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CASE REPORT

A case of fugitive acromegaly, initially presented as invasive prolactinoma

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Abstract Fugitive acromegaly is most commonly caused by pituitary acidophil stem cell adenomas, and is characterized by a relatively short clinical history, a large and locally invasive tumor, and relatively low hormonal activity. Here, we report an unusual case of fugitive acromegaly that initially presented as invasive prolactinoma. A 48-year-old man with a huge pituitary mass extending to the suprasellar area was referred to our hospital in December 2007. He had undergone transsphenoidal surgery in November 1999 because of a large invasive prolactinoma. The tumor had grown progressively, despite therapy with dopamine agonists. Subtle features of acromegaly were noted and serum IGF-1 levels were high (733 ng/ml). An oral glucose tolerance test revealed that basal and nadir levels of growth hormone (GH) were 1.56 and 1 ng/ml, respectively. As a therapeutic trial, long-acting octreotide (20 mg IM, monthly) was added, and the tumor size markedly reduced within 6 months on magnetic resonance imaging examination. Immunohistochemical staining of the tumor tissue obtained at the surgery in 1999 showed positive staining for GH and prolactin (PRL). Double immunofluorescence staining showed a mixed positivity for GH and PRL in the majority of tumor cells; however, the two hormones colocalized in a minority of tumor cells, indicating that the tumor was composed of three different cell types (GH, PRL, and GH/PRL). The diagnosis of fugitive acromegaly was initially overlooked in this patient because of normal serum GH levels and a lack of acromegalic features, although histological evidence for GH production was present. IGF-1 determinations would be helpful for the diagnosis of fugitive acromegaly.

Keywords Fugitive acromegaly · Pituitary tumor producing GH and PRL · IGF-1

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Introduction

Acromegaly is an acquired progressive disorder caused by excessive production of growth hormone (GH), which is characterized by somatic disfigurement and serious complicating conditions. Because of its insidious onset and slow progression, the diagnosis is usually made after 4–10 years of disease progression [1]. Biochemical evidence of the disease can be found in most patients, and strict criteria for its diagnosis have been developed [2]. However, some patients may exhibit physical stigmata of acromegaly without apparent biochemical evidence, which is called fugitive acromegaly [3]. Pituitary tumors causing acromegaly can be divided into several histological types.

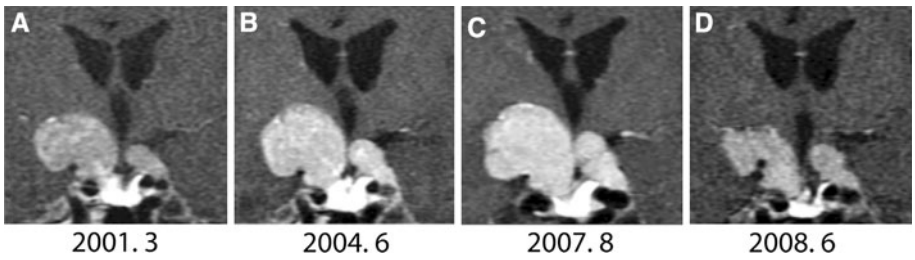

Fig. 1 The change in sellar mass according to medication. The patient had been taking bromocriptine after undergoing transsphenoidal adenomectomy in November 1999. Bromocriptine was administered until August 2005. An MRI (**a**) in March 2001 showed the remaining suprasellar mass after subtotal resection. An MRI (**b**) in June 2004 showed a recurrent tumor in the right suprasellar and left parasellar region involving the cavernous sinus. Cabergoline was administered for 2 years; however, an MRI (**c**) in August 2007 showed no interval change compared to March 2006. From January 2008, the patient was coadministered with Sandostatin LAR, and the tumor mass (**d**) had markedly decreased after 5 months

These include somatotroph adenoma, mixed somatotroph and lactotroph adenoma, mammosomatotroph adenoma, acidophil stem cell tumors, and plurihormonal tumors. Fugitive acromegaly is most commonly caused by acidophil stem cell tumors, from which GH and prolactin (PRL) are cosecreted.

Here, we report a 48-year-old male patient with fugitive acromegaly caused by a mixed GH/PRL adenoma. He had transsphenoidal neurosurgery 10 years previously; however, the disease recurred despite therapy with dopamine agonists.

Case description

A 48-year-old male patient was referred from Neurosurgery to Endocrinology in December 2007 for a huge pituitary mass extending to the suprasellar area and cavernous sinus. He had recently been treated with a dopamine agonist (DA) for giant prolactinoma because he had undergone transsphenoidal resection of a tumor in November 1999. His initial symptom was visual disturbance, which was first noted in 1995, after which it was gradually aggravated. In June 1999, an ophthalmologist advised him to visit a neurosurgeon, suspecting a pituitary tumor was compressing the optic nerve. Initial magnetic resonance imaging (MRI) showed a large pituitary sellar tumor invading the left cavernous sinus. Preoperative endocrinological analysis was performed and showed: serum PRL, 321 ng/ml (normal: 0–10 ng/ml); GH, 0.38 ng/ml (normal: 0–9.5 ng/ml); adrenocorticotropic hormone, 42.3 pg/ml (normal: 10–60 pg/ml); cortisol, 78.31 ng/ml (normal: 70–250 ng/ml); thyroid stimulating hormone, 2.1 μIU/ml (normal: 0.4–3.1 μIU/ml); free thyroxine, 1.65 ng/dl (normal: 0.73–1.95 ng/dl); luteinizing hormone, 2.59 mIU/ml (normal, adult male: 1.0–5.3 mIU/ml); follicle stimulating hormone, 1.3 mIU/ml (normal, adult male: 1.3–8.1 mIU/ml); and testosterone, 122.79 ng/dl (normal, male: 245–1836 ng/dl). The patient underwent transfenoidal surgery in November 1999 with subtotal resection of the tumor was performed. The pathology of the tumor revealed it was a pituitary adenoma. Immediately after the operation, serum PRL levels decreased to 139 ng/ml. The patient subsequently received treatment with bromocriptine (a dopamine D2 receptor agonist), and visited the outpatient clinic. Postoperative GH levels were 1.99 ng/ml; however, IGF-1 levels were not checked at that time. In October 2000, serum PRL had decreased to 37.35 ng/ml.

A sellar MRI examination 2 years after surgery showed that the pituitary macroadenoma had slightly increased in size and extended to the bilateral cavernous sinus encasing the right internal carotid artery (Fig. 1a). Another operation could not be performed because it was impossible to remove the tumor completely due to the risk of causing loss of vision. The tumor remained unchanged in June 2004 (Fig. 1b). Cabergoline (a long-acting D2 receptor agonist) treatment was started in August 2005. In an MRI study performed in March 2006, an increase in the size of the suprasellar mass was noted, especially the left portion, along with invasion of the left cavernous sinus and compression of the optic chiasm. At that time, serum PRL levels were 80.35 ng/ml without symptoms, and the patient was treated with a weekly dose of 2.5 mg cabergoline. During the follow-up, serum PRL levels progressively increased to 97.27 ng/ml and MRI showed no changes (Fig. 1c) despite the high dose of cabergoline (3 mg per week). The patient was then referred to Endocrinology in December 2007.

Upon referral, he was found to exhibit mild acromegalic features, such as thickened fingers (Fig. 2), a widened nose, pronounced eyebrows, broadened extremities, and obvious cheekbones, leading to the suspicion of acromegaly. His serum IGF-1 level was 733 ng/ml and an oral glucose tolerance test with 75 g glucose was performed. The basal GH level was 1.56 ng/ml and nadir GH level was 1 ng/ml. A subcutaneous injection of octreotide (a short-acting

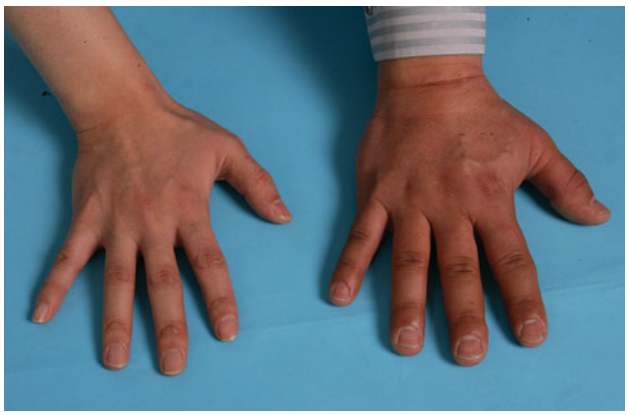

Fig. 2 The patient's hand (*right*) was enlarged and the fingers were thickened and stubby compared with the hand of a normal adult male (*left*)

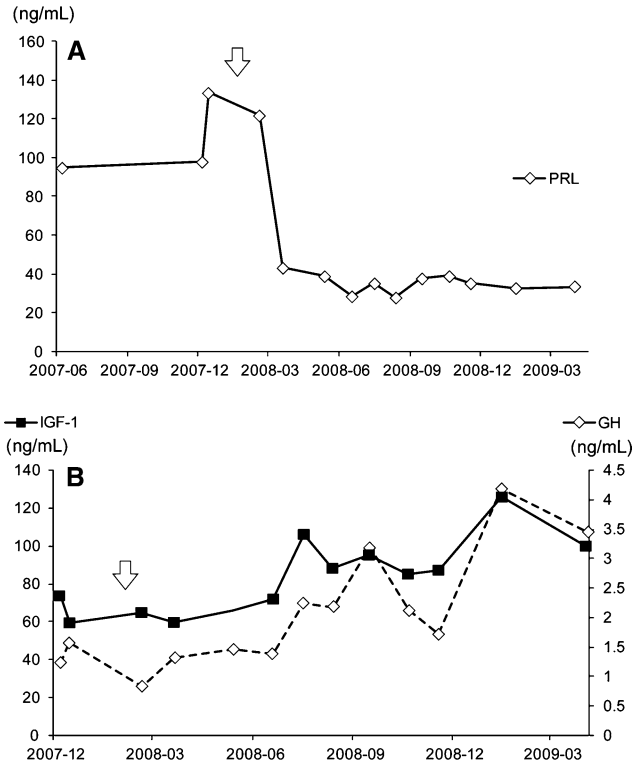

Fig. 3 The change in hormone levels and medications. This figure shows the PRL **a** levels of the patient from June 2007 to April 2009, and GH and IGF-1 **b** levels of the patient from December 2007 to April 2009. The white arrows indicate the time from the beginning of the administration of Sandostatin LAR. **a** Serum PRL levels tended to decrease after Sandostatin LAR was administered. **b** The dotted line indicates the GH hormone levels and the black line indicates the IGF-1 levels. Serum IGF-1 levels remained high despite treatment with Sandostatin LAR and cabergoline

synthetic somatostatin octreotide analog, 0.1 mg) reduced serum GH levels from 1.15 to 0.32 ng/ml (0 and 60 min after administration, respectively). Under the tentative diagnosis of fugitive acromegaly, a long-acting octreotide (Sandostatin LAR (long-acting release); 20 mg, intramuscularly, monthly) was given to the patient from January 2008. One month later, the dose of Sandostatin was increased to 30 mg per month because serum IGF-1 levels remained high (642.6 ng/ml). Four months later, in June 2008, PRL levels decreased to 28.06 ng/ml, although serum IGF-1 levels remained high (715.2 ng/ml). Moreover, a sellar MRI examination performed in June 2008 showed a marked reduction in the size of the pituitary adenoma, which decreased in volume by more than 35% compared to 5 months previously (Fig. 1d). Furthermore, the dose of cabergoline was increased to 3 mg per week because of persistently high IGF-1 levels. Figures 3 and 4 indicate the change in hormone levels and the medication history of the patient, respectively.

We analyzed tumor tissue that was processed in paraffin blocks at the time of initial surgery in 1999. Immunohistochemical analyses revealed a mixed adenoma that stained positive for GH (Fig. 5b) and PRL (Fig. 5c). Double immunostaining showed partial colocalization of the two hormones in a minor proportion (less than 5%) of tumor cells (Fig. 5d, e, f).

Discussion

This report is about a patient with fugitive acromegaly caused by a GH/PRL-secreting adenoma that was initially diagnosed as invasive prolactinoma because serum GH levels were within the normal range and no definite features of acromegaly were observed at the time of admission. Although acromegaly is caused by benign monoclonal pituitary somatotrophinomas in over 95% of patients [1], fugitive acromegaly is often related to acidophil stem cell adenomas (ASCAs). GH/PRL adenomas, except for ASCAs, are marked by acromegaly or gigantism [4] rather than fugitive acromegaly. Horvath et al. reported a 4.3% prevalence of ASCA in 347 surgically removed pituitary tumors [3, 5]. Clinically, ASCAs are more aggressive than other adenomas, and are always invasive and mostly resistant to drugs [4]. Since immunohistochemistry in ASCA may be similar to mixed somatotroph–lactotroph adenomas [3, 6], the detection of giant mitochondria using electron microscopy is essential to confirm the diagnosis of ASCA.

Although our immunohistochemical study revealed that the tumor tissue was composed of three cell types (GH, PRL, and GH/PRL), the tumor in this patient appeared to be closer to an ASCA than a mixed somatotroph–lactotroph adenoma or mammosomatotroph adenoma. This tumor showed invasive and relapsing features. Moreover, PRL immunostaining was more dominant than GH immunostaining. Failure to normalize PRL levels has been

Bromocriptine	Cabergoline	Cabergoline 2mg/week + LAR 20mg	Cabergoline 2mg/week + LAR 30mg	Cabergoline 3mg/week + LAR 30mg	Cabergoline 1mg/2days + LAR 30mg
1999/12~	2005/8~	2008/1~	2008/2~	2008/5~	2008/6~

Fig. 4 The medication history of the patient from December 1999 to April 2009. The dose of medications administered before 2007 is incomplete. In the case of bromocriptine, the minimum and maximum dose were 5 mg three times a day and 11.25 mg four times a day, respectively. Cabergoline doses, ranging from 1 mg to 3 mg per week, were administered until December 2007, and then Sandostatin LAR was added to cabergoline (2 mg per week) in January 2008, and administered for 15 months

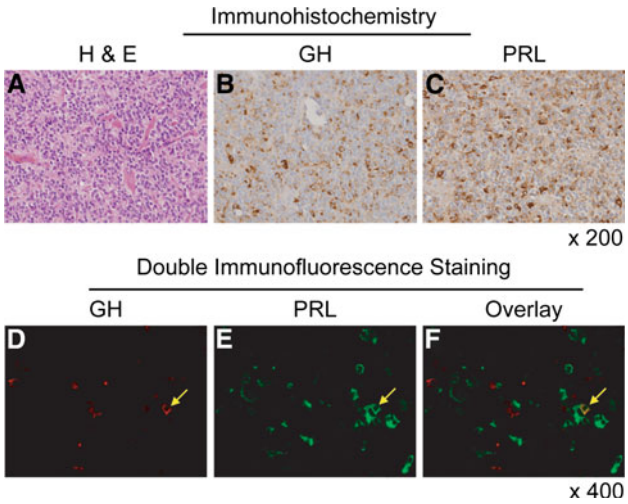

Fig. 5 Hematoxylin & eosin (H&E) stain (**a**), immunohistochemistry (**b**–**c**), and double immunofluorescence (**d**–**f**). H&E staining revealed a cellular mass with well-developed sinusoidal capillaries, consistent with typical pituitary adenomas (**a**). Immunohistochemical staining revealed that tumor cells were positive for GH (**b**) and PRL (**c**). Double immunofluorescence revealed that the tumor mass consisted of three cell populations: GH-positive (**d**) and PRL-positive (**e**) cells, and cells that were positive for both hormones (**f**). The yellow arrows indicate those cells that were positive for both PRL and GH

reported in only 11% of patients with prolactinoma who were treated with cabergoline [7]. In addition, mammosomatotroph adenomas are more sensitive to dopamine agonists (DAs) than ASCAs. Nevertheless, in our patient, tumor size was reduced with octreotide LAR treatment, suggesting that a certain component of the tumor might have somatostatin receptors responding to the somatostatin analog. Interestingly, serum IGF-1 levels remained high, which might be because of the heterogeneity of tumor populations that are resistant to somatostatin analogs (SSAs) or DAs.

IGF-1 might be the cause of the clinical features of acromegaly; thus, when acromegaly occurs without elevation of GH levels, one should pay attention to IGF-1 levels [8]. Swearingen et al. showed that the persistence of elevated IGF-1 levels was associated with a higher risk of mortality, regardless of GH levels [9]. Plasma IGF-1 concentrations also correlate better with the clinical manifestations of acromegaly than plasma GH levels, and successful treatment is associated with normalization of IGF-1 plasma concentrations [10]. For these reasons, only checking GH levels might overlook the presence of fugitive acromegaly.

Experimental therapies could be future alternatives for treating GH/PRL-secreting adenomas that show unclear characteristics. Pegvisomant, a GH receptor antagonist, is reportedly effective in normalizing IGF-1 levels in patients with acromegaly who are refractory to DAs and/or SSAs [11–13]. Rosiglitazone, which functions as a PPAR-γ agonist, also decreased GH and IGF-I secretion and improved acromegalic features; thus, PPAR-γ may be a novel molecular target in the treatment of pituitary tumors that are unresponsive to DAs and/or SSAs [14]. In contrast, there are medications that focus on DA-resistant prolactinomas. Although the incidence of estrogen receptors (ERs) on recurrent prolactinomas is significantly lower than the number of receptors on the original tumor [15, 16], Caronti et al. showed that tamoxifen has an inhibitory effect on cell proliferation of human pituitary adenomas, independent of ER expression [17, 18]. Therefore, antiestrogens are worth using for GH/PRL-secreting adenomas. Gefitinib, an epidermal growth factor receptor inhibitor, was recently reported to control PRL secretion and tumor burden in DA-resistant prolactinomas as well as in tamoxifen-resistant breast cancers [19, 20]. We performed immunostaining for ERα and ERβ; however, these receptors were not detected.

In GH/PRL-secreting adenomas, especially when accompanied by fugitive acromegaly, it is relatively difficult to make a correct diagnosis in the initial stages of the disease. Therefore, it is essential to carefully check a patient's general hormone levels, and the nature of invasive tumor growth should be kept in mind when managing patients because the possibility of ASCAs cannot be excluded [21]. In addition, according to the histological study we conducted on tissue that was obtained in 1999, the GH positivity was scattered and focalized. Considering the responsiveness of the tumor to SSAs, GH secreted from the regrowing tumor stimulated IGF-1 production, resulting in the gradual development of acromegalic features over many years. Although basal GH levels may be within the normal range, an IGF-1 measurement should be performed as a screening and follow-up test. If serum IGF-1 levels remain high, despite DAs and SSAs treatment, the

possibility of progression into cancer should also be considered. It remains unclear which treatment is effective for GH/PRL-secreting adenomas. Therefore, a more aggressive treatment plan should be established. In the future, it will be interesting to determine the relationship between serum IGF-1 levels and ASCAs.

Disclosure The authors have nothing to disclose.

References

1. P. Chanson, S. Salenave, Acromegaly. Orphanet J. Rare Dis. **3**, 17 (2008)
2. A. Avramidis, S.A. Polyzos, Z. Efstathiadou, M. Kita, Sustained clinical inactivity and stabilization of GH/IGF-1 levels in an acromegalic patient after discontinuation of somatostatin analogue treatment. Endocr. J. **55**(2), 351–357 (2008)
3. E. Horvath, K. Kovacs, W. Singer, H.S. Smyth, D.W. Killinger, C. Erzin, M.H. Weiss, Acidophil stem cell adenoma of the human pituitary: clinicopathologic analysis of 15 cases. Cancer **47**(4), 761–771 (1981)
4. W. Saeger, D.K. Ludecke, M. Buchfelder, R. Fahlbusch, H.J. Quabbe, S. Petersenn, Pathohistological classification of pituitary tumors: 10 years of experience with the German Pituitary Tumor Registry. Eur. J. Endocrinol. **156**(2), 203–216 (2007)
5. H.G. Maheshwari, T.R. Prezant, V. Herman-Bonert, H. Shahinian, K. Kovacs, S. Melmed, Long-acting peptidomimergic control of gigantism caused by pituitary acidophilic stem cell adenoma. J. Clin. Endocrinol. Metab. **85**(9), 3409–3416 (2000)
6. S.L. Asa, K. Kovacs, E. Horvath, W. Singer, H.S. Smyth, Hormone secretion in vitro by plurihormonal pituitary adenomas of the acidophil cell line. J. Clin. Endocrinol. Metab. **75**(1), 68–75 (1992)
7. M.E. Molitch, Dopamine resistance of prolactinomas. Pituitary **6**(1), 19–27 (2003)
8. G. Mohr, Z.P. Chen, M. Schweitzer, Acromegaly with normal basal growth hormone levels. Can. J. Neurol. Sci. **24**(3), 250–253 (1997)
9. B. Swearingen, F.G. Barker 2nd, L. Katznelson, B.M. Biller, S. Grinspoon, A. Klibanski, N. Moayeri, P.M. Black, N.T. Zervas, Long-term mortality after transsphenoidal surgery and adjunctive therapy for acromegaly. J. Clin. Endocrinol. Metab. **83**(10), 3419–3426 (1998)
10. D.R. Clemmons, J.J. Van Wyk, E.C. Ridgway, B. Kliman, R.N. Kjellberg, L.E. Underwood, Evaluation of acromegaly by radioimmunoassay of somatomedin-C. N. Engl. J. Med. **301**(21), 1138–1142 (1979)
11. A. Colao, R. Pivonello, R.S. Auriemma, M.C. De Martino, M. Bidlingmaier, F. Briganti, F. Tortora, P. Burman, I.A. Kourides, C.J. Strasburger, G. Lombardi, Efficacy of 12-month treatment with the GH receptor antagonist pegvisomant in patients with acromegaly resistant to long-term, high-dose somatostatin analog treatment: effect on IGF-I levels, tumor mass, hypertension and glucose tolerance. Eur. J. Endocrinol. **154**(3), 467–477 (2006)
12. C.E. Higham, T.T. Chung, J. Lawrance, W.M. Drake, P.J. Trainer, Long-term experience of pegvisomant therapy as a treatment for acromegaly. Clin Endocrinol (Oxf) **71**(1), 86–91 (2009)
13. M. Gradiser, M. Matovinovic, M. Vrkljan, Decrease in growth hormone and insulin-like growth factor (IGF)-1 release and amelioration of acromegaly features after rosiglitazone treatment of type 2 diabetes mellitus a patient with acromegaly. Croat. Med. J. **48**(1), 87–91 (2007)
14. A.P. Heaney, M. Fernando, S. Melmed, PPAR-gamma receptor ligands: novel therapy for pituitary adenomas. J. Clin. Invest. **111**(9), 1381–1388 (2003)
15. G.J. Kaptain, N.E. Simmons, T.D. Alden, M.B. Lopes, M.L. Vance, E.R. Laws, Estrogen receptors in prolactinomas: a clinico-pathological study. Pituitary **1**(2), 91–98 (1999)
16. S.W. Lamberts, L.J. Hofland, Future treatment strategies of aggressive pituitary tumors. Pituitary **12**(3), 261–264 (2009)
17. B. Caronti, G. Palladini, M.G. Bevilacqua, E. Petrangeli, B. Fraioli, G. Cantore, G. Tamburrano, C.M. Carapella, M.L. Jaffrain-Rea, Effects of 17 beta-estradiol, progesterone and tamoxifen on in vitro proliferation of human pituitary adenomas: correlation with specific cellular receptors. Tumour Biol. **14**(1), 59–68 (1993)
18. I. Vourliotaki, I.E. Bonapart, C. Stamataki, E.M. Tsapakis, C. Saridaki, A case of a prolactinoma resistant to dopamine agonists. Hormones (Athens) **4**(3), 165–170 (2005)
19. G. Vlotides, E. Siegel, I. Donangelo, S. Gutman, S.G. Ren, S. Melmed, Rat prolactinoma cell growth regulation by epidermal growth factor receptor ligands. Cancer Res. **68**(15), 6377–6386 (2008)
20. E. Gutteridge, A. Agrawal, R. Nicholson, K.L. Cheung, J. Robertson, J. Gee, The effects of gefitinib in tamoxifen resistant and hormone insensitive breast cancer: a phase II study. Int. J. Cancer. **126**(8), 1806–1816 (2010)
21. K. Kageyama, T. Nigawara, Y. Kamata, T. Takahashi, J. Anzai, S. Suzuki, Y.R. Osamura, T. Suda, A case of macroprolactinoma with subclinical growth hormone production. Endocr. J. **49**(1), 41–47 (2002)