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INTRAOPERATIVE PARATHYROID HORMONE MEASUREMENTS IN A FEMALE WITH PARATHYROID ADENOMA

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Summary

Primary hyperparathyroidism (PHPT) is a disorder characterized by increased and uncontrolled parathyroid hormone secretion, a cause of hyperfunction of one or more parathyroid glands. In 80-85% of cases PHPT is caused by parathyroid adenoma. Persistent hyperparathyroidism leads to altered osseous metabolism involving bone resorption and tissue changes. In rare cases, approximately in every thirteenth patient with PHPT, the bone mass is suspected of being a neoplastic lesion – a so-called brown tumor induced by primary hyperparathyroidism. The only way of PHPT correction is a surgical removal of the hyperactive parathyroid glands. In this article we report the first case of intraoperative parathyroid hormone measurements for primary hyperparathyroidism in the Republic of Croatia. The possibility of intraoperative PTH monitoring provides extra safety for both the patient and the operator. Intraoperative PTH becomes an exact instructor (navigator) to the operator – surgeon. Based on the decreasing value of this peptide with a very short half-life, the surgeon makes immediate decision if the operation is completed or further excision of the parathyroid glands is required because of hyperplasia. A guarantee for successful diagnosis, which is a prerequisite for a correct treatment, is a multidisciplinary, continuous, systematic and synchronized cooperation of the whole and heterogeneous medical team, which includes clinicians, radiologists, cytologists, pathologists and medical biochemists.

KEYWORDS: *primary hyperparathyroidism, intraoperative PTH, hypercalcemia, brown tumor*

INTRAOPERACIJSKO MJERENJE PARATIROIDNOG HORMONA U BOLESNICE S PARATIROIDNIM ADENOMOM

Sažetak

Primarni hiperparatireoidizam (pHPT) je stanje povećane i nekontrolirane sekrecije paratireoidne žlijezde radi hiperfunkcije jedne ili više paratireoidnih žlijezda. U 80-85% slučajeva pHPT je uzrokovan adenomom žlijezde. Ustrajan hiperparatireoidizam uzrokuje promjene u metabolizmu kostiju. Rijetko, približno u svakog tridesetog bolesnika s pHPT, mogu se razviti i ne-neoplastične lezije kostiju, tzv. smeđi tumor u primarnom hiperparatireoidizmu. Kirurško uklanjanje hiperaktivne žlijezde jedini je način korekcije stanja pHPT. Ovim se prikazom slučaja prvi put izvješćuje o intraoperativnom mjerenju koncentracije PTH u pHPT u Hrvatskoj. Monitoriranje intraoperativne koncentracije PTH pruža mogućnost dodatne sigurnosti za bolesnika i operatera, te ujedno postaje egzaktan *vodič (navigator)* operateru-kirurgu, koji na temelju pada vrijednosti ovog peptida izrazito kratkog vremena poluživota donosi trenutnu odluku o tomu je li operacija završena ili je potrebno daljnje uklanjanje paratireoidnih žlijezda zbog hiperplazije. Jamstvo uspješne dijagnoze, koja je preduvjet pravilnog liječenja, jest kontinuirana multidisciplinarna, sistematična i sinkronizirana suradnja cijelog i raznorodnog medicinskog tima koji uključuje kliničara, radiologa, citologa, patologa i medicinskog biokemičara.

KLJUČNE RIJEČI: *primarni hiperparatireodizam, intraoperacijski PTH, hiperkalcemija, smeđi tumor*

INTRODUCTION

Primary hyperparathyroidism (PHPT) is a disorder characterized by increased and uncontrolled parathyroid hormone secretion, a cause of hyperfunction of one or more parathyroid glands. Primitive hyperparathyroidism is the third most common endocrine disorder after diabetes mellitus and thyroid dysfunction (1). The estimated incidence of cases of PHPT in population is 0.5-1‰, it is more common among people older than 50 years of age and three times more common in women than in men (2). In 80-85% of cases PHPT is caused by parathyroid adenoma. The diagnosis of PHPT has classically been based on the demonstration of high blood calcium concentrations as a result of increased bone resorption and decreased renal elimination. Hypercalcemia is associated with calcuria and elevated level of parathyroid hormone (PTH). In most cases, primary hyperparathyroidism is diagnosed accidentally because of nonspecific symptoms: ending pain, pathological fractures, muscle ailments... The only way of PHPT correction is a surgical removal of the hyperactive parathyroid glands (3). PTH is a polypeptide containing 84 amino acids with a very short half-life (approximately 4 minutes) (4). It is possible to measure PTH level during the surgery, when the patient is under anesthesia, and that is a consequential sign of removal of the hyperactive parathyroid gland - the one with adenoma. Intraoperative PTH helps make a differential diagnosis and you can tell whether the cause of PHPT is parathyroid adenoma or parathyroid hyperplasia. Persistent hyperparathyroidism leads to altered osseous metabolism involving bone resorption and tissue changes. In rare cases, approximately in every thirteenth patient with PHPT, the bone mass is suspected of being a neoplastic lesion - a so-called brown tumor induced by primary hyperparathyroidism. Histologically, brown tumors are made up of mononuclear stromal cells mixed with multinucleated giant cells, among which recent hemorrhagic infiltrates and hemosiderin deposits (hence the brown color) are often found. Brown tumors may be the first indirect clinical sign of hyperparathyroidism, along with pain and fracture (5-7).

In this article we report the first case of intraoperative parathyroid hormone measurements for primary hyperparathyroidism in the Republic of Croatia.

CASE SUMMARY

A 36-year-old woman, who had a regular labor one month before, was complaining of persistent hip pain and difficult moving two months before labor and one month after. She was examined at the Orthopedics Department of an outdoor institution. She was diagnosed with fracture of the pubic bone and II, IV and V rib, with destruction of L5 and S1 vertebra. Neck ultrasonography identified a lesion of 3 cm located (at IB right region) the left thyroid lobe. Cytological examination of a fine-needle aspiration biopsy of the nodular lesion, that takes 2/3 of the left lobe of the thyroid gland, showed clusters of middle-sized papillary and acinous cells characteristic for parathyroid neoplasm (Figure 1).

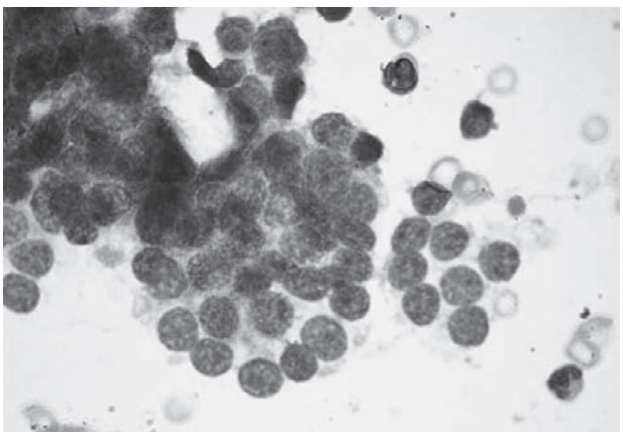

Figure 1. Cytological analysis of lesion punctate (clusters of middle-sized papillary and acinous cells characteristic for parathyroid neoplasm)

During that first medical and laboratory examination, an increase in serum calcium (3.1 mmol/L) and parathyroid hormone (PTH 170 pg/mL) levels was found. PET/CT (Positron Emission Tomography - Computed Tomography) examination showed multiple (secondary?) changes in almost all regions of the skeleton, particularly in the area of the mandibular angle.

The patient was referred to the University Hospital for Tumors for oncological treatment (chemotherapy or radiotherapy) of metastatic changes all over the body without known primary cancer site.

The patient was admitted to the Department of Head and Neck Surgery of the 'Sestre milosrd-

nice' University Hospital for Tumors. The Hospital Tumor Board decided to conduct a biopsy of a hard and steady perimandibular formation of 3 cm, in order to set the differential diagnosis, and make a plan for further examination and eventual treatment of malignant disease. Standard laboratory tests showed increased levels of serum calcium (3.20 mmol/L; reference range 2.14-2.53), alkaline phosphatase (575 U/L; reference range 54-119) and PTH (670 pg/mL**;** reference range 15-65).

Cytological examination of a fine-needle aspiration biopsy of the lesion in the right mandible through the mouth showed numerous multinucleated giant cells with prominent nucleoli (osteoclasts), osteoblasts, and frequent individual and clusters of oval and elongated mesenchymal cells of deficient hyaline stroma. The final report of the cytologist indicated the possibility of a brown tumor with multinucleated giant cells, including the cytologist's opinion that the changes might be associated with hyperparathyroidism.

Before surgery doctors tried to correct hypercalcemia (infusion, diuretics). After one-week therapy the results were not acceptable (serum calcium level was still above 3 mmol/L) and doctors were consulted and parathyroidectomy was performed. The image below shows the dynamics of serum calcium concentrations – 8 days before surgery, on the day of surgery (pre-operative and 2 hours after the operation), and 5 days after surgery (Figure 2).

Inferior left-side parathyroidectomy was performed through a 4 cm horizontal incision in the neck. During operation, the previously described tumor formation in the lower half of the left thyroid lobe was found. The tumor was about 3 cm in size and dark brown in color. Surgery was minimally invasive. During surgery, the suspect tissue was removed and healthy thyroid tissue preserved.

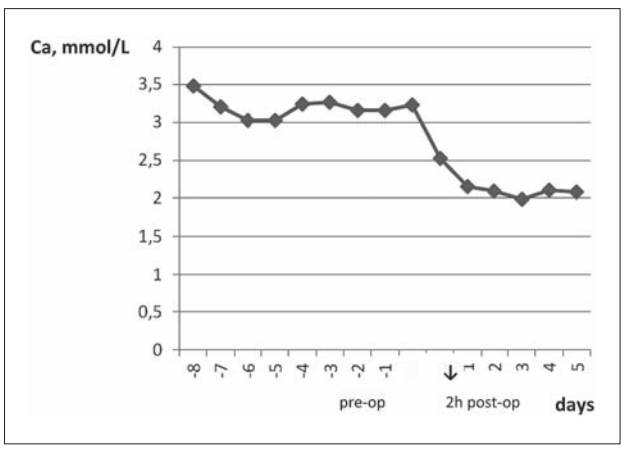

Figure 2. Dynamics of serum calcium concentrations before surgery, on the day of surgery and after surgery

Before and after the extirpation of the suspected tumor, venous blood was sampled and intraoperative plasma statPTH was measured. A significant decrease in statPTH after the extirpation as compared to the preoperative concentration pointed toward parathyroid adenoma. The operation was completed in the standard way for closing the incision in layers. The patient felt well after surgery, the postoperative period was regular with taking calcium support therapy due to an enormous deficiency of calcium in the bones as a result of an extremely large calcium extraction from the bone for a period of several months prior to surgery. The sutures were removed on the fourth postoperative day.

StatPTH concentration was measured using an electrochemiluminiscence immunoassay (Elecsys2010). The immunoassay was performed using original manufacturer's reagents, calibrators and controls by the Roche company. Blood sampling was done at three time-points: before surgery, during surgery and one day after surgery. Plasma samples were obtained in a tube with EDTA anticoagulant after whole blood centrifugation. The measured StatPTH values are shown in the table below (Table 1).

The results shown in Table 1 demonstrate that the removal of the first, and actually the proper hyperactive gland caused a significant drop in the PTH level, which was reduced to 1/6 of the value measured before surgery.

During the operation a piece of the removed tissue was taken and sent for histopathological analysis and the diagnosis of parathyroid adenoma was confirmed (Figure 3).

Table 1.
PTH CONCENTRATION BEFORE, DURING, AND ONE DAY AFTER SURGERY

Parameter	Reference range	Immediately before surgery	After excision of suspected glands	The day after surgery
PTH, pg/mL	15-65	511	78.4	40.3

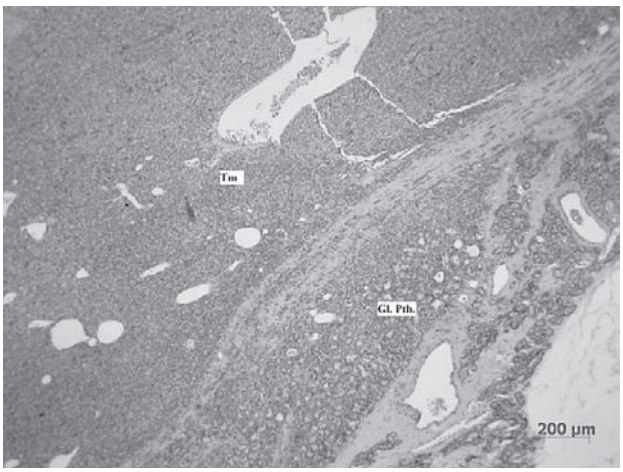

Figure 3. Histopathological analysis of the surgical specimens

DISCUSSION

Reparative granulomas of bones in hyperparathyroidism are cytologically characterized by intensive bone remodeling markers, osteoclasts, mononuclear cells and fibroblasts with local hemorrhage. Focal hemorrhage containing hemosiderin produces the grossly brown color after which the tumor is named – brown tumor (8-11).

According to literature data, changes in the skeleton due to brown tumors occur in less than 2% of patients suffering from any form of hyperparathyroidism. Bone lesions that are associated with hyperparathyroidism occur most frequently in the pelvis, ribs, limbs, and sometimes along the entire skeleton (12, 13). As rare as they are, multiple lesions distributed along the entire skeleton can be easily misdiagnosed as a metastatic tumor. It is possible to eliminate suspicion of tumor and direct the doctors to the right diagnosis by a careful and individual approach to patient, including a detailed family anamnesis, routine laboratory tests and combined visual techniques.

Brown tumors can cause many complications including a pathological fracture as reported in our case. In this case, multiple bone changes were present, probably as a consequence of a parathyroid adenoma - a cause of primary hyperparathyroidism.

The primary symptoms of the disease appeared during pregnancy, but attention was not focused on them as they were considered to be related the mentioned physiological condition. The literature data indicate the incidence rate of pHPT in reproductive age of 8 cases per 100 000 population (14, 15).

There are several cases of pHPT in pregnancy reported in the literature. They were usually detected by accident. The primary symptoms experienced by pregnant women included non-specific urinary tract infections, usually associated with urolithiasis becuse of hypercalcemia (16-18).

A multidisciplinary approach has a significant role in the diagnosis: clinical laboratory will confirm the pHPT (elevated levels of calcium, alkaline phosphatase and PTH) in suspected patients while radiological techniques will demonstrate the process of bone resorption. Unfortunately, these two diagnostic procedures cannot distinguish adenoma from carcinoma. Only preoperative cytologic and postoperative histopathological analysis can confirm the diagnosis. Preoperative treatments are important for the precise localization of tissue that needs to be removed (radiological diagnosis: MIBI scintigraphy; fine-needle aspiration biopsy). An isolated use of only one of diagnostic branches can be misleading. Miyakoshi et al. in 2007 presented a case of a multiple brown tumor in primary hyperparathyroidism that mimicked metastatic bone disease and provided a false positive image of the CT and MIBI scintigraphy (19). The possibility of intraoperative PTH monitoring provides additional patient and operator safety. Intraoperative PTH becomes an exact instructor (navigator) to the operator – surgeon. Based on decreasing levels of this peptide with a very short half-life, the surgeon makes an immediate decision if the operation is completed or requires a further excision of the parathyroid glands because of hyperplasia.

In Croatia, until now, doctors have not practiced the measurement of PTH during parathyroid gland surgery. The very first laboratory monitoring of operations was performed in the 'Sestre milosrdnice' University Hospital for Tumors. This way of monitoring the success of surgery is reasonable from a medical and economic standpoint because it significantly reduces the potential costs (reduced number of operations to only one, reduced total hospital stays, etc.). Therefore, it is not surprising that the intraoperative PTH measurement has become an indispensable part of the algorithm for approaching patients with pHPT provided by a number of associations.

A female patient was referred and admitted to our institution, a highly multidisciplinary hospital for cancer treatment, with the initial premise that she probably had a dissemination of an unknown primary tumor, which caused extensive lesions of the skeleton. This oncology center has been the patient's final destination, because it was expected that the patient would be exposed to radical methods of treatment, radio- and chemotherapy. In the end, the patient was operated on, measurable markers that indicate active disease have disappeared because the crucial factor of their imbalance, i.e. parathyroid adenoma was removed.

CONCLUSION

A guarantee of any successful diagnosis, which is a prerequisite for proper treatment, is a multidisciplinary, continuous, systematic and synchronized cooperation of the whole and heterogeneous medical team, involving the full and effective coordination of efforts of clinicians, radiologists, cytologists, pathologists and medical biochemists.

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