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Perspective

Post-Thyroidectomy Protracted Hypoparathyroidism: When Medicine Overhauls Surgery

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Perspective

Though thyroidectomy has undergone major surgical refinements over past few decades, post-operative hypoparathyroidism still remains the most common complication negatively impacting patient's quality of life due to requirement for lifelong medication, regular clinic visits and long-term costs [1-3]. As thyroid cancer has recently become the fastest growing malignancy globally [4], a sound knowledge of all predictive risk factors and management of hypoparathyroidism is increasingly becoming essential for the surgeons.

A 24-year old girl presented with multiple TIRADS-4 nodules (largest 3.4cm) in both lobes with suspicious left level VI node. FNA was suspicious of follicular variant of papillary thyroid cancer (Bethesda-V). She successively underwent total thyroidectomy, bilateral Central Compartment Neck Dissection (CCND) and left lateral (level II-IV) neck dissection. All four parathyroid glands were preserved intraoperatively, nevertheless, she became symptomatic for hypocalcemia on the first post-operative day (Day-1) itself. Corrected serum calcium, which was 2.25mmol/L preoperatively, dropped to 1.92mmol/L on Day-1. Serum intact Parathormone (iPTH) level plummeted to 0.5pg/ml. Endocrinology team was informed and calcium gluconate infusion was started as per the British Association of Endocrine and Thyroid Surgeons (BAETS) guideline [3] along with oral calcium and calcitriol replacement. Serum 25(OH)D levels were found to be low (9.87ng/ml) and cholecalciferol 60,000 units once weekly was added. Oral magnesium supplements were also started in view of reduced serum magnesium levels (0.58mmol/L). Calcium levels proved difficult to normalise and the patient remained clinically symptomatic and dependent on intermittent intravenous calcium supplementation in spite of increasing oral calcium and calcitriol till Day-8. In view of continuing hypocalcemia, hydrochlorothiazide (12.5mg twice a day) was added to prevent hypercalciurea. Serum calcium finally reached a near normal level (2.17mmol/L) on Day-9 on oral calcium at 5gm/day (divided in five doses), calcitriol 4mcg/day and elemental magnesium 1600mg/day, along with weekly doses of cholecalciferol (60,000 units). She was kept under close surveillance for two more days with these oral replacements, during which she remained asymptomatic, and was discharged. Histopathology confirmed follicular variant of papillary carcinoma without extrathyroidal extension (largest dimension 45mm); 4/10 metastatic central compartment lymph nodes (pT3aN1, *AJCC TNM staging 8th edition*). Considering her prolonged hypoparathyroidism, a multi-disciplinary tumor board decision was made to delay adjuvant radioactive iodine ablation till normalisation of calcium levels, and hence, thyroxine suppression was initiated. The patient was still requiring high dose of oral calcium and calcitriol replacement along with six instances of intravenous calcium gluconate even at 3rd postoperative month, and any attempt at tapering the dose led to prompt recurrence of hypocalcemic symptoms. The latest serum calcium was still suboptimal (1.5mmol/L) with an elevated serum phosphate (1.94mmol/L). Recombinant PTH (rPTH)(1–34) though considered for this patient, could not ultimately be offered due to financial constraint.

The incidence of post-thyroidectomy hypoparathyroidism differs in the literature. Increased risk has always been associated with thyroid malignancies; 30.1% in cases of total thyroidectomies, which further increases to 63.2% when CCND is performed additionally [5]. Female sex [6], preoperative serum calcium level <9.1mg/dL [7], vitamin-D deficiency, extrathyroidal extension, bilateral CCND [8] and difference (Δ) of ≥1.1mg/dL between pre- and postoperative serum calcium (in the present case, Δ=1.2mg/dL) [9] have been found to be independent predictors of postoperative hypoparathyroidism. Moreover, low serum iPTH (<13pg/ml) and need for calcium and Vitamin-D replacement at 12-weeks after surgery are two criteria defining protracted hypoparathyroidism [10]. The prevalence of protracted and permanent hypoparathyroidism was found to be inversely related to the number of parathyroid glands remaining in-situ [11]. Even when these glands are well preserved, postoperative normal serum parathormone level is not guaranteed [12].

The present case exhibited all risk factors; pre-, intra- and postoperatively, for development of post-thyroidectomy protracted hypoparathyroidism. However, even with institution of timely therapy, she proved to be difficult to treat and required much higher than usual recommended doses of calcium and calcitriol for achieving normocalcemia. An increased risk of permanent hypoparathyroidism should be considered too. Although estimated prevalence of permanent hypoparathyroidism is 0-3%, its true prevalence is probably underestimated due to various reasons; most importantly, conflicting data from single institutional studies and lack a clear definition [10]. The fourth national BAETS audit reported a 12.1% rate of permanent hypoparathyroidism after total thyroidectomy [13]. Mehanna *et al.* demonstrated how the rate of hypoparathyroidism varied from 0-46% depending on different definitions reported in literature [14]. Serum calcium <7.54mg/dL

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(1.88mmol/L) at 24 hours post-thyroidectomy, identification of <2 parathyroid glands intraoperatively, re-surgery for bleeding, Graves' disease and heavier thyroid specimens were identified as independent predictors of permanent hypoparathyroidism in multivariable analysis [15].

Whether *parathyroid autotransplantation* prevents permanent hypoparathyroidism is a matter of controversy. Some have proposed that in the long-term it prevents permanent hypoparathyroidism [16-18]; however, several studies have found a strong association between autotransplantation and permanent hypoparathyroidism [19-21]. *Parathyroid allotransplantation*, though relatively less explored, is an interesting alternative in treatment refractory permanent hypoparathyroidism achieving clinical remission in 70% patients in a single case series [22,23]. The time-to-recovery of parathyroid function is the biggest challenge in these scenarios. In a prospective cohort study (n=857), 16.6% total thyroidectomy recipients developed protracted hypoparathyroidism, and 25.4% of protracted hypoparathyroidism developed permanent hypoparathyroidism [24]. 74.6% recovered eventually; 51.4% before 6 months, 14.8% within 6-12 months, and 8.4% after 12 months. A waiting period of at least 12 months is, hence, justified before allotransplantation is considered. Maintenance of a higher serum calcium concentration with calcium and calcitriol replacements at the time of discharge have a positive effect on parathyroid function recovery. This phenomenon, known as '*parathyroid splinting*' [11], allows the injured and ischemic parathyroid glands to rest in a normal to high serum calcium environment. Parathyroid splinting shows a synergy with the number of parathyroid glands remaining in-situ to facilitate functional recovery. The addition of once daily rPTH(1-34) to conventional therapy helps to achieve normocalcemia and reduces daily requirements of calcium and calcitriol [25]. It also helps to reduce the risk of nephrocalcinosis. Parathyroid allotransplant may also be offered in select cases of treatment refractory permanent hypoparathyroidism under clinical trial setting.

The present case emphasizes that surgeons and endocrinologists often need to work in tandem for the management of such challenging cases. Meticulous evaluation, precise pre- as well as post-operative counselling, anticipation and thorough knowledge of guidelines on treatment of hypocalcemia are imperative to manage these delicate scenarios, and possibly avoiding medicolegal consequences. The delay in adjuvant radioactive iodine ablation can be considered in such cases in view of conflicting observational data regarding improved disease-free survival in ATA low-to-intermediate risk category [26]; though it was considered in this particular case due to presence of clinically evident central compartment lymph nodes found intraoperatively.

Ethical Atatement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was taken from the patient. Institutional Ethics Committee approval was obtained prior to submission (AIIMS/IEC/20/689).

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