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CASE REPORT

IFOSFAMIDE-INDUCED FANCONI SYNDROME: A RARE BUT RECOGNIZED COMPLICATION

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Abstract:
Ifosfamide is an alkylating chemotherapeutic agent that was approved for medical use in the United States in 1987. It is frequently prescribed either alone or in combination with other agents to treat a variety of cancers, such as sarcomas, lymphomas, and lung cancers. It has increasingly been associated with the development of acquired Fanconi Syndrome. Fanconi Syndrome is characterized by the dysfunction of the proximal renal tubule, leading to the inability to reabsorb essential nutrients and electrolytes from the urine. This causes a wide range of abnormalities in electrolyte levels which can lead to a host of metabolic complications if not recognized and efficiently treated. We describe a case of a patient who developed acquired Fanconi Syndrome after starting a chemotherapy regimen with Ifosfamide for a known malignancy. Upon discontinuation of the Ifosfamide and repletion of electrolytes, the patient improved clinically with resolution of renal injury and stabilization of electrolyte levels. This report aims to increase awareness for Fanconi Syndrome and demonstrate the necessity for having high clinical suspicion of this condition, especially when managing patients who are on chemotherapeutic agents, such as Ifosfamide.

Keywords: *Fanconi Syndrome, Chemotherapy, Ifosfamide, Electrolyte Abnormalities, Metabolic Acidosis*

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Introduction:

Fanconi Syndrome is an interesting disorder that requires a certain level of clinical suspicion to accurately diagnose and evaluate. This condition occurs from malfunctioning of the proximal renal tubule, a region that is important for reabsorbing electrolytes and essential nutrients from the urine.[1] Untreated, this dysfunction can lead to various metabolic complications. Fanconi syndrome (FS) presents as inherited or acquired, primarily affecting children and adults, respectively.[1] Acquired FS, the focus of this paper, arises from a multitude of factors including medications, chronic illnesses, or toxins as these can all affect and damage the proximal renal tubule.[2] Elucidating the precise etiology of this syndrome is crucial for developing targeted therapies to effectively treat this condition. We present an interesting case of a man who developed acquired Fanconi Syndrome following the induction of chemotherapy with Ifosfamide in the setting of known malignancy.

Case Report:

This is a case of a 47-year-old African American male with a history significant for muscular sarcoma of the right thigh with pathologic fracture of the right femoral shaft who presented to an outside hospital from a correctional facility for worsening swelling and pain in

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the right thigh and lower extremity. CT imaging demonstrated a right femoral neck fracture and duplex ultrasound of the right lower extremity revealed a DVT, so the patient was started on heparin drip and transferred to our hospital for further metastatic disease workup. He had severe pain and swelling in the right lower extremity upon arrival, but he denied symptoms of chest pain, shortness of breath, and paresthesia in distal extremities.

Patient notes he had a similar right thigh mass that was removed at age 10 and was asymptomatic afterwards. He reports insidious enlargement of the mass in his right anteromedial thigh over the past few years but is unsure of initial date of recurrence. MRI of right femur showed "pathologic fracture of the right proximal femur with associated mass involving the bone and anterior soft tissues measuring 10.6 x 13.2 x 8.9 cm" (Figure 1).

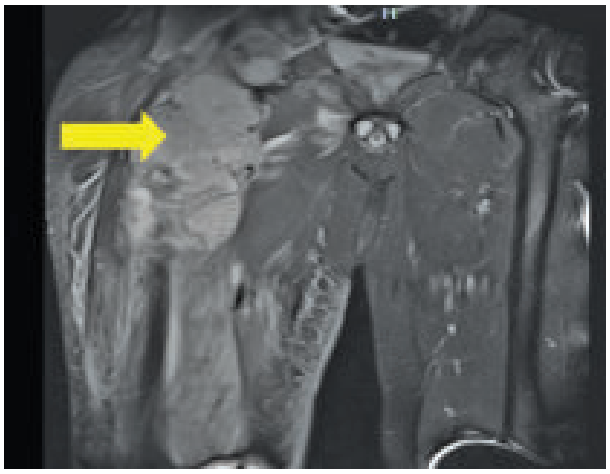

Figure 1: *MRI of right femur revealed mass at the right femur involving the bone and anterior soft tissues measuring 10.6 x 13.2 x 8.9 cm.*

CT Chest/ Abdomen/ Pelvis also demonstrated "numerous bilateral pulmonary nodules measuring up to 1.8cm (Figure 2), concerning for metastatic disease." Pathologies from CT guided core biopsies of both the mass in the right femur and a lateral pulmonary nodule revealed evidence of spindle cell sarcoma.

Treatment options at this time included surgical excision of the mass in the right femur or initiation of chemotherapy. The patient was evaluated by hematology/oncology and recommended to initiate a neoadjuvant regimen of Adriamycin, Ifosfamide, and Mesna (AIM) for 6 cycles in hopes of mass cytoreduction to salvage the right lower extremity. His chemotherapy regimen outlined 6 cycles of AIM for 4 days followed by G-CSF for 7 days. Complete blood count (CBC), complete metabolic panel (CMP), magnesium, and Urinalysis were monitored daily on the days of chemotherapy. Electrolyte levels were stable during his first two cycles of the AIM regimen.

Upon direct admission for cycle 3, CT Chest/Abdomen/ Pelvis demonstrated unchanged size of sarcoma in the right thigh and stable bilateral pulmonary nodules. On day 3 of this cycle, CMP was notable for hypokalemia (Potassium 2.9 mmol/L) and hypophosphatemia (Phosphorous 2.0 mg/dL), which were repleted and stabilized to 3.5 mmol/L and 2.3 mg/dL, respectively. Therapy was continued and on day 7 of this admission, labs were notable for an elevated Creatinine to 1.10 mg/dL (baseline 0.7), Potassium of 2.7 mmol/L, Phosphorous of 2.1 mg/dL, and Bicarbonate of 13(Table 1), indicating evolving acute kidney injury (AKI) and non-anion gap metabolic acidosis (NAGMA). Urinalysis was also notable for pH of 6.0, 2+ protein, 3+ glucose, urine creatinine 24.50mg/dL, urine potassium of 34.1mmol/L, fractional excretion of sodium (FeNa) of 3.4%, and fractional excretion of urea (FeUrea) of 63%. These

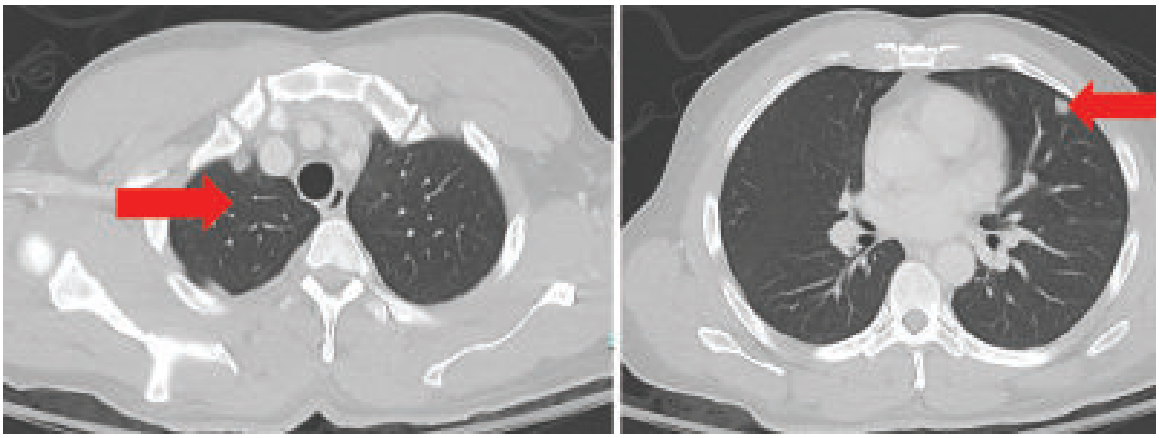

Figure 2. *CT chest, abdomen and pelvis revealed numerous bilateral pulmonary nodules, indicating metastasis.*

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Table-II

Laboratory Values Prior to and After Cycle 3 of Ifosfamide Therapy

		Pre Cycle 3	Post Cycle 3
CMP	Sodium (Na)	135	138
	Potassium (K)	3.7	2.7
	Chloride (Cl)	100	118
	Biocarbonate (HCO3)	26	13
	BUN	7	8
	Creatinine (Cr)	0.73	1.10
	eGFR	>90	83
	Glucose	109	103
	Magnesium (Mg)	1.6	1.9
	Phosphorous (Phos)	2.8	2.1
Urinalysis	pH	5.0	6.0
	Protein	2+	2+
	Glucose	Negative	2+

values indicate an intrinsic etiology of renal dysfunction, likely an acquired proximal renal tubular acidosis with Fanconi syndrome, secondary to the use of Ifosfamide in the patient's chemotherapy regimen.

Despite aggressive fluid resuscitation with intravenous lactated ringers and electrolyte supplementation (potassium and phosphorous), electrolyte abnormalities persisted for another week; subsequently, levels stabilized with potassium 3.6 mmol/L, phosphorous 3.0 mg/dL, and creatinine 0.75 mg/dL, consistent with resolution of AKI.

The consecutive cycle of chemotherapy was scheduled for the following week and the Ifosfamide and current AIM regimen was exchanged for Cyclophosphamide/ Doxorubicin to avoid further episodes of AKI. The patient tolerated the new chemotherapy regimen very well and his serum electrolyte levels remained stable and within normal limits during the final 3 cycles of his regimen.

Discussion:

Fanconi Syndrome (FS) is associated with renal proximal tubular dysfunction, resulting in significant wasting of electrolytes including bicarbonate, phosphate, glucose, and amino acids. There are many different causes of FS, including genetic conditions such as cystinosis, galactosemia, Wilson disease, and hereditary fructose intolerance among others.[3]In cases of acquired FS, as observed in this patient, a diverse range of etiologies can be implicated. The most common cause is medication induced, including certain antivirals (nucleoside reverse transcriptase inhibitors [NRTIs]), chemotherapeutic agents, and antibiotics.[1]As the proximal tubule represents the first part of the of the renal tubular system immediately following the glomerulus, it is the most common site for injury to occur in the kidneys. Many drugs enter the proximal renal tubule from the bloodstream via a range of transporters that are expressed on cell membranes, namely p-glycoprotein and organic anion and cation transporters.[3]There are various mechanisms that can result in reduced reabsorption of electrolytes and other solutes by the proximal tubule, including modifications in the functionality of these cell membrane transporters, disorders with cellular energy metabolism, and disruptions in the membrane permeability of the proximal tubule.[4] The most widely accepted explanation for this dysfunction is decreased adenosine triphosphate (ATP) due to defective cellular energy metabolism, resulting in impairment of secondary active transport mechanisms (glucose, amino acids, and phosphate).[4]

Many chemotherapeutic medications, especially alkylating agents such as ifosfamide and platinum-based compounds such as carboplatin/cisplatin are associated with toxicity of the proximal renal tubule. One study found that ifosfamide is rapidly taken up by tubular cells via the human organic cation transporter 2 (hOCT2)[5] and subsequently forms the toxic metabolite chloracetaldehyde. Its active metabolites bind with intracellular structures such as nucleic acids, namely DNA and RNA, leading to inhibition of protein synthesis.[6]Ifosfamide has been associated with the development of FS in approximately 5% of patients treated with this agent.[7]As such, it is most likely that the sudden changes in electrolyte levels

that occurred in this patient's case upon initiating his chemotherapy regimen were due to the ifosfamide in particular. The presentation of metabolic acidosis with normal anion gap, hypokalemia, hypophosphatemia, glucosuria, and proteinuria are sufficient to diagnose acquired drug induced Fanconi Syndrome. Furthermore, upon discontinuation of the ifosfamide, the patient's electrolyte levels normalized within a few days and remained stable upon continuation of a different chemotherapy regimen.

Although rare, it is important for providers' to have high clinical suspicion for Fanconi Syndrome when treating patients with medications that have been associated with this condition. Timely recognition and repletion of electrolytes is imperative to avoid more serious health consequences. A comprehensive evaluation for electrolyte imbalances should incorporate both daily laboratory serums testing to evaluate for electrolyte abnormalities and thorough physical examinations over the course of treatment. Clinical manifestations suggestive of electrolyte derangements may include new onset fatigue, confusion, lethargy, polydipsia, and polyuria. Prolonged hypokalemia can often lead to dangerous cardiac arrhythmias and hypomagnesemia and hypophosphatemia have been associated with seizures and lethargy/muscle weakness.[8] Studies have found that multidisciplinary efforts with inclusion of nursing and pharmacy in the care and monitoring of patients on chemotherapeutic agents such as Ifosfamide have also been very helpful in avoiding the development of Fanconi Syndrome and other adverse drug effects. An interprofessional healthcare team fosters optimal patient outcomes by facilitating streamlined communication, coordinated care, and therapy optimization in those taking ifosfamide.[7]

Conclusion:

Medication induced toxicity commonly leads to this syndrome and chemotherapeutic agents, such as ifosfamide, have been studied and are often implicated in the development of FS. When treating patients with ifosfamide, it is beneficial to have a high index of suspicion for the presentation of FS throughout the treatment period. The integration of interdisciplinary teams in the care of patients on ifosfamide has also been found to aid in the prevention of Fanconi syndrome and other serious adverse drug events.

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Consent:

Informed consent was obtained from the patient for the publication of this case report.

Declaration:

The authors declare no conflict of interest.

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