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## Innovative and effective immunosuppressive bitherapy for an unusual paraneoplastic opsoclonus-myoclonus-ataxia syndrome of the adult<sup>☆☆</sup>



### Biterapia inmunosupresora efectiva e innovadora en un síndrome opsoclono-mioclono-ataxia paraneoplásico e inusual del adulto

Dear Editor:

Opsoclonus-myoclonus-ataxia syndrome (OMAS) is a movement disorder whose origin is frequently paraneoplastic or parainfectious. It is characterised by acute or subacute rapid, multi-directional saccades associated with truncal ataxia and diffuse myoclonus; to a lesser extent, dysarthria, appendicular ataxia, and/or deterioration in level of consciousness also appear. In 50% of the cases, neurological symptoms manifest before a tumour is diagnosed and neuroimaging studies display no alterations. Adults with paraneoplastic OMAS show partial or no response to immunomodulatory therapy; in these patients, relapses are frequent and may lead to fatal diffuse encephalopathy. Furthermore, some patients experiencing relapses will need to resume treatment. OMAS is an extremely rare and probably immune-mediated disorder. Lack of clinical trials means that no treatment guidelines are available to date.<sup>1–16</sup> We present a case of recurrent OMAS in an immunocompetent

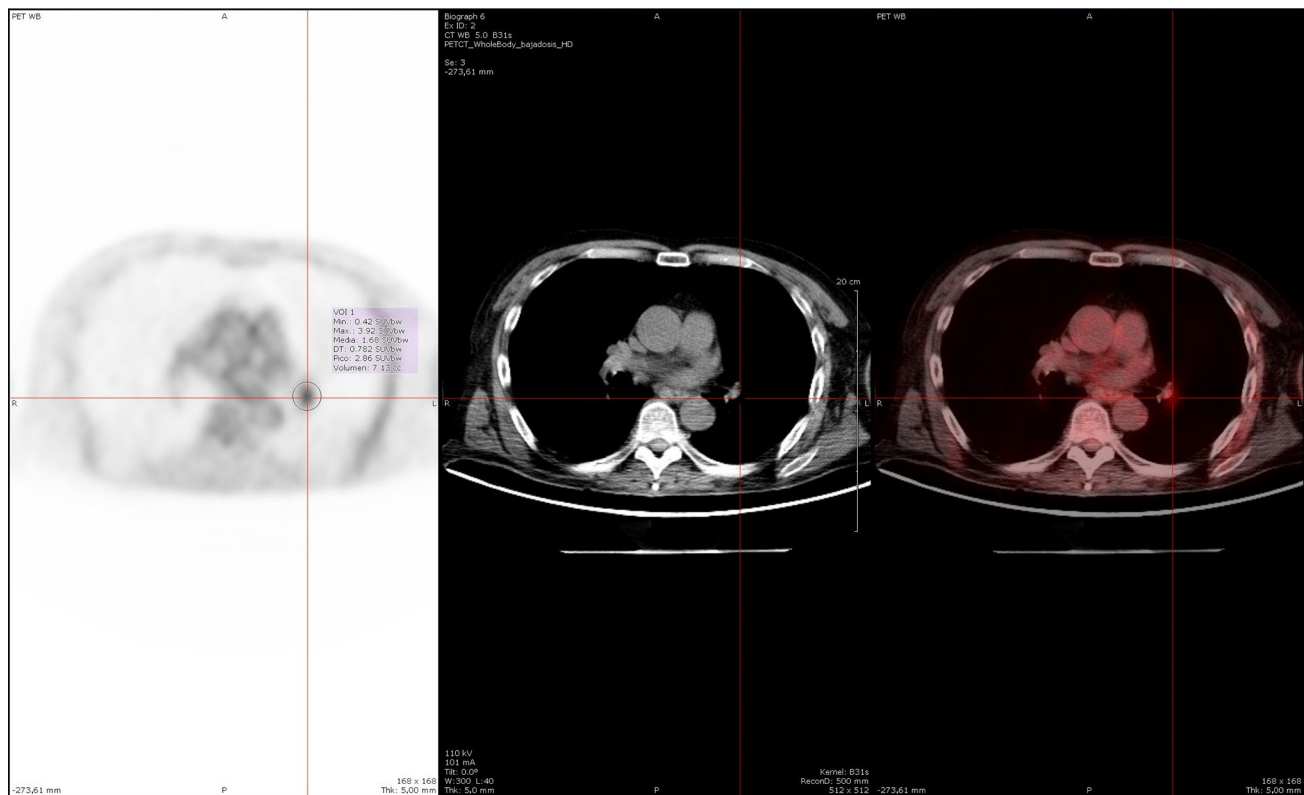
adult whose symptoms resolved with IV methylprednisolone and cyclophosphamide pulse therapy (MCPT).

Our patient was a 62-year-old man with a history of severe use of tobacco (94 pack-years) and alcohol (3–4 glasses of whisky/day) who came to the emergency department due to a 2-week history of ataxic gait with alternating bilateral lateropulsion resulting in falls. Since cerebellar involvement was suspected, he was admitted to the neurology department and underwent a complete analysis and a thorough radiological study. During the hospital stay, our patient's state worsened: he exhibited fluctuations in the level of consciousness, incoherent thinking, visual hallucinations, jargon aphasia, dysarthria, psychomotor agitation, multifocal myoclonus, and binocular nystagmus, which was horizontal-rotatory during the first few days and multidirectional thereafter (Appendix A. Additional material [video available online]). A general analysis ruled out a toxic, metabolic, or infectious aetiology; a brain MRI scan, a whole-body PET/CT study (Fig. 1), and testicular ultrasound revealed no signs of tumours. Our patient tested positive for anti-CV2 antibodies (Table 1) and the EEG displayed generalised grade 2 delta activity. Given the clinical suspicion of OMAS and the lack of response to megadose corticosteroid therapy (1g/day for 5 days) with 2 subsequent cycles of IV immunoglobulins (0.4g/day for 5 days), we decided to administer MCPT on a monthly basis (Fig. 2) based on the protocols described in paediatric literature; this treatment has been proven effective and significantly less costly than rituximab. Treatment achieved symptom resolution. Unfortunately, our patient experienced a relapse one year later, after reducing the medication. This time, small cell lung cancer (SCLC) was detected and confirmed by anatomical pathology studies (Fig. 3); extrathoracic metastases were also detected (pleura, liver, adrenal glands). Our patient was diagnosed with definite OMAS and died 7 months later during hospitalisation.

Paraneoplastic neurological syndromes (PNS) are extremely rare, with an incidence rate below 1% in patients with cancer. In adults, the types of cancer most frequently associated with PNS are SCLC (anti-Hu or anti-CV2 antibodies) and breast cancer (anti-Ri antibodies). On the other hand, SCLC represents 20% of all malignant lung tumours. This type of tumour, which originates in Kulchitsky cells, is normally central and frequently associated with mediastinal adenopathies. SCLC is very aggressive and spreads to

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<sup>☆☆</sup> This study was presented in poster format at the 66th Annual Meeting of the Spanish Society of Neurology (Valencia, November 2014).



**Figure 1** Whole-body  $^{18}\text{F}$ -FDG PET/CT study conducted one year after symptom onset, after our patient's second admission to hospital. Hypermetabolic mass in the root of the left lung with a maximum standardised uptake value (SUVmax) of 3.92 in the interlobar region (SUVmax  $\geq 2.5$  generally indicates a high probability of malignancy), with normal findings on IV contrast CT images. Suspicion of adenopathy was later confirmed with an endobronchial ultrasound-guided puncture in the hypermetabolic region, which detected no neoplasia.

extrathoracic structures very easily (95% of the cases). The percentage of patients with SCLC who develop PNS is estimated at 3%.<sup>1–18</sup> PNS progress rapidly, frequently resulting in irreversible neuronal damage in a few weeks. Due to their relapsing-remitting course, they have a poor prognosis.

Motor and cognitive-behavioural sequelae constitute the main challenge for patient management in the middle and long term. Early treatment is therefore essential. Management of patients with OMAS should target the cancer and include immunotherapy. Corticosteroids are the most

**Table 1** Antibody test results in serum and CSF samples.

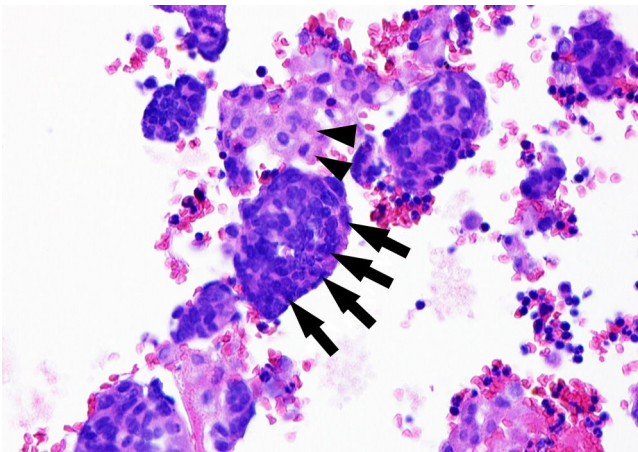
Antibodies against	Sample	Screening method	Confirmation method	Results
Hu	Serum	Immunohistochemical study	Immunoblot	Negative
CV2	Serum	Immunohistochemical study	Immunoblot	Positive
Ma1, Ma2	Serum	Immunohistochemical study	Immunoblot	Negative
Amphiphysin	Serum	Immunohistochemical study	Immunoblot	Negative
GAD	Serum	Immunohistochemical study	RIA	Negative
LG11 <sup>a</sup>	Serum	Immunohistochemical study	CBA	Negative
CASPR2 <sup>a</sup>	Serum	Immunohistochemical study	CBA	Negative
NMDAR	CSF	Immunohistochemical study	CBA	Negative
AMPA	CSF	Immunohistochemical study	CBA	Negative
GABABR	CSF	Immunohistochemical study	CBA	Negative

AMPA: alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor; CASPR2: contactin-associated protein-like 2; CBA: cell-based assay (immunohistochemical study using HEK cells [human embryonic kidney cells] transfected with the antigen); CV2 (CRMP-5-IgG): collapsin response mediator protein 5; GABABR:  $\gamma$ -aminobutyric acid type B receptor; GAD: glutamic acid decarboxylase; Hu (ANNA-1): type 1 antineuronal nuclear antibody; Ma1: neuron- and testis-specific protein 1; Ma2: onconeural antigen; NMDAR: N-methyl-D-aspartate receptor. LG11: leucine-rich glioma inactivated 1 protein; RIA: radioimmunoassay.

<sup>a</sup> Voltage-gated potassium channel (VGKC)-complex antibodies.

DAYS					Monthly dose (every 28 days)
1	2	3	4	5	
↓ ↓ ↓ ↓	↓ ↓ ↓ ↓	↓ ↓ ↓ ↓	↓ ↓ ↓ ↓	↓ ↓ ↓ ↓	Methylprednisolone (1 g/24 h) IV
	↓ ↓ ↓ ↓		↓ ↓ ↓ ↓		Cyclophosphamide (50 mg/kg/h) IV
↓ ↓ ↓ ↓	↓ ↓ ↓ ↓	↓ ↓ ↓ ↓	↓ ↓ ↓ ↓	↓ ↓ ↓ ↓	Pantoprazole (1 vial) (40 mg/24 h) IV
→					Fluid therapy, 0.9% saline solution (2000 cc/24 h): 15 mEq KCl/500 cc saline solution
→					Clinical and haemodynamic monitoring
→					Complementary tests to complete aetiological study

**Figure 2** Treatment protocol in our patient. The first dose of MCPT improved clinical alterations (behaviour and hallucinations); opsoclonus, myoclonus, and ataxia disappeared after the second pulse.



**Figure 3** Cytology test of bloody pleural fluid. Cell block (haematoxylin–eosin stain) showing tumour cells (nuclear moulding with an extremely high nuclear–cytoplasmic ratio, abundant mitotic figures, and minimal cytoplasm) (arrows) intermingled with reactive mesothelial cells (more abundant, eosinophilic cytoplasm, light pink in colour) (arrowheads). The immunohistochemical study of tumour cells was positive for thyroid transcription factor 1 (TTF-1, which points to a primary pulmonary origin), chromogranin/synaptophysin, CD56, and Ki-67 (MIB-1) (in 57% of all neoplastic cells). These findings were compatible with infiltration or metastasis of small-cell neuroendocrine carcinoma of the lung.

effective alternative to OMAS. Other available treatments include cyclophosphamide, azathioprine, ciclosporin A, rituximab, gamma globulins, and plasmapheresis. However, relapses are frequent after medication is reduced or discontinued. Multimodal treatment is therefore recommended to prevent relapses and improve long-term prognosis.<sup>1–16</sup> Good response to MCPT has been described in paediatric patients with OMAS,<sup>19</sup> but not in adults. After a thorough literature search on PubMed (MEDLINE), we can state that

ours is the first reported case of an adult whose recurrent OMAS resolved thanks to MCPT. We therefore suggest MCPT as an early treatment option in cases of OMAS refractory to corticosteroids and immunoglobulins. This may improve quality of life and reduce neurological and cognitive sequelae occurring in up to 80% of these patients.<sup>11,20</sup> Analytic and experimental studies with greater sample sizes would provide invaluable data on the effectiveness of this combined immunosuppressant treatment in adults.

## Conflicts of interest

The authors have no conflicts of interest to declare.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.nrleng.2015.02.005>.

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## Lipoid proteinosis or Urbach-Wiethe disease: description of a new case with cerebral involvement<sup>☆,☆☆</sup>



## Lipoidoproteinosis o enfermedad de Urbach-Wiethe: a propósito de un nuevo caso con afectación cerebral

Dear Editor:

Lipoid proteinosis (LP), also known as hyalinosis cutis et mucosae or Urbach-Wiethe disease (OMIM: 247100), is a rare recessive autosomal disorder. The disease follows a slow,

benign course. To date, some 250<sup>1</sup> to 300 cases<sup>2,3</sup> have been reported. LP is characterised by intracellular deposition of periodic acid-Schiff–positive (PAS-positive) hyaline material in the skin, mucous membranes, and internal organs.<sup>4–6</sup>

This type of genodermatosis results from loss-of-function mutations in the gene coding for extracellular matrix protein 1 (ECM1) on chromosome 1q21.<sup>1,7–9</sup> ECM1 contains 10 exons with 3 isoforms (ECM1a, the most frequent; ECM1b; and ECM1c), whose functions remain to be determined. ECM1 is expressed in the dermis, keratinocytes, endothelial cells, and developing bones. It is linked to keratinocyte differentiation, basement membrane regulation, collagen composition, and growth-factor binding (skin homeostasis).<sup>1,9</sup>

Clinical manifestations of LP are secondary to protein abnormalities and vary greatly among individuals.<sup>5</sup> The disorder affects multiple systems, especially the skin and mucosa of the upper aerodigestive tract.<sup>7</sup> Nearly pathognomonic for LP, the disease typically presents in childhood with a weak cry and hoarse voice due to laryngeal infiltration.<sup>10</sup> At the age of 3, infiltration and diffuse thickening of the skin occurs, resulting in papules and chickenpox-like scars. Around 50% to 60% of the cases

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<sup>☆☆</sup> The genetic part of this study has been published previously (J Clin Neurol. 2014;10:64–8).