Introduction
Parathyroid conditions causing primary hyperparathyroidism (pHPT) can be divided into single gland disease and multi gland disease. pHPT is most commonly caused by typical adenoma/single gland disease (PA) - this is 80-85% cases of pHPT. Parathyroid hyperplasia or multiple gland disease accounts for 10-15% of cases of PHPT. Atypical parathyroid adenoma (APA) and carcinoma (PC) - very rare conditions - are both responsible for pHPT in approximately 0.5 - 1.5% of cases. Objectives: To estimate occurrence of atypical parathyroid adenoma, parathyroid carcinoma and parathyroid hyperplasia along with characterize them based on their etiology, clinical presentation, diagnosis and treatment. Methods: We performed a retrospective study and enrolled 1,019 patients with primary hyperparathyroidism undergoing parathyroidectomy at academic Department of General and Endocrine Surgery between 1983 and 2018. Results: Out of 1,019 cases of primary hyperparathyroidism, 850 (83.4%) cases were due to typical parathyroid adenoma (PA), 135 (13.2%) cases were due to parathyroid hyperplasia, 29 (2.8%) cases were due to parathyroid carcinoma (PC), and 5 (0.5%) cases were due to atypical parathyroid adenoma (APA).
blood serum levels of calcium and parathyroid hormone. Additionally, we measured the success rate and result after performance of primary parathyroidectomy. We also compared the anatomical localization sites of patients with double parathyroid adenoma to those with single gland neoplasm (adenoma or hyperplasia). Every patient was diagnosed with primary hyperparathyroidism on the basis of biochemical results and radiological measures. Each of them had developed hypercalcemia which needed to be monitored, because 2 cases were in serious risk of hypercalcemic crisis occurrence. The signs and symptoms of each patient were established during the preoperative visit and directly during hospitalization period after the surgery. During the time of follow-up all patients had blood serum calcium levels monitored together with PTH.

**Methods of Statistical Analysis**

All of the collected data was included in a spreadsheet in Microsoft Office Excel 2019. The statistical analysis was performed in Statistica 12.5. After establishing and classifying the data using a Kolmogorov-Smirnov test, we used Student’s t-test to compare data with normal distribution, and for the non-normal distribution data, we used the Mann-Whitney U test. The results are presented as percentage changes, full numbers, means, and standard deviations. The level of significance was calculated at p<0.05. Effect size - ES - was determined using: Youle’s Phi coefficient and Cramer’s V.

**Results**

From the group of 1,019 patient’s APA were confirmed in 5 (2 women and 3 men) between 38 to 68, av 52 years. No history of irradiation to the neck or familial HPT was reported. 90.6% of the cases - including all APA patients - were symptomatic at the time of admission, although symptoms were mostly due to hypercalcemia, a variety of fatigue, weakness, depressed mood, bone, and muscle pain. Patients with APA were characterized by higher frequency of depression (80.0%), musculoskeletal symptoms (80.0%), nephrolithiasis (80.0%), osteoporosis (60.0%), and stomach/duodenal ulcers (40.0%) (Table 1).

The majority of tumors in a group of 1,019 patients were localized in the neck region 93.5% and 6.5% were in the mediastinum. In the group of patients with APA, lesions were located once in the mediastinum. In 84% of patients - including all APA patients - the lesions were singular and 16% had multiple with a predominance of 2 lesions, more than 3 lesions were also found sporadically. Characteristics of patients are presented in (Table 2).

**Table 2. Characteristics of the patients operated for APA and PA, PC**

<table>
<thead>
<tr>
<th>Factor</th>
<th>No of patients</th>
<th>test statistic</th>
<th>p value</th>
<th>ES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>APA</td>
<td>PA</td>
<td>PC</td>
<td></td>
</tr>
<tr>
<td>sex M</td>
<td>n=5</td>
<td>n=850</td>
<td>n=29</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>244</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>age years from-to (average)M</td>
<td>33-69 (53.3)</td>
<td>21-79 (55.0)</td>
<td>29-69 (55.9)</td>
<td>-1.18</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>606</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>symptoms</td>
<td>Yes</td>
<td>773</td>
<td>27</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>77</td>
<td>2</td>
<td>0.05</td>
</tr>
</tbody>
</table>

In a group of 1,019 patients operated for pHPT, the growths were almost equally distributed in the left or right parathyroid gland, but most were localized in the regions of inferior lobes of the thyroid. In the group of patients with APA, all lesions were so localized. We also performed a comparison of neoplastic glands occurrence between patients with single gland changes and those with multiple abnormal glands. The exact comparison with total number of patients, by the means of localization and number of disordered glands with the group of patients treated for APA is shown in [Table 3].

3 patients had parathyroidectomy. 1 patient had parathyroidectomy with the removal of thyroidlobe and 1 patient had en bloc resection. There were no patients which were re-operated for recurrences of hypercalcemia. All of the patients were alive with no evidence of disease. In the group of 1,019 patients, postoperative patient monitoring showed that in most of the cases parathyroidectomy was successful. Approximately 96.2% of patients did not have symptoms after treatment and their calcium and parathyroid hormone levels stabilized. Patients were monitored for 5 years and their symptoms did not reoccur and the levels of calcium and PTH stayed within normal ranges. In the group of APA patients, no signs of recurrence of hyperparathyroidism were found during the follow-up. In the APA group, we observed slightly higher levels of ionized calcium and PTH in the blood serum compared to the group of patients.

**Table 3. Localization of parathyroid glands in patients operated for APA and PA, PC**

<table>
<thead>
<tr>
<th>Factor</th>
<th>No of patients</th>
<th>test statistic</th>
<th>p value</th>
<th>ES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>APA n=5</td>
<td>PA n=850</td>
<td>PC n=29</td>
<td></td>
</tr>
<tr>
<td>localization left</td>
<td>superior</td>
<td>0</td>
<td>98</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>inferior</td>
<td>1</td>
<td>210</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>right</td>
<td>superior</td>
<td>0</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>inferior</td>
<td>4</td>
<td>503</td>
<td>10</td>
</tr>
</tbody>
</table>

with typical parathyroid adenomas (PA). Statistically, male group scored higher levels of calcium and PTH than women - similarly in patients with APA. After surgical management calcium and PTH levels dropped to normal values, as shown in Table 4, Figure 1, Figure 2.

Regardless of the cause of primary hyperparathyroidism, surgical therapy has a high curative rate. According to the study of 1,019 cases, 96.2% of patients - including patients with APA - after parathyroidectomy were cured and did not experience further episodes of hypercalcemia in the following 5 years. Surgical approach of treatment of hyperparathyroidism is very effective and even in the case of malignant cause of the hyperparathyroidism, the full resection of the tumor and fast diagnosis is a life saving measure with high survival rate.

**Discussion**

In our study we presented patients that developed primary hyperparathyroidism, that could becaused by typical adenoma (PA), atypical adenoma (APA), hyperplasia and cancer (PC). According to our research, most cases suffered the symptoms of hypercalcemia due to hyperplasia and typical adenoma (PA) that are benign conditions. The therapeutic outcome for this patients’ group was very satisfactory with a very high rate of curability [1,3,28]. On the other hand, patients with atypical parathyroid adenomas (APA) are at higher risk of development of parathyroid carcinoma (PC), thus it is very important from a surgical point of view to resect all of the tumor to prevent development of malignancy [2,7,33]. Patients will develop symptoms due to hypercalcemia, that mostly include fatigue, malaise, constipation, bone and muscle pain, decreased concentration and depressive episodes [5,28]. After obtaining laboratory blood examination results, we can observe increased levels of calcium and PTH that is indicative of hyperparathyroidism [6,27]. Later we have to distinguish the cause of the disorder. Neck USG can be performed to identify if the gland is enlarged, although the results are usually not enough for diagnosis of hyperplasia [7,8]. The Tc(99 m)-sestamibi scintigraphy can help with a diagnosis, by localization of changed parathyroid gland with a sensitivity of 70-90%, unfortunately its use is limited in multiple lesions of the gland, [9,30]. Therefore, use of USG and scintigraphy could markedly increase sensitivity of the diagnosis. Unfortunately, recent studies showed that even this method is not very accurate and many patients cannot be diagnosed only upon the results of both of these examinations [10]. APA are extremely rare and have only been described 23 times in literature [12,27]. They lack specific criteria from histopathological point of view, it is not possible to differentiate them from benign adenomas and cancerous lesions neither by imaging methods nor macroscopically. Microscopically, they have some features of carcinoma - they adhere to contiguous structures, bends of fibrosis, solid trabecular growth, mitotic activity, but they do not invade the capsule, what is a hallmark of malignancy [12,13,26]. Although, the lack of specific criteria for histopathologic makes it extremely hard to always correctly diagnose the atypical adenoma (APA). The proposed criteria require the presence of at least 2 of those symptoms: intraoperative adherence, bands of fibrosis, pronounced trabecular growth, strong mitotic activity, necrosis, small cells with high nuclear/cytoplasmic ratio, cellular atypia in the absence of unequivocal signs of malignancy [13,14,24]. Use of imaging studies like USG or scintigraphy is limited, because it is not giving a definitive diagnosis. Clinical picture can be very varying, generally, the hypercalcemia is slightly lower than seen in cancer, but higher than in typical adenoma (PA). All those similarities make it extremely difficult to distinguish atypical adenoma from carcinoma and benign lesion. The diagnosis of cancer should be supported if there is an invasion of the capsule, vessels, and neighboring structures [14,25]. The treatment of choice for atypical parathyroid adenoma (APA) is parathyroidectomy. Without evidence of macroscopic local invasion, the value of en bloc resection at initial surgery remains debatable. The surgeon performing the operation has to be very vigilant and check surrounding tissues for necrosis or any other abnormalities.

**Table 4. Levels of ionized calcium and PTH in blood serum in patients undergoing surgical treatment due to APA and PA, PC**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Examination</th>
<th>before operation</th>
<th>after operation</th>
<th>Z</th>
<th>p</th>
<th>h2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>value levels</td>
<td>average</td>
<td>value levels</td>
<td>average</td>
<td></td>
</tr>
<tr>
<td>Group of APA patients n=5</td>
<td>PTH</td>
<td>54.6-1560</td>
<td>57.12</td>
<td>22-69.1</td>
<td>37.42</td>
<td>26.78</td>
</tr>
<tr>
<td></td>
<td>Calcium</td>
<td>1.71-2.98</td>
<td>2.13</td>
<td>1.18-1.27</td>
<td>1.21</td>
<td>26.83</td>
</tr>
<tr>
<td>Group of PA patients n=850</td>
<td>PTH</td>
<td>45.6-1265</td>
<td>154.51</td>
<td>3.1-176.8</td>
<td>36.74</td>
<td>27.59</td>
</tr>
<tr>
<td></td>
<td>Calcium</td>
<td>1.43-2.99</td>
<td>1.88</td>
<td>0.78-12.01</td>
<td>2.43</td>
<td>27.58</td>
</tr>
<tr>
<td>Group of PC patients n=29</td>
<td>PTH</td>
<td>45.6-1265</td>
<td>154.51</td>
<td>3.1-176.8</td>
<td>36.74</td>
<td>27.59</td>
</tr>
<tr>
<td></td>
<td>Calcium</td>
<td>1.43-2.99</td>
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<td>2.43</td>
<td>27.58</td>
</tr>
</tbody>
</table>
Also helpful is intraoperative histopathological evaluation in case of doubt. After performing the procedure, the patient should be closely monitored, especially in unclear cases [15]. From a histological point of view the parathyroid carcinoma (PC) can be misdiagnosed as an atypical adenoma (APA) - due to inadequate histopathological sample or other causes. Clinically, the physician should consider diagnosis of carcinoma when the patient presents with renal and bone symptoms simultaneously because dual presentation is quite rare in case of adenomas. Laboratory studies of very high levels of calcium and PTH also can indicate presence of malignancy. On physical examination and sonographic evaluation masses bigger than 3 cm should be considered to be malignant [17,23]. Histopathological studies and genetic analysis of lesions can help with the diagnosis of cancerous lesions but are not always definitive. The diagnosis is confirmed if there is an obvious sign of invasive growth of the tumor, either invasion of the capsule, vessels, neighboring structure or presence of metastasis at the time of presentation. Although the metastatic progression of the tumor is very slow, usually cancer is in an earlier stage. Scintigraphy and USG studies are not very helpful because just upon them we cannot distinguish between adenoma and carcinoma [15,17]. Additionally, adjacent lymph nodes should be resected as well [16,17]. If the diagnosis was confirmed based on the result of pathological studies of tumor resected during primary surgery, the treatment becomes more complex. Reoperation is advised in cases in which the surgery did not restore levels of calcium and PTH. In cases where primary surgery resolved the symptoms, patients should be strictly monitored and the levels of calcium and PTH should be measured regularly for surveillance of cancer return [17,29]. Primary hyperparathyroidism is a clinical manifestation of benign and malignant conditions. A quick and precise diagnosis followed by surgical resection of hyperfunctioning tissue is the only curative approach [21,22,32]. A multidisciplinary approach should always be preferred in patients with this condition due to difficult differential diagnosis and not clear criteria [23].

**Conclusion**

1. Primary hyperparathyroidism can be a manifestation of growing adenoma, hyperplasia of the gland, carcinoma, or atypical parathyroid adenoma.
2. In case of diagnosis of atypical adenoma, patients after parathyroidectomy should be closely monitored for any evidence of malignant proliferation.
3. Although, the vast majority are caused by benign lesions, the malignancies can present very similarly making it very difficult to quickly diagnose and treat - especially in the case of atypical adenoma.
4. The laboratory examinations can be helpful, especially if very high levels of calcium and PTH are noted. The PTH and ionized calcium levels can be a good prognostic factor but are not definitive in the differential diagnosis between atypical adenoma, cancer, or parathyroid adenoma.
5. Some clinical features and histopathological evaluation of the lesion in many cases can be very helpful in the differential diagnosis, but not always is enough for the formation of a conclusive diagnosis.
6. In cases that are very suspicious of malignancy, an aggressive surgical approach is preferred and cautious monitoring of a patient after surgery is extremely important for establishing a good prognosis.

**References**

Kowalski G (2022) Atypical Parathyroid Adenomas as a Rare Cause of Primary Hyperparathyroidism - In an Academic Institution Experience


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