An intrasellar pituitary adenoma–gangliocytoma presenting as acromegaly

Melissa H Lee¹, Penelope McKelvie², Balasubramanian Krishnamurthy¹, Yi Yuen Wang² and Carmela Caputo¹

Departments of ¹Endocrinology and Diabetes, ²Anatomical Pathology, St Vincent’s Hospital Melbourne, Victoria, Australia, and ³Department of Neurosurgery and Surgery, The University of Melbourne, St Vincent’s Hospital Melbourne, Victoria, Australia

Summary

Most cases of acromegaly are due to growth hormone (GH)-secreting pituitary adenomas arising from somatotroph cells. Mixed pituitary adenoma and gangliocytoma tumours are rare and typically associated with hormonal hypersecretion, most commonly GH excess. Differentiating these mixed tumours from conventional pituitary adenomas can be difficult pre-operatively, and careful histological analysis after surgical resection is key to differentiating the two entities. There is little literature addressing the possible mechanisms for the development of mixed pituitary adenoma–gangliocytomas; however, several hypotheses have been proposed. It still remains unclear if these mixed tumours differ from a clinical perspective to pituitary adenomas; however, the additional neural component of the gangliocytoma does not appear to modify the aggressiveness or risk of recurrence after surgical resection. We report a unique case of acromegaly secondary to a mixed GH-secreting pituitary adenoma, co-existing with an intrasellar gangliocytoma.

Learning points:

• Acromegaly due to a mixed GH-secreting pituitary adenoma and intrasellar gangliocytoma is rare.
• These mixed tumours cannot be distinguished easily from ordinary pituitary adenomas on the basis of clinical, endocrine or neuroradiologic findings, and histological analysis is required for a definitive diagnosis.
• Surgical resection is usually sufficient to provide cure, without the need for adjuvant therapy.
• These mixed tumours appear to have a good prognosis although the natural history is not well defined.
• The pathogenesis of these mixed tumours remains debatable, and ongoing research is required.

Background

Acromegaly is most commonly due to a growth hormone (GH)-secreting pituitary adenoma arising from somatotroph cells, with a minority (<2%) of cases due to growth hormone-releasing hormone (GHRH) hypersecretion (1). Mixed pituitary adenoma and gangliocytoma tumours are rare, with less than 40 cases reported in the literature (2, 3). Pituitary gangliocytomas are benign and slow-growing tumours, composed of mature neurons resembling hypothalamic ganglion cells. Most intra-pituitary gangliocytomas are associated with hormonal hypersecretion, most commonly GH excess (4), and associated endocrine syndromes. The diagnosis of mixed pituitary adenoma–gangliocytomas is challenging and requires careful histological analysis. This unusual histopathological finding does not appear to change clinical practice and the risk of recurrence seems to be low; however, we recognise that the long-term outcomes of these mixed tumours are not well described. We describe...
a rare case of acromegaly secondary to a mixed pituitary adenoma–gangliocytoma and review the literature about this uncommon condition and its proposed pathogenesis.

Case presentation

A 60-year-old otherwise healthy male was referred for assessment of a pituitary mass found following investigation of chronic headaches over the preceding two years. MRI revealed a 1.9 × 1.7 × 2.4 cm pituitary adenoma with invasion into the right cavernous sinus (Knosp grade 3) but no compression of the optic chiasm (Fig. 1).

Clinical history was suggestive of acromegaly, with subtle change in his physical features over the preceding years. On examination, he had coarse facial features, increased interdental spaces, macroglossia, increased breadth of feet and hands, skin tags and excessive palmar sweating. There were no other symptoms or signs of endocrine dysfunction or family history of endocrinopathies.

Investigations

Static pituitary hormonal testing showed an elevated IGF1 level of 122 nmol/L (normal range: 11–29 nmol/L) and elevated morning GH level of 5.2 µg/L (normal range: 0–1.7 µg/L). His remaining anterior pituitary hormones were normal (morning cortisol: 242 nmol/L, TSH: 0.55 µU/mL, free T4: 15 pmol/L, prolactin: 178 IU/L, LH: 1.4 IU/L, FSH: 3.81 IU/L and testosterone: 8.8 nmol/L). His GH failed to suppress after a 75 g oral glucose tolerance test (OGTT), with a GH nadir of 3.1 µg/L. Based on these findings, a diagnosis of acromegaly due to a GH-producing pituitary macroadenoma was made.

Treatment

He underwent endoscopic transphenoidal surgery with complete resection of the lesion. Intraoperatively, the surgeon noted a different macroscopic appearance from a typical pituitary adenoma (Fig. 2). This tumour was red-purple in colour with a firm and rubbery texture, in comparison with a pituitary adenoma that tends to have a white-cream colour and soft consistency. Histopathology demonstrated a composite chromophobe pituitary adenoma with ganglion cells in a dense neutrophil matrix, consistent with a gangliocytoma (Fig. 3). The adenoma cells stained weakly for GH and the ganglion cells stained for neuN and synaptophysin. The Ki67 index was <2%, and P53 showed rare reactive nuclei.

Outcome and follow-up

Post-operatively, his hypothalamic–pituitary–adrenal axis remained intact with no glucocorticoid replacement requirement. A 3-month post-operative OGTT demonstrated adequate suppression of GH (GH nadir: 0.3 µg/L); however, a discordant but declining IGF1 level
of 44 nmol/L. Post-operative MRI at 12 months showed no evidence of residual adenoma. He remains in clinical and biochemical remission, with a repeat OGTT 18 months post-operatively demonstrating suppression of GH (GH nadir, 0.2 µg/L) and a normalised IGF1 level of 17 nmol/L.

Discussion

The first case of a mixed pituitary adenoma–gangliocytoma was reported in 1926, and since then, two literature reviews have described less than 40 cases of these mixed tumours (2, 3). These are a subset of ‘collision tumours’, defined as histologically different tumours close to each other. Occurrence in the sellar region is rare. They are biphasic tumours, composed of both adenomatous proliferation of adenohypophyseal cells and well-differentiated ganglion cells within a neuropil (4). There appears to be a strong female preponderance and most present as macroadenomas (4). Most are associated with GH excess (75%); however, these mixed pituitary tumours have also been reported with hyperprolactinaemia, Cushing's disease and Rathke's cleft cyst (4, 5). Sixty-five per cent of pituitary gangliocytomas are accompanied with pituitary adenomas, as demonstrated in this case (6).

Gangliocytomas, classified as WHO grade 1 tumours, are a benign and slow-growing differentiated form of neuroblastic tumours of the sympathetic nerve fibres. Most commonly, these tumours are found extracranially, with an incidence of 0.5% at intracranial sites (6). Intracranially, they are typically distributed in the third ventricle, frontal and temporal lobes and are rarely found in the sellar region. 40–60% of gangliocytomas occur in adolescents and young adults, but as seen in this case, can occur at any age. Although rare, gangliocytomas may also be implicated in genetic syndromes. For example, dysplastic gangliocytomas of the cerebellum can be associated with PTEN germline mutations linked to Cowden syndrome.

Mixed pituitary adenoma–gangliocytomas are difficult to distinguish from a pituitary adenoma on neuroimaging (6) as there are no specific features to differentiate the two tumours. The density, signal and contrast manifestations are similar on MRI (7), and thus, they are often mistaken for a pituitary adenoma pre-operatively. As noted by the neurosurgeon, their macroscopic appearances can be useful to distinguish the two entities; however, a definitive diagnosis is based on histological studies. The proportion of neuronal and adenohypophysial components can vary considerably and the ganglion cells can vary in both size and neuropil-like components. Immunohistochemistry (IHC) staining of the adenoma cells is typically positive for GH in cases of acromegaly.

The histogenesis of mixed pituitary adenoma–gangliocytomas remains unclear; however, multiple hypotheses have been proposed. Firstly, hypothalamic hormonal stimulation (e.g. GHRH) by the gangliocytoma may lead to somatotroph hyperplasia and GH hypersecretion (8). In multiple case reports, GHRH has been identified in ganglion cells. Due to lack of availability of IHC staining with anti-GHRH antibody, this could not be performed for our patient. Alternatively, there may be a common origin of both neuronal and adenohypophysial components from uncommitted stem/progenitor cells capable of multidirectional differentiation (4). Furthermore, gangliocytomas may represent neuronal differentiation of pre-existing pituitary adenoma cells which exhibits some developmental plasticity, evidenced by immunopositivity of neuronal components for cytokeratin and adenomatous tissue for neurofilament (1, 4, 5). Lastly, two tumours of different origins may occur coincidentally, with the development of a pituitary adenoma in a pre-existing neuronal choristoma; and neuronal elements then derived from abnormal migration of hypothalamic neurons within the adenohypophysial parenchyma during the early phase of embryogenesis (4). The histology from our case would suggest that the mechanisms leading to the development of these mixed tumours are due to a common embryonic progenitor cell origin or neuronal differentiation within an established pituitary adenoma.
The management of pituitary adenoma–gangliocytomas is similar to that of other pituitary lesions. It is a non-metastasising tumour; therefore, after surgical resection, adjuvant therapy is not usually required. The natural history and remission rates of these tumours is not well defined as many case reports are historical, have scanty descriptions of post-operative biochemical and tumour persistence and have varied follow-up times. Thus, it is not possible to assess meaningful success rates post-surgical resection. To date, there has only been one report of biochemical recurrence and tumour progression in a patient treated with radiotherapy 17 years prior, who did not undergo surgical resection (9). In those patients with mixed pituitary adenoma–gangliocytomas who underwent transsphenoidal surgery, the longest follow-up reported in case reports and case series has been 3 years (10). Eighteen months after surgery, our patient remains in remission with no evidence of tumour recurrence. There are no reports that these lesions behave aggressively or that they are malignant. Furthermore, gangliocytomas do not respond to radiotherapy or somatostatin analogues as these are slow-growing tumours (1). However, theoretically, one indication for adjuvant radiotherapy for these mixed tumours may be if there was persistent GH excess post-operatively as the hormonal hypersecretion is responsive to radiotherapy (1). Several case reports have trialled somatostatin analogues pre-operatively with disappointing results, with a lack of significant shrinkage of the tumour mass. An explanation for this may be that there is a lack of somatostatin receptors in the ganglionic cells (10); however, this needs to be further explored in future studies as the expression of somatostatin receptors in these tumours has not been well examined.

In conclusion, we describe a rare case of a mixed GH-secreting pituitary adenoma and gangliocytoma presenting with acromegaly. Careful histological analysis is key to differentiating these composite tumours from the typical GH-secreting pituitary adenomas. It remains unclear if these tumours differ from a clinical perspective to conventional pituitary adenomas. The histogenesis still remains controversial, and ongoing research is required to understand its pathophysiology and draw any firm conclusions to assist and guide clinical practice.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
Written informed consent has been received.

Author contribution statement
MHL, an endocrinology advanced trainee at St Vincent’s Hospital, provided the initial manuscript draft. B K and C C, specialist endocrinologists, have provided clinical details and managed this patient during the course of his treatment. Y Y W is a consultant neurosurgeon specialising in pituitary surgery who performed the surgery and has managed this patient during the course of his treatment. P M, a consultant pathologist, reviewed the histopathology and performed the immunohistochemistry staining for this patient. All authors were actively involved in the writing of this manuscript, and approved the final version of the manuscript.

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