Paraneoplastic opsoclonus-myoclonus syndrome in a patient with oesophageal adenocarcinoma☆

Síndrome opsoclono-mioclono paraneoplásico en paciente con adenocarcinoma de esófago

Dear Editor:

Opsoclonus-myoclonus syndrome (OMS) is characterised by rapid, multidirectional conjugate saccades; involuntary muscle jerks in the limbs; and truncal and gait ataxia.[1] It may be idiopathic, parainfectious, or toxic-metabolic, but most cases are paraneoplastic. We present a novel association between OMS and oesophageal adenocarcinoma.

Clinical case

Our patient was a 67-year-old man, a smoker, who was brought to the emergency department by his relatives due to a one-month history of behavioural disorder. The patient initially presented irritability and recent memory impairment, and frequently talked and moved his limbs vigorously during sleep. Fifteen days later, the patient complained of blurred vision, a feeling of instability while walking, and dyspnoea with minimal exertion.

The physical examination revealed eyelid myoclonia; erratic eye movements in all directions and in the primary position; horizontal diplopia with lateral gaze in both directions; fine distal intention and postural tremor without dysmetria; positive Romberg sign; and ataxic, wide-based gait, with inability to walk in tandem. No other relevant findings were observed in the general or neurological examination. The patient scored 26/30 on the Montreal Cognitive Assessment.

The patient was admitted to the neurology department with a diagnosis of OMS; complementary tests were performed to determine whether aetiology was paraneoplastic and to rule out other aetiologies. A blood analysis with tumour marker tests yielded normal findings. A CSF analysis revealed high levels of anti-Ma2 antineuronal antibodies and no other cytochemical alterations, except for slightly elevated protein levels (0.50 g/L). Serum levels of anti-Ma2 antineuronal antibodies were not tested.

The head CT scan revealed no alterations. A brain MRI scan showed punctiform hyperintensities in the pons on T2-weighted and FLAIR sequences, with no diffusion restriction; these probably indicated foci of inflammation, although the hypothesis of chronic vascular lesions cannot be ruled out. A body CT scan revealed segmental thickening of the distal portion of the oesophagus, with narrowing of the oesophageal lumen and adjacent, subcentimetre ganglia in the region of the hepatogastric ligament.

A digestive tract endoscopy revealed Barrett oesophagus with thickening of the distal third; samples were taken from this area for biopsy.

The anatomical pathology study revealed oesophageal adenocarcinoma; endoscopic ultrasound classified the malignancy as stage T3N2. The patient was diagnosed with paraneoplastic OMS secondary to oesophageal adenocarcinoma with anti-Ma2 antineuronal antibodies.

He was treated with boluses of methylprednisolone, which caused irritability and insomnia and were therefore replaced by intravenous immunoglobulins. Treatment improved behavioural symptoms and gait.

The treatment plan included chemoradiotherapy, according to the CROSS protocol; surgery would be considered subsequently, depending on the patient's response to treatment. Unfortunately, the patient died suddenly at home, 20 days after treatment onset.

Discussion

OMS is paraneoplastic in 39% of cases.[2] The syndrome may present without the full set of symptoms (ie, without opsoclonus or without myoclonus),[3] resulting in a mean diagnostic delay of 11 weeks.[4] According to a group of experts in paediatric OMS[5] and a review on the syndrome,[6] diagnosis should meet 3 of the following 4 characteristics in both children and adults: *1)* opsoclonus, *2)* myoclonus or ataxia, *3)* changes in the sleep pattern or behavioural alterations, and *4)* presence of tumour or onconeuronal antibodies. Our patient met all 4 diagnostic criteria.

Nonparaneoplastic OMS is more frequent in young adults (30-40 years) without encephalopathy and showing better treatment response. Paraneoplastic OMS predominantly affects individuals older than 40 years (mean of 66 years), is usually associated with encephalopathy, and shows poorer response to treatment.[7] As patient presented encephalopathy and was older than 40, it was more likely that OMS was secondary to a tumour; the paraneoplastic origin was subsequently confirmed.

Lung cancer, particularly small-cell lung cancer,[7] and breast cancer[8,9] are the types most frequently associated with OMS in adults, whereas neuroblastoma is by far the most frequent in paediatric patients.[1] The literature also includes cases of OMS associated with other types of cancer, such as oesophageal squamous-cell carcinoma,[10] but this is the first reported case of OMS secondary to oesophageal adenocarcinoma.

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It has been suggested that the syndrome is of humoural autoimmune origin.[7] Antibodies target the fastigial nucleus of the cerebellum, causing GABAergic inhibition of omnipause neurons, which control saccadic eye movements, leading to opsoclonus.[11] However, most patients with OMS do not present onconeuronal antibodies (only detected in 11% of cases), and no specific association has been established between the type of tumour and the antibodies detected, with the exception of anti-Ri antibodies (ANNA-2), which have been detected in 70% of patients with breast cancer and OMS.[7–9] Other antibodies described in association with OMS include anti-Hu (ANNA-1), anti-Yo (PCA-1), and anti-NMDA antibodies; however, these are not routinely measured in patients with suspected OMS since they appear very rarely.[6] The only potential exception is HNK-1 antibodies in the case of lung cancer.[2]

Anti-Ma2 antibodies recognise Ma family proteins, which are found exclusively in neurons and testicular germ cells; they were first described in young men with symptoms of cerebellar or diencephalic involvement and testicular tumours.[12,13] Testicular cancer is the predominant type in more recent series, although it does not account for half of the total (40%).[13] In fact, anti-Ma2 antibodies have been detected in patients with lung, stomach, or salivary gland adenocarcinoma; testicular germ cell cancer; breast cancer; and poorly differentiated lymphoma.[2,13] However, anti-Ma2 antibodies have not previously been associated with oesophageal adenocarcinoma, except for a case presented by Ortega Suero et al.[14] (no clinical description is provided) in a series of 32 patients with paraneoplastic neurological syndromes associated with anti-Ma1 and anti-Ma2 antibodies. The patient presented diplopia and oscillopsia, and a brain MRI scan revealed inflammatory lesions in the temporal lobe and diencephalon. The series also included a patient with opsoclonus and gait alterations who presented anti-Ma antibodies (case included in a table; no clinical description is provided); she had a lung tumour that was not confirmed by an anatomical pathology study. In a series of 22 patients, Hoffman et al.[13] also report the case of a patient (patient no. 4) with metastatic oesophageal cancer associated with anti-Ma antibodies who presented gait ataxia, ophthalmoplegia, and mnestic deficits. However, this patient did not present OMS, and MRI revealed lesions compatible with limbic/thalamic encephalitis. Therefore, ours is the first reported case of paraneoplastic OMS associated with oesophageal adenocarcinoma and one of the few reported cases of OMS where presence of anti-Ma antibodies (anti-Ma2 in our case) could be confirmed.

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