CASE REPORT

Application of MR spectroscopy and treatment approaches in a patient with extrapituitary growth hormone secreting macroadenoma

Duško Kozić [1], Milica Medić-Stojanoska [2], Jelena Ostojić [1], Ljubomir Popović [3] & Nada Vučković [4]

1. Institute of Oncology, Diagnostic Imaging Center, Sremska Kamenica, Serbia
2. Clinic of Endocrinology and Metabolic Disorders, Clinical Center of Voivodina, Novi Sad, Serbia
3. Clinic of Neurosurgery, Clinical Center of Voivodina, Novi Sad, Serbia
4. Department of Pathology, University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia

Correspondence to: Dr. Jelena Ostojić
Institute of Oncology, Diagnostic Imaging Center
Institutski put 4, 21204 Sremska Kamenica, Serbia
PHONE: +381 21 480 5607
FAX: +381 21 661 3741
EMAIL: ostojic.jelena@onko.onk.ns.ac.yu

Submitted: September 6, 2007 *Accepted: October 9, 2007*

Key words: **extrapituitary growth hormone secreting adenoma; MR spectroscopy**

Neuroendocrinol Lett 2007; **28**(5):560–564 **PMID:** 17984954 NEL280507C01

Abstract

MR spectroscopy (MRS) of hormonally active pituitary adenomas has not been published in literature. We report MR imaging and spectroscopy findings in a 41-year-old man with extrapituitary growth hormone-secreting adenoma. Application of the single voxel proton MRS, SE 135 technique, with voxel size 11×11×11 mm, revealed the elevated choline peak (resonance at 3.2 ppm) in the paramedial aspect of the tumor, while no metabolic activity in the mentioned region was noted using the same method 11 months after Lanreotide treatment. Elevation of choline peak in functional pituitary adenomas could represent an active marker of cellular proliferation, compatible with increased hormonal activity.

INTRODUCTION

Ectopic pituitary adenomas are rare neoplasms, most frequently arising along the cranio-pharyngeal migration path of the Rathke's pouch. Approximately 80 extrapituitary adenomas have been reported in literature, most of them located in the sphenoid sinus and suprasellar region. Majority of ectopic pituitary adenomas are either non-functional or adrenocorticotropin (ACTH) secreting, while only several reports of patients with growth hormone (GH) producing extrapituitary adenoma are available [1–4,6,10]. Numerous studies regarding MR spectroscopic characteristics of malignant brain tumors are available in literature. MR spectroscopic features of hormonally active pituitary adenomas are however unknown. The purpose of this report is to present the appearance of MR spectrum of ectopic GH secreting macroadenoma before and after the Lanreotide treatment.

REPORT

A 41-year-old man noticed gradual enlargement of his nose, lips, hands and feet over the past 7 years and complained on headaches and infrequent periods of blurred vision. Physical examination revealed the acromegalic appearance and hypertension (160/80 mmHg). Other clinical findings were unremarkable. Laboratory examination revealed

Table. Plasma hormone levels on admission and after surgical procedure, radiation therapy and Lanreotide treatment.

	Levels on addmission	Levels after neurosurgical procedure	Levels 30 days after radiation therapy	Levels after 11 months of continous Lanreotide treatment	Normal range
GH	>40	36.9	33.7	Morning 7.17 Before noon 8.43 Evening 6.6	0.06–5.0 ng/ml
IGF-I	1128	1 054	747	472	101–267 ng/ml
FSH	5.6	5.0	6.48	9.44	1.5–12.4 IU/l
LH	1.8	1.8	2.1	3.2	1.7–8.6 IU/l
TESTOSTERONE	9.2	9.2	8.0	9.84	9.9–27.8 nmol/l
PROLACTIN	Morning 9.7 Evening 12	14.0	16	16.2	4.6–21.4 ng/ml
FREE T4	17.7	19.4	18.9	19.6	12–22 pmol/l
FREE T3	4.2	4.7	4.5	4.27	2.8–7.1 pmol/l
TSH	1.71	1.01	1.44	1.41	0.32–5.16 mIU/l
ACTH	40	51.4	35.1	32.3	<46pg/ml
CORTISOL	Morning 522 Evening 81	299.6 90.6	457.5 102.0	431 156	171–650 nmol/l 64–330 nmol/l

the presence of GH and IGF-I elevation. Absence of GH suppression during oral glucose tolerance test (54.3-43.3-44.8-39.1 ng/ml) was evident. Low-normal levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were found, associated with decreased level of testosterone, suggesting the presence of central hypogonadism. The remaining hormonal activity of the adenohypophysis was preserved (Table). No functional abnormalities of neurohypophysis were detected. The visual acuity and visual fields were normal. MR examination revealed the presence of a huge mass involving the sellar floor, invading the clivus and extending into the sphenoid sinus and the region of the posterior ethmoid cells, measuring 40 mm in antero-posterior and 53 mm in oblique cranio-caudal dimension. Bilateral parasellar spreading of the tumor was seen with dislocation of the cavernous segments of the internal carotid arteries, more prominent on the left, associated with no consequent disturbance of the flow. The pituitary stalk was deviated to the left. The tissue of the pituitary gland was completely intact and clearly demarcated from the tumor (Figure 1). The tumor was partly extirpated via a trans-sphenoidal approach. The presence of unaffected pituitary tissue was confirmed during the procedure. The histological examination of the obtained specimen showed the features of pituitary adenoma. No clinical improvement was noted after the partial tumor reduction. Slightly decreased, but still high levels of GH and IGF-I

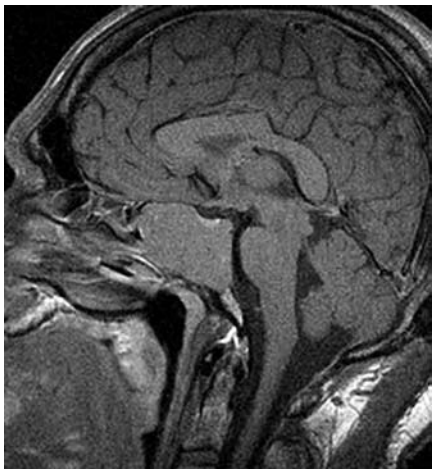

Figure 1. Huge ectopic GH-secreting macroadenoma involving the sellar floor, invading the clivus and extending into the sphenoid sinus and the region of the posterior ethmoid cells, associated with parasellar extension, but intact pituitary gland tissue.

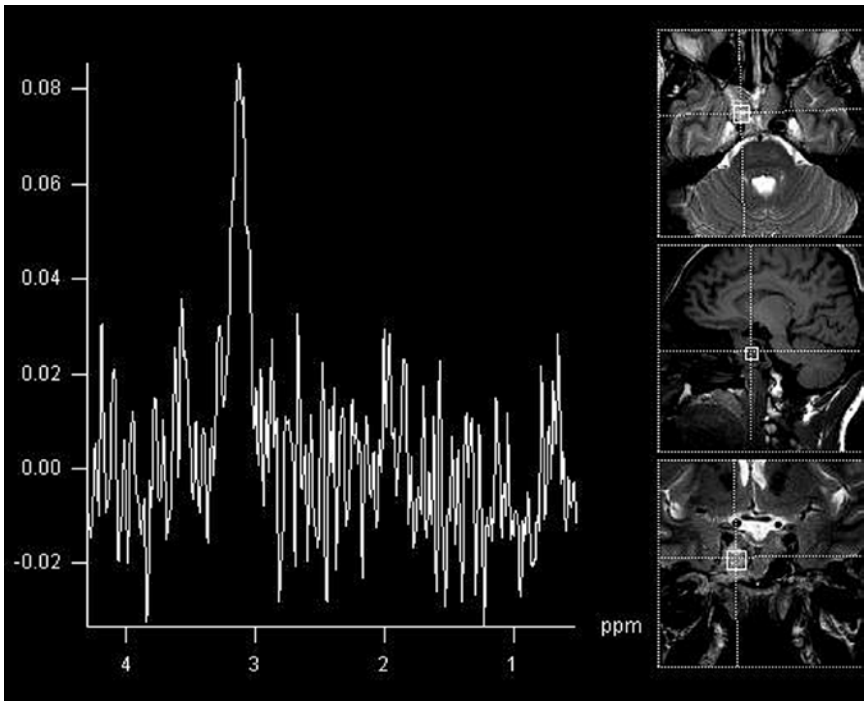

Figure 2. Single voxel spectroscopy SE 135 technique with voxel size 11×11×11 mm, revealed the elevated choline peak in the medial aspect of the tumor, compatible with hormonal activity.

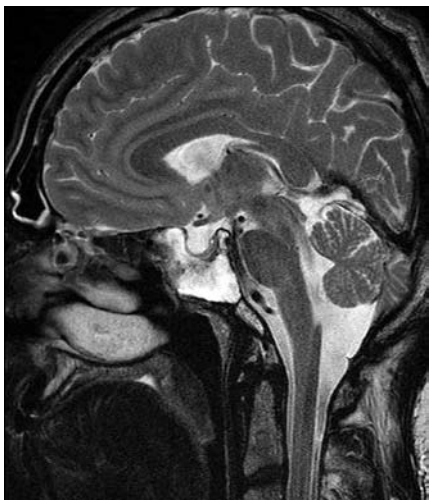

Figure 3. Marked shrinkage of the tumor associated with cystic degeneration, compatible with positive effect of the Lanreotide treatment.

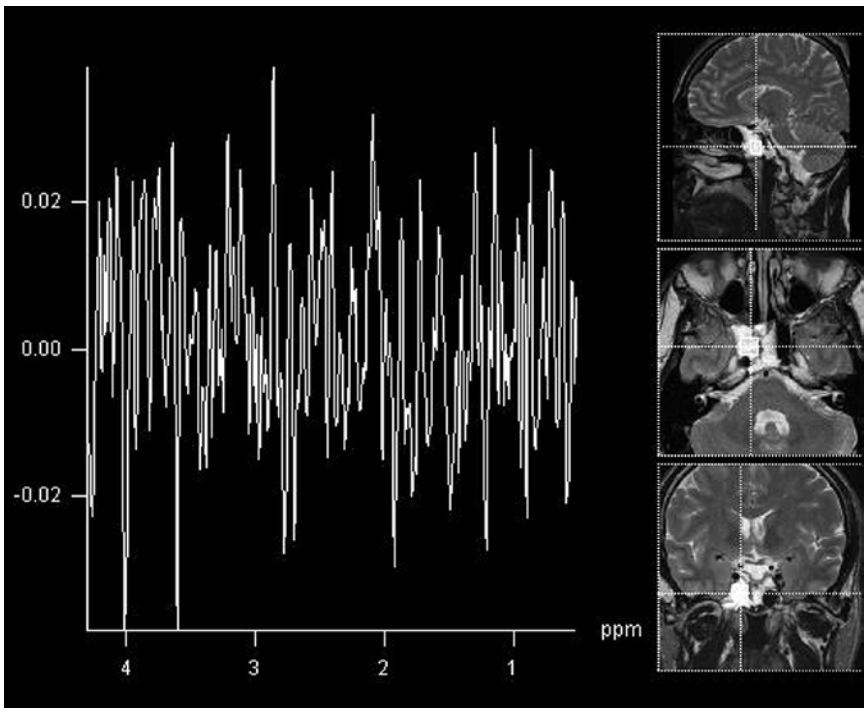

Figure 4. Post Lanreotide treatment single voxel MRS (SE 135 technique) with voxel (size 11×11×11 mm) positioned at the place of previously elevated choline peak, revealed electronic noise only.

and the signs of central hypogonadism were evident. The remaining hormonal activity of the adenohypophysis was normal (Table). Conformal radiation therapy was indicated and performed (total dose 54 Gy/30 fractions). Slightly decreased, but still high levels of GH and IGF-I and the signs of central hypogonadism without any signs of clinical improvement were evident thirty days after radiation therapy. The remaining hormonal activity of the adenohypophysis was normal (Table). MR examination, performed after surgical procedure and radiation therapy revealed partial reduction of the tumor size, measuring 33 mm in antero-posterior and 43 mm in oblique cranio-caudal dimension. Application of the single voxel spectroscopy SE 135 technique

with voxel size 11×11×11 mm, revealed the elevated choline peak in the paramedial aspect of the tumor (Figure 2). Owing to persistent acromegaly and no signs of clinical improvement, the treatment with long-acting somatostatin analogue (Lanreotide, Somatulin autogel 120 mg subcutaneously/4weeks) was initiated. Marked clinical improvement with significant regression of acromegaly, associated with marked decrease of GH and IGF-I levels was observed after 11 months of treatment. The improvement of FSH, LH and testosterone levels was also evident (Table). MR examination revealed the presence of a marked shrinkage of the tumor associated with cystic degeneration of the adenoma, consistent with the positive effect of the medical treatment (Figure 3). Several repeated applications of the single voxel MRS (SE 135 technique) with voxel (size 11×11×11 mm) positioned at the place of previously elevated choline peak, revealed electronic noise only – a complete lack of any metabolites (Figure 4).

DISCUSSION

In order to establish the diagnosis of extrasellar pituitary adenoma, adenomatous transformation of the ectopic pituitary remnants has to disclose no morphologic continuity with the normal appearing intrasellar content [10,12]. Since the sellar floor was secondarily involved in our patient, we decided to use the more accurate term of extrapituitary instead of ectopic macroadenoma. MR examination is a reliable diagnostic modality capable to clearly distinguish ectopic pituitary adenomas from aggressive intrasellar tumors with suprasellar, parasellar or infrasellar extension. Maximal surgical reduction followed by external radiotherapy is usually considered as a treatment of choice for ectopic pituitary macroadenomas. The endocrine nature of these neoplasms could frequently be detected only after immunohistochemical evaluation of the extirpated tissue [12]. The hormonal secretion of the ectopic adenoma, clearly identified in the blood sample, like the one in our patient, has been rarely assessed. The determination of IGF-I level is important since they may reflect more reliably the acromegalic activity compared to GH. The level of circulating GH can fluctuate during the day and its level in the serum might be within normal range during measurement. The somatostatine long-acting analogue octreotide has been used as adjunctive therapy for GH-secreting adenomas and has resulted in normalization of GH levels in 30–45% of patients [2,6]. Pungale et al. have reported a presence of pharyngeal pituitary non-functioning (somatostatin receptor scintigraphy positive) adenoma in a 60 year-old woman, with normal morphology of the intrasellar gland. A massive tumor shrinkage was observed after a successful treatment with long-acting preparation of octreotide [12]. The impressive tumor mass reduction in our patient associated with significant T2 elevation of the tumor tissue, compatible with cystic and necrotic changes, has also been observed.

Spectroscopic studies of intraaxial brain tumors showed significant role in characterization of different histological types and in prediction of the degree of malignancy. The proton MR spectroscopy of benign extraaxial cranial lesions has not been usually performed since enough information important for clinical or surgical purposes are obtained from conventional MR imaging. Therefore, no MR spectroscopy studies regarding the metabolic profile of pituitary adenomas are available in literature. The best of our knowledge, MRS has only been performed in one patient with chromophobic adenoma and in one patient with craniopharyngeoma in the proton MR spectroscopy study of Poptani et al. where 120 patients with intraaxial or extraaxial brain tumors were included. Chromophobic adenoma exhibited only noise and no metabolic resonances were observed, while the presence of "lactate only spectrum" was detected in the patient with craniopharyngeoma [11].

In our patient, the presence of elevated choline peak on single-voxel MRS within the adenoma, noted before the Lanreotide treatment, seems to be most consistent with the region of the hormonally active part of the mass. Choline and its derivates most likely represent important constituents of the phospholipid metabolism of cell membranes (Mahashari, Miller). Choline peak at 3.2 ppm consists of choline, phosphocholine, glycerophosphocholine and phosphatidylcholine. This metabolite is found to be increased both in benign and malignant tumors. This elevation is associated with increased membrane phospholipid biosynthesis and represents an active marker for cellular proliferation and/or cell density [5,7,13]. Elevated choline peak is therefore not specific for GH overproduction and concentration of this metabolite increases in all quickly proliferaling tumors, not necessarily hormonally active. Compared to intraaxial brain tumors, a complete absence of creatine and N-acetyl aspartate (marker of neuronal activity) peaks was evident, giving the typical extraaxial tumor spectroscopic pattern – ("choline only" spectrum). No peak of lactate, a product of anaerobic glycolysis, was also noted. The presence of "noise only" spectrum using the same methodology after the continuous Lanreotide administration, seems to correlate with significant interruption of GH secretion, that is in accordance with posttreatment decrease of the hormone level just minimally above the normal range.

However, single-voxel MRS failed to detect biochemical abnormality within the tumor since IGF-I level, although markedly reduced, was still significantly above the normal range. This diagnostic modality, although useful and relatively rapid for obtaining the information regarding the metabolic activity, is undoubtedly unable to contribute in defining the special heterogeneity of the mass. Multivoxel MRS may, however, contribute in adding new information, relevant not only to diagnostic purposes, but also to the clinical management [9]. The importance of multivoxel MRS in routine practice is still under investigation. However there is a reason to expect that this modality could provide the information relevant

to choosing the adequate treatment, like in our patient, the possible targeting of active tumor particle during radiosurgical procedure.

REFERENCES

1 Anand VK, Osborne CM, Harkey HL III. Infiltrative clival pituitary adenoma of ectopic origin. Otolaryngology – Head and Neck Surgery. 1993; **108**: 178–183.
2 Davis SH, Laws ER, Ilstrup DM, Speed JK, Caruso M, Shaw EG, Abbond CF, Scheithauer BW, Root LM, Schleck C. Results of surgical treatment for growth-hormone-secreting pituitary adenomas. Journal of Neurosurgery. 1993; **79**: 70–75.
3 Hori E, Akai T, Kurimoto M, Hirashima Y, Endo S. Growth hormone-secreting pituitary adenoma confined to the sphenoid sinus associated with normal sized empty sella. Journal of Clinical Neuroscience. 2002; 1996–1999.
4 Hou L, Harshbarger T, Herrick MK, Tse V. Suprasellar adrenocorticotropic hormone-secreting ectopic pituitary adenoma: case report and literature review. Neurosurgery. 2002; **50**: 618–625.
5 Kozic D, Nagulic M, Samardzic M, Ostojic J, Milic-Rasic V, Skender Gazibara M, Sener RN. Malignant peripheral nerve sheath tumor of the oculomotor nerve. Acta Radiologica. 2006; **47**: 595–598.
6 Madonna D, Kendler A, Soliman AM. Ectopic growth hormone-secreting pituitary adenoma in the sphenoid sinus. Annals of otology, rhinology and laryngology. 2001; **110**: 99–101.
7 Maheshwari S, Mukherji S, Neelon B, Schiro S, Fatterpekar G, Stone J, Castillo M. The choline/creatine ratio in five benign neoplasms: comparison with squamous cell carcinoma by use of in vitro MR spectroscopy. Am J Neuroradiol. 2000; **21**: 1930–1935.
8 Miller BL. A review of chemical issues in 1-H NMR spectroscopy: N-acetyl-aspartate, creatine and choline. NMR Biomed. 1991; **4**: 47–52.
9 Nelson S. Multivoxel magnetic resonance spectroscopy of brain tumors. Molecular Cancer therapeutics. 2003; **2**: 497–507.
10 Pasquini E, Faustini-Fustini M, Sciarreta V, Saggese D, Roncaroli F, Serra D, Frank G. Ectopic TSH-secreting pituitary adenoma of the vomerosphenoidal junction. European Journal of Endocrinology. 2003; **148**: 253–257.
11 Poptani H, Gupta R, Roy R, Pandey R, Jain V, Chhabra D. Characterization of intraaxial mass lesions with in vivo proton MR spectroscopy. Am J Neuroradiol. 1995; **16**: 1593–1603.
12 Pungale N, Waridel F, Bouzourene H, Boubaker A, Pungale M, Gaillard R, Gomez F. Pharyngeal pituitary non-functioning adenoma with normal intra-sellar gland: massive tumor shrinkage on octreotide therapy. European Journal of Endocrinology. 2003; **148**: 357–364.
13 Ruiz-Cabello J, Cohen JS. Phospholipid metabolites as indicators of cancer cell function. NMR Biomed. 1992; **5**: 226–233.