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Case Report

Orthopaedics Section

Uranium-Toxicity and Uranium-Induced Osteosarcoma Using A New Regimen and Surgery : A First-Time Experience

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ABSTRACT

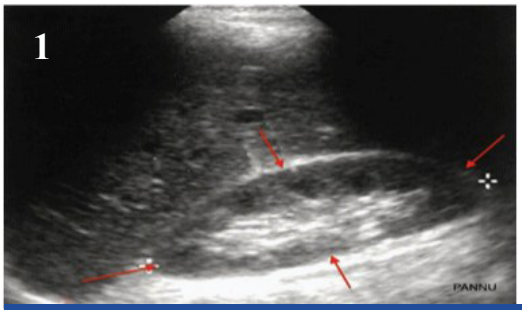
Uranium isotopes have always been problematic to mankind since many centuries. Different studies all over the world have been unable to reveal causal relationship between uranium and its toxic effects on kidneys, bone and lungs. In this case report, we present a rare association of uranium toxicity with renal dysfunction and possibility of induction of osteosarcoma by an unknown mechanism. The presentation of the 12-year-old patient was reduction in urine output along with joint pains, seemed like that of diabetes mellitus, as he was already on insulin. The patient later diagnosed to have uranium toxicity. This case is an instance of strong association between medicine and public health. With complete history, physical examination and required investigations, all common causes like NSAID toxicity, aminoglycoside toxicity and exacerbation of diabetes were ruled out. Uranium investigations were done lastly based on the toxicology report of drinking water (South African toxicologist, Caron Smith). In the management strategy, the new regimen CBMIDA, supported by studies in Europe, was used. However, to our surprise, joint symptoms tracked their way to a diagnosis of osteosarcoma, which was later operated upon by our orthopaedic surgery team. Histopathologically, it was found to be a chondroblastic type of osteosarcoma.

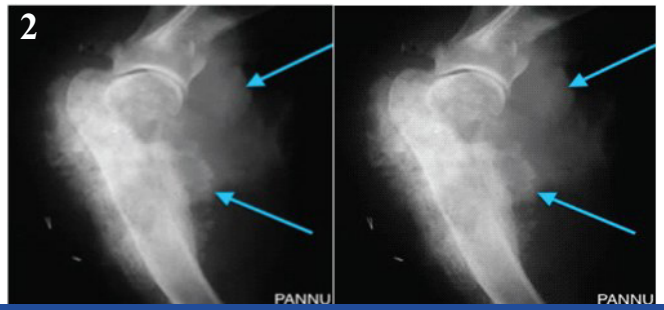
Keywords: Chondroblastic Orthopedics pediatric, Nephrology

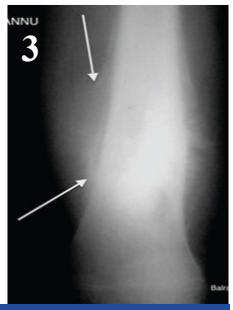
CASE REPORT

A 12-year-old child, presented with chief complaints of decreased urine output since three months and joint pains (especially knee joint) with limitation of movement since 10 days. Urine output decrease was gradual in onset and progressive with no associated pain, dribbling, burning or blood in urine. Limitation of movement was associated with knee pain with minor involvement of hip joint 10 days back. Patient experienced pain only while playing, which later becomes worse at night time, thus disturbing his sleep. There was a history of associated fever, which was gradual in onset, documented as 101° F, by a previously consulted physician, not associated with rigors, chills or rashes, which earlier was intermittent but became continuous later on. It was temporarily relieved by medication as prescribed by a local practitioner. There was a history of significant weight loss in the last three months. There was no associated history of sore throat, respiratory infection or morning stiffness of joints or redness of eye (reactive arthritis).There was no history of consumption of lead paint [1] or ethylene glycol [2]. The patient denied any history of periorbital swelling, palpitations or chest pain. History of past illness revealed that he was a known case of type 1 Diabetes receiving daily two injections (morning 15 units, evening 12 units) of NPH Insulin (one unit/kg). There was no history of hypoglycaemic episodes, hospitalisations or diabetic ketoacidosis. In the family, there was no history of renal or cardiac disease or cancer. There was no history of NSAID exposure for knee-pain or aminoglycosides exposure, though patient took homeopathic medicine for about three days (Dosage—Bryonia taken 6C four times a day for up to 14 days). Contrast CT scan was not done. After obtaining a diligent history, we formed two provisional diagnosis: Diabetic nephropathy with accompanying bone tumour, Uranium nephrotoxicity and bone tumour.

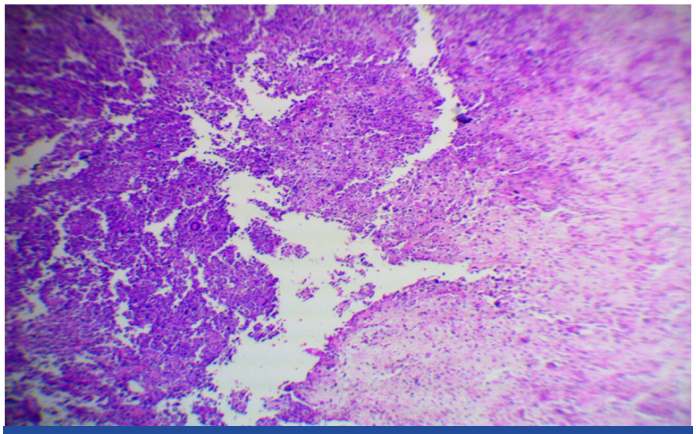
On physical examination, the height and weight of child were 43 inches and 16 kg, respectively, his blood-pressure was 115/70mmHg. There was no icterus, clubbing, cyanosis or lymphadenopathy.







[Table/Fig-1]: Ultrasonography of Kidney **[Table/Fig-2]:** X-ray knee demonstrating possible uranium induced osteosarcoma (Sun-ray appearance)
[Table/Fig-3]: Radiograph demonstrated lytic-lesion involving metaphysics of femur,new bone formation and periosteal reaction (Codman's triangle)



[Table/Fig-4]: High grade chondroblastic osteosarcoma on histopathology of the resected mass

[Table/Fig-5]: Monitoring uranium-levels during chelation-therapy

No hepatomegaly, splenomegaly and no peripheral oedema was detected. His ophthalmologic, neurologic and cardiac examinations were normal (on auscultation, no abnormal sounds or murmurs were heard in the chest). Renal pathology due to congestive heart failure and nephritic syndrome was ruled out. With respect to congestive heart failure, there was no history of chest pain, breathlessness or palpitations. Jugular-venous pressure was not raised.

On further laboratory examination, his serum creatinine level was found to be 2.8mg/dl, fasting blood glucose concentration was 5.2mmol/L, HbA1c was 4.8%, and blood profile tests to measure the amount of protein and cholesterol were within normal limits. Serum protein electrophoresis results were as follows: albumin (67), alpha 1 (1.4), alpha 2 (7.2), beta-globulin (9.3), gamma globulin (8.0), antinuclear antibodies (ANA), hepatitis B, hepatitis C, and HIV were negative. Full urine analysis colour and odour were normal, clear with specific gravity 1.010,pH 5.5, no casts, bacteria or debris.+1 glycosuria, with no ketones and 24 hour urine collection showed <3 grams protein. On repeat analysis after a week, urine albumin to creatinine ratio was 0.029 and 0.016 (normal) after one month [3,4]. On radiographic examination, ultrasonography abdomen [Table/Fig-1], with focus on kidneys: right kidney measured 10.33*4.12*2.04 and left kidney measured 10.5*4.7*2.45. There was no evidence of any mass, hydronephrosis, calculus or cortical-thinning; but had normal echo texture and normal demarcation between outer cortex and middle pyramids and columns of Bertin.

Meanwhile, in March 2009, South African Board Certified Clinical metal toxicologist Carin Smith [5] collected drinking-water samples from Faridkot, Punjab, India. They were preserved at 4°C with nitric acid. Levels were found to be 54 times higher than normal levels [6]. The type of uranium was 238 U and same was found in water of Faridkot region by toxicologists. The use of phosphorus fertilisers in the region might be the source of uranium, which reach water after leaching from the soil [7]. Since, the patient was also a resident of Faridkot, a 24 hour urine sample examination of the patient was conducted, with inductively coupled plasma mass spectrometry after microwave assisted digestion and online separation using UTEVA extraction chromatographic-resin) [8] and uranium levels were found to be 785.9 ngd(-1) [9,10]. Thus, the diagnosis of uranium-toxicity was made [11]. The patient was referred to radiology department for roentgenographic investigation of knee. The radiographs demonstrated lytic-lesion involving metaphyses of femur, new bone formation, periosteal reaction (Codman's triangle) as shown in [Table/Fig-2,3]. MRI was helpful in staging the malignancy as stage1B.The diagnosis of osteosarcoma [12] was confirmed histopathologically as high grade osteosarcoma [Table/Fig-4] and chest X-ray was done to rule out any lung-metastases. The patient was taken to hospital to prevent any further exposure and was externally decontaminated. The patient received sodium bicarbonate 840mg/kg/day orally in divided doses (to alkalinise urine to pH 8 to increase the renal excretion of toxic uranium) titrated to urine pH 8 along with chelating therapy with CBMIDA {Catechol-3,6-bis (methyliminodiacetic acid)} [13]. 1200mg/kg once daily for two weeks. Uranium levels were regularly monitored as depicted in [Table/Fig-5]. On revaluation, uranium levels dropped to 124.7ngd (-1). Therapy was repeated till uranium levels reached normal-limit {6.45ngd(-1)}. Chemotherapy was started with high-dose methotrexate with leucovorin rescue(MTX-L) administrated over 6 hours with a mean peak concentration 900umol/l at the completion of infusion, then,10 mg leucovorin was administered intravenously 24 hours after initiation of MTX-infusion.

Proper monitoring prevented toxicity of MTX. Hydration was maintained to prevent tumour lysis syndrome, which could have been severe with lack of normal kidney function. After suppression of osteosarcoma with chemotherapy, MRI was done which showed an enhancement, infiltrating into soft tissue spaces containing nerves and blood vessels and high signal intensity peritumoural oedema. Pre-surgical evaluation of tumour which involved blood vessels and nerves led to a decision of amputation which was unavoidable and a prosthetic limb was fitted so that the child can join in normal activities. Histopathological examination of the resected part revealed high grade chondroblastic type osteosarcoma.

DISCUSSION

The present case documents a rare presentation relating chronic exposure to uranium and induction of osteo-sarcoma. Until now, physicians have been reluctant to the use of chelation therapy in toxicities in humans. CBMIDA, a chelating agent [14] was administered based on a study by Fukude S et al., Therapy was continued for three weeks with regular monitoring of uranium levels. Chemotherapeutic combination of high dose methotrexate with leucovorin was preferred over other combinations, including Ifosfamide, cisplatin or carboplatin [15] because their potential nephrotoxicity [16] would have further compromised kidney function in our patient [17]. NSAID induced kidney damage [18] has been reported in children in many case reports but we ruled it out in negative history.

Similarly, nephrotoxicity caused by aminoglycosides [19] in children has also been documented. However, these toxicities do not present with any accompanying joint symptoms. Lead nephrotoxicity is common among children. Consumption of antifreeze ethylene glycol can also result in kidney dysfunction. There is no documented evidence of induction of osteosarcoma [20] on chronic-uranium exposure, though, a study conducted in South Carolina by Wagner SE et al., claimed evidence of carcinogenic-potential of uranium in drinking water. Another study from United Kingdom provides evidence of induction of osteosarcoma in mice with alpha emitting nuclides from uranium-233.

Population studies like ATSDR [21], Jacob [22], and Konietzka [23] suggested that kidney is the main target of uranium [24,25] and in addition, bone can be the next target. To the best of our knowledge, the indexed case is the first successful treatment of uranium toxicity and uranium-induced osteosarcoma. The literature is limited on possibility of uranium as a causative factor for development of osteosarcoma [26,27]. Molecular and intracellular signalling research is encouraged in future to ascertain the mechanism of carcinogenesis. More case-control studies are warranted to ascertain odds ratio of development of osteosarcoma in children exposed or unexposed to uranium.

CONCLUSION

Our experience raises a high possibility of more cases of cancers on long-term exposure to uranium in Punjab. This association merits large scale study to ascertain the high-risk individuals living in environment polluted with depleted uranium in Punjab, India.

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