CASE REPORT

When dizziness becomes sinister: oropharyngeal carcinoma presenting as a paraneoplastic neurological disorder

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SUMMARY

Paraneoplastic neurological disorders are uncommon presentations of head and neck cancers. We present a case of a 68-year-old male patient who presented with dizziness, nausea and memory problems. MRI of his brain showed bilateral cerebellar leptomeningeal enhancing signal abnormality with cervical lymphadenopathy. CT imaging of his neck raised the suspicion of a tonsillar primary, which was later confirmed on biopsy. His poorly differentiated HPV positive squamous cell carcinoma was treated with chemoradiotherapy. Subsequent MRI imaging showed progressive cerebellar atrophy and his presenting symptoms persisted, but he remained disease free 6 months post-treatment for his primary malignancy.

His medical history included type 2 diabetes mellitus and non-arteritic anterior ischaemic optic neuropathy in his left eye. He was a lifelong non-smoker.

On examination, he was fully orientated to time, place and person with intact language skills and frontal lobe function and was therefore deemed to have an unaffected higher mental function. He had a rather hesitant, tottering gait which was not Parkinsonian but looked more like 'gait ignition failure' as seen in cerebrovascular disease. He also required immediate support when he attempted heel-to-toe walking. Cranial nerve, upper and lower limb examinations were otherwise normal. He was faultless on finger/nose and heel/shin testing, with symmetrical reflexes and plantar flexors.

BACKGROUND

Paraneoplastic syndromes present with systemic signs and symptoms that are not directly related to the primary malignancy or its metastases. Paraneoplastic neurological disorders (PNDs) are estimated to affect fewer than 1% of patients with cancer.¹ This becomes even rarer in the subset of head and neck malignancies. They may precede the clinical manifestations of the primary tumour and present as the first sign of malignancy.

Oropharyngeal carcinoma can present with sore throat, neck lump and referred otalgia. Locally advanced tumours can present with dysphagia and airway obstruction. Our patient did not present with any of these symptoms. To the best of our knowledge, this is the first reported case of squamous cell oropharyngeal carcinoma presenting with symptoms consistent with PND.

CASE PRESENTATION

A 68-year-old man was referred for neurological assessment by his general practitioner with a 10-month history of dizziness and deterioration in memory. His symptoms of feeling 'off balance' with a light-headed, swimmy sensation were initially intermittent and lasted for a few hours. This gradually became a persistent sense of disequilibrium with a low-grade background of nausea. He also described a short-term memory problem as well as being unable to recall stories which he used to tell frequently at dinner parties. In addition, he was having difficulties with orientation and felt that his handwriting had deteriorated. Alongside all of this, he felt that his mood was low.

INVESTIGATIONS

He underwent an MRI scan of his brain with gadolinium which showed subtle high signal peripherally in the cerebellum (figures 1 and 2), but without any associated mass effect, and also multiple enlarged right-sided upper cervical nodes. No obvious primary was seen to account for the bilateral cerebellar leptomeningeal enhancement on initial MRI. He underwent lumbar punctures on three separate occasions which did not show any malignant cells, but was consistent with a non-specific chronic inflammatory process.

He had further MRI imaging a few weeks later following a deterioration in his clinical condition. This showed progression of the bilateral cerebellar leptomeningeal enhancing signal abnormalities. Because of some right-sided level II cervical lymphadenopathy evident on MRI imaging (figure 3), a CT of the neck, chest, abdomen and pelvis was performed. Although no abnormalities were seen on the imaging of his chest, abdomen and pelvis, the neck images showed a right-sided oropharyngeal primary tumour with regional metastatic lymphadenopathy (figures 4 and 5).

A panendoscopy showed right tonsillar inferior pole thickening with no ulcers and a right level II neck fullness. Supraglottis, glottis, hypopharynx and oesophagus up to 22 cm were noted to be normal. Biopsies of the right lower pole tonsil showed a poorly differentiated squamous cell carcinoma which was p16 positive. Expression of p16 is highly correlated with human papilloma virus infection in head and neck squamous cell carcinoma. PET scan showed no disease out with the

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Figure 1 Postcontrast MRI fluid attenuation inversion recovery (FLAIR) image sagittal views with high signal peripherally in the cerebellum.

Figure 2 Postcontrast MRI fluid attenuation inversion recovery (FLAIR) image axial views with high signal peripherally in the cerebellum.

head and neck region. The patient was negative for anti-Hu, Ri, Yo antibodies and western blot was negative for anti-Hu, Ri, Yo, Ma1, Ma2, CV2/CRMP5, amphiphysin, Sox-1, Zic-4 and anti-Tr antibodies.

DIFFERENTIAL DIAGNOSIS

Leptomeningeal enhancing signal abnormality can be secondary to infection (eg, meningitis or encephalitis), leptomeningeal carcinomatosis, lymphoma, haemorrhage, granulomatous conditions (eg, sarcoidosis) or vasculitis.

TREATMENT

Following discussion by the regional multidisciplinary team, his T1N1M0 oropharyngeal squamous cell carcinoma was treated

Figure 3 Axial T2 image with gadolinium contrast showing right level II enlarged lymph node with central necrosis.

Figure 4 Axial CT image with contrast showing an enlarged right level II lymph node.

with radical carboplatin and radiotherapy. Treatment was complicated by multiple episodes of sepsis and delirium. He was started on sertraline to help with his low mood. Mirtazapine was added as an antiemetic and also as an adjunct to improve his psychological status.

Figure 5 Axial CT imaging with contrast showing soft tissue thickening and enhancement in the right glossotonsillar sulcus and at the lower pole of the right faucial tonsil, adjacent to the enlarged lymph node.

OUTCOME AND FOLLOW-UP

Subsequently, he reported of ocular flutter, and square wave jerks were identified, but he retained reasonably good vision. These features were thought to be part of the paraneoplastic process.

He was transferred for a period of rehabilitation following completion of treatment with radical chemotherapy and radiotherapy. A repeat MRI 3 months later showed progressive cerebellar atrophy with persisting dentate nucleus signal abnormality and minimal reduction in the extent of meningeal enhancement. A post-treatment CT scan showed complete response at the primary site with a small residual right IIa node. PET scanning showed no metabolically active disease.

He was eventually discharged home with increased support. He was able to mobilise with a frame although he required supervision, and he was unsafe on stairs. His mood improved together with his cognitive function, although this did not return to his baseline. Subsequent post-treatment surveillance MRI scans have shown progressive cerebellar atrophy. His long-standing subjective dizziness persisted, but it was hoped that this would not progress further following successful treatment of his primary cancer.

DISCUSSION

Head and neck cancers have seldom been reported with paraneoplastic neurological syndromes. These syndromes are more commonly associated with lung, haematological or gynaecological malignancies.² Literature review in the English language revealed only two previous case reports on a paraneoplastic cerebellar degeneration associated with head and neck cancers. This included a lymphoepithelial tonsillar carcinoma and a spindle cell carcinoma of the nasal cavity.³⁻⁴ To the best of our knowledge, this is the first case of an association of a head and

neck squamous cell carcinoma with paraneoplastic cerebellar degeneration. Although no paraneoplastic antibodies were identified in the present case, the neurological and radiological opinions were that this presentation did represent a paraneoplastic phenomenon.

The patient with lymphoepithelial tonsillar carcinoma presented initially with a history of dizziness, slurring of speech and disturbance of gait and balance. Whole body PET/CT scan revealed mild hypermetabolism in the right tonsil. He underwent a tonsillectomy and neck dissection. Histology revealed a low-grade differentiated lymphoepithelial carcinoma of the lower tonsil and tongue base. The mitosis marker Ki67 was present in 40% of tumour cells. Immunohistochemical workup revealed numerous CD3+T-lymphocytes and CD20+B-lymphocytes with positivity for bcl2. Staining was negative for CD23, CD30, CD34, CD138 and the macrophage marker KiM1P, and he did not test positive for any onconeural antibodies. He subsequently underwent additional resection of the neighbouring tongue base and neck dissection followed by intense neurorehabilitation. In the course of the next 18 months, he had a stable cerebellar dysfunction with only slight progression of dysarthria which was treated every 3 months with steroid pulses.

The patient with spindle cell carcinoma presented with progressive gait instability with nausea and vertigo. She had previously been diagnosed with spindle cell carcinoma of the nasal cavity which was resected by functional endoscopic sinus surgery. Histology revealed epithelial as well as mesenchymal differentiation and absence of molecular translocation t(X,18), and she was staged T3 N0 M0. MRI revealed two nodes beneath the angle of the jaw with intense tracer uptake on PET/CT imaging. She underwent a level II neck dissection which confirmed locoregional recurrence and underwent adjuvant concomitant chemoradiotherapy of the left neck. She was positive for anti-Hu antibodies. Complete remission of her cancer was confirmed, and she remained stable neurologically at 3 years follow-up.

PNDs are thought to be immune mediated, whether antibody or T-cell mediated. There are classical (eg, cerebellar degeneration, limbic encephalitis, encephalomyelitis particular to the brain) and non-classical syndromes (eg, brainstem encephalitis and optic neuritis, again particular to the brain). The diagnosis is difficult to establish because other diseases may have similar pathological signs. Two clinical signs shared by most PND patients are the rapid progression of symptoms and signs of inflammation in the central nervous system. In 70% of patients with PND, neurological symptoms are the first manifestation of a tumour.⁵

Diagnostic criteria divide PND into definite and probable PND. Patients with definite PND fulfil any of the following: classic syndrome with cancer diagnosed within 5 years of neurological symptom development, non-classic syndrome that resolves or significantly improves after cancer treatment without concomitant immunotherapy, provided that the syndrome is not susceptible to spontaneous remission; non-classic syndrome with cancer diagnosed within 5 years of neurological symptom development and positive neuronal antibodies; neurological syndrome (classic or not) without cancer and with well-characterised antineuronal antibodies (Hu, Yo, CV2/CRMP5, Ri, Ma2, or amphiphysin). Probable PND is defined as a classic syndrome with high risk of cancer, without antineuronal antibodies; neurological syndrome (classic or not) without cancer and with partly characterised antineuronal antibodies or non-classic syndrome with cancer diagnosed within 2 years of neurological symptom development, without neuronal antibodies.²⁻⁶

Despite the diagnostic value of antineuronal antibodies, they have a low-to-moderate sensitivity with almost 50% of patients with PND testing negative for antibodies,⁷ as in the present case. The presence or absence of such antibodies does not influence therapeutic decisions but has however some prognostic value.⁸

Treatment for PND is directed at the underlying malignancy. The early destruction of neural structures unfortunately prevents clinical improvement in some patients, despite treatment of the underlying lesion. The best chance of stabilising the paraneoplastic syndrome is achieved only when complete removal of the underlying lesion is effected.⁹

Learning points

- ▶ Head and neck malignancies rarely present without upper aerodigestive tract symptoms.
- ▶ Paraneoplastic neurological disorders are rare but may be the only symptom of an underlying head and neck cancer.
- ▶ A high index of suspicion is necessary to make the diagnosis with early use of appropriate imaging modalities.
- ▶ Treatment should be directed at the underlying malignancy.

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Contributors All coauthors have equally contributed to this case report and consented in the final draft. CM is the treating neurologist, and IFN is the treating oncologist. LY and PA are trainees involved in the management of the patient discussed in the case report under the guidance and supervision of CM and IFN.

Competing interests None declared.

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