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RESEARCH ARTICLE

TUMOR INDUCED OSTEOMALACIA: A CASE REPORT

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Abstract

Background: Tumor-induced osteomalacia (TIO), which is also known as oncogenic osteomalacia, is an uncommon paraneoplastic syndrome characterized by a renal phosphate loss causing hypophosphatemia, leading to rickets in children and osteomalacia in adults. It is caused by mesenchymal tumors, which secrete FGF-23 (fibroblast growth factor-23) and rarely other phosphotonins. It can present with a wide range of symptoms and there is often a delay in its diagnosis. Early diagnosis is important and surgical excision can cure the disease in most patients, thus preventing the complications.We report a case of TIO, who was diagnosed at an early stage and underwent curative surgery.

Case presentation: A 30 years old female presented with pain in both legs, more severe in the left leg since about 1 year. She also had difficulty in walking, low back ache, muscle pain, mild pain in both the knee joints as well. On examination, she had limping gait, muscle power in the left leg was grade 3-4; otherwise, there was no significant findings on examination. Blood investigations showed elevated alkaline phosphatase (ALP)- 387IU/ml, low serum phosphorus- 1.2mg/dl, normal calcium - 9.8mg/dl, 25-OH Vitamin D- 24.69ng/ml, Parathyroid hormone (PTH)- 61pg/ml.Other blood tests were unremarkable. X- rays of both the legs and pelvis showed a classicalpseudo-fracture in proximal part of both the fibulae and proximal part of the right femur. This suggested hypophosphatemicosteomalacia. TmP/GFR was found to be very low (1.4mg/dl), which confirmed renal phosphate wasting. Later we got Fibroblast growth factor – 23 (FGF-23)- 617RU/ml, which was elevated. This confirmed FGF-23 related hypophosphatemicosteomalacia. In view of the patient's age, onset of symptoms, lack of family history, absence of dental and hearing abnormalities, we suspected an acquired rather than a genetic cause. The patient underwent whole body Gallium-68 DOTANOC PET scan, which revealed somatostatin receptor expressing soft tissue density lesion in subcutaneous plane in the mid- anterior right leg, suggestive of FGF-23 secreting mesenchymal tumor.The patient was initially treated with replacement dose of oral phosphorus and calcitriol, along with calcium and vitamin D supplements. Later the patient underwent surgery for excision of the tumor in the right leg. The tumor was

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around 2cm size and the histopathology was suggestive of gaint cell rich tumor- possibly a phosphaturic mesenchymal tumor. Post surgery, the patient had significant improvement in her symptoms, gait improved and pain reduced. The serum phosphorus level was 3.8mg/dl post-operatively. The serum phosphorus level was maintained without phosphorus replacement. The patient was advised to repeat FGF-23 levels, but the patient failed to get it done.

Conclusion: The diagnosis of TIO requires high index of suspicion and should always be looked as a differential diagnosis when we are evaluating a patient with osteomalacia. A detailed history and examination followed by a step wise biochemical evaluation and imaging is important to diagnose TIO in early stages. Surgical resection of the causative tumor will lead to definitve cure of the disease in most patients and avoids the complications like osteoporosis and fractures, thus improving the quality of life of the patients.

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Introduction:-

Tumor-induced osteomalacia (TIO), which is also known as oncogenic osteomalacia, is an uncommon paraneoplastic syndrome characterized by a renal phosphate loss causing hypophosphatemia, leading to rickets in children and osteomalacia in adults. It is caused by a mesenchymal tumors, which secrete FGF-23 (fibroblast growth factor-23) and rarely other phosphotonins, which lead to hypophosphatemia. It can present with a wide range of severity of symptoms, which can delay the diagnosis in many patients. (1) Early diagnosis is important and surgical excision can cure the disease in most patients, thus preventing the complications.

We report a case of TIO, who was diagnosed at an early stage and underwent curative surgery.

Case Report

A 30 years old female presented with pain in both legs, more severe in the left leg since about 1 year. She also had difficulty in walking, low back ache, muscle pain, mild pain in both the knee joints as well. She was initially treated by a Family Doctor with analgesics, Calcium, Vitamin D and Vitamin B12 supplements with which she had a temporary pain relief after which she had a recurrence of her symptoms. Because of her persistent and worsening symptoms, she visited our hospital, where she was evaluated further. On examination, she had limping gait, muscle power in the left leg was grade 3-4; otherwise, there were no significant findings on examination.

Based on her symptoms, we subjected her to baseline blood and radiological investigations. Hemoglobin was 12.6gm/dl, peripheral smear showed a normocytic normochromic picture, total leukocyte count was 9400/microL; platelet count was 3.86 lakhs/microL; erythrocyte sedimentation rate (ESR) was 30mm after 1 hour. Renal function tests showed Serum creatinine of 0.7mg/dl; Liver function tests revealed albumin of 4.7gm/dl, alkaline phosphatase (ALP) of 387IU/ml, SGOT was 31IU/ml, SGPT was 27IU/ml. Thyroid stimulating hormone (TSH) was 1.82microIU/ml, C-reactive protein was 2.6mg/L and RA factor was negative. Serum Calcium was 9.8mg/dl, 25-OH Vitamin D was 24.69ng/ml. These initial blood investigations showed elevated ALP levels. Based on her predominant symptom of leg pain, X- rays of both the legs were done which showed a classical pseudo-fracture in proximal part of both the fibulae. In view of elevated ALP levels and pseudo-fractures in both fibulae, we suspected a metabolic bone disease and got the X-ray of pelvis, which showed another pseudo-fracture in upper part of right femur, rest of the pelvis X-ray was normal. Elevated ALP levels and presence of pseudo-fractures narrowed down the diagnosis to Osteomalacia. Then, we got few other blood tests done: repeat serum calcium was 9.9mg/dl, serum phosphorus was 1.2mg/dl, Parathyroid hormone (PTH) was 61pg/ml. This confirmed that the patient was having hypophosphatemicosteomalacia. Further investigations included tests to calculate TmP/GFR, where the following tests were done in an early morning sample: serum creatinine was 0.7mg/dl, serum phosphorus was 1.4mg/dl, urine creatinine was 45.47mg/dl and urine phosphorus was 15.26mg/dl. Then, we calculated the TmP/GFR, which was found to be very low (1.4mg/dl), which confirmed renal phosphate wasting. Later we got Fibroblast growth factor – 23 (FGF-23), which was 617RU/ml, which was elevated. This confirmed FGF-23 related hypophosphatemicosteomalacia. In view of the patient's age, onset of symptoms, lack of family history, absence of

dental and hearing abnormalities, we suspected an acquired rather than a genetic cause. Tumor induced osteomalacia (TIO) is the common acquired cause and hence subjected the patient to whole body Gallium-68 DOTANOC PET scan, which revealed somatostatin receptor expressing soft tissue density lesion in subcutaneous plane in the mid-anterior right leg, suggestive of FGF-23 secreting mesenchymal tumor.

The patient was treated with replacement dose of oral phosphorus and calcitriol, along with calcium and vitamin D supplements. Later the patient underwent surgery for excision of the tumor in the right leg. The tumor was around 2cm size and the histopathology showed admixture of bland round, oval to spindle mononuclear cells along with multi-nucleated gaint cells and pigmented cells in grungy calcified matrix focally, suggestive of gaint cell rich tumor- possibly aphosphaturic mesenchymal tumor. Post surgery, the patient had significant improvement in her symptoms, gait improved and pain reduced. The serum phosphorus level was 3.8mg/dl post-operatively. The serum phosphorus levels normalized and was maintained even without oral phosphorus replacement. The patient was advised to repeat FGF-23 levels, but the patient failed to get it done.

Discussion:-

Tumor-induced osteomalacia (TIO), also known as oncogenic osteomalacia, is a paraneoplastic syndrome which is characterized by renal phosphate loss causing hypophosphatemia, leading to rickets in children and osteomalacia in adults. (2) It is a very rare syndrome with less than 2000 cases being reported world-wide.

TIO is mostly caused by phosphaturic mesenchymal tumors (PMTs). These are usually small, benign, and slow-growing polymorphous neoplasms, affecting bone or soft tissues. They secrete fibroblast growth factor 23 (FGF23) which is the most important phosphatonin, which decreases the renal tubular phosphate reabsorption and causes significant hypophosphatemia. (3) Rarely other phosphotonins like secreted frizzled-related protein-4, FGF7, and matrix extracellular phosphoglycoprotein (MEPE) can be involved in the etiology. (1,4). Rarely, malignant tumors can be the cause in about less than 10 percent of TIO patients.

The clinical features vary and are non-specific. The common symptoms are bone pain, debilitating muscle weakness, gait disturbances; while some patients can present with pathological fractures and/or pseudo-fractures, and bone deformities. Rarely, they can have local symptoms related to the tumor. (4) Our patient presented with leg pain as the predominant symptom, which is in concordance with most review articles. Some of these patients can show low bone mineral density. (4,5) However, DEXA scan was not done in our patient. It can be rarely associated with nephrocalcinosis and nephrolithiasis. The increased levels of FGF-23 is linked to increased cardiovascular and kidney disease as well. (4)

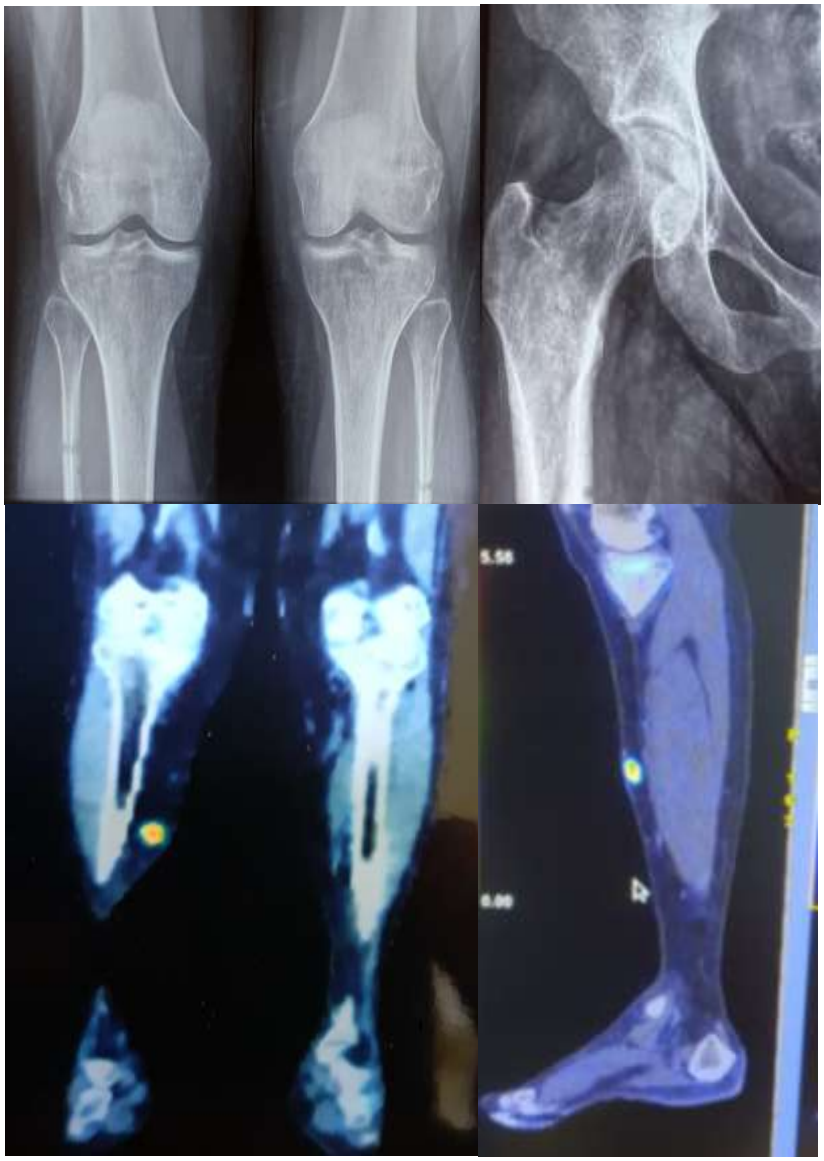
Biochemically, the patients have hypophosphatemia and reduced 1,25-dihydroxy vitamin D levels, while the calcium, parathyroid hormone (PTH) and 25- hydroxy vitamin D levels are normal. (6) They also show a significant reduction of bone mineral density. (1). Our patient had moderate hypophosphatemia (serum phosphorus: 1.2mg/dl), which is consistent with most patients with TIO. (4)

The diagnosis of TIO is delayed for years, most of the times because of its rarity and non-specific presentation. The diagnosis requires a step wise approach to first biochemically confirm and identify the cause of hypophosphatemia, followed by measurement of phosphotonins (FGF-23) levels. This is followed by imaging modalities to localize the tumor. The tumor localization canbe challenging because of it's small size and variable anatomical location. Functional imaging is commonly used to localize the tumor, with Ga-68 DOTATATE PET/CT showing the greatest accuracy(7) and others like 18F-fuorodeoxyglucose (FDG) PET/CT, Technetium 99 m octreotide scintigraphy/SPECT/CT being less accurate. Anatomical imaging techniques like ultrasonography, computed tomography (CT) or magnetic resonance (MR) are used in some patients. Venous sampling of FGF-23 levels and fine needle aspiration cytology (FNAC) is usually not required routinely in all patients. (4)

Initial treatment includes Phosphorus replacement and active Vitamin D supplementation. This should be followed by Surgical resection of the causative tumor, which is the curative treatment. The resection of the tumor leads to a rapid normalization of biochemical parameters and to marked improvement or resolution of the symptoms in almost all patients. (6) Rarely, patients can have a persistent or recurrent disease following surgery. Medical treatment includes oral phosphorus replacement and vitamin D supplementation with regular follow up, Cinacalcet, Octreotide and anti FGF-23 antibody- Burosumab. Radiotherapy can be used in some rare patients. (4)

Conclusion:-

The diagnosis of TIO requires high index of suspicion and should always be looked as a differential diagnosis when we are evaluating a patient with osteomalacia and hypophosphatemia, after ruling out vitamin D deficiency and other causes of low phosphorus. A detailed history and examination followed by a step wise biochemical evaluation and imaging to localise the lesion is important to diagnose TIO in early stages. Surgical resection of the causative tumor will lead to definitve cure of the disease in most and hence avoiding the complications like osteoporosis and fractures, thus improving the quality of life of the patients.



1) Looser's zones in bilateral fibulae; 2) Looser's zones in right femur; 3,4) Ga-68 DOTANOC scan showing SSTR expressing tumor in right leg.

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