CASE BASED DISCUSSIONS

Paraneoplastic phenomenon in mesothelioma

Ali Bin Waqar,[1] Daniel Menzies,[2] Mared Casey,[3] Mark Doran[4]

ABSTRACT

A 71-year-old man presented with breathlessness and visual disturbance. On examination of the chest, he had signs suggestive of a right-sided pleural effusion and a neurological examination yielded conjugate vertical gaze palsy. Subsequent investigations revealed pleural thickening and mesothelioma. His anti-Ma2 antibodies were positive indicating a paraneoplastic syndrome as the cause of the vertical gaze palsy.

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2019-213176).

[1]Respiratory Medicine, Betsi Cadwaladr University Health Board, Bodelwyddan, UK
[2]Respiratory Medicine, Glan Clwyd Hospital, Bodelwyddan, UK
[3]Pathology, Glan Clwyd Hospital, Bodelwyddan, UK
[4]Neurology, Glan Clwyd Hospital, Rhyl, UK

Correspondence to
Dr Ali Bin Waqar, Respiratory Medicine, Betsi Cadwaladr University Health Board, Bodelwyddan LL18 5UJ, UK; alibinwaqar@gmail.com

Received 4 February 2019
Revised 29 March 2019
Accepted 1 April 2019
Published Online First 20 May 2019

To cite: Waqar AB, Menzies D, Casey M, *et al*. *Thorax* 2019;**74**:719–720.

ABW: A 71-year-old male patient was referred to the respiratory clinic with a 1-month history of progressive breathlessness. Prior to the onset of symptoms, his exercise tolerance had been unlimited, whereas at the time of evaluation, he was only able to walk 200 yards because of dyspnoea. His only other symptom was alteration in his vision that appeared to coincide with the onset of breathlessness. His medical history was significant for benign prostatic hypertrophy and ischaemic heart disease. He had a 50 pack-year smoking history. He was a retired building surveyor and reported incidental exposure to asbestos. Physical examination revealed dullness to percussion, and decreased air entry and vocal resonance over the left hemithorax consistent with the presence of a pleural effusion. Examination of his eyes was remarkable for a conjugate gaze palsy affecting the volitional upward and downward movement of his eyes (online supplementary video 1). A large left-sided pleural effusion was subsequently confirmed on chest X-ray. A CT scan revealed areas of irregular soft-tissue pleural thickening and a pleural effusion on the left side (figure 1). Using ultrasound guidance, diagnostic and therapeutic pleural aspiration of 1.1 L of straw coloured fluid was performed. The results of the pleural fluid protein levels were 49 g/L (total protein content in the serum was 71 g/L) and the pleural fluid LDH (lactate dehydrogenase) levels were 271 U/L (in comparison to serum LDH levels which were 214 U/L). The results confirmed the presence of an exudative effusion.

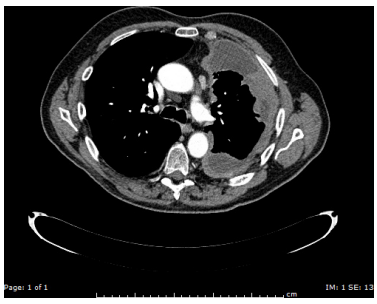

Figure 1 Pleural nodularity and thickening suggesting mesothelioma.

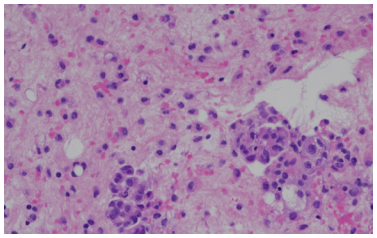

Figure 2 Pleural-based mass lesion comprising a malignant epithelioid neoplasm with solid and tubulopapillary architecture.

MC: Pleural fluid cytology shows abundant mesothelial cells that stain positive with calretinin, CK 5/6 and podoplanin which is suggestive of mesothelioma. Pleural biopsies obtained during subsequent local anaesthetic thoracoscopy confirm epithelioid type malignant mesothelioma (figure 2).

DM: This is a common presentation and would be familiar to most chest physicians. However, the gaze paralysis is unusual. Can you speculate as to how the neurological abnormalities and the new diagnosis of mesothelioma may be linked?

ABW: It is possible that this represents a paraneoplastic syndrome, although this is not a diagnosis usually associated with mesothelioma and is a clinical scenario encountered more frequently with lung tumours arising within the lung parenchyma, particularly small-cell lung cancer. Paraneoplastic syndromes are a group of heterogeneous disorders with a mechanism of action which is immune mediated. These syndromes can affect any part of the nervous system ranging from the cerebral cortex to the neuromuscular junction and can result in an array of neurological disorders including encephalomyelitis, cerebellar degeneration, sensory neuropathy and Lambert-Eaton myasthenic syndrome (LEMS). As our patient has an unusual neurological condition, and this is in the context of a tumour not ordinarily associated with paraneoplastic disease, the opinion of a neurologist should be sought.

MD: This patient has supranuclear ophthalmoparesis and the differential diagnosis for this finding includes progressive supranuclear palsy (PSP) and Niemann-Pick type C, with less likely possibilities of myasthenia gravis (MG) and LEMS all of which tend to begin insidiously and progress slowly, unlike our patient.[1] The only abnormal neurological sign present in this patient is a severe restriction of vertical gaze with no associated limb or proximal muscle weakness, normal reflexes, no muscle fatigability and no other cranial nerve deficit present which would lessen the likelihood of MG or LEMS.

Patients with PSP often have fatigue, headaches and dizziness, have bulbar involvement and display extrapyramidal features with axial rigidity and develop monotone dysarthria—none of which is the case in this patient. Measurement of paraneoplastic antibodies may be of value in this circumstance. Antiacetylcholine receptor antibodies are highly specific and can be used along with other tests like antimusk antibodies for MG.[2] Voltage-gated calcium channel antibodies (VGCCs) aid in diagnosing LEMS.

ABW: Paraneoplastic antibodies that affect the neurological system are often grouped in two categories:

1. Antibodies directed against synaptic proteins—these are antibodies against VGCC, NMDA (N-methyl-D-aspartate) and the AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors.
2. Antibodies directed against intracellular neuronal proteins—these antibodies belong to the category of 'well-characterised' paraneoplastic antibodies and their detection almost always indicates the presence of an underlying tumour.[3] These include anti-Hu, anti-Ri, anti-Yo, anti-Ma2, anti-Tr and antiamphiphysin antibodies.

DM: Our patient has positive anti-Ma2 antibodies and because of the presence of a confirmed malignancy and a non-classical neurological syndrome would now meet the agreed definition of a definite paraneoplastic syndrome.[4] Although lung tumours are commonly associated with paraneoplastic syndromes, there are only rare reports of this condition developing in patients who have mesothelioma.[5] Paraneoplastic syndromes occur more frequently than previously considered and because they present in a wide variety of symptoms and signs, they can often be a challenge to diagnose. Treatment options are limited and the mainstay of therapy is to control the primary tumour which in turn should reduce antibody formation and ameliorate symptoms. In a patient with mesothelioma anticancer treatments, particularly chemotherapy, are often relatively ineffective. As this patient has anti-Ma2 antibodies directed against cellular antigen, it is conceivable that removal of the antibodies from his system could lead to an improvement in symptoms. A trial of plasma exchange should be considered to determine if it leads to any clinical resolution.

Collaborators Ali Waqar; Daniel Menzies.

Contributors ABW and DM conceived the case study. MC supplied slides and provided expertise on the histopathological specimen. MD was consulted for neurology opinion and helped in exhibiting patient symptoms on the video provided.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Parental/guardian consent obtained

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Wirtz PW, Sotodeh M, Nijnuis M, *et al*. Difference in distribution of muscle weakness between myasthenia gravis and the Lambert-Eaton myasthenic syndrome. *J Neurol Neurosurg Psychiatry* 2002;73:766–8.
2 Padua L, Stalberg E, LoMonaco M, *et al*. SFEMG in ocular myasthenia gravis diagnosis. *Clin Neurophysiol* 2000;111:1203–7.
3 Dalamau J, Rosenfeld M. *Overview of paraneoplastic syndromes of the nervous system*. Waltham, MA: UptoDate, 2018.
4 Graus F, Delattre JY, Antoine JC, *et al*. Recommended diagnostic criteria for paraneoplastic neurological syndromes. *J Neurol Neurosurg Psychiatry* 2004;75:1135–40.
5 Archer HA, Panopoulou A, Bhatt N, *et al*. Mesothelioma and anti-Ma paraneoplastic syndrome; heterogeneity in immunogenic tumours increases. *Pract Neurol* 2014;14:33–5.