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PARATHYROID CARCINOMA

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Abstract

Parathyroid carcinoma is the rare type of endocrine malignancy. The causes of parathyroid carcinoma are unknown. Men and women are equally affected. The most effective method of treatment is surgical resection and palliation. Parathyroid carcinoma is progressive but slow growing. Pseudoparathyroidism is the severe complication. It comprises metabolic disorders which are characterized by physical findings. The physical findings variably include short bones, short stature, a stocky build early onset obesity and ectopic ossifications as well as endocrine defects that often include resistance to parathyroid hormone. Parathyroid glands are the two pairs of the small, oval-shaped glands. They are located next to the two thyroid gland lobes in the neck. Each gland is usually about the size of the pea. The management of parathyroid carcinoma is done on the basis of surgery, radiation therapy, chemotherapy. The management of hypercalcemia is done by using the agents such as biophosphonates, Plicamycin, Calcitonin, Gallium, Calcimimetics, WR-2721, Octreotide, Immunization.

Keywords : Parathyroid gland, Parathyroid carcinoma, Pseudoparathyroidism, Hypercalcemia, etc.

Introduction:

Parathyroid carcinoma is the rare type of endocrine malignancy. The patients usually present with the severe signs and symptoms of hypercalcemia. The causes of parathyroid carcinoma are unknown, but the clinical correlations with different genetic syndromes exist. The men and women are equally affected by the parathyroid carcinoma. The most patients are presented with signs and symptoms of hypercalcemia. The most effective method of treatment is surgical resection and palliation treatment. Parathyroid carcinoma is progressive but slow growing. A parathyroid tumor it may be benign or malignant that can cause significant problems because, this type of tumor causes the amount of Calcium in the blood rise, which results in serious conditions called as hypercalcemia.

Pseudoparathyroidism :

The Pseudoparathyroidism and the related disorders, these comprise the metabolic disorders and these are characterized by physical findings that variably include short bones, short stature, a stocky build early onset obesity and ectopic ossifications as well as endocrine defects that often include resistance to parathyroid hormones. The pseudoparathyroidism and related disorders are also associated with the spectrum of abnormal physical characteristics as well as neurocognitive and endocrine abnormalities. This is caused by the molecular defects that impairs the hormonal signaling through the receptors, that are coupled through the alfa-subunits of the stimulatory G protein (Gs alpha), to activation of adenylyl cyclase. The common features of pseudoparathyroidism is represented by the impaired signaling of various hormone. This indicates a group of heterogeneous disorders. There are mainly two subtypes of

pseudoparathyroidism i.e. Type-1a and Type-2b. These are caused by molecular alterations within or upstream of impaired GNAS gene. This gene encodes Gs alpha and other translated and untranslated products.

Etiology :

The etiology of parathyroid carcinoma is unknown. However, there are no. of clinical situations that may cause parathyroid carcinoma. Parathyroid carcinoma is reported in the patients with history of neck irradiation, patients with prolonged secondary hyperparathyroidism, secondary to celiac disease. It is also described in patients with end stage renal disease. The other factors also lead to parathyroid carcinoma such as the mutation of HRPT2 (CDC73) , a tumor suppressor gene has been described in the molecular pathogenesis of parathyroid carcinoma. This gene has located on chromosome 1. This gene encodes for the protein parafibromin which is involved in the inhibition of cell proliferation. The mutation of the same gene is also found in hyperparathyroidism-jaw tumor syndrome and sporadic parathyroid carcinoma. Studies have shown that 15% of patients with hyperparathyroidism-jaw tumor syndrome surely develop the parathyroid carcinoma. Multiple endocrine neoplasia type 1 (MEN1), Familial isolated hyperparathyroidism (FIHP) also causes the parathyroid carcinoma. The past radiation therapy for head or neck can also increase your risk of parathyroid cancer.

Pathophysiology :

The pathogenesis of parathyroid carcinoma is explained as it is usually of soft consistency, round or oval in shape and of a reddish-brown colour. In contrast it is frequently described as a lobulated firm to stony-hard mass. In about 50% of cases the parathyroid carcinoma is surrounded by a dense, fibrous, grayish, white capsules. These adheres tenaciously to the adjacent tissues and make the tumor difficult to separate from contiguous structures. The diagnosis of parathyroid carcinoma is not difficult if there is gross infiltration of adjacent thyroid nerve, muscle, esophagus and obvious cervical node metastasis. The causes of pseudoparathyroidism are unknown. The several types of mutations have been implicated in the pathogenesis of parathyroid carcinoma that include retinoblastoma (Rb), breast carcinoma susceptibility (BRCA), cyclin D1/ parathyroid adenomatosis gene 1 (PRAD1) genes.

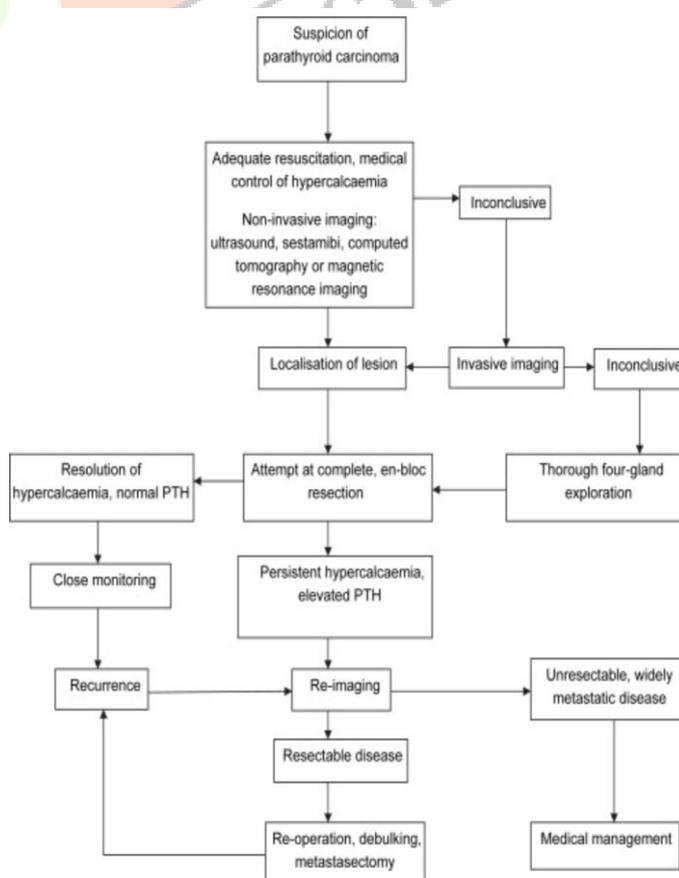
Functions :

The functions parathyroid gland are as follows –

It maintains serum calcium homeostasis through synthesis and release of parathyroid hormones. At the bones, the parathyroid hormones inhibit osteoblast activity and stimulate osteoclast activity leading to bone breakdown and calcium release. At the kidneys, the parathyroid hormones increases calcium reabsorption and block phosphate reabsorption from the tubules. The parathyroid hormones also act on kidneys to stimulate the formation of vitamin D. The vitamin D is the essential component of calcium and phosphate homeostasis.

The functions of parathyroid gland on various systems are as follows :

Skeletal System : By indirectly stimulating osteoclast to break down the bone the parathyroid hormones works at the cellular level. The parathyroid hormone binds to the cell receptors



situated on the osteoblasts that stimulates the release of receptor activator of nuclear factor kappa-B ligand (RANKL). The RANKL binds to its receptors on osteoclast precursors, that stimulates them to fuse into mature osteoclast that increase the calcium resorption from bone.

Renal System : The parathyroid hormone having the two main roles in the kidney. It works on various parts in the kidney such as ascending loop of henle, distal convoluted tubules, proximal convoluted tubules and collecting ducts that increase reabsorption of calcium by upregulating TRPV5 and calcium transporter on the tubular epithelium. The parathyroid hormones block the phosphate reabsorption by binding to the sites in the proximal tubule. The net effect of parathyroid hormone is to decrease the calcium excretion and increase phosphate excretion in the urine.

Gastrointestinal System : About 70%-80% absorption of calcium occurs in the small intestines. The parathyroid hormone has no direct effect on the small intestine. But the downstream effect of parathyroid hormones on vitamin D synthesis occur at this level. The calcium and phosphate absorption is done by vitamin D from the gut.

Clinical Features :

The clinical features of parathyroid carcinoma are as follows :

Elevated serum parathyroid hormone levels, elevated serum calcium i.e. hypercalcemia. The typical clinical picture of parathyroid gland in carcinoma is characterized by signs and symptoms of severe hypercalcemia with renal involvement are nephrocalcinosis, nephrolithiasis, impaired renal function. The bone involvement such as : subperiosteal resorption, osteitis fibrosa cystica, salt & pepper skull diffuse osteopenia. On physical examination up to 76% of patients with parathyroid carcinoma have a palpable neck mass, renal colic, muscle weakness, fatigue, depression, nausea, polydipsia, bone pain and fractures, recurrent severe pancreatitis, elevated levels of alpha and beta subunits of HCG, recurrent laryngeal nerve palsy, sub periosteal bone resorption, peptic ulcer disease, anemia and weight loss, etc.

Management of Parathyroid Carcinoma :

The parathyroid carcinoma can be managed by the complete surgical excision, radiation therapy and chemotherapy, etc.

Surgery : The single and most effective therapy for parathyroid carcinoma is the complete resection of the primary lesion at the time of initial operation when the extensive local invasion and distant metastases are less likely.

The following steps should be taken :

Complete removal of lesion together with the ipsilateral thyroid lobe and isthmus. And the skeletonization of the trachea & removal of any contiguous tissues to which the tumor adheres. The serum calcium levels should be observed in the post operative patients. The deposition of calcium and phosphorus into the skeleton is regarded as the surgery has been successful.

Radiation Therapy : The parathyroid carcinoma is not the radiosensitive tumor, though to control tumor growth & decrease hormone production the use of radiation therapy is done. For prevention of the tumor regrowth, the radiation to the neck after surgery for recurrence may be helpful.

Chemotherapy : Several regimens are utilized in chemotherapy for parathyroid carcinoma such as nitrogen mustard : vincristine, cyclophosphamide, actinomycin D, adriamycin, and 5-fluorouracil and adriamycin alone.

Management of hypercalcemia :

The prognosis of parathyroid carcinoma is poor when the parathyroid carcinoma has become widely disseminated and the surgical resection is no longer effective. Controlling the hypercalcemia is the only therapeutic goal at this point. The management of hypercalcemia include infusion of saline to restore fluid volume and enhancing the urinary calcium excretion and loop diuretics to further increase the calciuresis. Other agents are also utilized for managing the hypercalcemia such as, biophosphonates, plicamycin, calcitonin, gallium, calcimimetics, WR- 2721, octreotide, Immunization, etc.

Biophosphonates : These agents mainly inhibit the osteoclast mediated bone resorption.

Clodronate (Cl2MDP) : This agent lowers the serum calcium in parathyroid carcinoma. It is administered by intravenously.

Etidronate : It also lowers the serum calcium levels. It is also administered by intravenously over a 2 hour period at a dose of 7.5 mg/kg. The dose of etidronate may be repeated daily or until the serum calcium falls to normal for maximum of 7 days. It is also available in oral form. The more potent biophosphonate is Pamidronate which is widely available for intravenous route. The dose of Pamidronate is about 45-90 mg/day. The new and more potent biophosphonates are Ibandronate and Zoledronate.

Plicamycin : (Mithramycin) It is the another type of inhibitor of bone resorption. It also lowers the serum calcium levels in parathyroid carcinoma. It is also administered by intravenous route. The dose of plicamycin is about 25 mcg/kg over 4-8 hours. It may be repeated at daily intervals for upto 7 days, until the serum calcium levels falls to the normal range. The Plicamycin shows the toxic effects on liver, kidney and bone marrow.

Calcitonin : It shows both of the functions such as

It inhibits osteoclast mediated bone resorption and increase the urinary calcium excretion also. The dose of calcitonin is about 200-600 Medical Research Council Units/day. It is given in combination with glucocorticoids (300 mg hydrocortisone) and in the occasional patients when used alone.

Gallium : The gallium nitrate inhibit the bone resorption by preventing dissolution of hydroxyapatite crystals. It is administered as a continuous 5 day infusion at a dose of 200 mg/ m2 day.

Calcimimetics : By using these agents the serum calcium levels was controlled for 2 years without any adverse effects.

WR-2721 : WR-2721 [5-2-(3-aminopropyl) amino] ethylphosphorothoric acid. It is the hypocalcemic agent which acts by inhibiting parathyroid hormone secretion and bone resorption.

Octreotide : The long acting somatostatin analogue. It also inhibit the parathyroid hormone secretion.

Immunization : The studies show that a patient with parathyroid carcinoma which is metastatic to the lungs and pleura had the severe hypercalcemia which was resistant to the agents such as, oral clodronate, iv pamdronate, octreotide, 5-fluorouracil and streptozotocin, etc. So, that patient was immunized with the human and bovine parathyroid hormone peptides followed by the booster doses at 4 and 11 weeks. After 4 weeks of immunization the antibodies against parathyroid hormone were detected. The rapid improvement and no any significant adverse effects were absorbed in that patient. This would be a novel and relatively simple approach to control of hypercalcemia in patients who having parathyroid carcinoma, if confirmed.

Conclusion :

Parathyroid carcinoma is the rare type of endocrine disorder. The causes of parathyroid carcinoma are unknown though many things cause the cancer of parathyroid gland. Mainly hypercalcaemia is the cause of parathyroid carcinoma and the pseudoparathyroidism is the complication of parathyroid carcinoma. Parathyroid gland shows the function on renal, skeletal and gastrointestinal system. To manage parathyroid carcinoma various measures are used such as surgery, radiation therapy and chemotherapy. The surgery is followed by making complete excision of tumor. The radiation therapy is followed by using radiations though the parathyroid tumor is not radiosensitive. It is also done to control tumor growth and to decrease hormone production. Chemotherapy is done by using various agents such as nitrogen mustard, vincristine, cyclophosphamide and actinomycin D, etc. The hypercalcaemia is managed by using various agents such as bisphosphonates, plicamycin, calcitonin, gallium, calcimimetics, WR-2721 and octreotide, etc. In this way parathyroid carcinoma is explained.

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