Case report

Analgesic Nephropathy and Hyperparathyroidism -a case report

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Summary

Chronic kidney disease (CKD) is very common in our country and most of the cases progress to end stage renal disease (ESRD) and ultimately die due to inadequate facilities of renal replacement therapy especially in the remote rural areas of Bangladesh. Disturbances in mineral and bone metabolism are prevalent in CKD and have traditionally been termed renal osteodystrophy. A young male is described here having regular non steroidal anti-inflammatory analgesics drugs (NSAIDs) for about one and half years for traumatic low back pain who presented with severe dyspnea, disorientation, hypertension, edema and anemia. On admission his serum creatinine was found very high. He was promptly resuscitated by several settings of hemodialysis, necessary medications and blood transfusions following which he gained consciousness with relief of dyspnea. The patient was totally hopeless to know that he is suffering from kidney disease, and he was also not economically very much solvent. With further dialysis, total avoidance of analgesics and other appropriate supportive management the patient ultimately recovered completely from chronic renal failure (CRF) but his hyperparathyroid state persisted inspite of maintaining serum calcium to normal level by calcitriol (1, 25 dihydroxycholecalciferol) and calcium supplements. On follow-up in addition to elevation of serum parathyroid hormone he developed some soft tissue calcification which warranted stopping calcium supplements. Otherwise he was found well and maintaining good health. CKD is usually irreversible and progressive, and reversible causes are very less among which analgesic nephropathy is one of the important one.

Keywords: analgesic nephropathy; chronic kidney disease; mineral bone disease; hyperparathyroidism; soft tissue calcification.

Introduction

Analgesic nephropathy is an established condition resulting from prolonged use of NSAIDs. Renal papillary necrosis and tubulo-interstitial nephritis with progressive scarring are characteristic of the histopathology of analgesic nephropathy. Typically, papillary necrosis in these patients is bilateral and affects almost all renal papillae1. Minimal or membranous glomerular lesions can also develop2. Clinically analgesic nephropathy can present as hematuria, proteinuria, nephritic syndrome, nephrotic syndrome, acute renal failure or CRF.

These conditions are usually reversible if analgesics are stopped before the renal condition is sufficiently protracted with scarring and shrinkage of the kidneys resulting irreversible damage and ESRD2. In CRF, hypocalcemia results from inadequate production of calcitriol by the kidneys needed for calcium retention and resorption. Hypocalcemia and decreased calcitriol stimulates the parathyroid glands for secretion of parathormone which regulates calcium levels and helps to maintain these levels mainly by bone resorption causing renal osteodystrophy. Secondary hyperparathyroidism can be prevented by providing calcium carbonate and calcitriol.

Disturbances in mineral and bone metabolism are prevalent in CKD and an important cause of morbidity, decreased quality of life, and extraskeletal calcification especially vascular, which has been associated with increased cardiovascular mortality. These disturbances have traditionally been termed Renal Osteodystrophy3. In 2005, the organization of Kidney Disease: Improving Global Outcomes (KIDGO), proposed replacing the term Renal Osteodystrophy by Chronic Kidney Disease-Mineral Bone Disorders; (CKD-MBD) as the disorder is not confined to the skeleton4. CKD-MBD is manifested by an abnormality of any one or a combination of the following: laboratory-abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism; bone-changes in bone turnover, mineralization, volume, or strength; and calcification in the soft-tissue and the arterial vessels3,4,5,6.

Hyperparathyroidism is overactivity of the parathyroid glands resulting in excess production of PTH. Excessive PTH secretion may be due to problems in the glands themselves, in which case it is referred to as primary hyperparathyroidism and which leads to hypercalcemia . It may also occur in response to low calcium levels, as encountered in various situations such as vitamin D deficiency or chronic

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kidney disease; this is referred to as secondary hyperparathyroidism. Tertiary hyperparathyroidism result from autonomous hyperplasia of the parathyroid glands and a loss of response to serum calcium levels. This disorder is most often seen in patients with CRF. In all cases, the raised PTH levels are harmful to bone, and treatment is often needed. Recently, vitamin D receptor activation on parathyroid hormone suppression has been suggested in the survival of patients undergoing dialysis for treatment of hyperparathyroidism7.

In 2009 KDIGO clinical practice released guidelines on the management of CKD-MBD8,9. According to these guidelines, parathyroid intervention, such as parathyroidectomy and percutaneous ethanol injection therapy, should be indicated if mineral disorders cannot be managed by pharmacological means. Recently, several novel therapeutic tools, including sevelamer hydrochloride (a phosphate binding agent), vitamin D analogs, and cinacalcet hydrochloride have been introduced in the clinical setting in Japan. Cinacalcet is a calcimimetic which enhances the calcium sensing receptors of the parathyroid glands resulting in increase binding of calcium thereby reducing the secretion of PTH. The other side 2009 KDIGO guideline suggests that, if the intact PTH levels fall below two times the upper limit of normal for the assay, calcitriol, vitamin D analogs, and/or calcimimetics be reduced or stopped. And in patients with CKD stages 3-5 with severe hyperparathyroidism who fail to respond to medical/pharmacological therapy, this guideline suggests parathyroidectomy.

Case report

Md Harez Ali, 20 years old male (A 09089088, R 071101842) was admitted in Khwaja Yunus Ali Medical College & Hospital in the emergency department on the afternoon of 06th June 2008 with severe dyspnea, disorientation, hypertension, edema and moderate anemia. His blood pressure was 160/110 mmHg and auscultation of the chest revealed bilateral basal crepitations. On admission his Serum Creatinine was found 2675 umol/L, serum urea: 23.34 mmol/L, Sodium: 128.9 mmol/L, Potassium 7.0 mmol/L, Chloride: 91.4 mmol/L, bicarbonate: 6.9 mmol/L, Hemoglobin: 7.8 gm/dL and Serum Calcium: 2.09 mmol/L. Chest X-ray revealed mild cardiomegaly with pulmonary edema and ECG-sinus tachycardia. Hemodialysis (HD) was done on the day of admission and was continued at frequent intervals. Blood transfusions were given at the time of dialysis. Other emergency drugs and supportive measures were provided (oxygenation, loop diuretics, antihypertensives, calcium carbonate supplements, restriction of fluid, potassium and proteins) following which he gained consciousness with relief of dyspnea. His urine output was only 200ml on the 1st 24 hours of admission. Urine examination revealed protein +++ and RBC plenty. Serum albumin was found 2.4 gm/dL. HBsAg: negative and anti HCV: negative. X ray lumbar spine revealed compression collapse of 3rd lumbar vertebra & osteoporosis of spines. Renal ultrasound revealed normal findings. The patient was stabilized by total 6 times of HD with 8 units of blood transfusion {B (+)} by 2 weeks. He was totally hopeless to know that he is suffering from CKD, as he was not economically very much solvent. He mentioned that in the past, in January 2007, he sustained traumatic compression collapse (wedge) of 3rd lumbar vertebra (Fig-1a, Fig-1b) developed paraparesis, was bed ridden initially and underwent treatment by local quacks with various analgesics. He also was treated by different orthopedic surgeons of various clinics and hospitals and recovered from paraparesis. Since January 2007 he was taking different analgesics in considerable doses both parenteral and oral (Naproxen, Clofenac, Ketorolac, Piroxicam, Paracetamol) daily to control his low back ache in addition to the use of lumbar corset. Subsequently he developed diarrhea, anorexia, nausea, vomiting, gradual edema, weakness, undue tiredness with scanty urine for about one month before admission in a critical stage with disorientation and convulsion. Shortly after several HD & blood transfusions the patient improved hemodynamically. On 07th July 2008 he was discharged with advice to continue diuretics, antihypertensives, calcium carbonate, calcitriol, prednisolone (60 mg/day orally) restriction of fluid, and proteins and to visit at frequent intervals for follow up. His edema subsided; blood pressure, serum creatinine and urine output returned to normal. During further follow up the individual was found to develop gradual and complete recovery by 6 months; but needed admission twice for blood transfusions and renal checkup only. He was also evaluated for collapsed vertebra and osteoporosis of spines. Urinary Bence Jones protein and serum protein electrophoresis were found negative. Routine examination of the urine was found normal and serum calcium also returned to normal level. A follow up X ray dorsolumbar spine (Fig-2a, Fig-2b) revealed additional features of soft tissue (renal/pancreatic) calcifications, osteoporosis of thoracic and lumbar vertebrae and partial collapse of thoracic 5, 6, 9 and 11 vertebrae. Than PTH assay was done, which was found high (78 pg/ml, normal 7 to 53 pg/ml) suggestive of hyperparathyroidism which warranted stopping of calcium supplements. He was discharged with advice for periodic follow up.

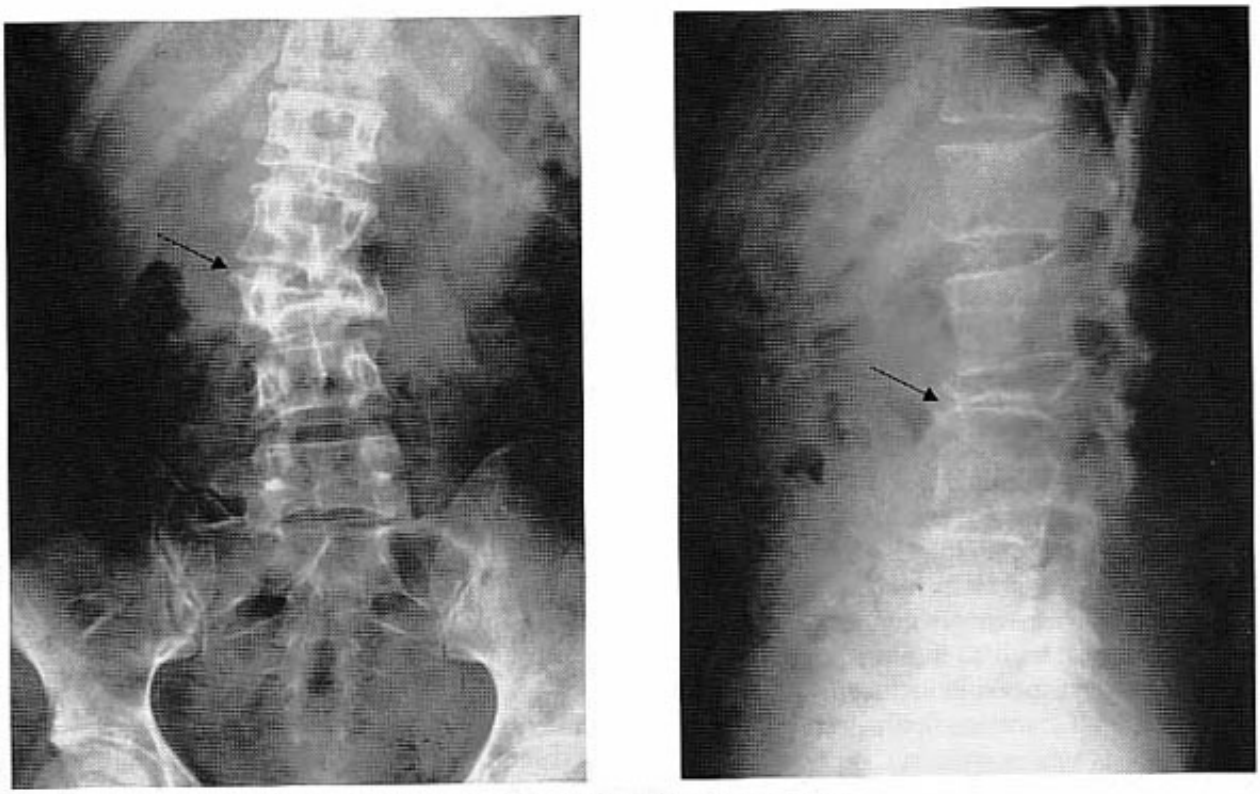

Fig-1a & Fig-1b showing compression collapse of 3rd lumbar vertebra

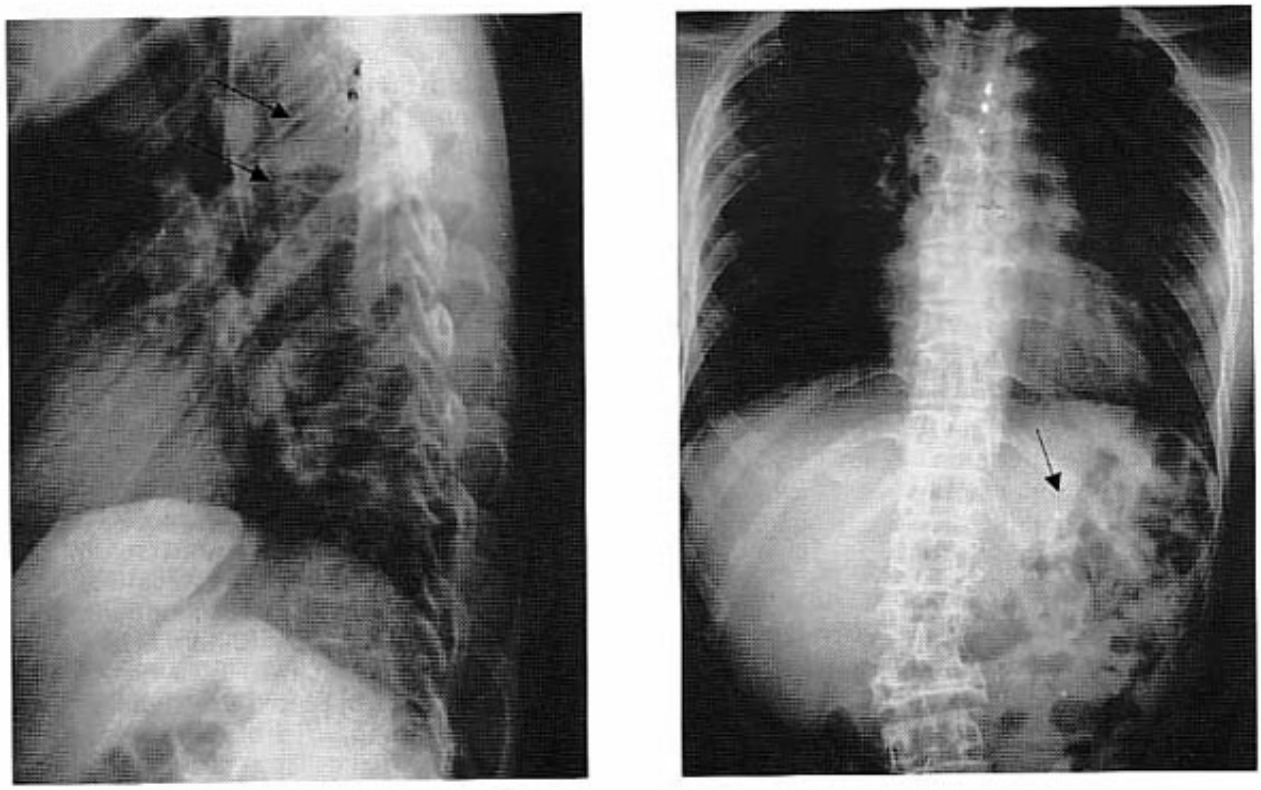

Fig-2a & Fig-2b showing additional features of soft tissue (renal/pancreatic) calcifications, osteoporosis of thoracic and lumbar vertebrae and partial collapse of thoracic 5, 6, 9 and 11 vertebrae.

Discussion

Analgesic nephropathy is most commonly seen in patients who ingest large quantities of analgesic combinations. The drugs of concern are phenacetin, paracetamol, aspirin, and other NSAIDs. Chronic ingestion of 1 g/d for 3 years is the typical amount needed for renal dysfunction10. Analgesic nephropathy is recognized since long. Many of the renal abnormalities that are encountered as a result of NSAIDs use can be attributed to the inhibition of prostaglandins synthesis. There are various analgesics associated renal syndromes. Révai T & Harmos G published a case report that developed ARF and nephrotic syndrome after 6 months of diclofenac where histopathology revealed membranous nephropathy and interstitial nephritis11. After discontinuation of diclofenac and treatment with prednisone 1 mg/kg/day, furosemide 400 mg/day and simvastatin at a dose of 20 mg/day, creatinine clearance gradually increased and after 5 months of treatment complete remission of the nephrotic syndrome was observed. Jochum E & Janssen U published a case report where a male of 18, developed chronic renal damage following use of analgesics for 4 years12.

Conclusion

CKD is recognized as one of the significant public health concern in Bangladesh and is associated with increased morbidity and mortality. NSAIDs are still indiscriminately used in our country. Most patients grossly underestimate their analgesic use. Even in patients on long term NSAIDs without acute or chronic renal failure, subclinical renal dysfunction such as reduced creatinine clearance and impaired urine concentrating ability has been shown to be present. Although this subclinical dysfunction is reversible on withdrawal of NSAIDs, some reports have suggested a persistent residual dysfunction13. Even with a wide range of NSAIDs at our disposal, a renal safe NSAID is yet to be discovered13. Physicians should consider screening heavy users of acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) for evidence of renal disease and discourage the use of these drugs14.

References:

1. Granese J, Brightbill K, Osborne P, Cox CE, Gaber LW. Analgesic nephropathy selectively affecting a unilateral non-functioning hypoplastic kidney. Clin Nephrol 2007 Aug; 68(2):115-20.
2. Kleinknecht D. Interstitial nephritis, the nephrotic syndrome, and chronic renal failure secondary to nonsteroidal anti-inflammatory drugs. Semin Nephrol 1995 May;15(3):228-35
3. Moe SM, Drüeke T, Lameire N, Eknoyan G. Chronic kidney disease-mineral-bone disorder: a new paradigm. Adv Chronic Kidney Dis 2007 Jan; 14(1):3-12
4. Suchowierska E, My?liwiec M. Mineral and bone disturbances associated with chronic kidney disease. Pol Merkur Lekarski 2010 Feb; 28(164):138-43. Review. Polish. PMID: 20369744
5. Moe SM, Drüeke T. Improving global outcomes in mineral and bone disorders. Clin J Am Soc Nephrol 2008 Nov; 3 Suppl 3:S127-30
6. Lameire N, Eknoyan G, Barsoum R, Eckardt KU, Levin A, Levin N, Locatelli F, MacLeod A, Vanholder R, Walker R, Wang H. A new initiative in nephrology: 'Kidney disease: improving global outcomes'. Contrib Nephrol 2005; 149:90-9
7. Gal-Moscovici A, Sprague SM. Use of vitamin D in chronic kidney disease patients. Kidney Int. 2010 May 26
8. Uemura K, Kakuta T. Clin Calcium. CKD-MBD (Chronic Kidney Disease-Mineral and Bone Disorder). Parathyroid interventions : Final one piece in the management of uremic SHPT patients.2010 Jul;20(7):1104-10. Japanese. PMID: 20585190
9. Moe SM, Drüeke TB, Block GA, Cannata-Andía JB, Elder GJ, Fukagawa M, et al. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl 2009 Aug; (113):S1-130
10. Watnick S, Morrison G. Kidney Disease. In McPhee S J & Papadakis MA. Current Medical Diagnosis and Treatment, 49th ed. McGraw Hill Companies, New York. 2010: pp 844-846
11. Révai T, Harmos G. Nephrotic syndrome and acute interstitial nephritis associated with the use of diclofenac. Wien Klin Wochenschr 1999 Jul 9; 111(13):523-4
12. Jochum E, Janssen U. Chronic interstitial nephritis in an 18-year-old due to intake of a compound analgesic. Med Klin (Munich) 2006 Oct 15; 101(10):830-4. German. PMID: 17039326
13. Ejaz P, Bhojani K, Joshi VR. NSAIDs and kidney. J Assoc Physicians India 2004 Aug; 52:632-40
14. A S L, Brenner B M, Tubulointerstitial Diseases of the Kidney. In Fauci AS, Kasper DL, Longo DL, Braunwald E, Hauser SL, Jameson JL, Loscalzo J. Harrison's Principles of Internal medicine, 17th ed. Mc Graw Hill, New York. 2008: pp 1806-1810