A null cell adenoma of the pituitary detected seven years after removal of a prolactinoma. Recurrence or de novo tumourigenesis?

Hajime Watanobe, Kenji Kudo, Toshimi Okushima, Yohshoh Fukita and Kazuo Takebe

Third and First Departments of Internal Medicine, Hirosaki University School of Medicine, Hirosaki, Aomori, Japan

Abstract. We report an extremely unusual case of prolactinoma which emerged at recurrence as a null cell adenoma. A 53-year-old woman sought medical attention for progressive visual loss and headache. A pituitary tumour was detected by a computed tomographic scan, and hyperprolactinemia was noted. The tumour, removed by a transfrontal surgery, was a chromophobe adenoma, and immunohistochemically the adenoma cells were selectively positive for PRL, which indicated a prolactinoma. Postoperatively, her plasma PRL level was normalized. Seven years later, she noted blurred vision and again sought medical attention. A CT scan demonstrated recurrence of a pituitary tumour. On this occasion, however, she was not hyperprolactinemic. She underwent again a transfrontal resection of the pituitary tumour. Its histology was again a chromophobe adenoma, but the adenoma cells showed no positive immunostaining for any anterior pituitary hormone including PRL, which indicated a null cell adenoma. We have no clear explanation of the pathogenesis underlying her very unusual course. However, null cells (assuming that the original tumour was a mixed adenoma) left behind at the first surgery, or unidentified hypothalamic and/or pituitary derangements might possibly have been responsible for the recurrence. We learned from this patient that recurrent pituitary adenomas may not necessarily have the same endocrine features as did the original tumours. This information appears to make a valid clinical point, because if hormone levels alone are followed after pituitary surgery, recurrent pituitary tumours may be overlooked.

Pituitary tumours may recur, mostly within the first 10 years after the initial treatment (1-5). Recurrence rate following surgery alone has been reported to be 16-30% (1-3); a combined surgery and radiation therapy reduces the rate to 3-15% (1-5). It is known that irradiation of the pituitary fossa may induce the development of a sellar or parasellar tumour of non-pituitary origin, such as an osteogenic sarcoma (6), fibrosarcoma (7,8) or glioma (9). Apart from such radiation oncogenesis, it is commonly held that most, if not all, recurrent pituitary tumours are expected to show the same histopathological and endocrine features as did the original tumours. This observation is clinically important in the follow-up of patients with functioning pituitary tumours, because re-increases in hormone levels may suggest tumour regrowth.

In this context, a previous case report by Tera¬moto et al. (10) appears extremely unusual. Their patient was initially diagnosed to harbour a GH-producing adenoma and was operated on, but 7.5 years later it recurred as a null cell adenoma. Recently, we have experienced a similar case of pituitary tumour. Our patient was initially diagnosed to have a prolactinoma and operated on, but it recurred 7 years later as a null cell adenoma. We attempted to explain the pathogenesis of this unusual transformation.

Methods

Hormone assays
Determination of PRL, LH, FSH, TSH, ACTH, GH, cortisol and IGF-I were performed by RIAs using commercial kits. In the PRL kit used (Daiichi Radioisotope Co, Tokyo, Japan), V-L-S # 2 (NIH) was employed as a reference preparation.
Immunohistochemical staining
Paraffin-embedded specimens of pituitary adenomas obtained at surgery were immunostained for PRL, LH, FSH, TSH, ACTH and GH by an indirect peroxidase technique. For this study, old blocks of the first tumour were re-cut at the same time as the second tumour, and the same reagents were used to stain both tumours (immunohistology kits purchased from BioGenex Laboratories, Dublin, CA). The specificities of the primary antibodies against the six pituitary hormones were established by performing control immunostains, consisting in the application of antibodies pre-incubated with excess antigens, and the application of non-immune rabbit serum in place of the primary antibodies.

Case report
In May 1982, a 53-year-old woman sought medical attention for progressive visual loss and headache. A computed tomographic (CT) scan of her sella turcica pointed to a pituitary tumour presenting ring enhancement. Routine non-hormonal laboratory tests were unremarkable, but endocrine examinations revealed hyperprolactinemia (105-120 µg/l). Detailed hormonal data are shown in Table 1. Responsiveness of plasma PRL (110 µg/l (basal) \(\rightarrow\) 160 µg/l (peak); 1.5-fold increase) to TRH (500 µg) was markedly lower than that of 10 normal postmenopausal women (4.5-9.0 times the basal). Secretory reserves of LH and FSH were markedly impaired, and that of GH was slightly impaired. TSH, ACTH and cortisol secretions were within the normal range. She underwent a transfrontal pituitary surgery. A round adenoma with a diameter of 12 mm was visualized in the anterior pituitary lobe. The tumour had a large cystic component in the centre in agreement with its ring enhancement on the CT scan. The adenoma, not impinging on the pituitary stalk, was macroscopically completely removed. Histopathological examinations revealed that the adenoma consisted exclusively of chromophobic cells. Immunohistochemically, 40-50% of the adenoma cells were positive for PRL (Fig. 1, top), and no other pituitary hormone staining was present. A postoperative CT scan of the sella turcica did not suggest the presence of a residual tumour tissue. Within two weeks of surgery, her basal plasma PRL was restored to normal (5-8 µg/l), and its responsiveness to TRH (7.1 µg/l (basal) \(\rightarrow\) 29.1 µg/l (peak); 4.1-fold increase) also became near normal, although the absolute peak level was clearly lower than normal (Table 1). Secretory reserve of LH was further diminished compared with the

<table>
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<th>Plasma hormone level¹</th>
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<th>1st Surgery</th>
<th>2nd Surgery</th>
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<tr>
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1) Basal or basal and stimulated plasma hormone levels at iv administrations of TRH (500 µg, for PRL and TSH), GnRH (100 µg, for LH and FSH) and arginine (30 g in 30 min, for GH). Maximum responses were obtained 15-30 min postadministration for all of the five anterior pituitary hormones.
2) Determined in 10 normal postmenopausal women (aged 46-60 years).
pre-operative value, and those of ACTH and cortisol also became subnormal (Table 1), which subsequently necessitated substitution with hydrocortisone (20 mg/day). Secretory reserves of the remaining hormones examined were similar to the pre-operative values (Table 1). These findings suggested that her pituitary adenoma was a prolactinoma. No other known causes of hyperprolactinemia (11) were present. Her vision and visual fields were gradually improved without additional radiation therapy.

In November 1989, she noted blurred vision and again sought medical attention. Visual fields showed a bitemporal defect. A CT scan demonstrated recurrence of a pituitary tumour with lateral and suprasellar extensions. Hormonal examinations revealed, however, that she was not hyperprolactinemic (3.5-4.0 µg/l) on this occasion. As shown in Table 1, on TRH test the plasma PRL increased with a normal amplitude (3.7 µg/l (basal) → 19 µg/l (peak); 5.1-fold increase), although the absolute peak level was markedly lower than normal. Secretory reserves of the remaining pituitary hormones were largely similar to those after the first surgery (Table 1). She underwent again a transfrontal resection of the pituitary tumour. The tumour (31 mm in its largest diameter) was nearly completely removed, and its histology was again a chromophobe adenoma. The pituitary stalk was not visualized. Immunohistochemically, the adenoma cells were negative for all of the pituitary hormones including PRL (Fig. 1, bottom), which indicated a null cell adenoma. Hormonal data after this second surgery were very similar to those before surgery (Table 1). Thereafter, the patient received a total irradiation of 46 Gy to the sellar and parasellar areas. Her subsequent course was unevent-

Fig. 1.
Immunohistochemical staining for PRL of the pituitary adenomas obtained at the first (top) and second (bottom) operation. Forty to 50% of adenoma cells from the first tumour were positive for PRL (top), but the second tumour was negative for PRL (bottom). Magnification, × 100. Bar indicates 50 µm.
ful, although her vision and visual fields remained stable. She is now closely followed-up as an out-patient.

Discussion
That the first pituitary tumour of this patient probably was a prolactinoma is supported by several lines of circumstantial evidence. First, the elevated plasma PRL concentration before the first surgery was restored to normal after adenomectomy. Second, the surgery did not reveal impingement by the adenoma on the pituitary stalk that could cause hyperprolactinemia by preventing PRL-inhibiting factor(s) from reaching the pituitary (11). Third, the observed poor PRL response to TRH was not only indicative of a prolactinoma, but a usual finding (11). In addition, the most convincing support for the diagnosis of prolactinoma was the immunohistochemical demonstration of the selective immunostaining for PRL of the adenoma cells. However, this diagnosis may not be in full agreement with her mildly or moderately elevated PRL levels (105-120 µg/l). This is because it is generally accepted that macroprolactinomas are usually associated with plasma PRL concentrations of 200 µg/l or greater (11). This discrepancy may, however, be explained by the existence of the large cystic component in the first tumour.

In turn, that the second pituitary tumour detected 7 years after the first operation was a null cell adenoma, is convincingly supported by the immunohistochemical findings. None of the pituitary hormones examined, including PRL, was positively stained in the adenoma cells, nor any of them had high levels in the general circulation. Of the hormonal data, it is to be noted that after the first operation and before and after the second, she showed a normal or near normal PRL responsiveness to TRH, although the absolute peak level of PRL was clearly subnormal. This finding suggests that after the first surgery most PRL in the general circulation originated in normal lactotropes. However, the impairment of PRL reserve indicates that normal pituitary tissues may have been massively removed by surgery together with the tumour, and/or already compressed prior to surgery. This may be in agreement with the postoperative marked decrease in LH and ACTH reserves and/or the pre-operatively demonstrated decrease in LH, FSH and GH reserves.

It is generally accepted that most, if not all, recurrent pituitary tumours retain the same biological natures as did the original tumours. In this context, our patient appears extremely unusual in that two biologically different pituitary tumours developed 7 years apart. Although we have no clear explanation of the pathogenesis underlying her very unusual clinical course, several possibilities may be offered. First, the prolactinoma might have originally contained a small subset of null cells, and such cells left behind at surgery might have later acquired a significant mitotic activity and proliferated. Unfortunately, the in vitro studies on the first tumour were not enough to confirm or deny this possibility. However, recent studies have reported that a single pituitary adenoma may occasionally comprise various compositions of different cell types (12). In a similar case report of an acromegalic patient by Teramoto et al. (10), they speculated that irradiation might possibly have induced the proliferation of residual null cells. In our patient, however, radiation therapy was not performed for the first tumour. Therefore, even if the remnant null cells played a pivotal role in the recurrence, the trigger for their proliferation is unknown. A second possibility is that the relapse may have represented new tumour formation (de novo tumourigenesis) rather than the late regrowth of tumour remnants, perhaps due to inherent hypothalamic and/or pituitary abnormalities. Although this possibility is interesting and may point to a new way of perception of pituitary pathology, it is no more than a speculation at present.

We are unable to think of any other pathogenetic factor which may have contributed to the unusual endocrine presentation of this patient. Perusal of the literature did not reveal any previous case of prolactinoma showing a similar postoperative course. However, our patient with prolactinoma, together with the only one reported acromegalic patient (10), allowed us to learn that recurrent pituitary adenomas may not necessarily have the same endocrine features as did the original tumours. This information appears to make a valid clinical point, because it implies that if hormone levels alone are followed after pituitary surgery, recurrent tumours may be overlooked.

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References


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Dr Hajime Watanobe,
Third Department of Internal Medicine,
Hirotsaki University School of Medicine,
5 Zaifu-cho,
Hirotsaki,
Aomori 036,
Japan.