Acromegaly due to a mixed Growth Hormone secreting adenoma-gangliocytoma – A rare cause of GH excess

South Tees Hospitals NHS Foundation Trust

Max Wood, Anil Varma[2], David Scoones[3], Sath Nag[1]

Departments of Endocrinology[1], Surgery[2] and pathology[3], The James Cooks University Hospital, Middlesborough, United Kingdom

1 Introduction

Adeno-gangliocytomas are a rare form of pituitary tumour, with less than 40 cases being described in the literature worldwide.[1] They are mixed lesions consisting of adenocytic and gangliocytic components.[2,3] These tumours have in most cases been found in patients with features of acromegaly, although less frequently can present with cushingnoid features or hyperprolactinemia.[3] Uncomplicated pituitary adenomas and neural gangliocytomas tend to exhibit a high degree of cellular differentiation and low proliferative potential. As such they are often slow benign tumours that may be resolved with complete surgical resection.[2] The clinical course of mixed Adeno-gangliocytomas are however not well characterised. The histogenesis of Adeno-gangliocytoms also remains unclear although the histological specimens show histogenetic distinction between the two components.[2,4] Reports on these rare tumours can provide insight in to the effectiveness of current treatment modalities.

2 Case Details

A 64-year-old man presented with symptoms of urolithiasis and was admitted for stone fragmentation and ureteric stent insertion. During anaesthetic recovery he developed sudden onset severe frontal headache with nausea, photophobia and visual field disturbance. Urgent cranial CT scanning showed pituitary apoplexy. Subsequent pituitary MRI scan confirmed a pituitary macroadenoma with evidence of tumoral haemorrhage. [Figure 1] On examination he had classical clinical features of acromegaly including prognathism, interdental separation, large hands and macroglossia.

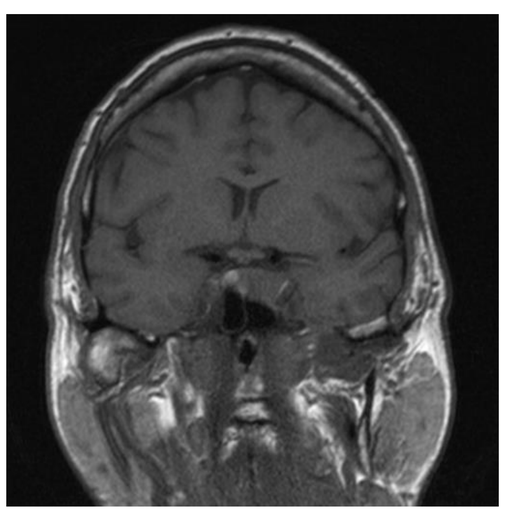

Figure 1: Pituitary macroadenoma measuring 14.1 mm with area of haemorrhage in the right side of the gland indicating apoplexy.

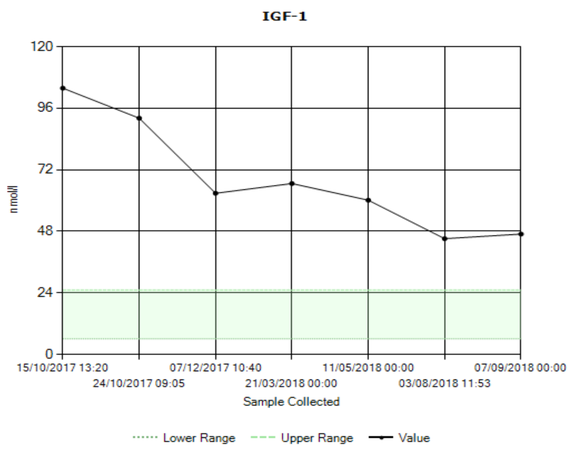

Figure 3: Graph depicting serum IGF-1 levels against date collected. There is an over 50% drop in IGF-1 levels from 103.8 nmol/l to 46.9nmol/l post treatment with surgery and adjuvant radiotherapy and somatostatin analougue therapy.

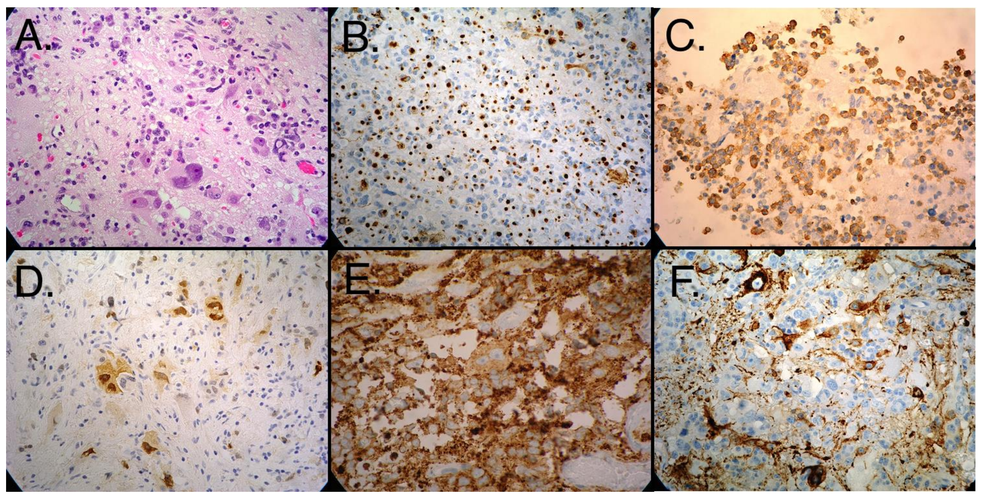

Figure 2: Immunostaining of adeno-gangliocytoma histology sections . A. H and E staining of histological specimen. B. Adenocytes expressing HGH. C. Adenocytes expressing AE1/AE3 paranuclear dot like staining D. NueN expression in gangliocytes. E. Synaptophysin expression in gangliocytes. F. Prolactin expression in gangliocytes.

Investigations showed raised GH (5.32 mcg/l) and IGF-1 (103.8 nmol/l) with non-suppression of GH levels during an OGTT. Thyroid and gonadal axes were normal. Pituitary apoplexy was managed with Dexamethasone in the acute phase. Endoscopic trans-sphenoidal pituitary surgery was undertaken electively. At operation a hard fibrous tumour was noted and decompression of the macroadenoma was undertaken. Resection was incomplete due to the fibrous nature of the tumour and risk to surrounding structures. Histology of the excised tumour showed a composite lesion consisting of adenocytes and ganglion cells confirming the diagnosis of an adeno-gangliocytoma. The adenocytic component is shown with paranuclear dot like staining for AE1/AE3 [Figure 2,B] and expressing HGH [Figure 2,C], in keeping with a sparsely granulated GH adenoma. The ganglion cell component demonstrated ganglion cells expressing NueN [Figure 2,D] and Synaptophysin [Figure on immunostaining. The ganglion cell component also showed strong staining for other hormonal markers including prolactin [Figure 2,F]

Post operative assessment showed a 20% overall reduction in tumour size on MRI and evidence of residual GH hypersecretion. [Figure 3] Adjuvant treatment with pituitary radiotherapy along with somatostatin analogue therapy in the interim was effective in conjunction with surgery in reducing the IGF-1 level from 103.8 nmol/l on initial measurement to 46.9 nmol/l post surgery. [Figure 3]

3 Discussion

Ganglion cell containing tumours within the pituitary gland have been rarely described in the literature.[5] Mixed adenoma and ganglion cell containing tumours, also described as collision sellar lesions, were found to account for 0.52% of lesions in a series of 1322 sellar tumours.[3] Another study quoted a figure of 0.55%, highlighting the rarity of these tumours.[3]

The origins of these tumours remains controversial. Theories include the neuronal metaplasia of pituitary adenoma cells in to ganglionic cells with evidence that trans-differentiation may occur with adenoma cells being shown to express receptors for nerve growth factor as well as neuronal components including cytokeratin supporting this hypothesis.[1,2,3] Another hypothesis stipulates that there is common stem cell progenitor for both adenoma and ganglionic cells could account for these mixed lesions.[1,2,3] A third theory involves abnormal migration of neuronal tissue during embryogenesis accounting for these lesions.[1,2,3] In our histological sample, the ganglion cell component demonstrated staining for hormonal markers including prolactin [Figure 2,F]. A previous report by Li et al. also demonstrated pituitary hormones within the neuronal element of the tumours including prolactin and ACTH.[5]This lends support to the theory that at least some of the lesions described are the result of trans-differentiation of adenocytes into neuronal cells.

In this case, the fibrous nature of the tumour made resection very difficult and only 20% of the tumour could be safely resected. The treatment did result in an over 50% reduction in IGF-1 levels in conjunction with radiotherapy and somatostatin analogue therapy, demonstrating the effectiveness of the treatment modality in reducing the initial tumour mass. [Figure 3].

4 Conclusion

Conventional macro pituitary adenomas and neural gangliocytomas tend to respond well to surgery and may not need adjuvant therapy post surgery. The risk of recurrence in mixed Adeno-gangliocytomas is not well characterised. Although initial tumour reduction seems effective, further research is needed to determine the role of adjuvant medical therapies in this group of patients if complete surgical resection is achieved.

References: **1.** Lee MH, McKelvie P, Krishnamurthy B, Wang YY, Caputo C (2017), "An intrasellar Pituitary adenoma-gangliocytoma presenting as acromegaly", *Endocrinology, Diabetes and Metabolism Case Reports*, 17-0035. **2.** Wang Z, Li P, Zhou Q, Yang Z, Liu P (2016), "Gangliocytoma combined with pituitary adenoma: Report of three cases and literature review", *Transl. Neurosci*, 2(3): 165-171. **3.** Koutourousiou M, Kontogeorgos G, Wesseling P, Grotenhuis AJ, Seretis A (2010), "Collision Sellar Lesions: experience with eight cases and review of the literature", *Pituitary,* 13(1): 8-17. **4.** Pace V, Perentes E (2001), "Mixed Pituitary adenoma-gangliocytoma in a female albino rat", *Acta Neuropthol* 101: 277-280. **5.** Li JY, Racadot M, Kujas M, Kourdri M, Peillon F, Racdot J (1989), "Immunocytochemistry of four mixed pituitary adenomas and intrasellar gangliocytomas associated with different clinical symptoms: Acromegaly, amenorrhoea, Cushings disease and isolated tumoral symdrome", *Acta Neuropathologica*, 77(3): 320-328