CASE REPORT

Paraneoplastic overlap syndrome in non-small squamous cell lung carcinoma

Romy Hoque, Lourdes DelRosso

Department of Neurology,
Louisiana State University
School of Medicine,
Shreveport, Louisiana, USA

Correspondence to

Dr Romy Hoque,
romy.hoque@gmail.com

Received 29 August 2013
Revised 7 January 2014
Accepted 23 January 2014

SUMMARY

This is a case of paraneoplastic overlap of limbic encephalitis and opsoclonus myoclonus in a patient with non-small squamous cell lung carcinoma.

BACKGROUND

We report a case of the coexistence of limbic encephalitis (LE), and opsoclonus myoclonus (OM) in a single patient with non-small squamous cell lung carcinoma. Our report adds to the spectrum of presentation of peripheral nerve hyperexcitability disorders.

CASE PRESENTATION

A 60-year-old woman with hypertension and 90-pack-year smoking history presented with 2 months of blurred vision, tremulousness, intermittent extremity twitching, severe sleep onset and sleep maintenance insomnia, visual/auditory hallucinations, severe constipation and weight loss. Complex behaviours during presumed sleep were witnessed by family and included semipurposeful arm movements such as reaching for objects that were not present, and mumbling. She denies dry eyes, dry mouth, excessive sweating or excessive daytime sleepiness.

On examination she exhibited fluctuating confusion, delusions and impaired short-term recall. Opsoclonus was noted on fixed gaze ([video 1](#)). Strength was mildly decreased throughout, and deep tendon reflexes were brisk throughout. Sensation was normal in all extremities. Postural, kinetic and resting tremor with spontaneous and stimulus-evoked myoclonus were noted. No ataxia was noted. Gait was wide based with steps of short height and length. Lung auscultation revealed

diminished breath sounds in the left lower lung. Physical examination of the heart and abdomen revealed no further pathological results.

INVESTIGATIONS

Chest CT revealed a 5 cm peribronchial mass with postobstructive left lower lobe pneumonia. Bronchoscopy with endobronchial biopsy was performed. Biopsy confirmed non-small squamous cell lung carcinoma with basoid features and strong immunostaining for p63 and cytokeratin 5/6. Immunostaining for thyroid transcription factor 1 (TTF1) is negative. She was diagnosed with stage IIIa lung cancer. Abdominal and pelvis CT was unremarkable.

Serum autoantibodies were detected for P/Q voltage-gated calcium channel (P/Q-VGCC), and antineuronal nuclear antibodies (ANNA)-2/Ri. Serum autoantibody testing was negative for voltage-gated potassium channel, leucine-rich, glioma inactivated 1, contactin-associated protein 2, ANNA-1/Hu, Yo, glutamic acid decarboxylase, N-methyl-D-aspartate, CV2, γ -aminobutyric acid class-B, Ma-1, Ma-2/Ta, amphiphysin and acetylcholine receptor. Serum testing for hepatitis B, hepatitis C, HIV and herpes simplex virus (HSV) 1/2 were negative. Severe hyponatraemia with syndrome of inappropriate antidiuretic hormone was noted.

Cerebrospinal fluid (CSF) analysis was unremarkable. CSF was negative for xanthochromia, cryptococcal antigen, malignant cells and HSV PCR testing. CSF immunoglobulin testing was negative for syphilis, HSV1/2, California encephalitis, Eastern Equine encephalitis, St Louis encephalitis, Western Equine encephalitis, lymphocytic choriomeningitis, West Nile virus, measles and mumps.

MRI of the brain showed mild T2-weighted image (WI) hyperintensities of the insular cortex bilaterally without gadolinium-contrast enhancement. Bright lesions on T2-WI are non-specific and may be seen with oedema, infarction, inflammation or infection. Fluorine-18-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) revealed bilateral insular/mesial temporal hypermetabolism ([figure 1](#)), consistent with an active metabolic lesion. The combined MRI and 18F-FDG-PET findings are consistent with a diagnosis of LE. 18F-FDG-PET of abdomen and pelvis revealed no lesions.

Nerve conduction studies, repetitive nerve stimulation and concentric needle electromyography were normal. Polysomnogram with 16-channel electroencephalography (EEG) showed a total time in bed of 380 min with a total sleep time (TST) 70 min. Sleep latency was normal at 31 min. Sleep

Video 1 Clinical Exam Findings.

CrossMark

To cite: Hoque R, DelRosso L. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-201571

Figure 1 (A) Polysomnography hypnogram showing severely decreased sleep efficiency of 18%. (B) MRI of the brain showing mild T2-weighted image hyperintensity in the insular cortex bilaterally (arrow). (C and D) Fluorine-18-fluorodeoxyglucose positron emission tomography brain imaging axial (C) and sagittal (D) views showed hypermetabolism in the insular/mesial temporal cortex (arrows). CA, central apnea; HR, heart rate; HYPO, hypopnoea; LegMvt, leg movements; MA, mixed apnoea; MIC, microphone; OA, obstructive apnoea; Pos, position; RERA, respiratory effort-related arousals; SpO₂, pulse oximetry.

efficiency was poor at 18% of total time in bed with an increased amount of wake after sleep onset (WASO) of 258 min during the recording. Sleep stage 1 (N1) consisted of 87.2% of TST. Sleep stage 2 (N2) consisted of 0.7% of TST. Slow wave sleep (N3) was not present during sleep (0% of TST). Rapid eye movement (REM) sleep was 12.1% of TST. Mild background slowing was noted with frequent right-middle temporal derivation sharp waves. Cyclic sleep organisation, and sleep spindles were absent. Few apnoeas and hypopnoeas were noted.

TREATMENT

The patient was diagnosed with paraneoplastic overlap syndrome consisting of LE and OM. After completion of a single course 5-day course of intravenous immunoglobulin (IVIG) repeat polysomnography (PSG) with 6-channel EEG was performed, and showed: total time in bed 400 min, TST 27 min, sleep efficiency 6%, sleep latency 239 min, WASO 133 min and N1% 100%. A single non-convulsive electrographic seizure of 1 min duration was noted in the right frontal and right central derivations. Few apnoeas and hypopnoeas were noted. Periodic limb movements of sleep and complex abnormal behaviours during sleep were not seen on either PSG.

Levetiracetam was initiated and 24 h video EEG revealed no further electrographic seizures. A single course of radiation therapy was instituted rather than chemotherapy or intravenous corticosteroids due to severe postobstructive pneumonia.

OUTCOME AND FOLLOW-UP

No clinical improvement was noted. In particular, opsoclonus, tremor and stimulus-induced myoclonus all persisted despite treatment with IVIG. Patient and family declined further treatment. The patient was placed under hospice care.

DISCUSSION

Our case demonstrates an unusual presentation of squamous cell lung cancer associated paraneoplastic overlap of LE; and OM. Positive antibodies found in our patient included ANNA-2 (associated with LE and OM); and P/Q-VGCC (associated with cerebellar degeneration).

LE is characterised by subacute short-term memory loss, temporal lobe seizures, behavioural abnormalities, confusional states and hallucinations.¹ Diagnostic criteria include clinical presentation, radiological evidence of limbic system involvement and demonstration of cancer within 5 years of diagnosis, most commonly, lung cancer.² In a study by Irani *et al*,³ 8/64 patients with LE had insomnia.

Although small cell lung cancer (SCLC) is the most common lung neoplasm associated with paraneoplastic disease, a non-small cell lung carcinoma (NSCLC) component can be identified in up to 30% of SCLC.⁴ Combined NSCLC–SCLC are difficult to exclude outside of autopsy. Our patient's neoplasm was consistent with squamous cell carcinoma both histologically and by immunostaining. Coexpression of p63 and cytokeratin 5/6 is almost exclusively restricted to squamous cell carcinoma and is not seen in SCLC.⁵ TTF1 staining, commonly seen in adenocarcinoma, was absent in our patient.

Chaotic saccadic eye movements with myoclonus, ataxia and encephalopathy characterise OM. The paraneoplastic form of OM is commonly seen in older women with breast or SCLC.⁶ In a review by Klaas *et al*,⁷ 4/131 patients with OM had seizures; 7/131 patients had non-SCLC and 3/131 patients had unspecified sleep issues. None of the patients with OM were diagnosed with LE.

Complex nocturnal behaviours were not observed on the video recordings from the patient's two PSGs. It is not clear if the patient's complex behaviours during presumed sleep witnessed by family were either a consequence of visual/auditory hallucinations during periods of wakefulness in fragmented sleep, an acute confusional state during wakefulness, seizure disorder or a true sleep-related behaviour.

Our report adds to the spectrum of paraneoplastic syndrome associated with non-small squamous cell carcinoma. Paraneoplastic overlap of LE and OM may be under-recognised

Learning points

- Squamous cell carcinoma of the lung may be associated with paraneoplastic limbic encephalitis, opsoclonus myoclonus and insomnia.
- Limbic encephalitis is characterised by subacute short-term memory loss, temporal lobe seizures, behavioural abnormalities, confusional states and hallucinations.
- Chaotic saccadic eye movements with myoclonus, ataxia and encephalopathy characterise opsoclonus myoclonus.
- Establishment of diagnosis of paraneoplastic disease often requires an extensive evaluation including: polysomnography, electroencephalography, MRI and fluorine-18-fluorodeoxyglucose positron emission tomography.

and requires extensive neurophysiological and neuroimaging evaluation with full head montage PSG, MRI, 18F-FDG-PET and serum autoantibody testing to establish the diagnosis.

Contributors RH and LD contributed fully to the preparation of this manuscript.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Gultekin SH, Rosenfeld MR, Voltz R, *et al.* Paraneoplastic limbic encephalitis: neurological symptoms, immunological findings and tumour association in 50 patients. *Brain* 2000;123:1481–94.
- 2 Graus F, Saiz A. [Limbic encephalitis: a probably under-recognized syndrome]. *Neurologia* 2005;20:24–30.
- 3 Irani SR, Alexander S, Waters P, *et al.* Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan's syndrome and acquired neuromyotonia. *Brain* 2010;133:2734–48.
- 4 Wagner PL, Kitabayashi N, Chen YT, *et al.* Combined small cell lung carcinomas: genotypic and immunophenotypic analysis of the separate morphologic components. *Am J Clin Pathol* 2009;131:376–82.
- 5 Kaufmann O, Fietze E, Mengers J, *et al.* Value of p63 and cytokeratin 5/6 as immunohistochemical markers for the differential diagnosis of poorly differentiated and undifferentiated carcinomas. *Am J Clin Pathol* 2001;116:823–30.
- 6 Zuliani L, Graus F, Giometto B, *et al.* Central nervous system neuronal surface antibody associated syndromes: review and guidelines for recognition. *J Neurol Neurosurg Psychiatry* 2012;83:638–45.
- 7 Klaas JP, Ahlskog JE, Pittock SJ, *et al.* Adult-onset opsoclonus-myoclonus syndrome. *Arch Neurol* 2012;69:1598–607.

Copyright 2014 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.

BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow