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*Source / Izvornik:* **Collegium Antropologicum, 2010, 34, 25 - 29**

**Journal article, Published version**

**Rad u časopisu, Objavljena verzija rada (izdavačev PDF)**

*Permanent link / Trajna poveznica:* <https://um.nsk.hr/um:nbn:hr:105:105722>

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*Download date / Datum preuzimanja:* **2024-07-13**



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# Diagnostic Pitfalls in Parathyroid Gland Cytology

Anka Knežević-Obad<sup>1</sup>, Hrvojka Tomić-Brzac<sup>1</sup>, Kamelija Žarković<sup>2,4</sup>, Damir Dodig<sup>1,4</sup>  
and Ivana Knežević Štromar<sup>3</sup>

<sup>1</sup> Clinical Department of Nuclear Medicine and Radiation Protection, University Hospital Center Zagreb, Zagreb, Croatia

<sup>2</sup> Clinical Department of Pathology, University Hospital Center Zagreb, Zagreb, Croatia

<sup>3</sup> Polyclinic »Sunce«, Zagreb, Croatia

<sup>4</sup> University of Zagreb, School of Medicine, Zagreb, Croatia

## ABSTRACT

*The aim of this study is to establish possibilities of using cytology in the diagnosis of parathyroid gland adenoma. 475 patients, all suspected to have parathyroid gland disease, were examined over a three-year period (from 1 of January 2006 to 31 of December 2008) in the Clinical Department of Nuclear Medicine and Radiation Protection, University Hospital Center Zagreb, Croatia. Ultrasound guided fine needle aspiration biopsy (UG-FNAB) of suspected occurrences determined by ultrasound was done. Samples obtained by UG-FNAB were air-dried and stained using the May-Grünwald-Giemsa (MGG) staining procedure. PTH levels were determined in all punctate and sera obtained on the day of UG-FNAB. Samples adequate for cytological analysis were obtained from 288 patients, while 187 punctates did not contain epithelial elements. The parathyroid hormone (PTH) analysis was made for all punctates. The adenoma was diagnosed via morphological characteristics in 71 out of 288 punctates that were proven adequate for cytological analysis. Increased PTH levels were later on established in all diagnosed adenomas. All patients with cytology-based diagnosis of parathyroid gland adenoma were sent to surgery, and the cytological diagnosis was confirmed by pathohistology. In three cases, the parathyroid gland adenoma was established by pathohistology, although in these cases the cytological diagnosis was negative. The cytological diagnosis of parathyroid gland adenoma can be considered reliable in 96% of cases, provided that the echosonographic structure and localisation of the punctured node is noted, and assuming that material adequate for cytological analysis is obtained by FNAB. Possible pitfalls are oncocytic types of parathyroid adenoma, intranuclear inclusions and papillary formation of epithelial cells, and cystic degeneration of nodules. These errors can be avoided by defining the PTH level on the same punctate.*

**Key words:** parathyroid gland cytology, UG-FNAB, parathyroid adenoma

## Introduction

Parathyroid glands can be visualised by ultrasound only if they are affected by a pathological change. Solitary hypoechoic nodules, situated next to the lower or upper pole of thyroid gland lobes are usually adenomas or, very rarely, carcinomas. The hyperplasia of parathyroid glands almost always affects all or several glands and is manifested during ultrasound examination as a number of hypoechoic nodules in the area where they are normally found. However, the cases of atypical localisation are not rare, and they may cause a problem during diagnosis<sup>1,2</sup>. An ultrasound-guided fine needle aspiration biopsy (UG-FNAB) may be useful in pre-surgery

diagnostics, provided that the material for cytological analysis is of good quality. Cytology may be used to differentiate adenoma from parathyroid gland tissue hyperplasia, but it cannot be used to differentiate adenoma from carcinoma<sup>3-6</sup>. Some authors dispute the possibility of differentiating adenoma from hyperplasia by cytological procedure<sup>7,8</sup>.

Possible pitfalls in the cytological pre-surgery diagnostics of parathyroid adenoma, i.e. the causes of erroneous negative findings generated by cytological analysis, are analyzed in this study.

## Material and Methods

475 patients, all suspected to have parathyroid gland disease, were examined over a three-year period (from 1 January 2006 to 31 December 2008) at the Clinical Department of Nuclear Medicine and Radiation Protection, University Hospital Center Zagreb, Croatia. 347 patients were female, and 101 male, aged 20 to 88, and most of them were 50 to 69 years old.

The ultrasound examination was made using the 7–13 MHz linear probe. UG-FNAB was performed on all of them, using the 25 gauge needle.

Some of the material obtained by puncture was spread onto the glass using the glass-on-glass method, and then it was air-dried and stained using the May Grünwald-Giemsa (MGG) staining procedure. After that, the material was analysed using the light microscope. The rest of the material obtained by FNAB was diluted with 1 ml of physiological solution and placed in ice for determination of PTH level in the punctate. PTH level was also determined in serum samples obtained from the patients on the day of UG-FNAB.

The parathormon was determined by immuno-radiometry.

The punctate samples were treated in the same way as the serum samples. The analytical sensitivity of the method is 0.2 pmol/L, and the measuring range is 0.2–250 pmol/L. The 1–6 pmol/L values in the serum were considered normal. The PTH values in the punctate were determined using the semi-quantitative procedure.

In this study, the researchers used only the material that proved suitable for cytological analysis after the first FNAB, i.e. the samples for which the parathyroid gland adenoma diagnosis was made and based on that patients were sent to surgery. The patients that had to undergo surgery because of hyperplasia of parathyroid glands (long-term haemodialysis patients) were not considered in this study. The cytological results for patients sent to surgery under clinicians suspicion of parathyroid adenoma, despite the fact that the pre-surgical cytological diagnosis was negative (i.e. it did not point to the parathyroid gland disease), were also reviewed.

## Results

During the first puncture, a material adequate for cytological analysis was obtained from 288 patients out of the total of 475 patients that were initially subjected to UG-FNAB. This shows that as much as 40% of material obtained by the UG-FNAB of parathyroid glands did not prove suitable for cytological analysis, which is almost three times more when compared to UG-FNAB of thyroid gland (12%).

36 out of 187 materials that were proven inadequate for cytological analysis, were characterized by elevated PTH levels in the punctate.

In the cytologically acceptable material, the pre-surgery cytological adenoma diagnosis was made for 71 pa-

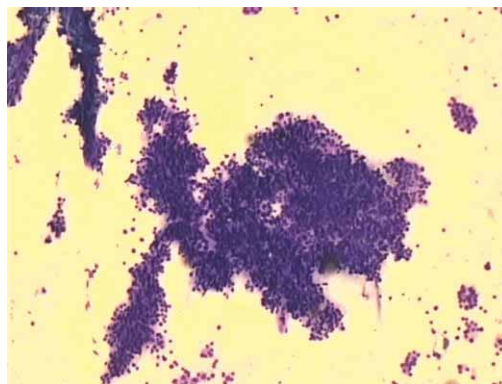


Fig. 1. Parathyroid gland adenoma, MGG x200. High cellularity, three dimensional cell clusters with visible overlapping of nuclei, denuded nuclei near the clusters, traces of blood capillary endothelium.

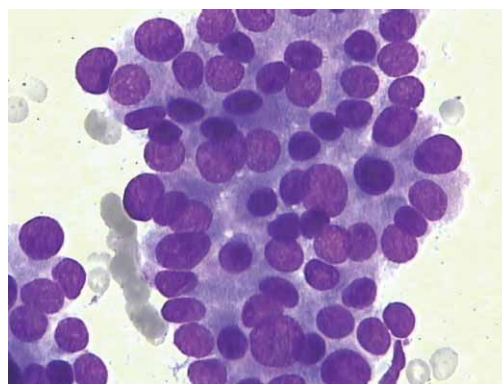


Fig. 2. Parathyroid gland adenoma, MGG x1000. Cell polymorphism.

tients (Figures 1 and 2). In all these cases, PTH levels were elevated in both punctate and serum. As to ultrasound analysis, all of them were solitary, hypoechogetic nodules, situated in 84% of cases next to the lower pole of the right or left thyroid lobe. None of the nodules was palpable. All of the above data, and the Ca and P findings in the serum, were available to the cytologist prior to delivery of cytological opinion. The PTH levels in the punctate were not known to the cytologist at the time of cytological analysis of the punctate.

After the review of pathohistological findings of patients sent to surgery by the clinician suspecting the parathyroid gland tumour, without the pre-surgery cytological diagnosis of adenoma, the histology revealed the presence of adenoma in three patients. In one case, the cytological diagnosis was the cystically altered thyroid gland, in the second case it was the oncocyctic tumour of the thyroid gland (Figures 3 and 4) and, in the third case, the papillary carcinoma of the thyroid gland was diagnosed (Figures 5 and 6). In all three cases, the parathormon was positive in both punctate and serum. One of 71 adenoma diagnosed by cytological procedure was histologically confirmed as parathyroid gland carcinoma.

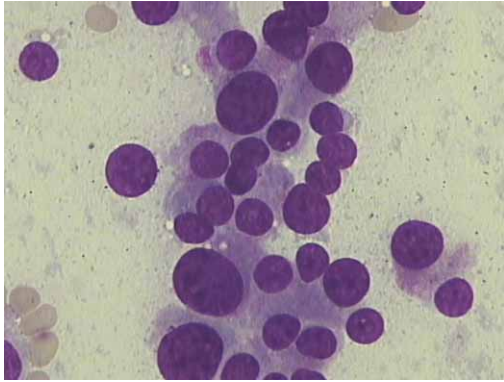


Fig. 3. Atypical adenoma of parathyroid gland, MGG x1000.

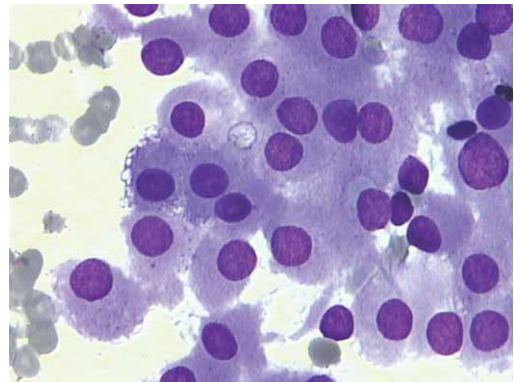


Fig. 4. Oncotic adenoma of parathyroid gland, MGG x1000.

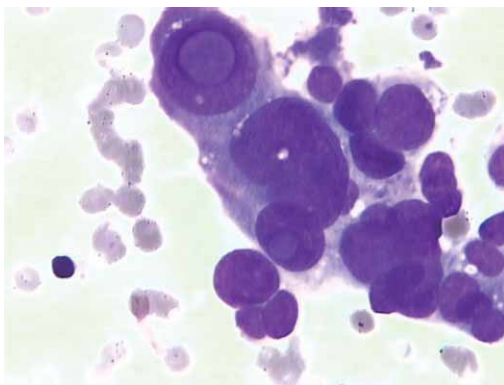


Fig. 5. Intranuclear inclusions in parathyroid gland adenoma, MGG x1000.

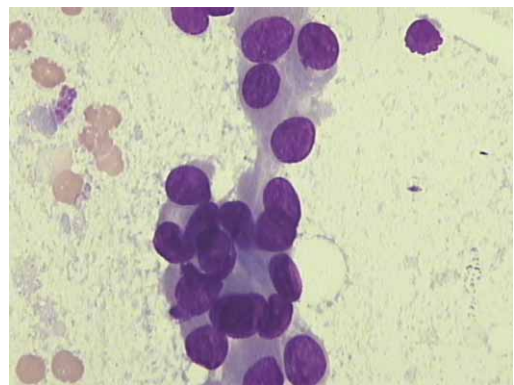


Fig. 6. Parathyroid gland adenoma, MGG x1000. Follicular cluster of epithelial cells.

## Discussion

The number and location of parathyroid glands is variable. Most often there are four of them, and they are located next to the lower and upper pole of the thyroid gland lobes<sup>1</sup>. If they are pathologically unaltered, they can not be visualized due to small size, and they can not be differentiated from thyroid gland tissue by ultrasound. However, if they are pathologically altered, then the ultrasound and the UG-FNAB are both highly suitable for pre-surgical diagnosis of parathyroid glands<sup>2</sup>.

In our material, 84% of pre-surgical cytologically diagnosed parathyroid-gland adenomas were situated next to the lower pole of the right or left lobe of the thyroid gland. The others were situated next to the back contour of the central or top third of lobes, in the iugulum, and only 2 were intrathyroid adenomas. Other localities described in literature (on the neck, para-cardiac adenomas, etc.) were not identified in our material.

All adenomas were solitary, and none of them was palpable. The ultrasound examination revealed that these are the hypoechogenic, well delimited nodules, devoid of visible calcifications, and with visible parts of cystic degeneration of nodule. The examination by Colour Dopp-

ler revealed capsular vascularisation. Such ultrasound findings correspond to those described in literature<sup>9</sup>.

As already indicated during presentation of results, the material adequate for cytological analysis was not obtained in 40% of nodules punctured because of suspected change of parathyroid gland. The percentage of such inadequate material is much higher when compared to nodule puncture in thyroid gland conducted in the same period and in the same laboratory. We have not found discussion of similar issues in the literature. The above information opens the topic of validity of cytological puncturing in pre-surgical diagnosis of change to parathyroid gland. In our opinion, such great percentage of inadequate material is due to location of parathyroid glands and to intensive blood circulation in the capsule and the gland itself, which is why a lot of blood is present in the punctate. It seems that reaching the gland is not the problem, as shown by the positive PTH in the punctate, even in 19% of material inadequate for cytological analysis due to lack of epithelial elements in the punctate. This information corresponds to that found in literature where it can be seen that the punctate-based PTH determination method is more sensitive than the cytological analysis for detection of changes to parathyroid gland, and for proving whether the parathyroid gland has really been punctured<sup>10</sup>.

When making the cytological diagnosis of parathyroid adenoma, we used morphological criteria described in the literature: cellularity of smear, three dimensional cell clusters with visible overlapping of nuclei, cell polymorphism with many denuded nuclei near the clusters, traces of blood capillary endothelium and clear background in smear<sup>3,6,7</sup>. The adenoma can be differentiated from hyperplasia of parathyroid gland using morphological properties of cells and ultrasound findings (localisation, structure and number of nodules), and the data about the calcium and phosphorus levels in the serum. Some adenoma can even be differentiated in greater detail: oncocyctic adenoma, chief cell adenoma and, in one case, an atypical adenoma<sup>6,7</sup>. In one case out of 71 diagnosed adenomas, the pathohistological analysis pointed to the parathyroid gland carcinoma. During subsequent review of cytological findings, it was established that there are no cytological criteria that would justify the carcinoma diagnosis. According to data available in the literature, the cytological differentiation between adenoma and carcinoma can not be made based on morphological properties, while opinions differ as to the differentiation between adenoma and hyperplasia<sup>3,6-8</sup>.

In our material, the pre-surgical diagnosis of parathyroid gland adenoma was based on morphological properties of cells in smear, on clinical data (calcium and phosphorus levels in serum), and on ultrasound properties of the punctured substance. In 4% of cases (i.e. in three cases) the cytological diagnosis was wrong although the above mentioned data were known. In one case, the ultrasound revealed that nodule was affected by cystic degeneration and, from the standpoint of morphology, the epithelial elements found in this cystic matter pointed to degenerative change of thyrocytes. Such cases are described in the literature as a possible cytological error<sup>11,12</sup>. In the described punctate, the PTH was positive, which was not known at the time the cytological diagnosis was made. In the second case, the oncocyctic type of parathyroid gland adenoma was mistaken for the onco-

cytic adenoma of the thyroid gland. The subsequent review of the cytological findings revealed that oncocytes in the parathyroid gland tumour present morphological properties that differ from those in the thyroid gland. The nuclei of these cells in parathyroid gland adenoma are smaller, the cells come in denser clusters, and traces of blood capillary endothelium are almost always visible in smear, which is not the case in thyroid gland adenoma. Here also, the positive PTH result for punctate was obtained at a later time. Elevated PTH level in this case justifies the former name of this tumour: »functional oxifilic adenoma«<sup>13</sup>. In the third case, the cytological diagnosis was »papillary carcinoma of thyroid gland«. Smears revealed papillary formations of epithelial cells, partly well delimited basophilic cytoplasm, and also intranuclear inclusions. Here, the subsequent PTH findings for punctate were also positive. It can be seen from literature that such cytological pattern can be seen in 7% of parathyroid gland adenoma and in as many as 43% of parathyroid gland carcinoma<sup>14,15</sup>. Intranuclear inclusions are not pathognomonic only for papillary carcinoma of thyroid gland. They can be found in medullar carcinomata in case of hyalinised trabecular adenoma of thyroid gland, and were described in parathyroid gland adenoma already in 1983<sup>16</sup>.

## Conclusion

Cytological diagnosis of parathyroid gland adenoma is possible if relevant clinical data are available: calcium and phosphorus levels in serum, ultrasound properties, and punctured nodule location. The diagnosis is accurate in as many as 96% of cases, provided that the material adequate for cytological analysis is obtained by UG-FNAB. Possible pitfalls are oncocyctic types of parathyroid adenoma, intranuclear inclusions and papillary formation of epithelial cells, and cystic degeneration of nodules. These errors can be avoided by defining the PTH level on the same punctate.

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A. Knežević-Obad

Clinical Department of Nuclear Medicine and Radiation Protection, University Hospital Center Zagreb, Kišpatićeva 12, 10000 Zagreb, Croatia  
e-mail: ivana.stromar@gmail.com

## DIJAGNOSTIČKE POGREŠKE U CITOLOGIJI ADENOMA PARATIROIDNIH ŽLIJEZDA

### SAŽETAK

Cilj ovog rada bio je utvrditi mogućnosti citologije u dijagnostici adenoma paratiroidnih žlijezda. U trogodišnjem periodu (01. siječnja 2006. – 31. prosinca 2008. godine) u Klinici za nuklearnu medicinu i zaštitu od zračenja, KBC Zagreb, pregledano je 475 bolesnika pod sumnjom na bolest paratiroidnih žlijezda. Ultrazvučno suspektne tvorbe su citološki punktirane pod kontrolom ultrazvuka (UZV). Razmazi dobiveni punkcijom sušeni su na zarku i bojeni metodom May-Grünwald-Giemsa (MGG). Adekvatan materijal za citološku analizu dobiven je kod 288 bolesnika, a 187 punktata nije sadržavalo epitelne elemente. Iz svih punktata vršena je analiza PTH. Od 288 punktata adekvatnih za citološku analizu u 71 bolesnika je citološki dijagnosticiran adenom temeljem morfoloških karakteristika. U svih dijagnosticiranih adenoma kasnije je potvrđena i povišena vrijednosti PTH u punktu. Svi bolesnici sa citološki postavljenom dijagnozom adenoma paratiroidne žlijezde upućeni su na operativni zahvat te je dijagnoza patohistološki potvrđena. U tri slučaja postavljena je patohistološka dijagnoza adenoma paratiroidne žlijezde, dok je citološka dijagnoza u tim slučajevima bila negativna. Citološki smo bili u mogućnosti na osnovu bojanja po MGG-u te bojanja na argirofilna zrnca po Grimeliusu dijagnosticirati adenom paratiroidne žlijezde u 96% slučajeva, pa čak i njegove subtipove: onkocitni adenom, atipični adenom i adenom glavnih stanica. Lažno negativnih nalaza je bilo 4% (3 slučaja). Citološku dijagnozu adenoma paratiroidne žlijezde moguće je postaviti u 96% slučajeva uz naznaku ehografske strukture i lokalizacije punktiranog čvora te uz pretpostavku da smo punkcijom dobili adekvatan materijal za citološku analizu. Moguće pogreške u dijagnostici su onkocitni adenom, nalaz intranukleranih inkluzija i papilarnih formacija epitelnih stanica te cistična degeneracija čvora. U kombinaciji s nalazom PTH iz istog punktata i te se pogreške mogu izbjeći.