e - ISSN - 2349 - 8005

INTERNATIONAL JOURNAL OF ADVANCES IN CASE REPORTS

Journal homepage: www.mcmed.us/journal/ijacr

VINCRISTINE-INDUCED BILATERAL VOCAL CORD PARALYSIS IN A CHILD WITH RHABDOMYOSARCOMA

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Article Info
Received 15/08/2015
Revised 27/08/2015
Accepted 12/09/2015

Key words:
Rhabdomyosarcoma, Neuropathy, Vincristine, Vocal cord palsy.

ABSTRACT
Vincristine-induced vocal cord paralysis is a rare but potentially dangerous condition. Its neurotoxicity is dose limiting and resolves spontaneously upon withdrawal of the vincristine in most of the cases. We describe a child with rhabdomyosarcoma who developed bilateral vocal cord paralysis causing progressive stridor during treatment with vincristine. A high index of suspicion of vincristine-induced vocal cord palsy is needed in a child on chemotherapy with new onset stridor with prompt otolaryngology consultation. Concomitant use of azoles possibly enhance the neurotoxicity effect of vincristine thus should be used with caution.

INTRODUCTION

Vincristine is a vinca alkaloid and one of the widely used antineoplastic drugs. It has a well-known efficacy for the treatment of acute lymphoblastic leukemia and many solid tumors. Its dose limiting neurotoxicity is a well-described entity, which may include peripheral (motor/sensory), autonomic, cranial neuropathies, or encephalopathy. However, cranial neuropathy is not widely recognized and so far no more than 25 pediatric patients with vincristine-induced vocal cord palsy have been reported. The pathogenesis of the vincristine-induced neurotoxicity is still ill defined. We report a child who developed progressive bilateral vocal cord palsy during induction treatment of rhabdomyosarcoma of mandible receiving Vincristine chemotherapy along with local radiation.

CASE REPORT

We present the case of a 5 year- old male, who presented with huge swelling over left buccal region. He was admitted under the care of oncology department for work-up and was diagnosed to have intermediate risk rhabdomyosarcoma. He was started on therapy based on Children's Oncology Group, ARST0531 protocol consisting of Vincristine, Dactinomycin and Cyclophosphamide (VDC) along with local control. On and off he also needed supportive medications including antibiotics for febrile neutropenia and fluconazole for mucositis.

On day 2 of the week 10 chemotherapy (VC), he developed stridor and hoarseness. He was received ten doses of vincristine (1.5mg/m2; maximum dose 2 mg) and currently on local radiation therapy as per protocol. He was otherwise asymptomatic. This respiratory symptoms was initially felt to be associated with an upper respiratory tract infection; however it progressed over the next 3 weeks. There were no previous clinical symptoms of neuropathy and no positive history for inherited neuropathies. Physical examination of the oropharynx followed by a CT scan of

the neck revealed no cause for hoarseness. ENT was taken on board and a flexible fiber optic endoscope done showed both vocal cords to be in abducted position with loss of movement of both vocal cords. There was loss of deep tendon reflexes. The nerve conduction velocity studies showed motor predominant axonal neuropathy involving the upper and lower extremity. Electromyography of larynx could not be done. His subsequent doses of vincristine were put on hold as the vocal cord paralysis was most likely related to vincristine.

Stridor improved after ten days and hoarseness of voice resolved 35 days after the onset of palsy. Subsequent laryngoscopy and flexible fiber optic endoscope showed normal movement of both vocal cords. Vincristine was re-introduced with 75% reduction dose and gradually increased up to full dose as per protocol. The patient's symptoms did not progress further and in the past 2 months have shown significant improvement.

DISCUSSION

Vincristine (VCR) is a widely used chemotherapeutic drug for different types of hematological and solid malignancies. It is well associated with dose limiting neurotoxicity which is known to manifest in different forms. Its manifestation ranges from peripheral sensorimotor neuropathies (neuritic pain, paresthesia) to autonomic (constipation, urinary retention) neuropathies. It is also known to cause cranial neuropathies but they are infrequent [1]. The cranial nerve manifestations related to vincristine neurotoxicity include hearing loss, facial palsy, transient cortical blindness, oculomotor nerve dysfunction [2]. Vocal cord paralysis is another of the cranial nerve manifestations related to VCR neurotoxicity. The primary mechanism of action of vincristine is inhibition of mitotic spindle fibers this inhibits the fast axonal transport by microtubules which is why it is thought to cause the neurotoxicity [3]. Vincristine toxicity is reported as being cumulative. Increased dose strength and frequency both lead to manifestation of VCR toxicity [4, 5]. The toxicity is also known to be enhanced when there is concomitant use of other drugs which interfere with CYP3A4 liver enzymes [6]. Some of the drugs included are allopurinol, erythromycin, isoniazid, mitomycin C, phenytoin and azoles. Our patient was taking fluconazole for mucositis chemoprophylaxis which might have added to the neurotoxicity effect of vincristine.

To date there have been around 20 reported cases of VCR induced VCP as found out by searching the English literature. Most of the reported pediatric patients had a primary diagnosis of ALL which is the most common cancer reported in children. The patient we report had rhabdomyosarcoma and to the best of our knowledge this is the fourth reported case in the available literature. The ages reported for VCR induced VCP vary from infants of 0.4 years (2) to 15 years old in the pediatric age group [7]. Cases in adults have also been reported. The VCP can be both either bilateral, as in our case or unilateral. Although bilateral VCP is more common but among unilateral VCP specifically left cord paralysis is seen more often [5, 8]. The reason for this is thought to be due to the greater length of the left laryngeal nerve [5]. The laryngeal dysfunction is often associated with other neurotoxic manifestation although in cases where there were no obvious neurotoxic manifestations however subsequent nerve conduction study often shows evidence of axonal neuropathy [9]. Our patient had laryngeal dysfunction along with loss of deep tendon reflexes as well after which the nerve conduction study performed showed motor predominant axonal neuropathy.

All reported cases resolved spontaneously after withholding VCR doses with no recurrence of the paralysis on subsequent re-administration of VCR. The recovery period ranges from 1 month to 10 months with a median period of 6 weeks [8]. Supportive measures for respiratory and swallowing difficulties were necessary for only a few reported cases until recovery. Airway measures included intermittent positive airway pressure, tracheostomy and cordectomy [2, 5, 10].

CONCLUSION

Our case illustrates that a high index of suspicion of vincristine-induced vocal cord palsy is needed in a child on chemotherapy with new onset stridor with prompt otolaryngology consultation. Flexible laryngoscopy is required in the diagnostic evaluation of such a patient who has received vincristine. Concomitant use of azoles possibly enhance the neurotoxicity effect of vincristine thus should be used with caution.

ACKNOWLEDGEMENT: NIL

CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

STATEMENT OF HUMAN AND ANIMAL RIGHTS

All procedures performed in human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

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