilms tumor patient who previously achieved remission for 10 months. **[Paediatr Indones. 2020;60:223-5; doi: http://dx.doi.org/10.14238/pi60.4.2020.223-5**].

Keywords: *Wilms tumor; Fanconi syndrome; ifosfamide; nephrectomy*

The Case

A 3-year-old boy was admitted to the hospital due to sudden weakness in both legs from the prior day. He had difficulty walking and moving his body. There was no history of trauma, falls, familial disease, or diarrhea. He had completed the polio vaccination regimen. He had been diagnosed with Wilms tumor stage IV and underwent unilateral nephrectomy, 15 cycles of chemotherapy (actinomycin, vincristine, and ifosfamide) over 50 weeks, and radiation, achieving complete remission for the previous 10 months.

The patient was alert and conscious. Vitals signs were within normal limits. Physical examination was unremarkable. Neurological examination revealed a decrease in muscle strength of both legs (point 3 of manual muscle testing). Sensory and autonomic function showed no abnormalities. Physiological reflexes were diminished and no pathological reflexes were observed in both legs. Complete blood count and biochemical parameters revealed anemia and severe

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Submitted July 15, 2019. Accepted July 8, 2020.

hypokalemia, with potassium level at 1.9 mEq/L. Glomerular filtration rate was otherwise normal. Blood gas analysis confirmed the presence of metabolic acidosis. Urinalysis was done to evaluate for a possible urinary cause of these abnormalities. Glucose and protein were detected in his urine. Given his history and work up, a diagnosis of ifosfamide-induced Fanconi syndrome was suspected. He underwent potassium and bicarbonate correction. The patient was closely monitored by assessing his laboratory abnormalities. After 3 days of treatment, his general condition improved. The motor function in both legs returned to normal and the patient was discharged.

Discussion

One major concern for a survivor of Wilms tumor is nephrotoxicity. Nephrotoxicity manifests in several forms, from glomerular to tubular dysfunction or even acute renal failure.[5] It can have a primary etiology or be due to drug-induced process.

Renal tubular dysfunction is categorized into proximal and distal tubular dysfunction depending on the affected site. Proximal tubular dysfunction implies an impairment of fractional electrolyte excretions or reabsorption of substances such as amino acids, low molecular weight proteins (LMWPs), phosphate, bicarbonate, glucose, and urate. In contrast, distal tubular abnormalities are expected to impair the osmolality of the urine.[6]

Proximal tubular toxicity, known as Fanconi syndrome is a generalized reabsorption defect resulting in clinical features such as aminoaciduria, low molecular weight proteinuria, normoglycemic glycosuria, metabolic acidosis, hypokalemia, organic aciduria, hypophosphatemia, hypouricemia, and polyuria.[7] According to his urinalysis, blood work, and blood gas analysis results, our patient likely fulfilled the first five of the aforementioned conditions. In addition, glomerular damage in our patient was excluded as the glomerular filtration rate was within normal limits. Distal tubular dysfunction was not fully measured due to the lack of urine osmolality data.

Fanconi syndrome has a wide spectrum of clinical manifestations. The presentation can be growth failure, rickets, dehydration, or hypokalemia. The obvious symptom in our patient was severe hypokalemia. The low level of potassium may have been due to an increase in urinary potassium secretion, worsening with acidosis that contributes to an increase of filtered potassium load. Metabolic acidosis in the patient primarily reflects a defect in bicarbonate reabsorption in the proximal tubule.[8]

The pathomechanism by which ifosfamide, in this case, may induce Fanconi syndrome remains unclear. Ifosfamide, one of the alkylating antineoplastic prodrugs, requires CYP3A5 and CYP2B6 located in the kidney and liver, respectively, to form acrolein, chloracetaldehyde (CAA), and isophosphoramide (active drug). The CAA, the metabolite of ifosfamide, is known to induce proximal tubular cell injury. An in vitro study showed that the accumulation of CAA reduces glutathione and ATP level through inhibition of Na/K/ATPase as well as V-ATPase.[3] The ATP is essential for endocytosis and transport across the basolateral membrane.[9] A decrease in endocytosis and membrane transport automatically diminishes any reabsorption. Another study found that ifosfamide itself readily binds to the organic cation transporter (OCT) receptor and leads to a higher intake of ifosfamide in the tubular epithelial cells.[1,10]

Renal dysfunction in Wilms tumor patients may be associated with the previous treatment. Past studies revealed a tendency to acute renal failure in patients following nephrectomy. A study showed that uninephrectomised children with Wilms tumor have a higher risk of renal impairment.[11] Nephrectomy was comparable to other nephrotoxic chemotherapy (cisplatin) in inducing renal damage in patients receiving ifosfamide.[12] However, another study reported that patients treated with only unilateral radical nephrectomy were at low risk for long-term renal dysfunction.[13] The filtration rate has been postulated to increase after a reduction of renal mass, leading to the high uptake of ifosfamide in the nephrons and tubules.[4] This theory may explain the main role of the nephrotoxic regimen in diminishing renal function in our patient.

Our patient successfully achieved remission after unilateral nephrectomy combined with chemotherapy. However, durable remission suggests that ifosfamide therapy at fairly high doses (>50 g/m^2) retained the potency to cause late complications.[1] Therefore, identifying high-risk pediatric patients for acute kidney injury,[14] e.g., those with younger age, concomitant use

of other nephrotoxic agents, or history of renal failure before starting the treatment, may be mandatory in the future. In spite of the therapeutic effectiveness of ifosfamide, regular monitoring of complete renal function and electrolytes should be performed in conjunction with assessment of disease progression and further complications of Fanconi syndrome, e.g., rickets and osteomalacia.

Conflict of Interest

The authors declare no conflict of interest.

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