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Case Report

Ifosfamide-induced nephrogenic diabetes insipidus and Fanconi syndrome in a patient with femur osteosarcoma

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Abstract

Background: Ifosfamide-induced Fanconi syndrome is a relatively infrequent complication that generally occurs in young patients with a high cumulative dose of ifosfamide; and is commonly characterized by glycosuria, proteinuria, electrolyte abnormalities, and a normal anion gap metabolic acidosis.

Case Presentation: In this study, we present the case of a 16-year-old male patient with of osteosarcoma of the right femur with pulmonary metastasis, who received ifosfamide as part of chemotherapy 1 year and 2 months ago and required hospitalization for cellulitis. During inpatient management, he presented with hypokalemia, hypophosphatemia, polyuria, glycosuria, and proteinuria, by which he was diagnosed with Fanconi syndrome and nephrogenic diabetes insipidus, induced by ifosfamide. Management was focused on the control of the internal environment and use of potassium supplements and potassium-sparing diuretics.

Conclusion: Patients receiving ifosfamide should be periodically monitored for kidney function and internal environment to detect any potential complications. It is thus important to carefully observe the cumulative dose of ifosfamide to prevent its associated nephrotoxicity, since its appearance can impoverish the prognosis in patients with neoplasms. Therefore, physicians should always be aware about the possibility of nephrotoxicity development.

Keywords: Fanconi syndrome, Nephrogenic diabetes insipidus, Ifosfamide.

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The proximal renal tubule is the primary place where many solutes are reabsorbed, including 65% sodium and 90% glucose (1, 2). The dysfunction of the proximal tubule presenting inadequate solute reabsorption is known as Fanconi syndrome (FS); this is often characterized by glucosuria, phosphaturia, aminoaciduria, and type II renal tubular acidosis (3) and mainly caused, in the adulthood, by medications, exogenous toxins, and heavy metals (4, 5). The medications associated with FS are antimicrobials, anticonvulsants, and chemotherapy drugs such as ifosfamide (6), which has been reported as its etiology in up to 5% of the patients treated (7, 8), as well as causing also nephrotoxicity, proximal tubulopathy, and glomerulopathy (9). According to the literature, ifosfamide-related FS mainly occurs in children due to a high cumulative dose of ifosfamide (greater than 119 g/m^2), renal mass reduction, or joint treatment with cisplatin and renal irradiation (3, 10, 11), but the reported cases show that there is no age distinction (9, 10, 12–28). The pathophysiology of the renal tubular damage caused by ifosfamide is not well established, but it is likely to be that chloroacetaldehyde, one of the ifosfamide metabolites, is the main driver of the development of proximal tubulopathy. Chloroacetaldehyde is known to deplete intracellular glutathione in the renal tubules, favoring cellular damage (29, 30). The sodium 2-mercaptoethanesulfonate (MESNA) is a usually prescribed antioxidant for urinary bladder protection as it binds to acrolein, which is another ifosfamide metabolite, to prevent cellular damage.

However, MESNA is not sufficient in avoiding tubular glutathione depletion and is unable to prevent the tubular toxicity of ifosfamide (3, 12). It is believed that ifosfamide can lead to mitochondrial dysfunction and energy depletion in the proximal renal tubules, but how this defect would affect some transporters more than the others is yet to be determined (13). Nephrogenic diabetes insipidus (NDI) is the failure of the kidneys to concentrate urine, despite having normal or elevated plasma concentrations of arginine vasopressin (31) and, currently, there are proposals to change its name from NDI to "arginine vasopressin resistance" (32). NDI causes polyuria, polydipsia and hyposthenuria leading to severe dehydration and electrolyte abnormalities (elevation in sodium and chlorine concentration) (33). There are congenital and acquired forms, with the latter being caused by infiltrative disorders, electrolyte abnormalities, and antimicrobial, psychotropic, and chemotherapeutic agents, such as ifosfamide (31, 34). NDI is a rare complication of ifosfamide treatment (14), and it usually occurs with FS, manifesting as tubular toxicity (15, 16, 35). Ifosfamide-related NDI mainly occurs due to a high cumulative dose of ifosfamide (greater than 40–60 g/m2), under the age of 16 years, or joint treatment with cisplatin (14). The pathophysiology of the ifosfamide-related NDI remains unknown. In this present article, we describe the case of a 16-year-old male patient with a diagnosis of osteosarcoma of the femur, who, because of the use of ifosfamide, developed FS and NDI.

Case Presentation

A 16-year-old male with the diagnosis of osteoblastic osteosarcoma in the distal right femur (figure 1) with lung metastasis 1 year and 2 months ago received carboplatin, ifosfamide, and MESNA, which led him to develop severe neutropenia 2 months later, after which he used cisplatin and doxorubicin. Finally, it was changed to etoposide 100 mg/m^2 and ifosfamide 3.5 g/m^2. Five days after the last cycle, he was admitted to the emergency room because of vomiting and fever, signs of phlogosis in the right inguinal region, and increased right lower limb volume. Physical examination revealed the following: blood pressure 80/50 mmHg, heart rate 110 beats/minute, respiratory rate 30 breaths/minute, axillary temperature 38.3°C, weight 40 kg, height 155 cm, body surface area 1.33 cm^2, body mass index 16.64 kg/cm^2, and signs of phlogosis in the proximal third of the right lower limb. The rest of the exam was normal. The initial blood tests showed pancytopenia (leucocytes 120 cells/mm^3, hemoglobin 4.7 g/dl, platelets 9000/mm3) and mild metabolic acidosis with a normal anion gap (pH 7.285, K^+ 1.9 mmol/L, Na^+ 156 mmol/L, lactate 0.9 mmol/L, and $HCO3^-$17 mmol/L). The initial diagnosis was dermal-onset sepsis, and the patient underwent hydration, red blood cell transfusions, filgrastim, meropenem 2g I.V. t.i.d., and vancomycin 1 g I.V. b.i.d. Later, the patient was transferred to the internal medicine service, where he was treated with poor clinical response.

Caspofungin was then added to his treatment, and his evolution became favorable with this management; however, 18 days after his hospital admission, he presented with hypocalcemia (8 mg/dl), hypokalemia (2.0 mmol/L), hypomagnesemia (0.95 mmol/L), hypophosphatemia (0.9 mmol/L), non-quantified glycosuria and proteinuria, hyperphosphaturia (24-hour urine phosphate/creatinine ratio: 3717 mg/g), and hypercalciuria (24-hour urine calcium/creatinine ratio: 1493 mg/g); this, together with the metabolic acidosis on admission, confirmed that the first diagnosis was FS attributed to the use of ifosfamide, wherein his cumulative dose received since diagnosis was found to be 55 g/m^2. Furthermore, concomitantly, the patient presented with episodes of hypotonic polyuria (urine osmolarity 250 mOsm/kg, plasmatic osmolarity 300.61 mOsm/kg, diuresis 8 L/day), for which he was subjected to a fluid restriction test with administration of nasal desmopressin, without changes in the urinary osmolarity finishing the test, being the second diagnosis NDI, attributed to persistent hypokalemia secondary to FS, persisting the possibility of the ifosfamide contribution to the nephrotoxicity. Due to the coexistence of both pathologies, the patient received hydrochlorothiazide and oral potassium supplements daily. At the end, he presented with slight clinical improvement after receiving oral potassium supplements. Ifosfamide was suspended, and I.V. chemotherapy based on docetaxel 108 mg/day and gemcitabine 1250 mg/day was initiated.

Discussion

Ifosfamide, which is a synthetic structural isomer of cyclophosphamide, is an alkylating antineoplastic agent used to treat many solid tumors, especially in children (9), with hemorrhagic cystitis being its most frequent adverse effect (3). However, its increasingly frequent use has revealed that nephrotoxicity is a potentially serious complication that can include tubular dysfunction and even glomerular deterioration, these effects being first described in 1972 (36). There are few cases reported in the literature (9, 10, 12–28), and those show that the mean age of the affected population is 29 years (95% CI = 19.2–38.9), without sex predominance (52% males).

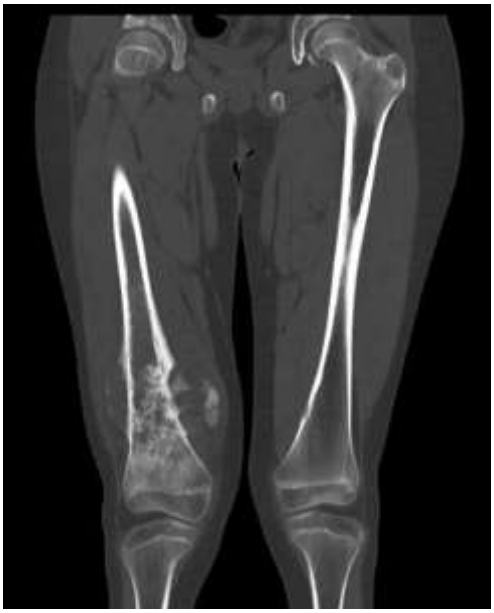

Figure 1. Computed axial tomography scan with contrast of the right lower limb prior to the start of chemotherapy. Sagittal section. Note tumor lesion at the level of the distal third of the right femur compatible with osteosarcoma.

The mean time from ifosfamide use to the development of complications in more than half of the cases was less than 20 days, but it was noted to range from 3 days to 2 years. Children often presented with dyspnea, leg pain, growth retardation, rickets, polydipsia, and polyuria, whereas adults presented with weakness, asthenia, dyspnea, polydipsia, polyuria, hypovolemia, and febrile neutropenia at admission. Mean phosphate was 1.50 mg/dl (95% CI = 1.15–1.85), and mean bicarbonate was 16.75 mmol/L (95% CI = 14.12–19.37).

Moreover, 67% of the patients developed only FS, 19% FS and NDI, 10% partial FS, and 5% only NDI. All cases were treated with electrolyte reposition, and some with hydration, diuretics, desmopressin, and indomethacin. However, 14% of the patients died despite the treatment used, while the rest had total or partial resolution of the symptoms. During hospitalization, our patient with presented signs of proximal tubular dysfunction, evidenced by hypokalemia, hypophosphatemia, hypomagnesemia, hypocalcemia, glycosuria and proteinuria, compatible with FS, which was induced by ifosfamide, being an infrequent complication (26, 37).

Our patient had three of the risk factors described: age, joint treatment with cisplatin and a high cumulative dose of ifosfamide. Notwithstanding, there are reported cases that did not present risk factors (10, 16). FS can develop acutely (10, 15, 16, 23) or up to 2 years after ifosfamide has started (12, 13, 36). In our case, it started approximately after 5 days of the last ifosfamide cycle, in the context of a sepsis, due to cellulitis in the lower right limb, which is a common comorbidity in this type of reported cases (10, 13). The development of hypotonic polyuria (diuresis > 2 L/m^2 in 24 hours in children, with a urine osmolarity< 300 mOsmol/kg) and the lack of response to desmopressin in the fluid restriction test, confirmed the diagnosis of NDI (31).

The characteristic hypokalemia of the FS may explain the coexistence of secondary NDI (34). However, this could be an effect of ifosfamide nephrotoxicity, occurring in patients with other signs of tubular dysfunction, such as FS (10, 16). How ifosfamide alters the concentration of urine in the distal tubule to result in NDI remains unknown (14). There is no specific management of ifosfamide-induced NDI (36, 37), but controlling the internal environment by means of free water intake, oral potassium supplements, and the use of diuretics such as hydrochlorothiazide, which is known to reduce urinary flow by reducing salt reabsorption and inhibiting SLC12A3 cotransporter in the distal tubule, has been proposed (38).

However, hydrochlorothiazide can lead to hypokalemia, which can exacerbate NDI in these patients, the reason why the concomitant use of potassium-sparing diuretics such as amiloride is considered (14, 39). The use of intravenous desmopressin at supratherapeutic doses (80 ug every 6 to 8 hours) could reduce polyuria in patients with ifosfamide-induced NDI (14). The signs of tubular dysfunction attributed to ifosfamide nephrotoxicity are initially transient but become persistent in some patients as the cumulative dose increases (11, 26). Preventing this toxicity is vital to

minimize complications during the chemotherapy regimen (40). Thus, the primary method to prevent nephrotoxicity is to limit the cumulative dose of ifosfamide especially in patients with risk factors (11).

Other preventive strategies, such as the co-administration of MESNA (11, 40), N-acetylcysteine (30, 41), resveratrol, melatonin, L-carnitine, and thymoquinone have been evaluated, but their efficacy has not been proven (10). Based on our case and others available in the scientific literature, timely diagnosis of this entity, support with electrolyte replenishment and hydration, as well as the possibility of suspension of ifosfamide have been shown to restore tubular function in most cases (30). In conclusion, this reported case reminds us that ifosfamide can result in FS and NDI simultaneously, which should be prevented by assessing the harm/benefit associated with its use and carefully observing the cumulative dose of ifosfamide, since these nephropathies impoverish the prognosis of patients with neoplasms. Other safer therapeutic alternatives should be evaluated.

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