Introduction

Paraneoplastic syndrome affects various organ systems, such as the endocrine, neurological, dermatological, rheumatological and haematological systems (1). These disorders are due to hormones, peptides, or cytokines secreted by the tumour or to immune cross-reactivity between the malignant and the normal tissue. Paraneoplastic neurological disorder (PND) is a rare condition which affects any part of the central and peripheral nervous system. It occurs in any patients with known or occult malignancies and also in patients without a neoplasm (2).

Most instances of PND are thought to be caused by an autoimmune reaction directed against the “onconeural” antigens expressed by the neurons and the tumour cells (2). It must be differentiated from other neurological disorders caused by the invasion of the tumour, metastasis, infection, ischaemia, a metabolic cause, and cancer therapy toxicity. More than 260 cases of nasopharyngeal carcinoma (NPC) associated with paraneoplastic syndrome have been reported (3). The most common is dermatomyositis (4). Others include immune thrombocytopenia (5), syndrome of inappropriate antidiuretic hormone secretion, Cushing’s syndrome, tumour fever, leukemoid reaction, osteoarticular syndrome, sensory neuropathy, demyelinating motor neuropathy (6), and optic neuritis.

We report on the case of an elderly man with known NPC who presented with peripheral neuropathy of the lower limbs and bowel and urinary incontinence, without evidence of spinal or leptomeningeal metastasis. The possibility of PND in NPC is discussed in this paper.

Case Report

A 76-year-old man who was a chronic smoker with underlying hypertension, ischaemic heart disease, peripheral vascular disease, and chronic obstructive airway disease was diagnosed with NPC World Health Organisation type III...
(undifferentiated) T1N2M0 with neck metastasis in January 2014. He was referred for radical radiotherapy. However, he refused the treatment and opted for traditional medication. He defaulted on his follow-up until October 2014, when he presented complaining of progressive bilateral lower limb weakness and numbness over a four-month duration and urinary and bowel incontinence for a period of two weeks. He was unable to walk and was ambulated with the use of a wheelchair. He did not have symptoms of hypercalcaemia, such as bony pain, abdominal pain, or constipation. He had nasal blockage, but denied having epistaxis, a hearing problem, and tinnitus. His cervical lymph node was increasing in size but was painless with no discharge. There was no dysphagia, shortness of breath, reduced effort tolerance, and hoarseness.

The neurological examination revealed a lower motor neuron lesion of the bilateral lower limb, with power of 2/5 and reduced sensation at the level of L4/L5/S1. The anal tone was lax but bulbocavernous reflex was present. The upper limbs were normal neurologically. The cerebellar examination was negative. The cranial nerve examination was normal. Bilateral cervical lymph node swelling was observed, which was larger on the left neck and measured 4 cm × 4 cm, was firm to the touch, and fixed to the underlying structures. A huge nasopharyngeal mass, occupied the whole nasopharynx, extending inferiorly to the oropharynx. The clinical staging remained as T1N2M0.

The full blood count and electrolytes were normal, as was the creatine kinase. Brain metastasis, infarction, and meningeval enhancement was not demonstrated on contrasted computed tomography (CT). Magnetic resonance imaging (MRI) of the spine did not reveal spinal metastasis and cord or root compression. The nerve conduction study (NCS) and electromyography (EMG) results were normal. The patient did not consent to lumbar puncture and muscle biopsy, and neither of these was performed. The anti-neuronal antibody level was unavailable and was not sought.

An obvious cause for the patient’s neurological disorder was not indicated in the investigations. A diagnosis of PND was made. He was given palliative radiotherapy, consisting of three fractions of radiotherapy, six Gy each, given daily to the face and neck. He completed the radiotherapy which resulted in a slight improvement in his neurological function. However, he was lost to follow-up at our centre.

Discussion

Paraneoplastic syndrome was first described in the 1940s and remained poorly understood until recently. PND results from immune cross-reactivity between the tumour cells and the nervous system. The tumour-directed antibodies, known as “onconeural” antibodies, inadvertently attack the normal components of the nervous system owing to antigenic similarity (7).

The natural course of PND is subacute progression for weeks or months. This corresponded with the identified neurological dysfunction in our patient of progressive lower limb weakness that had happened five months following the initial diagnosis of NPC. Depending on the affected components, PND is classified into different sub-types; the central nervous system, peripheral nervous system, neuromuscular junction, and muscular system. The most commonly reported cases involve limbic encephalitis; paraneoplastic cerebellar degeneration; Lambert-Eaton myasthenic syndrome; myasthenia gravis; autonomic, sensory or motor neuropathy; and myopathy (7). Frequently, these cases relate to carcinoma of the lung, breast or ovary, and lymphoma. The differential diagnosis for these syndromes is broad and includes infectious, toxic or metabolic causes; metastases; nerve compression; and adverse treatment effects (1). These are usually the cause of the neurological disorder, rather than paraneoplastic syndrome (2). Therefore, the PND is a diagnosis of exclusion.

Investigations should incorporate imaging, serology, electroencephalography, NCS, EMG, and cerebrospinal fluid (CSF) and anti-neuronal antibody analysis (1).

In this case, the patient presented with lower limb weakness and sensory loss, with urine and bowel incontinence. L2–S1 motor neuropathy and L4–S1 sensory neuropathy was observed. MRI of the spine was normal, with no evidence of spinal cord or nerve compression and spinal metastasis. Pathology was also not noted on contrasted CT of the brain. The patient’s neurological dysfunction was attributed to be as a result of PND.

From the clinical features, this patient may have had sensorimotor neuropathy, a PND subtype which affects the peripheral nervous system. In sensorimotor neuropathy, an NCS will show mixed sensory and motor axonal neuropathy, with demyelinating features (6). However, our patient’s NCS was unremarkable.
Chronic inflammatory demyelinating polyradiculopathy (CIDP), in which acellularity with raised protein levels is demonstrated in the CSF analysis, and typical demyelinating feature is demonstrated in the NCS, was another possible subtype. This diagnosis could not be made in our case because a lumbar puncture was not performed as the patient did not consent to it.

Motor neuronopathy was another possible subtype, involving subacute progression. It presents as a slowly progressive lower motor neuron syndrome that affects the lower limbs. This condition is more common in non-Hodgkin’s lymphoma (6). It is associated with prominent neuronal degeneration, restricted to the anterior horns of the spinal cord, and mild posterior column demyelination, which were not detected in this case.

The absence of the characteristic fatigability of proximal weakness and autonomic dysfunction made the diagnosis of Lambert-Eaton myasthenic syndrome (LEMS) unlikely. Furthermore, the electrophysiological findings for our patient were not consistent with presynaptic neuromuscular dysfunction. LEMS is commonly associated with small cell lung carcinoma in 60% of cases (1).

NPC is commonly associated with dermatomyositis, which accounted for 61% of all dermatomyositis cases seen in a 12-year retrospective review in Kuala Lumpur Hospital, Malaysia (4). Classically, patients with dermatomyositis have a photodistributed rash, Gottron’s papules, and heliotrope rash. They have proximal muscle weakness, raised creatine kinase, and myopathic changes demonstrated in an EMG, as well as inflammatory involvement which can be observed on the muscle biopsy sample. This patient did not have any dermatological manifestation suggestive of dermatomyositis, and his creatine kinase and EMG results were normal. However, a muscle biopsy was not performed and this diagnosis could not be excluded.

To achieve a definite diagnosis, the patient needed to undergo a lumbar puncture to exclude micrometastases of the spinal cord or CIDP. He needed to have a muscle biopsy to exclude dermatomyositis or necrotising myopathy. Finally, it was necessary to determine his anti-neuronal antibody levels. However, it has been shown in the literature that the results for 30% of patients with presumed PND were found to be negative following anti-neuronal antibody screening (2).

Treatment of PND with immunomodulatory treatment, such as corticosteroids, azathioprine, cyclophosphamide, plasma exchange, and intravenous immune globulin has not resulted in successful outcomes. Discovery and treatment of the underlying tumour is the mainstay of management, leading to an improved chance of neurological stabilisation or improvement (2).

In this case, the patient refused to undergo radical radiotherapy and chemotherapy and was only given palliative radiotherapy. The suggestion that palliative radiation therapy is effective in PND is not in evidence in any reports. However, localised palliative radiation is a known treatment option for paraneoplastic hypertrophic osteoarthropathy (1).

**Conclusion**

PND is a diagnosis of exclusion in patients with malignancies who present with neurological dysfunction. This case illustrates the difficulties in managing patients with NPC and neurological disorders. All causes, including infection, toxic and metabolic, metastasis, compression, and adverse treatment effects, must be excluded in view of the rarity of PND. Despite the unusual association of NPC and PND, clinicians need to be aware of these conditions as such knowledge may be helpful in making an accurate diagnosis, the provision of prompt treatment at an early stage, and contributing to a better survival rate. Treatment of the tumour is the cornerstone of PND management and should not be delayed as this is a devastating and progressive condition.

**Conflict of Interest**

There are no potential conflicts of interest, including specific financial interests and relationships and affiliations (other than those affiliations listed in the title page of the manuscript) relevant to the subject of this manuscript.

**Authors’ Contributions**

Conception and design: SYN
Analysis and interpretation of the data: SYN
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Critical revision of the article for important intellectual content: MHK, MRMY
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