Published in final edited form as:

Clin Neuropathol. 2021 May 01; 40(3): 160–164. doi:10.5414/NP301343.

A Case Report of Metastatic Renal Cell Carcinoma Causing Corticobasal Syndrome

Melanie P. Jensen¹, James B. Rowe², Kieren S. J. Allinson³

¹Department of Pathology, Charing Cross Hospital, Imperial College Healthcare NHS Trust, London, UK

²Department of Clinical Neurosciences, University of Cambridge, and Cambridge University Hospital NHS Trust, Cambridge, UK

³Addenbrooke's Hospital, Department of Pathology, Cambridge, UK

Abstract

We present a case report of a patient with a history of renal cell carcinoma in which corticobasal syndrome had been diagnosed ante-mortem. However distinguishing features of corticobasal degeneration pathology were absent at post-mortem. Instead, neuropathological examination revealed features consistent with the patient's history of renal cell carcinoma: micrometastatic renal cell carcinoma in cerebellar and cerebral white matter, including within the gyral white matter of the primary motor and somatosensory cortices. There was also Purkinje cell loss and mild lymphocytic inflammation in the cerebellum, but the significance of this was unclear. A number of 'corticobasal degeneration mimics' have been described in the literature; but micrometastatic carcinoma causing corticobasal syndrome is a novel finding. This case expands the range of clinical disorders which may mimic corticobasal degeneration to include micrometastatic carcinoma.

Keywords

Renal cell carcinoma; corticobasal syndrome; case study

Introduction

Corticobasal syndrome (CBS) is a progressive parkinsonian syndrome characterised by insidious onset extrapyramidal motor features (typically asymmetric limb rigidity/akinesia, dystonia, or myoclonus) and cognitive dysfunction (including alien limb, apraxia, aphasia, executive or visuospatial functions), often with dysphagia in later stages [1]. The clinical diagnosis of CBS can be challenging, because of the heterogeneity of symptoms and signs [2]. Although most cases are caused by the primary tauopathy of corticobasal degeneration,

Correspondence to: Melanie P. Jensen.

Corresponding author: Melanie Jensen, Postal address: Department of Pathology, Charing Cross Hospital, Fulham Palace Road, London, UK, m.jensen@cantab.net, Telephone: 020 3311 1234.

Conflicts of interest

There are no conflicts of interest to disclose.

there are many mimics, including Alzheimer's disease, Lewy-body disease and progressive supranuclear palsy [3]. The present report documents a case report of metastatic renal cell carcinoma mimicking corticobasal degeneration, highlighting the importance of considering broad differential aetiologies in CBS-type presentations.

Case report

A 63-year old right-handed man presented with a 7-year history of declining mobility, indistinct speech, behavioural and cognitive change. His wife described new apathy, use of profanities and emotional lability. The patient had also lost a significant amount of weight despite a normal appetite, which is sometimes attributable to dysphagia in CBS but not in this case. He had a past history of hypertension and asthma with no hospital admissions since childhood. There was no family history of neurological disease. The patient did not smoke and drank 4 units of alcohol per day. Examination at initial presentation revealed bilateral apraxia with mild rigidity and fine myoclonus in the upper limbs. He had prominent palmomental reflexes and an extensor Babinski response on the left. Speech was non-fluent and apraxic with occasional myoclonic interruptions. There was cortical sensory loss with dysgraphia and stereognosis bilaterally. The revised Addenbrooke's Cognitive Examination score was 74/100 (losing points in the domains of verbal fluency and visuospatial function).

The patient was reviewed in neurology clinic and given the clinical diagnosis of probable CBS. Levodopa and citalopram were initiated with mild improvement in the patient's speech and mobility.

The MRI head revealed moderate diffuse cerebral atrophy and one or two small white matter lesions in keeping with chronic small vessel ischaemia, but was otherwise unremarkable. Given the background of weight loss, the patient underwent a CT scan of chest, abdomen pelvis which revealed a 7.3 cm heterogeneously enhancing mass arising from the interpolar region of the left kidney, suggestive of renal cell carcinoma (RCC). He underwent a successful laparoscopic radical left nephrectomy, revealing a pT2a Fuhrman grade 4 clear cell RCC (Leibovich score 8). Subsequent to the operation he made a good recovery and gained weight.

Over the subsequent four years the patient's neurological syndrome slowly progressed. He developed increasing difficulty with praxis requiring assistance for all aspects of personal care. An increase in his levodopa had no symptomatic benefit. His mobility deteriorated and he developed dysphagia resulting in frequent choking episodes and chest infections. He had regular interval CT scanning to monitor for RCC recurrence. Two years after the nephrectomy, this revealed a lobulated soft tissue mass in the right lobe of the lung. This was thought likely to represent lung metastases of RCC. Tests for paraneoplastic antibodies associated with paraneoplastic cerebellar degeneration, including anti-Hu, Ri, Yo, MA1, MA2, CV2, TR and amphiphysin were negative. The patient was deemed unsuitable for further invasive interventions due to his dementia, immobility and co-morbidities.

The patient died aged 67, 11 years after the onset of symptoms. His brain was donated to the Cambridge Brain Bank.

The fresh, unfixed whole brain weighted 1351 grams. The formalin-fixed left cerebral hemisphere, left hemi-brainstem, right cerebellar hemisphere and residual slices of the left cerebellar hemisphere were available for neuropathological examination. Macroscopic examination of the brain showed moderate pallor in the locus coeruleus but was otherwise unremarkable, with a well-pigmented substantia nigra. There was no significant cerebral cortical atrophy. There were no macroscopic focal lesions within the brain parenchyma.

Microscopy revealed intravascular and perivascular micrometastatic carcinoma. This was present within cerebellar and cerebral white matter, including the white matter of the pre- and post-central gyri (primary motor and somatosensory cortices). The malignant cells were epithelial in quality, with large irregular nuclei, well-defined cell membranes and cytoplasmic clearing, in keeping with the cytomorphology of his known RCC. The micrometastases did not appear to elicit a surrounding inflammatory cell or glial reaction. There was marked but patchy Purkinje cell loss from the cerebellar cortex associated with a mild T-cell lymphocytic infiltrate on immunohistochemistry. The differential diagnosis of the cerebellar pathology was broad and included ischaemia / small vessel disease. Paraneoplastic cerebellar degeneration was a possibility but the patchy nature of the changes, and the associated granular cell layer depletion, made an ischaemic / vascular aetiology more likely. There was no evidence of inflammation elsewhere, either in the cerebral cortex, white matter, subcortical nuclei or limbic areas. There was no increase in Alzheimer Type II astrocytes within the basal ganglia or elsewhere to suggest a metabolic encephalopathy. There was mild small arterial arteriosclerosis within white matter and deep grey matter.

There was no evidence of a conventional neurodegenerative disease: the midbrain demonstrated a well-preserved substantia nigra and immunohistochemical preparations for alpha synuclein were negative in midbrain regions. Immunohistochemistry for phosphorylated tau protein showed neurofibrillary tangles, neurites and dots limited to transentorhinal and entorhinal cortices (Braak stage II), commensurate with the patient's age and not indicative of a neurodegenerative tauopathy. There was no pathological aggregation of TDP-43 or alpha synuclein. There were no p62 positive inclusions to suggest a C9orf72 expansion. Beta-amyloid staining revealed very mild and focal leptomeningeal cerebral amyloid angiopathy. There were no amyloid plaques.

Discussion

We report a case of corticobasal syndrome in which neuropathological examination demonstrated micrometastatic renal cell carcinoma and evidence of paraneoplastic cerebellar degeneration. Clinically the patient presented with a typical corticobasal syndrome, defined by the consensus international diagnostic criteria: insidious onset and gradual progression of an asymmetric akinetic rigid syndrome, limb apraxia, myoclonus, progressive non-fluent aphasia, and cognitive impairment [1]. However distinguishing features of corticobasal degeneration pathology were absent: neither macroscopic (frontal and temporal, often asymmetric, atrophy) nor microscopic (ballooned neurones in cortical convexity areas, tau-positive astrocytic plaques, "coiled bodies", and tau-positive thread-like lesions in the neocortex, basal ganglia, and brainstem nuclei), were present at post-mortem [4] and

nor was there evidence of any other significant neurodegenerative pathology, including Alzheimer's disease, Parkinson's disease or frontotemporal lobar degeneration.

Instead, neuropathological examination revealed features consistent with the patient's history of RCC. The main neuropathological finding was of micrometastatic RCC in cerebellar and cerebral white matter. This is consistent with the clinical finding of a cortical-predominant syndrome in life and the history of known RCC with lung metastases. The onset of corticobasal symptoms occurred 7 years prior to the finding of the RCC, but RCC can be very indolent, even when metastatic [5]. The patient's MRI of the head did not reveal metastases, but current neuroimaging modalities demonstrate limited potential in the detection of micrometastases, especially in the absence of contrast [6].

There was also severe patchy Purkinje cell loss and associated mild lymphocytic inflammation. This may be secondary to paraneoplastic cerebellar degeneration [7]. Other possible causes of the Purkinje cell loss include spinocerebellar ataxia, severe and prolonged episodes of brain hypoxia, ischaemic changes secondary to small vessel disease, chronic alcohol excess and long-standing epilepsy but none of these alternatives would typically be associated with a lymphocytic infiltrate. However, the patient did not have a cerebellar syndrome clinically, and paraneoplastic antibodies associated with paraneoplastic cerebellar degeneration were not detected in life, arguing against paraneoplastic cerebellar degeneration. The patchy nature of the Purkinje cell loss, and its association with depletion of the underlying granular cell layer, perhaps make ischaemic changes secondary to vascular disease most likely.

The clinicopathological correlation between CBS and corticobasal degeneration (pathology) is low, owing to the heterogeneity of pathologies underlying CBS and the heterogeneity of phenotypes caused by corticobasal degeneration. Whilst the neuropathological consensus diagnostic criteria for corticobasal degeneration clearly distinguish it from other forms of frontotemporal lobar degeneration, the diagnosis of CBS and its underlying pathology is more challenging [1].

In a longitudinal clinicopathological evaluation of 27 patients with clinical CBS in life, half were found to have non-corticobasal degeneration pathology at post-mortem [3]. These 'corticobasal degeneration mimic' patients displayed a range of pathology: ten had Alzheimer's disease pathology, two had frontotemporal lobar degeneration (FTLD-tau), two had mixed Lewy body and Alzheimer's pathology, and one had Lewy bodies in the brainstem only [3]. Although the well-established Armstrong criteria broaden the clinical phenotype associated with corticobasal degeneration, only 9/14 (64%) of patients with pathologically-confirmed corticobasal degeneration were classified as having probable corticobasal degeneration ante-mortem using these criteria [1] [3]. Motor features regarded as characteristic of corticobasal degeneration, namely myoclonus and alien-limb phenomenon, were present in less than half of patients with established disease, and less than a third of patients at first clinic visit [3]. Metastatic carcinoma has not previously been identified as a cause of CBS, but indolent metastatic cancers like RCC need to be considered if there are atypical features, such as the early unexplained weight loss.

In conclusion, we present the clinico-pathological findings of a case of metastatic renal cell carcinoma causing a corticobasal syndrome. This case expands the range of clinical disorders which may mimic corticobasal degeneration, to include micrometastatic carcinoma.

Acknowledgements

This work was supported by the NIHR Cambridge Biomedical Research Centre including the Cambridge Brain Bank, and the Wellcome Trust (103838). The authors thank the patient's family for their support of this research. We acknowledge Cambridge Brain Bank, part of the Human Research Tissue Bank which is supported by the NIHR Cambridge Biomedical Research Centre.

References

- [1]. Armstrong MJ, Litvan I, Lang AE, Bak TH, Bhatia KP, Borroni B, Boxer AL, Dickson DW, Grossman M, Hallett M, Josephs KA, et al. Criteria for the diagnosis of corticobasal degeneration. *Neurology*. 2013; 80 :496–503. [PubMed: 23359374]
- [2]. Parnera JB, Rodriguez RD, Studart Neto A, Nitrini R, Brucki SMD. Corticobasal syndrome: A diagnostic conundrum. *Dement Neuropsychol*. 2016; 10 :267–275. [PubMed: 29213468]
- [3]. Alexander SK, Rittman T, Xuereb JH, Bak TH, Hodges JR, Rowe JB. Validation of the new consensus criteria for the diagnosis of corticobasal degeneration. *Journal of Neurology, Neurosurgery & Psychiatry*. 2014; 85 :925.
- [4]. Constantinides VC, Paraskevas GP, Paraskevas PG, Stefanis L, Kapaki E. Corticobasal degeneration and corticobasal syndrome: A review. *Clinical Parkinsonism & Related Disorders*. 2019; 1 :66–71. [PubMed: 34316603]
- [5]. Azawi NH, Lund L, Fode M. Renal cell carcinomas mass of <4 cm are not always indolent. *Urol Ann*. 2017; 9 :234–238. [PubMed: 28794588]
- [6]. Zhou Z, Qutaish M, Han Z, Schur RM, Liu Y, Wilson DL, Lu Z-R. MRI detection of breast cancer micrometastases with a fibronectin-targeting contrast agent. *Nature Communications*. 2015; 6 :7984. doi: 10.1038/ncomms8984
- [7]. Venkatraman A, Opal P. Paraneoplastic cerebellar degeneration with anti-Yo antibodies - a review. *Ann Clin Transl Neurol*. 2016; 3 :655–663. [PubMed: 27606347]

Figure 1.

T2 weighted MRI showing generalised prominence of the supratentorial ventricles and cerebral sulci, indicating mild diffuse cerebral atrophy. There were one or two small white matter lesions, in keeping with cerebral small vessel disease. There were no focal lesions. The cerebellar hemispheres and vermis (b) appeared to be preserved.

Figure 2.

(a) Coronal section of the left cerebral hemisphere showing relative preservation of the cerebral cortex, subcortical nuclei and hippocampus without any macroscopic focal lesions. The site of the histological micro-metastases are shown with asterisks.

(b) Sections of the brainstem and cerebellum showing preservation of these structures, including a well-pigmented substantia nigra. The site of the histological micro-metastases are shown with asterisks.

(c) and (d) Micro-metastases of renal cell carcinoma in a perivascular distribution.

(e) Cerebellar cortex showing a severe loss of Purkinje cells and (f) a sparse mainly leptomeningeal T-cell infiltrate (CD3).