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# Vocal fold palsy following vinca alkaloid treatment

B. V. Burns, M.B., Ch.B., J. C. Shotton, F.R.C.S.

**Abstract**
We report two patients with Hodgkin's disease on chemotherapy, one with vincristine, the other with vinblastine, who were referred to the ENT department with a vocal fold palsy. These drugs are commonly used in the treatment of haematological malignancies, and head and neck sarcomas. Examination showed a unilateral immobile fold. No causative local pathology was identified, and they were otherwise thought to be achieving remission, but the development of a fold palsy suggested a poor response to treatment. One patient's palsy resolved following completion of chemotherapy, but the other patient's persists, despite an otherwise good response to the treatment. The vinca alkaloids are neurotoxic, usually causing a peripheral neuropathy, but cranial mononeuropathies are a rare side-effect. A total of 27 previous cases of vocal fold palsy have been reported with the use of the vinca alkaloids, and such a lesion should not be assumed to be due to advancing lymphoma.

**Key words: Vinca alkaloids, complications; Vincristine; Vinblastine; Vocal fold palsy**

## Introduction

Vincristine has been used as an anti-cancer drug since the 1960s, for the treatment of haematological malignancies and solid tumours of the head and neck. It lacks the usual emetic and myelotoxic effects of other anti-cancer drugs, but its use is limited by its neurotoxicity (Legha, 1986; Postma *et al.*, 1993; Donaghy, 1996). Most patients experience a peripheral neuropathy, predominantly sensory (Postma *et al.*, 1993), which may progress to motor involvement. Autonomic neuropathy is also relatively common, manifesting as constipation or urinary difficulties. Cranial mononeuropathies are rare, but have been described and can affect most of the cranial nerves. Such manifestations of toxicity were more common in the first two decades of its use when higher doses were administered. Vinblastine is a related drug, neurotoxic but usually less so than vincristine, more myelosuppressive and with a tendency to damage epithelium causing ulceration.

Vocal fold paralysis caused by the vinca alkaloids has been described previously in eight papers – a total of 27 cases, 24 from vincristine and three from vinblastine (Bohannon, 1963; Bradley, 1970; Brook and Schrieber, 1971; Holland *et al.*, 1973; Whittaker and Griffith, 1977; Delaney, 1982; Tobias and Bozeman, 1991; Annino *et al.*, 1992). Only six children and two adults have been added since 1977. Most have unilateral lesions, with four cases having a bilateral palsy. Dysphagia is also reported as an associated symptom in four patients. Peripheral neuropathy, manifesting as pain or paraesthesia of the extremities is usually present, as is constipation. The neurotoxicity appears to be dose-related, and cumulative with repeated doses. Adverse effects are usually reversible on interruption of therapy, where most patients can be expected to make a full recovery in one to two months. Failure to do so may result in a permanent disability (Donaghy, 1996).

We report on a further two cases where the vinca alkaloids were thought to be the cause of a vocal fold palsy.

## Case reports

### *Case 1*

A 48-year-old male presented with a swelling in the left submandibular region. This was excised, and the histology showed nodular sclerosing Hodgkin's disease. Chemotherapy was begun with the VEEP regimen (vincristine, etoposide, epirubicin and prednisolone). The patient started experiencing lethargy and mild neuropathic symptoms, predominantly paraesthesia of his hands and feet. This is typical of vincristine toxicity, but the symptoms were mild and the chemotherapy was continued. Two further computed tomography (CT) scans showed sustained regression by the third month, but the patient had developed intermittent hoarseness. By the fifth month this had progressed to periods of almost complete aphonia, with excessive coughing when drinking fluids. He was re-referred for examination of his larynx. Indirect laryngoscopy (IDL) showed a left vocal fold palsy, but otherwise normal larynx. His neck lymphadenopathy had resolved. No mediastinal involvement had been demonstrated in this patient from his recent staging investigations, including a chest CT scan. He received his final dose, and a CT scan at that time showed complete remission. He was reviewed in our clinic five weeks later. All laryngeal symptoms had completely resolved, and both folds were fully mobile on IDL. His peripheral neuropathy had also improved.

### *Case 2*

A 49-year-old female presented with hoarseness. She was on a six-month chemotherapy regimen of adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) for

From the Department of Otolaryngology, Kent County Ophthalmic and Aural Hospital, Maidstone, Kent, UK.
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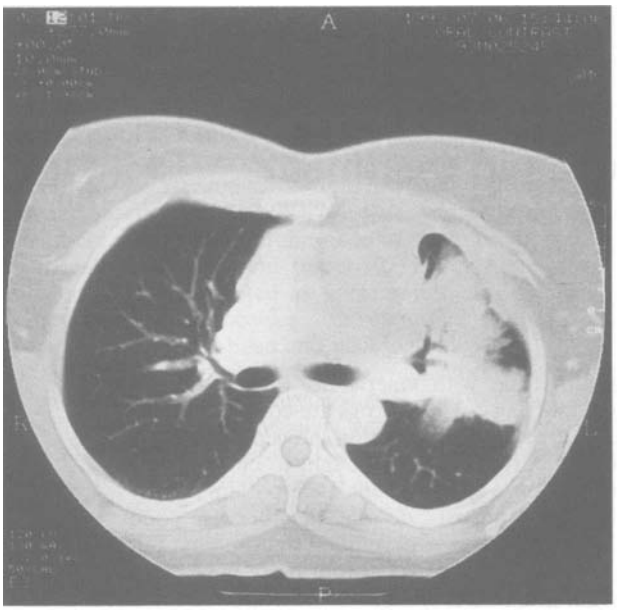

FIG. 1

Chest CT scan of *Case 2*, showing left hilar lymphadenopathy close to the aortic arch. It was initially assumed that advancing disease here led to hoarseness by involvement of the left recurrent laryngeal nerve to give a left-sided fold palsy.

nodular sclerosing Hodgkin's disease with mediastinal involvement. This had been diagnosed four years earlier following investigation of a left hilar mass seen on a chest X-ray peformed for repeated chest infections. Treatment was initially with chlorambucil, procarbazine, vincristine and prednisolone (the Chl.VPP regimen). She responded well, although did develop some tingling of her extremities which had improved following completion of the course. She had remained in remission during the subsequent four year follow-up until she developed a cough and breathlessness, and enlargement of her left hilar lymphoid mass (Figure 1). This represented a relapse, and the ABVD regimen was commenced. She improved symptomatically, with reduced breathlessness, but developed pain in her limbs, stiffness and oral ulceration, typical of vinblastine toxicity. Her white cell count had reduced to $1.9 \times 10^9$/litre, an effect which any component of her medication could have caused, but the regimen was continued because of failure of the aorto-pulmonary lymphadenopathy to regress on CT, and the development of a hoarse voice. This was assumed to represent advancement of her hilar disease affecting the left recurrent laryngeal nerve. The voice symptoms progressed, and she was referred for laryngeal examination. Indirect laryngoscopy showed a very sluggishly mobile *right* vocal fold, which could not be explained by left-sided chest disease. There was no clinical evidence of local neck disease, in particular no palpable neck nodes. A microlaryngoscopy and bronchoscopy with washings were performed, and no pathology found to explain a palsy. On recovery from anaesthetic, the right fold appeared almost completely immobile on direct examination, confirming the appearances in clinic. Six months later she remains in remission, but continues to have marked hoarseness.

## Discussion

The vinca alkaloids have their anti-neoplastic effect by inhibiting the M phase of mitosis. This occurs by binding of the drug to the cells' microtubule system, which may affect axoplasmic flow in neurones, and their ability to conduct impulses (Wisniewski *et al.*, 1968; Bradley *et al.*, 1970). This has been proposed as the mechanism by which these drugs have their neurotoxic effects, and how a neuropathy is reversible on stopping the drug. However, histological examinations of biopsy and post-mortem material have shown primary axonal degeneration in nervous tissue in patients with vincristine neuropathy (Bradley *et al.*, 1970; Casey *et al.*, 1973). Sensory and motor nerve conduction velocities and neuromuscular transmission are unimpaired in even the most severe neuropathies (Bradley *et al.*, 1970; Casey *et al.*, 1973; Rosenthal and Kaufman, 1974), suggesting neuronal loss rather than impaired function. Neurones do not divide, and loss of the cell body is a permanent loss. If too many neurones are irreversibly damaged, recovery of function may be incomplete.

Our first case progressed to almost complete aphonia from his third to sixth month on chemotherapy. This occurred alongside the more usual peripheral neuropathy, and both improved spontaneously five weeks following completion of treatment. Two other possible causes of a left-sided palsy exist in this case – the lymphoma and the excision biopsy. Neither the vagus or the recurrent laryngeal nerves were in the operative field at the time of his biopsy, and symptoms did not begin until four months later. Scarring is also unlikely, because his palsy resolved spontaneously. Furthermore, the patient's cervical nodes had shown a good response, both clinically and on CT scan, by the third month – when his laryngeal symptoms began.

Our second case had demonstrated other toxic effects of vinblastine prior to the onset of a voice change, with epithelial necrosis, and a peripheral neuropathy. No neck disease was ever demonstrated to account for a right-sided lesion. Her vocal fold symptoms did not improve on withdrawal of the drug, but less is known about the natural history of vinblastine induced palsies, with only three cases previously been described. The neurotoxicity of the vinca alkaloids is dose-related, and cumulative with repeated doses (Legha, 1986). It must be remembered that this patient had received vincristine four years earlier, sufficient to cause a peripheral neuropathy. Sub-clinical neuronal injury from previous vincristine treatment may have made this patient more susceptible to the effects of vinblastine, resulting in irreversible neuronal injury or loss.

Sensory involvement in vinca alkaloid toxicity is commonly experienced as pain. Involvement in the distribution of the trigeminal and glossopharyngeal nerves was well documented by McCarthy and Skillings in two papers (1991, 1992). Pain was primarily experienced in the temporomandibular joint, ears, throat, mandible and mandibular teeth. Difficulty in mastication was described in some patients. Interestingly, in this study, 40 patients were specifically asked about voice changes, and 10 per cent were found to be hoarse.

Dysphagia is another symptom of vagal nerve palsy. Dysphagia was associated with four of the previously documented cases, as well as with our first case. Chisholm and Curry (1978) observed dysphagia in two patients treated with vincristine for carcinoma of the breast. Oesophagoscopy was normal. The patients' symptoms improved on stopping the drugs, but returned in one patient who was recommenced on vincristine, again improving when the drug was withdrawn. No mention was made of vocal fold pathology.

Various papers document involvement of the optic nerve, which range from night-blindness (Ripps *et al.*, 1984) to severe visual loss following a single dose of vincristine (Teichmann and Dabbagh, 1988). Two cases of sudden sensorineural hearing loss have been described. Mahajan *et al.* first suggested an ototoxic effect of the drug

in 1981. This was followed up by a report in 1990 by Lugassy and Shapira, whose patient developed two episodes of severe, bilateral sensorineural deafness, which completely recovered within two months of stopping vincristine, on both occasions. One patient in Annino *et al.*'s (1992) series had a weak vocal fold, right seventh nerve palsy, blurred vision, and paraesthesia of the extremities.

## Conclusion

Patients with a variety of malignant diseases may be treated with various chemotherapeutic agents, including the vinca alkaloids. The ENT surgeon rarely needs to know about the side-effects of such specialist drugs, but vincristine-induced neuropathy may present to clinic in a variety of ways. A vocal fold palsy may be thought to represent a deterioration in the patient's response to chemotherapy, when in actual fact, the malignancy may be responding well. It is important to recognize that this may be a drug-induced lesion, to prevent inappropriate prolongation of therapy, and possible worsening of symptoms. Improvement usually occurs gradually over one to two months if the drug is withdrawn, as suggested by most papers. Failure to do so may result in a permanent disability. Bilateral fold palsies have occurred in four of the 27 previously reported cases and such patients may require tracheostomy until the neurotoxic effects have worn off. Hoarseness is probably more common than we realize with these drugs, but it is rarely looked for, and only the worst patients are referred for further investigations of the cause. Furthermore, if indirect examination of the larynx is otherwise normal, expensive, invasive diagnostic procedures to look for local pathology may not be necessary.

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Address for correspondence:
Dr B. V. Burns, M.B., Ch.B.,
Department of Otolaryngology,
Kent County Ophthalmic and Aural Hospital,
Church Street,
Maidstone,
Kent ME14 1DT.