Cent. Eur. J. Med. • 5(1) • 2010 • 53-58
DOI: 10.2478/s11536-009-0116-4

VERSITA

Central European Journal of **Medicine**

A complex case of Multiple Endocrine Neoplasia type 1 with Metastatic Parathyroid Carcinoma

Case Report

Shyam Kalavalapalli, Indrajit Talapatra*, Ian Patrick Michael O' Connell

Department of Endocrinology, Royal Albert Edward Infirmary, WN1 2NN Wigan, United Kingdom

Received 7 May 2009; Accepted 6 October 2009

Abstract: We describe below a patient with Multiple Endocrine Neoplasia type 1 (MEN type 1) who presented with features of Primary Hyperparathyroidism. However, the actual diagnosis of Parathyroid Carcinoma was delayed until metastases to the lung were discovered. She was also found to have Pituitary Macro adenoma with Silent Acromegaly, with no clinical features whatsoever. She underwent transphenoidal hypophysectomy with postoperative radiotherapy. However, the disease process remained biochemically active necessitating commencement of somatostatin analogues. There is also a tumour at the head of the pancreas which at present is non functional with normal gut hormone profile and normal 24 hour urinary 5-hydroxyl indole acetic acid (5-HIAA) excretion assay. Our case highlights the pitfalls in diagnosing the parathyroid carcinoma due to lack of initial proper histological features. The diagnosis of parathyroid carcinoma was based on histologically confirmed metastases to the lungs. We also discuss below the entity called Silent Acromegaly where patients have biochemically and/or histologically confirmed growth Hormone (GH) excess with no clinical features suggesting Acromegaly. We discuss the benefits of somatostatin analogues in indirectly controlling the rest of the tumours in MEN1 and hypothesise the same for metastatic parathyroid carcinoma. Metastatic parathyroid carcinoma with multiple endocrine neoplasia type 1 is extremely rare. Our case highlights the complexities of managing MEN1 with metastatic parathyroid carcinoma and the dilemmas in dealing with the various aspects of the care.

Keywords: *Parathyroid Carcinoma • Multiple Endocrine Neoplasia Type1 • Acromegaly*

1. Introduction

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant disorder characterized by predisposition to tumours of the parathyroid glands (which occur in nearly all patients by age 50 years), anterior pituitary, and pancreatic islet cells. The tumours are usually benign, except for some islet cell and gastrointestinal tract tumours. Here we present a complex case of MEN1 with metastatic parathyroid carcinoma.

2. Case Report

A 44 year old lady presented at the age of 40 years with two years history of right sided neck pain and generalised aches and pains. She was found to have biochemical evidence of Primary Hyperparathyroidism with corrected calcium of 2.71mmol/L (normal: 2.05-2.60) and an inappropriately high PTH of 8.7pmol/L (normal: 1.1-6.9). She underwent parathyroidectomy of her right lower parathyroid gland which was found to have a nodule measuring 2 x 1x 0.5 cm. Histology revealed very cellular parathyroid gland and was difficult to differentiate between parathyroid adenoma and hyperplasia as that depended on the state of other glands. She felt better with normalisation of her calcium.

However, her wellbeing was short lived as her symptoms reappeared within two years with recurrence of her primary hyperparathyroidism as suggested by a corrected calcium of 2.66 mmol/L and a PTH of 68pg/ml (normal: 15-65). This raised the suspicion of possible MEN1 syndrome. She did not have any family history of parathyroid problems. Her past history was unremarkable except that she had vaginal hysterectomy with conservation of her ovaries in the same year as her presentation. Clinical examination revealed bilateral

* *E-mail: Indratala@aol.com*

Table 1. Insulin Tolerance Test (pre hypophysectomy).

Time (min)	Glucose mmol/l	Cortisol nmol/L
0	5.0	379
30	1.5	325
60	2.3	768
90	3.7	685

Table 2. OGTT (pre hypophysectomy).

Time (min)	GH mU/l
0	10.4
30	59
60	88
120	49

Table 3. TRH Test (pre hypophysectomy).

Time	TSH mU/L
0 min	1.79
20min	18.30
60 min	10.26

galactorrhoea. The visual fields were normal. Further tests were carried out looking for MEN1.

For her recurrent primary hyperparathyroidism she had resection of her remaining three parathyroid glands with half of the left upper gland clipped and left in situ and post operative calcium remained normal at 2.58 mmol/L with a PTH of 4.39 pmol/L.

Rest of her endocrine profile revealed normal thyroid functions with FT4 (free thyroxine) of 12.7 pmol/l (normal: 12-22) and TSH of 1.28 mU/L (normal: 0.27-4.7), LH, FSH and oestradiol were in the normal range particularly as there were no clues with her periods in view of her previous hysterectomy.

In the interim, while awaiting other endocrine tests she developed severe abdominal pain with CT scans showing a right sided ovarian cyst and incidentally also showing lung nodules. She ended up having bilateral salpingo-oophorectomy for endometriosis with chocolate cyst. She was started on Raloxifene as patient was not keen on hormone replacement for prophylaxis of osteoporosis.

On the endocrine front, her prolactin was elevated at 1841 mU/L (normal: 71- 511) with normal macroprolactin screen of 89% (>60% indicates no significant macroprolactin). Her dynamic pituitary function test results are shown in Tables 1,2 and 3.

The high growth hormone (GH) levels favoured acromegaly with normal adrenal, thyroid and gonadal axes. In view of evidence of acromegaly with raised prolactin (repeat levels were 1744 mU/L) which could be either due to stalk disconnection or due to pituitary

Figure 1. Pituitary adenoma.

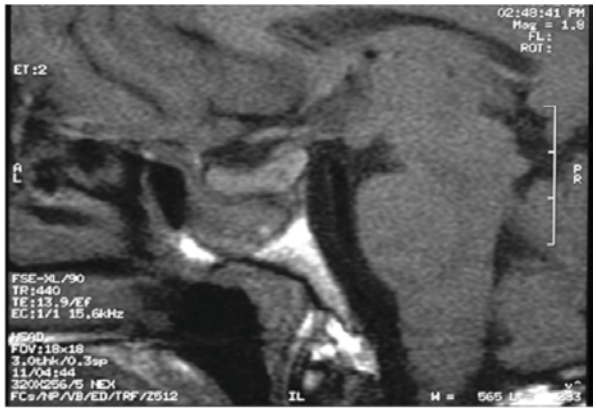
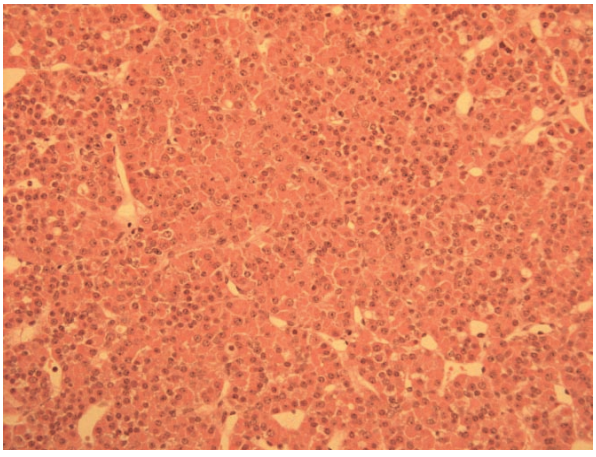


Figure 2. Pituitary histology.



adenoma, a MRI scan of the pituitary was arranged. The scan showed a pituitary macroadenoma measuring 19 x 15 x 14 mm abutting the optic chiasm and extending into the right cavernous sinus (Figure 1). She had transphenoidal hypophysectomy and the histopathology showed adenomatous architecture and cytology with mixture of acidophilic cells (Figure 2) but elsewhere also more basophilic and chromophobic cells.

Though her post operative MR Scan showed good clearance, she however continued to have biochemically active acromegaly with IGF-1 at 99.5 (8.6-29.4 nmol/L) and high GH profiles as shown in Tables 5,6,7 and 8. After close consideration of all the options she was given radiotherapy following discussing with the patient the long term risk of hypopituitarism. She was placed on Somatostatin analogues (octreotide 30mg intramuscularly) every four weeks.

In the mean time, the patient had one single episode of haemetemesis thought to be due to Mallory Weiss tear and to exclude the possibility of Zollinger Ellison syndrome as part of MEN1 and primary hyperparathyroidism she had an endoscopy which was

Table 4. LHRH Test (pre hypophysectomy).

Time	FSH IU/L	LH IU/L
0 min	4	9
30 min	7	63
60 min	11	101

Table 5. Insulin Tolerance Test - post hypophysectomy

Time	Glucose mmol/l	GH mU/l	Cortisol nmol/L
0	5.5	11.3	433
30	1.2	22.0	345
60	3.8	39.0	621
90	3.3	16.7	

Table 6. LHRH Test - post hypophysectomy.

Time	FSH IU/L	LH IU/L
0 min	41	21
20 min	69	99
30 min	81	124
60 min	99	141
90 min	82	99
120 min	76	84

Table 7. TRH Test - post hypophysectomy.

Time	TSH mU/L
0 min	0.78
20min	6.99
60 min	5.31

entirely normal. Her fasting gut hormones were normal. Her CT scan of the abdomen showed a 9 mm lesion in the head of pancreas. She was screened for carcinoid with 24 hr 5HIAA which was normal.

With regards to her lung lesions a repeat CT scan confirmed multiple nodules in both lungs. They increased in size particularly the one in the right middle lobe measuring 3 cm x 3 cm x 1.5 cm (Figure 3). She underwent wedge resection of nodules in medial segment of the right middle lobe and apical segment of right lower lobe both of which showed parathyroid tissue on histology (Figure 4), hence confirming metastatic parathyroid carcinoma

Again unrelated to her MEN1, she was found to have ischaemic colitis at splenic flexure on colonoscopy when she presented with one episode of rectal bleeding which was confirmed histologically.

Figure 3. Lung CT.

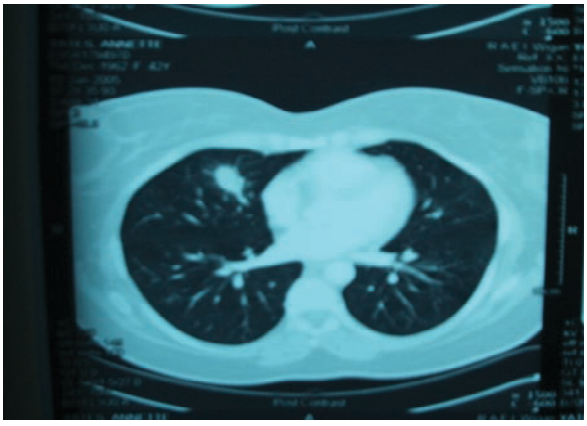
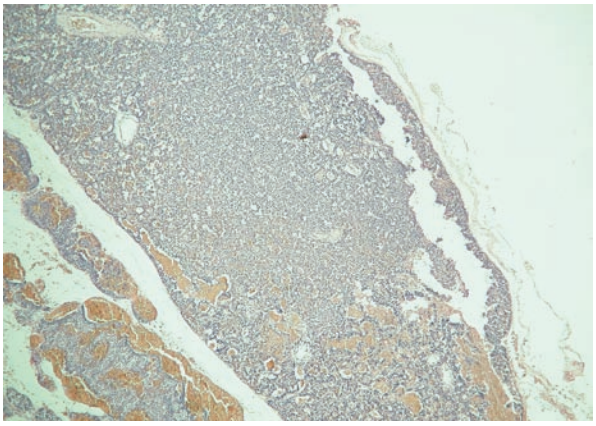


Figure 4. Lung histology.



At the present time she appears to remain in remission with a corrected calcium of 2.46 mmol/L (2.05-2.60) and a PTH of 4.01 pmol/L (1.1-6.9) after her primary hyperparathyroidism has been treated with three and half gland parathyroidectomy and she is maintained on Raloxifene 60mg daily and Adcal D3 one tablet twice daily.

The pituitary status also appears to be in remission with good clearance following her hypophysectomy with post-operative radiotherapy. Presently she is on Octreotide LAR 30mg intramuscularly every four weeks. Her most recent IGF-1 was 31.4 nmol/L (8.6-29.4). Her latest prolactin was 441 mU/L (130-640) with a normal gut hormone profile (Table 9).

Table 8. Growth Hormone Profile (Post Operative).

Time (min)	07:00	08:00	09:00	10:00	11:00	12:00	13:00	14:00	16:00
GH mU/L	10.5	18.6	2.1	0.6	0.9	2.9	3.2	2.2	4.2

Table 9. Gut Hormone.

VIP (<30pmol/L)	Pancreatic Polypeptide (<300pmol/L	Gastrin (<40pmol/L)	Glucagon (<50pmol/L)
<4	25	<4	17
Neurotensin (<100pmol/L)	Somatostatin (<150pmol/L)	ChromograninA (<60pmol/L)	ChromograninB (<150pmol/L)
33	70	42	57

3. Discussion

We describe a patient with multiple endocrine neoplasia type 1 presenting with primary hyperparathyroidism. However, the actual diagnosis of parathyroid carcinoma was delayed until metastases to the lung were discovered.

Our patient presented with what was presumed to be a straightforward primary hyperparathyroidism secondary to a parathyroid adenoma but was later confirmed to have a metastatic parathyroid carcinoma as part of MEN1 syndrome. Our case highlights the complexities of managing MEN1 with metastatic parathyroid carcinoma and the dilemmas in dealing with the various aspects of the care.

Primary hyperparathyroidism is usually caused by a parathyroid adenoma, occasionally by primary parathyroid hyperplasia, but only rarely by parathyroid carcinoma. In one summary of 4239 patients with hyperparathyroidism, 2.1 percent had functioning parathyroid carcinoma [1]. However to have metastatic parathyroid carcinoma as part of the Multiple endocrine neoplasia type 1 (MEN1) is extremely rare [2]. There are only three case reports so far associating parathyroid carcinoma with MEN1. Of those three, one was diagnosed at autopsy and other two were diagnosed histologically [3]. But ours is the first case report where metastatic parathyroid carcinoma as part of MEN1 was diagnosed based on metastases alone.

Our patient was shown to have metastatic parathyroid cancer after having found distant metastases in her lungs. The characteristic histopathology of parathyroid carcinoma consists of uniform sheets of cells arranged in a lobular pattern separated by dense fibrous trabeculae, mitotic figures in the tumour cells, and capsular and blood vessel invasion [4]. However, these features have been noted occasionally in parathyroid adenomas thereby rendering the above feature not completely reliable. DNA content of tumour cell nuclei is also not specific for parathyroid carcinoma [5].

Gross capsular and vascular invasion appear to correlate best with subsequent tumour recurrence because of the nonspecificity of these histologic features. The two criteria upon which a definitive diagnosis of parathyroid carcinomas can be made are: Local invasion of contiguous structures or Lymph node or distant metastases [6].

The aetiology of parathyroid carcinoma is unknown; however, an increased risk of parathyroid cancer has been associated with MEN1 and with autosomal dominant familial isolated hyperparathyroidism [7]. Parathyroid cancer has also been associated with external radiation exposure; however, most reports describe an association between radiation and the more common parathyroid adenoma [8,9].

At the time of presentation though she had single gland parathyroidectomy, due to her later recurrence of primary hyperparathyroidism with confirmation of MEN1 syndrome, she underwent resection of the remaining parathyroid glands except half of the left upper gland, which was left in situ. The metastases into the lungs found later and confirmed on biopsy infact led to the correct diagnosis of parathyroid carcinoma.

Her parathyroid condition is presently managed with selective oestrogen receptor modulator, Raloxifene, calcium with vitamin D3 and she remains in remission. Infact, she never had very high levels of hypercalcaemia suggesting the possibility of non functioning parathyroid carcinoma [10,11]. Nonproducing parathyroid carcinoma compares unfavourably with producing parathyroid carcinoma in terms of tumour progression and prognosis.

Few data on choice of therapy in nonproducing parathyroid carcinoma are available [12]. However, treatment of parathyroid carcinoma is surgical in the first instance, with the initial aim of achieving a cure by complete tumour resection [13]. Recurrence is common [14] and usually occurs locally in the neck. Parathyroid carcinoma is slow growing and metastasises late, with the most frequent sites of deposits being the lung (40%), cervical lymph nodes (30%), and liver (10%) [9]. Treatment of recurrent disease relies on surgical resection of local and distant deposits to palliate hypercalcaemia because the primary cause of mortality is hormonally driven biochemical disturbance, rather than direct tumour invasion.

Few other treatment options exist for patients for whom surgery is not possible because parathyroid carcinoma**s** are not radiosensitive and respond poorly to cytotoxic chemotherapy [13]. Bisphosphonates, which reduce PTH-induced osteoclast activity, have beneficial but transitory effects on calcium levels; however, they have no impact on tumour progression. Other options include calcitonin, octreotide, gallium, and mithramycin, which are occasionally transiently effective. Collins *et*

al. [15] successfully used a calcimimetic compound, cinacalcet, to decrease PTH secretion (via increased parathyroid cell sensitivity) and improved symptoms in an elderly patient with refractory parathyroid carcinoma.

Therapeutic immune targeting of cancer cells is a topic of growing interest as the mechanisms of antigen presentation, autoimmunity, and immune tolerance become more clearly defined. A variety of methods have been used to induce and augment targeting of antigens expressed by cancer cells. Previously, Bradwell and Harvey [16] reported the successful treatment of a patient with refractory parathyroid carcinoma by immunization with fragments of the PTH molecule to break natural tolerance and induce an antibody reaction against PTH. This method proved successful in reducing hypercalcaemia and concomitantly improved the patient's physical status, but there was no antitumour effect. In a recent study by Betea et al. [17], they reported for the first time the long-term hormonal, biochemical, and antitumor effects of anti-PTH immunotherapy in a patient with refractory metastatic parathyroid cancer.

The pituitary component of her MEN1 comprised of a pituitary macroadenoma with excess secretion of GH and prolactin. GH excess eventually develops in up to 60 percent of patients affected with MEN1, usually with onset in the fourth and fifth decades of life [18].

In spite of aggressive treatment with hypophysectomy and post operative radiotherapy, she continued to have GH excess necessitating the need to start somatostatin analogues. The concerns were mainly two fold, the direct effects of excess GH on her well being and indirectly, the negative impacts the excess GH might have on other endocrine organs, particularly in our case, the metastatic parathyroid carcinoma [19,20]. Infact, both her acromegaly and the parathyroid status appear to remain in remission since she was commenced on the Somatostatin analogues [21].

Interestingly, our patient did not manifest any of the features of acromegaly [22] and was confirmed only on actively screening by biochemical testing. Though her lack of symptoms could be due to early diagnosis, however, the fact that her hormone levels were significantly high does raise the possibility of silent acromegaly [23,24].

Silent somatotroph adenomas are defined as tumours showing morphological features consistent with GH production, but no clinical evidence of GH excess. Silent somatotroph pituitary tumours are defined as GH-secreting tumours with no clinical stigmata of GH excess [24-26]. Random GH and IGF-I values in these patients varied from mildly elevated to normal [27].

Screening for excess gut hormones was normal. However, she has the pancreatic head adenoma which is yet not clear whether it represents a functioning tumour or just an incidental adenoma. Though this could be clarified by further investigations both invasive (eg Calcium stimulation test) or noninvasively (eg octreotide scan, PET scan etc.), we felt that as she remained relatively asymptomatic it may be better to defer further tests at present. However, her 24 urinary hydroxy indole acetic acid were normal

Our patient is one of the few who as part of MEN1 syndrome ended up having metastatic parathyroid carcinoma. Fortunately, she remains well and relatively asymptomatic with her present treatment.

The management of MEN1 should be multi fold with a good rapport/understanding with the patient and keeping them well informed about their progress. The management should be tailor made individually for each patient separately after carefully thought over investigations and vigilance should be executed of various possibilities and appropriate but not unnecessary investigations. Finally, the goal of management for MEN1 should be to thrive to achieve a relatively normal life with minimal inconvenience.

References

[1] Obara T., Fujimoto Y., Diagnosis and treatment of patients with parathyroid carcinoma: an update and review, World J Surg., 1991,15(6), 738-744

[2] Dionisi S., Minisola S., Pepe J., et al., Concurrent parathyroid adenomas and carcinoma in the setting of multiple endocrine neoplasia type 1: presentation as hypercalcemic crisis, Mayo Clin Proc., 2002, 77 (8), 866-869

[3] Agha A., Carpenter R., Bhattacharya S., J Monson JP., Parathyroid carcinoma in multiple endocrine neoplasia (MEN) type 1: two case reports – poster presentation, Endocrine Abstracts., 2006, 11, P106

[4] Schantz A., Castleman B., Parathyroid carcinoma. A study of 70 cases, Cancer., 1973, 31, 600

[5] Bondeson L., Sandelin K., Grimelius L., Histopathological variables and DNA cytometry in parathyroid carcinoma, Am J Surg Pathol., 1993, 17(8), 820-829

[6] El-Hajj G., Arnold A., Parathyroid carcinoma, Uptodate Medicine, 2008

[7] Wassif W.S., Moniz C.F., Friedman E., Wong S., Weber G., Nordenskjold M., Peters T.J., Larsson C., Familial isolated hyperparathyroidism: A distinct genetic entity with an increased risk of parathyroid cancer., J. Clin. Endocrinol. Metab., 1993, 77, 1485-1489

[8] Fraker DL., Parathyroid Tumour. In: DeVita VT Jr, Hellman S, Rosenberg SA., Cancer: Principles and Practice of Oncology. 7th ed. Philadelphia, Pa: Lippincott Williams & Wilkins., 2005, 1521-1527

[9] Shane E., Clinical review 122: Parathyroid carcinoma, J Clin Endocrinol Metab., 2001, 86 (2): 485-493

[10] Sieracki J.C., and Horn R.C, Jr., Nonfunctional carcinoma of the parathyroid gland, Cancer., 1960, 13, 502-506

[11] Aldinger K.A., Hickey R.C., Ibanez M.L., and Samaan N.A., Parathyroid carcinoma: A clinical study of seven cases of functioning and two cases of nonfunctioning parathyroid cancer, Cancer., 1982, 49, 388-397

[12] Eurelings M., Frijns C.J.M., Jeurissen F.J.F., Painful ophthalmoplegia from metastatic nonproducing parathyroid carcinoma: Case study and review of the literature, Neuro-oncol., 2002, 4(1), 44 - 48

[13] Kebebew E., Parathyroid carcinoma, Curr Treat Options Oncol., 2001, 2, 347–354

[14] Kebebew E., Arici C., Duh QY., Clark OH., Localization and reoperation results for persistent and recurrent parathyroid carcinoma, Arch Surg., 136, 878–885

[15] Collins MT., Skarulis MC., Bilezikian JP., Silverberg SJ., Spiegel AM., Marx SJ., Treatment of hypercalcemia secondary to parathyroid carcinoma with a novel calcimimetic agent, J Clin Endocrinol Metab., 1998, 83, 1083–1088

[16] Bradwell AR., Harvey TC., Control of hypercalcaemia of parathyroid carcinoma by immunisation, Lancet., 1999, 353, 370–373

[17] Betea D., Bradwell AR., Harvey TC., Mead GP., Schmidt-Gayk H., Ghaye B., Daly AF., Beckers A., 2004 Hormonal and biochemical normalization and tumour shrinkage induced by anti-parathyroid hormone immunotherapy in a patient with metastatic parathyroid carcinoma, J. Clin Endocrinol Metab., 2004, 89, 3413–3420

[18] Marx S., Spiegel AM., Skarulis MC., Doppman JL., Collins FS., Liotta LA., Multiple endocrine neoplasia type 1: clinical and genetic topics, Ann Intern Med., 1998 , 129(6), 484-94

[19] Baris D., Gridley G., Ron E, Weiderpass E., Mellemkjaer L., Ekbom A., Olsen JH., Baron JA., Fraumeni JF Jr., Acromegaly and cancer risk: a cohort study in Sweden and Denmark, Cancer Causes Control., 2002, 13(5), 395-400

[20] White H.D., Ahmad A.M., Durham B.H., Chandran S., Patwala A., Fraser W.D., and Vora J.P., Effect of Active Acromegaly and Its Treatment on Parathyroid Circadian Rhythmicity and Parathyroid Target-Organ Sensitivity, J. Clin. Endocrinol. Metab., 2006, 91, 913 - 919

[21] Orme S.M., McNally R.J.Q., Cartwright R.A., Belchetz P.E., Mortality and Cancer Incidence in Acromegaly: A Retrospective Cohort Study, J. Clin. Endocrinol. Metab., 1998, 83, 2730 - 2734

[22] Utiger R. D., Treatment of Acromegaly, N Engl J Med., 2000, 342,1210-1211

[23] S Yamada S., T Sano T., L Stefaneanu L., K Kovacs K., T Aiba T., S Sawano S.,ShishibaY., Endocrine and morphological study of a clinically silent somatotroph adenoma of the human pituitary, J. Clin. Endocrinol. Metab., 1993, 76, 352 - 356

[24] Sakharova A.A., Dimaraki E.V., Chandler W.F., Barkan A.L., Clinically Silent Somatotropinomas May Be Biochemically Active, J. Clin. Endocrinol. Metab., 2005, 90, 2117 - 2121

[25] Yamada S., Sano T., Stefaneanu L., Kovacs K., Aiba T., Sawano S., Shishiba Y., Endocrine and morphological study of a clinically silent somatotroph adenoma of the human pituitary, J Clin Endocrinol Metab., 1993, 76, 352–356

[26] Klibanski A., Zervas N.T., Kovacs K., Ridgway E.C., Clinically silent hypersecretion of growth hormone in patients with pituitary tumours, J Neurosurg., 1987, 66, 806–811

[27] Kalavalapalli S., Reid H, Kane J., Buckler H., Trainer P., Heald AH., Silent growth hormone secreting pituitary adenomas. IGF-1 is not sufficient to exclude growth hormone excess, Ann. Of Cli. Biochem., 2007, 44, 89-93