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CASE REPORT

Post-COVID-19 opsoclonus myoclonus syndrome

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Abstract

Background: Opsoclonus-myoclonus syndrome (OMS) is a rare neurological disorder, which most commonly is a paraneoplastic manifestation. We report a case of OMS occurring as an immunological sequalae of COVID-19.

Case presentation: A 69-year-old woman developed subacute onset opsoclonus, multifocal myoclonus and truncal ataxia following moderately-severe COVID-19. Extensive evaluation revealed no underlying malignancy. There was only a partial response to steroids and intravenous immunoglobulin, but she significantly improved with plasmapheresis.

Conclusion: SARS-COV-2 infection can induce an immune-mediated OMS, which responds to plasmapheresis.

KEYWORDS
SARS-COV-2, plasma exchange, opsoclonus-myoclonus syndrome

INTRODUCTION

SARS-COV-2 infection has a clinical spectrum that ranges from asymptomatic infection to severe and fatal illness. Neurologic complications in SARS-COV-2 infected patients have been reported among hospitalized individuals with moderate to severe respiratory symptoms.[1,2] Neurologic symptoms may affect around half of the hospitalized patients at some point in their disease course.[1] Headache, encephalopathy, dizziness and muscle aches are the most frequently reported neurological manifestations.[1]

Opsoclonus-myoclonus (OMS) is a rare neurological syndrome that includes opsoclonus, an ocular motility disorder defined as spontaneous chaotic, conjugate, multi-vector, back-to-back, saccadic eye movements without intersaccadic latency, along with multifocal myoclonus and truncal ataxia. OMS most commonly occurs as a paraneoplastic manifestation.[3] We report a case of OMS occurring as an immune-mediated complication of COVID-19 with no evidence of an associated neoplasm at the time of presentation.

CASE PRESENTATION

A 69-year-old woman with a history of chronic kidney disease and hypertension presented with high fever, sore throat and respiratory symptoms for three days. On admission, her nasopharyngeal rapid antigen test was positive for SARS-COV-2 infection. She progressed to develop moderately severe COVID-19 with desaturation on minimal exertion. She was managed with supplemental oxygen, intravenous dexamethasone and enoxaparin.

During the recovery stage of COVID pneumonia (COVID day 12), she developed subacute onset chaotic, conjugate, arrhythmic and large amplitude eye movements in all directions followed by tremulousness of her body and difficulty in walking. On examination, she was alert and oriented with a Glasgow Coma Scale score of 15/15. Ocular examination showed prominent opsoclonus. Voluntary eye movements were full, but exacerbated the opsoclonus. All other cranial nerves were normal. She had truncal ataxia with limb myoclonus. Limb examination was normal except for bilateral exaggerated tendon reflexes. Her haemodynamic parameters remained stable with normal body temperature and a saturation of 96% on room air. Systemic examination including respiratory, cardiovascular, abdominal, thyroid, breast and per-vaginal examination were unremarkable. Initial investigation reports are summarised in the table below (Table 1).

TABLE 1 Initial investigations

	Results	Reference range
White cell count (per L)	9.47 *10^9	4.5 -11×10^9
Haemoglobin (g/dL) / MCV (fL)	10.1 / 88	11.5 - 15.5 (Haemoglobin)
Platelet (per L)	324 *10^9	150-400 ×10^9
Blood picture including thick and thin film	Normocytic normochromic red cells. No malarial parasites.	
C-reactive protein (mg /L)	16	<6
Erythrocyte sedimentation rate (mm 1st hour)	87	<20
Serum creatinine (mg/dL)	1.7	0.7 - 1.2
Serum sodium (mmol/L)	137	135 - 145
Serum potassium (mmol/L)	4.6	3.5 - 5.1
Urine full report	Normal	
Aspartate transaminase (U/L)	15	5 - 34
Alanine transaminase (U/L)	11	0 - 55
Albumin (g/dL)	3.5	3.5 - 5
Globulin (g/dL)	3.3	2.3 - 3.4
Serum ionized calcium (mmol/L)	1.12	1.05 - 1.30
Lactate dehydrogenase (U/L)	270	140 - 280
HbA1C (%)	5.8	<6.5
Blood culture	No growth	
Urine culture	No growth	
Sputum culture	No growth	
2D-echocardiogram	Normal	
Thyroid stimulating hormone (mIU/L)	1.9	0.4 - 4.0
Anti-thyroid peroxide antibodies	Negative	
CSF Herpes simplex virus (1 & 2) PCR	Negative	
HIV 1 & 2 antibody	Negative	
EBV IgM & IgG	Negative	
Serum CMV PCR	Negative	
Antinuclear antibodies	Negative	
Serum protein electrophoresis	No monoclonal gammopathy	
Urine protein electrophoresis	Negative	
Chest X-ray	COVID related peripheral shadows	
Sputum AFB x3	Negative	
Sputum gene-Xpert	Negative	
Mantoux	7mm	
Ultrasound scan abdomen	Normal	
Non- contrast CT Brain	Normal	
Mammogram	Normal	

CSF: cerebrospinal fluid; PCR: polymerase chain reaction; HIV: human immune deficiency virus; EBV: Epstein-Barr virus; CMV: cytomegalovirus; AFB: acid fast bacilli; CT: computed tomography

Cerebrospinal fluid examination was non-reactive with a normal protein of 41 mg/dL and 4 lymphocytes /mm^3; CSF glucose was 3.8 mmol/l (corresponding random blood glucose was 5.1 mmol/l). Her magnetic resonance imaging (MRI) of the brain was normal. Electroencephalogram showed bilateral periodic lateralized epileptiform discharges.

A diagnosis of post-COVID OMS was considered since there was no evidence of other para-infectious or paraneoplastic causes in our initial evaluation. She was treated with intravenous methylprednisolone 500 mg daily for five days and oral clonazepam. As there was no significant response noted, she was treated with intravenous immunoglobulin (2g/kg in five daily doses). Her opsoclonus improved significantly after two weeks, but her multifocal myoclonus and truncal ataxia persisted.

As there was only partial response to initial immunotherapy, further evaluation was done to screen for an occult neoplasm. Contrast-enhanced computed tomography of her chest, abdomen and pelvis were normal except for COVID related residual lung changes. A positron emission tomography (PET) scan did not reveal any abnormality. Neuronal antibody panel (enzyme-linked immunosorbent assay (ELISA)) was negative for anti-CRMP5, anti-amphiphysin, anti-PNMA2 (Ma2/Ta), anti-Ri, anti-Yo and anti-Hu.

Subsequently, she was treated with five cycles of therapeutic plasma exchange which resulted in significant improvement in the myoclonus and ataxia.

DISCUSSION

Opsoclonus-myoclonus syndrome (OMS) also referred to as "dancing eyes-dancing feet syndrome" and myoclonic encephalopathy (Kinsbourne syndrome), is a rare neurological disorder that occurs at a prevalence of 1 in 10,000,000 population.[4] Among the causes of OMS, a paraneoplastic aetiology has been reported to be the commonest.[3,5]

Among the tumours associated with OMS, small cell lung carcinoma, ovarian carcinoma and breast carcinoma have been commonly reported in the adult population.[3,5] Paraneoplastic opsoclonus-myoclonus syndrome precedes the diagnosis of a malignancy in more than 50% of cases regardless of the type of neoplasm. Except for breast adenocarcinoma associated anti-Ri antibody, OMS does not have characteristic onco-neuronal antibodies.[5]

The next most frequent cause associated with OMS is infection. Of the viruses, human immunodeficiency virus, Epstein Barr virus, cytomegalovirus, hepatitis C virus, enterovirus, varicella zoster virus, West Nile virus, Japanese encephalitis virus and SARS-COV-2 infection have been reported to cause OMS [5] while of the bacteria, *mycoplasma pneumoniae, mycobacterium tuberculosis, salmonella enterica, borrelia burgdorferi and streptococcus* have been implicated.[5] Although antibodies against NMDAR, LGI1, and CASPR2 have been reported in association with a few cases of OMS,[6] their role in OMS is not understood. These antibodies were not tested in our patient since our patient did not manifest any clinical features suggestive of either NMDAR-antibody encephalitis or limbic encephalitis.

Para-infectious or post-infectious OMS has been reported to be mild and monophasic, without overt encephalopathy and have a good response to immunotherapy compared to paraneoplastic aetiologies which demonstrated a severe clinical course with prominent encephalopathy and resistance to immunotherapy.[3,5]

OMS following SARS-COV-2 infection has been previously reported.[7] It is interesting to note that the majority of COVID-19 patients who developed OMS had mild-to-moderate respiratory symptoms, manifested no features of encephalopathy, had normal brain MRI scans and normal CSF findings, as was observed in our patient.[7] The precise pathogenesis of OMS in COVID-19 is not known. Proposed pathogenesis of OMS involves neuro-inflammation due to antibodies that target cerebellar Purkinje cells. The spike protein of SARS-CoV-2 has been hypothesized to be a trigger for autoimmune responses in OMS.[8]

For non-paraneoplastic OMS, immunotherapy and clonazepam are considered as the first line treatment. Steroids, ACTH, intravenous immunoglobulin and plasmapheresis have been used alone or in combination, but the evidence for benefit has not been conclusive.[5,9] Post-COVID OMS has been reported to have a good response to immunotherapy.[7,10]

Although there was a partial response to steroids and immunoglobulin, therapeutic plasma exchange (PLEX) led to a substantial improvement in our patient. This suggests that the immunopathogenesis of post-COVID-19 OMS is likely to be more humoral than cell-mediated. In general, paraneoplastic disorders are mediated by a cell-mediated immune response (CD8+) and respond poorly to immunotherapy such as PLEX that removes pathogenic antibodies. Onconeuronal antibodies that are found in paraneoplastic disorders are directed against intracellular proteins and are usually not pathogenic. Thus, immunotherapy that target onconeuronal antibodies usually fail to improve the neurological syndrome.

The close temporal relationship of OMS with COVID-19 in our patient, the remarkable response to immunotherapy, particularly PLEX, and the negative screen for an associated tumour including onconeural antibodies and PET scanning favours an immune-mediated post-COVID-19 OMS than a paraneoplastic OMS in our patient.

CONCLUSION

SARS-CoV-2 infection can induce an immune-mediated OMS. A course of immunotherapy is warranted in all patients presenting with OMS if a paraneoplastic aetiology is not evident on initial screening.

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