Opsoclonus-myoclonus paraneoplastic syndrome in nasopharyngeal carcinoma

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TITLE OF CASE

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SUMMARY

Summary

Nasopharyngeal carcinoma can present with epistaxis, cervical lymphadenopathy, audiological symptoms secondary to eustachian tube dysfunction, pain, or neurological symptoms from tumours directly invading the skull base. It is unusual for patients to present with indirect systemic manifestations. Paraneoplastic neurological syndrome can precede clinically overt malignancy by up to 5 years; therefore, a combination of thorough clinical, laboratory and radiological investigations are required to reach a diagnosis. Intravenous immunoglobulin and steroids may improve neurological symptoms initially and prevent irreversible neuronal damage, but treatment of the underlying cancer is important for long term resolution. Our case adds to a small but growing body of literature related to anti-Ri antibodies, opsoclonus-myoclonus syndrome presentations, and is the first reported association of this combination with nasopharyngeal carcinoma.

BACKGROUND

A paraneoplastic neurological syndrome occurs when antibodies targeting a malignancy inadvertently react against the host nervous system. It can involve a single-system or be multifocal [1]. Several “classical” paraneoplastic neurological syndromes have been described [2].

Many other organ systems as well as the neurological system can be affected by paraneoplastic syndromes, including the endocrine, dermatological, rheumatological and haematological systems. Non-neurological paraneoplastic syndromes are more frequently encountered [3]. Dermatomyositis is the most frequent of the paraneoplastic syndromes associated with nasopharyngeal carcinoma.

We report the rare case of a patient with nasopharyngeal carcinoma (NPC) presenting with anti-Ri antibody positive opsoclonus-myoclonus syndrome (OMS). We describe this patient’s clinical course and compare this with the literature.

CASE PRESENTATION

A Caucasian male in his mid-50s presented by ambulance to the accident & emergency department with irregular breathing, extreme fatigue and abnormal eye movements. Four weeks previously he had received oral antibiotics for a lower respiratory tract infection from his general practitioner (GP). He reported nausea and dizziness and received vestibular sedatives for presumed labyrinthitis. His mobility deteriorated, and he was spending most of his time in bed. One week previously, his GP had noticed that his left eye was twitching and he complained of diplopia. There were abnormal facial movements and his speech was impaired.

Past medical history included hypertension and obesity. He was a non-smoker and consumed 12 units of alcohol per week.

On general observation he appeared flushed, shaky and had a stuttering voice. His temperature was 37.9°C, heart rate 70bpm, blood pressure 147/68mmHg, respiratory rate 18/minute, and oxygen saturations 95% on air. He was alert and oriented and neurological examination found full power in all four limbs but evidence of facial and limb myoclonus. Truncal ataxia was evident, and there were uncontrolled irregular eye movements in all directions of gaze (opsoclonus). He was found to be in severe type II respiratory failure, with admission blood gas results included in table 1. He required admission to the intensive care unit (ICU) for intubation and ventilation.

INVESTIGATIONS

Lumbar puncture found white cell count 52cells/μL (0-5cells/μL) predominantly lymphocytes, protein 510mg/L (<450mg/L), normal glucose and unmatched oligoclonal bands. MRI brain showed abnormal signal involving the brain stem with particular involvement of the left posterior medulla and extension into the adjacent left cerebellar peduncle with no enhancement. Intravenous (IV) meropenem 2g, clarithromycin 500mg, and acyclovir 800mg were initiated to treat

possible infective meningoencephalitis. Other differential diagnoses included autoimmune encephalitis, Bickerstaff encephalitis, paraneoplastic syndrome and multiple sclerosis.

One day following admission he was commenced on a five-day course of 500mg IV methylprednisolone once daily followed by immunoglobulin 0.4g/kg per day for five days (adjusted for body weight) for treatment of OMS and a good response was achieved.

Onconeural antibody screen identified positive anti-Ri antibody (anti-neuronal nuclear antibody 2). Peripheral blood cultures, urine culture, bacterial meningitis screen, and respiratory virus tests were negative. Investigation results are summarised in table 1. He was ambulant and independent with activities of daily living and was discharged from hospital. He returned to driving two weeks later.

Outpatient FDG-PET/CT imaging found a 2cm metabolically active mass in the right nasopharynx and activity in a right retropharyngeal node (figure 1). Flexible nasoendoscopy by the Otolaryngologists found an irregularity in the right nasopharynx. General anaesthetic incisional biopsy was arranged and pathology confirmed a lymphoepithelial carcinoma which was Epstein–Barr virus latent membrane protein-1 (EBV/LMP-1) positive. Staging CT and MRI imaging demonstrated a T2 N1 M0 NPC.

DIFFERENTIAL DIAGNOSIS

Initial antibiotic and antiviral treatment was commenced to manage possible infective meningoencephalitis. Other differential diagnoses included autoimmune encephalitis, Bickerstaff encephalitis, paraneoplastic syndrome and multiple sclerosis.

TREATMENT

One month following discharge from hospital, he reported a two-week mobility deterioration and upper limb myoclonus. Methylprednisolone 500mg daily orally for five days and IVIG 100g daily

for two days produced a clear improvement in his mobility. The head and neck cancer multidisciplinary team discussion recommended induction chemotherapy followed by combined chemoradiotherapy treatment with curative intent. He received cisplatin 100mg/m^2 and 5-fluourouracil (5FU) 1000mg/m^2. A lower limb deep vein thrombosis (DVT) was diagnosed and managed. 5FU and cisplatin were given again one month following the first chemotherapy treatment. Due to a further 7-day episode of myoclonus, opsoclonus and vertigo, oral methylprednisolone (100mg daily for three days) wasrequired again 2 weeks later. Symptom improvement lasted only three days so further methylprednisolone 500mg daily for three days was given. He had planned pre-treatment gastrostomy tube insertion. Concurrent chemoradiotherapy with cisplatin 100mg/m^2 three-weekly combined with radiotherapy 70 Gy in 33 fractions over 6.5 weeks was then commenced. Neurological symptoms improved within one week of starting radiotherapy. Four months later he had returned to driving, was walking unaided and had no vertigo or oscillopsia.

OUTCOME AND FOLLOW-UP

CT imaging 3 months following treatment illustrated a good primary site response with no evidence of residual or recurrent primary site tumour. However, unfortunately multiple pulmonary metastases were identified. Second-line treatment with intravenous nivolumab 480mg four-weekly was then commenced. The risk of encephalitis was explained given the presentation with paraneoplastic neurological syndrome. He tolerated nivolumab well and received 10 cycles over 10 months.

He was admitted to hospital with respiratory distress, type II respiratory failure and reduced level of consciousness 10 days following intravenous nivolumab. Treatment was commenced for pneumonitis with non-invasive ventilation (BiPAP), and 1mg/kg methylprednisolone and he responded well initially. There had been progressive lower limb weakness over the preceding 4 weeks. Full neurological examination found him to be oriented in time and space with fluent speech and normal cranial nerve examination. There was no opsoclonus or myoclonus. Upper

limb examination was normal. Lower limb examination found normal tone, but reduced power worse proximally, flexor plantar responses but reduced tendon reflexes. Non-radicular paraesthesia in the lower limbs was reported. There was no back pain or dysmetria and no pyramidal signs. The underlying cause of the axonal neuropathy required further investigation to ascertain if this was related to nivolumab treatment, or Guillain-Barre syndrome, or chronic inflammatory axonal polyneuropathy. Urgent CT head, nerve conduction studies and an MRI brain and spinal cord were requested. Lumbar puncture was not performed. Chest radiograph found prominent lung metastases. Despite the initial treatment response, he subsequently deteriorated and active treatment was withdrawn prior to further neurological investigation. He died on day 4 of his admission.

DISCUSSION *Include a very brief review of similar published cases*

Presenting symptoms of NPC can include epistaxis, cervical lymphadenopathy, audiological symptoms secondary to eustachian tube dysfunction, pain, or neurological symptoms from tumours directly invading the skull base. It is unusual for patients to present with indirect systemic manifestations. Paraneoplastic neurological syndrome is rare and more frequently associated with small cell lung carcinoma (SCLC). Treatment includes management of the underlying neoplasm, immunotherapy, and supportive therapy.

A literature review of paraneoplastic neurological syndrome in NPC found one other case describing neurological symptoms preceding NPC diagnosis. A middle-aged male presented with progressive lower limb weakness, weight loss and gaze-evoked nystagmus with saccades [4]. Serum anti-Yo antibodies were positive and MRI imaging of the brain found leptomeningeal enhancement around the cerebellum and oculomotor nerves. A fullness in the left fossa of Rosenmuller was biopsied confirming NPC. This patient had positive anti-Yo antibodies, not anti-Ri as in our case, and his neurological symptoms failed to improve with treatment. His cancer was last reported to be in remission following chemoradiotherapy.

There are 2 other case reports [5, 6] detailing patients who developed paraneoplastic neurological syndrome following a diagnosis of NPC. A comparison of their clinical presentation and management has been summarised in table 2. Neither had onconeural antibodies identified.

Paraneoplastic neurological syndrome is immune system activated, with damage occurring to neural tissues by immune-mediated inflammation. Onconeural proteins are co-expressed by the tumour. Well-characterised onconeural antibodies have been described, including anti-Hu, -Yo, -Ma2, -CRMP-5, -amphiphysin, -Ri. Anti-Yo antibodies are associated with paraneoplastic cerebellar degeneration (PCD) and gynaecological malignancy [7]. Anti-Hu antibodies are most commonly associated with small-cell lung cancer [8]. Anti-Ri antibodies are associated with brainstem encephalitis, cerebellar syndrome, OMS and myelopathy [9]. Anti-Ri antibodies have been most frequently linked to SCLC and gynaecologic malignancy [10].

Opsoclonus-myoclonus syndrome is characterised by rapid, chaotic, but conjugate, eye movements and generalized jerks, predominantly involving proximal muscles. Axial and abdominal muscles can be involved. It has been described in young children with neuroblastoma and reported in adults with SCLC or breast cancer. Anti-Ri antibodies are associated [11]. Aetiology includes malignancy, parainfectious, idiopathic and toxic/metabolic causes. A 2012 Mayo clinic review of adult OMS patients found 116 reported cases, of which 55 had a cancer detected; most commonly SCLC. A paraneoplastic antibody was identified along with a corresponding cancer in 21 patients, with anti-Ri the most frequent in 14 cases. Review of outcomes found that 73% of patients had complete remission or residual mild symptoms. In total, 28 patients died (24%) with 10 of these attributed to cancer [12].

Paraneoplastic neurological syndrome can precede clinically overt malignancy by up to 5 years; therefore, a combination of thorough clinical, laboratory and radiological investigations are required to reach a diagnosis. IVIG and steroids may improve neurological symptoms initially and prevent irreversible neuronal damage, but treatment of the underlying cancer is important for long term resolution. This case adds to a small but growing body of literature related to anti-Ri antibodies, OMS presentations, and is the first reported association of this combination with NPC to our knowledge.

Table 1 – Investigation results

Arterial Blood Gas (on 40% oxygen)			
pH	7.12		
$PaCO_2$	14.99	kPa	
PaO_2	9.17	kPa	
HCO_3^-	23.7	mmol/L	
Base excess	1.57	mmol/L	
Oxygen saturation	90%		
Haematology			
White blood cells	8.4	$x10^9$/L	
Red blood cells	5.34	$x10^{12}$/L	
Haemoglobin	166	g/L	
Haematocrit	48.5	%	
Platelets	234	$x10^9$/L	
Neutrophils	5.31	$x10^9$/L	
Lymphocytes	1.87	$x10^9$/L	
Monocytes	1.03	$x10^9$/L	High
Eosinophils	1.03	$x10^9$/L	
Basophils	0.07	$x10^9$/L	
Prothrombin time	11	s	
APPT	23	s	
Fibrinogen	3.2	g/L	
ESR	5	mm/hr	
Biochemistry			
Sodium	139	mmol/L	
Potassium	4.7	mmol/L	
Urea	2.5	mmol/L	
Creatinine	59	µmol/L	
eGFR	>60	$mL/min/1.73m^2$	
Bicarbonate	34	mmol/L	High
Albumin	45	g/L	
Alkaline phosphatase	58	U/L	
Alanine transaminase	67	U/L	High
Bilirubin	13	µmol/L	
Glucose	7	mmol/L	High
C-reactive protein	1.3	mg/L	
Lactate	1.7	mmol/L	
Calcium	2.18	mmol/L	Low
Corrected calcium	2.24	mmol/L	
Phosphate	1.73	mmol/L	High
Magnesium	0.82	mmol/L	
Chloride	91	mmol/L	Low
Creatine kinase	51	U/L	
Procalcitonin	1.18	ng/mL	High

TSH	1.78	mU/L	
Serum osmolality	299	mmol/kg	High
Urine osmolality	553	mmol/kg	
Urine sodium	176	mmol/L	

Lumbar puncture	**Result**	**Unit**
CSF glucose	5.7	mmol/L
CSF protein	510	mg/L
CSF microscopy	clear & colourless	
CSF white cell count	52 cells/µL (predominantly lymphocytes)	
CSF oligoclonal bands	multiple IgG oligoclonal bands (nil in serum)	
CSF gram stain	No bacteria seen	
CSF culture	No growth	
CSF viral & bacterial screen	Negative	
Microbiology		
Aerobic peripheral blood culture	Negative	
Anaerobic peripheral blood culture	Negative	
Urine	Negative	
Legionella antigen	Negative	
MRSA swab	Negative	
Respiratory virus swab PCR	Negative	
Bacterial meningitis screen	Negative	
Hepatitis B virus PCR	Not detected	
Immunology		
Borrelia burgdorferi serology (Lyme disease)	Not detected	
Connective tissue disorder screen	Negative	
C3	Negative	
C4	Negative	
HIV Ag/Ab	Negative	
Syphilis EIA screening test	Negative	
Anti-GMB	Negative	
Anti-PR3	Negative	
Anti-MPO	Negative	
Anti-Ri antibody	Positive	
IgA	7.05	g/L
IgA	2.76	g/L
IgM	0.49	g/L
Hepatitis B core total Ab	Positive	
Hepatitis B surface Ab	319	mIU/mL
Hepatitis B surface Ag	Negative	
Hepatitis C Ag/Ab	Negative	
HEV IgM VIDAS	Negative	

Imaging	
Chest radiograph	Cardiomegaly, pulmonary venous congestion and perihilar oedema. No effusions.
CT head	Non-contrast. No acute intracranial pathology
MRI head	Multiple small areas of abnormal signal in the deep white and subcortical white matter of both hemispheres. Focal abnormal signal in the brainstem particularly the left posterior medulla extending to the adjacent left cerebellar peduncle, but with normal enhancement. Appearances consistent with a form of encephalitis.
CT venogram intracranial	No acute focal intracranial structural abnormality is demonstrated, no features to suggest venous sinus thrombosis.
CT chest, abdomen & pelvis	Non-contrast. No evidence of malignancy. Bibasal lung consolidation.
PET FDG Whole body	2cm mass in the right nasopharynx which is metabolically active (SUV max 14.6g/ml). Right retropharyngeal nodes which is enlarged and metabolically active (SUV max 17.4g/ml).
CT neck and chest with contrast	Right sided nasopharyngeal tumour extending into parapharyngeal space, with involved right retropharyngeal and right level II cervical lymph nodes, and further suspicious right level III and V nodes. No pulmonary metastases.
MRI neck with contrast	Right sided nasopharyngeal tumour with involved right retropharyngeal and right level II cervical lymph nodes, and further subcentimetre but asymmetric suspicious right level II, III and V nodes.
Pathology	
Tissue post-nasal space	Lymphoepithelial carcinoma (undifferentiated). EBM (LMP-1) positive, Cytokeratin AE1/3 positive, P63 positive, P40 positive

Table 2: Nasopharyngeal carcinoma and paraneoplastic neurological syndrome – summary of cases

Authors	Presentation	Symptoms	Tumour type	Tumour stage	Antibodies	Syndrome	Tumour treatment	Neurological treatment	Outcome
Our case	Before cancer diagnosis	Vertigo, nausea, dyspnoea, opsoclonus, myoclonus, abnormal facial movements	Nasopharyngeal carcinoma	T2 N1 M0 (TNM-8)	Anti-Ri	Opsoclonus-myoclus, brainstem encephalitis	Induction chemotherapy, and combined chemoradiotherapy	IVIG, steroids	Good neurological response to IVIG & steroids. Developed pulmonary metastases.
Bhardwaj S, et al[4]	Before cancer diagnosis	Lower extremity weakness	Nasopharyngeal carcinoma	Not reported	Anti-Yo	Cerebellar degeneration	Chemoradiotherapy	IVIG, steroids	Poor neurological response to IVIG. Cancer in remission.
Ng SY et al[5]	After cancer diagnosis	Progressive bilateral lower limb weakness and numbness, urinary and bowel incontinence	Nasopharyngeal carcinoma undifferentiated	T1 N2 M0	None tested	Mixed sensory and motor neuropathy	Initially refused radical radiotherapy, then had palliative radiotherapy	None	Partial early improvement in neurological function. Then lost to follow-up.
Chan KH et al[6]	After cancer diagnosis	Subacute generalised weakness, dysphagia, dyspnoea	Nasopharyngeal carcinoma	Not reported	Anti-Hu negative, no others tested	Inflammatory myelopathy, predominantly motor polyneuropathy/polyradiculopathy	Radical radiotherapy, chemotherapy, palliative radiotherapy to cervical metastases	IVIG, steroids	Partial neurological response to IVIG. Died from metastatic NPC.

LEARNING POINTS/TAKE HOME MESSAGES *3-5 bullet points*

- Nasopharyngeal carcinoma can present with paraneoplastic neurological syndrome
- Paraneoplastic neurological syndromes are uncommon but can indicate clinically covert malignancy and thorough clinical, laboratory and radiological investigations are required in paraneoplastic neurological syndrome
- A multidisciplinary approach is required and should include neurology and oncology

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FIGURE/VIDEO CAPTIONS

Legends

Figure 1 - FDG-PET/CT axial head image showing a 2cm metabolically active area in the right nasopharynx

PATIENT'S PERSPECTIVE

N/A

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