

CASE REPORT

Unilateral Palpebral Ptosis Associated with Vinblastine Therapy

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ABSTRACT Vinblastine is a plant-derived alkaloid, that is clinically used as an antineoplastic drug. An important complication of vinca alkaloid therapy is neurotoxicity; the ocular system can be involved, with bilateral ophthalmoplegia, diplopia, and bilateral seventh nerve palsy with lagophthalmos. Palpebral ptosis is always bilateral and usually associated with vincristine therapy; rarely has it been reported in association with vinblastine. We report the case of a two-year-old child with systemic Langerhans' cell histiocytosis (LCH), who developed unilateral palpebral ptosis in his left eye six weeks after vinblastine therapy was initiated. This is the first case reported in the literature of unilateral palpebral ptosis during vinblastine therapy.

KEYWORDS Vinblastine; neurotoxicity; ptosis

INTRODUCTION

Vinblastine and vincristine are purified alkaloids derived from the common flowering periwinkle, *Vinca rosea*. Vinca alkaloids have become clinically useful since the discovery of their antitumor properties in 1959. An important complication of the clinical use of vinca alkaloids is neurotoxicity; this adverse effect is qualitatively similar among these drugs, but quantitatively different (vincristine > vindesine > vinblastine).¹ The ocular system can be variously involved. In 1967, Albert *et al.*² described 20 cases with ocular complications induced by vincristine and vinblastine therapy. Among the ocular findings, ptosis was the most frequent presentation, followed by recti and oblique paresis, lagophthalmos associated with seventh nerve palsy, and corneal hyperesthesia. In only two patients was vinblastine sulfate (Velban) used: one patient presented with bilateral palpebral ptosis, the other with seventh nerve palsy and lagophthalmos.

Palpebral ptosis is always bilateral and usually associated with vincristine therapy; rarely has it been reported in association with vinblastine. A Medline search showed that the case of ptosis described by Albert and colleagues in 1967 is the only case report describing this vinblastine-induced adverse effect.

Here, we report the case of a two-year-old child affected by systemic Langerhans' cell histiocytosis (LCH), who developed unilateral ptosis

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in his left eye during vinblastine therapy without any sign of ophthalmoplegia.

CASE REPORT

40 A two-year-old male child presented with systemic Langerhans' cell histiocytosis (LCH). A general examination showed a multi-organ disease with skin, bone marrow, liver, and intestine involvement. LCH was diagnosed after skin biopsy and histopathologic examination. Bone marrow and hematological investigations were also performed. He was started on continuous prednisone (Deltacortene; Bruno, Q4 40 mg/m²/die), methotrexate (Methotrexate; Wyeth Q5 Lederle, 500 mg/m² every two weeks), and vinblastine Q60 (Velbe; Eli Lilly, 6 mg/m² every week) chemotherapy. After six weeks of therapy and a total dose of 12 mg vinblastine, the patient developed unilateral palpebral ptosis in his left eye, with a total blockage of the pupillary axis (Fig. 1); ophthalmologic examination disclosed 55 no sign of ophthalmoplegia. Findings from anterior segment and fundus examinations with dilated pupils were normal. Considering the high dose of steroids, applanation tonometry was also performed and normal results were achieved (12 mmHg in both eyes). Radiological investigations ruled out any orbital involvement of the disease. Vinblastine was immediately discontinued, and anti-amblyopic treatment with patching of the right eye and left palpebral suspension with 60 strips[®] were started. After three weeks, palpebral ptosis progressively resolved without any complication. Palpebral suspension and anti-amblyopic treatment were 65 stopped.



FIGURE 1 Left palpebral ptosis with a total blockage of the pupillary axis.

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DISCUSSION

Vinblastine is a plant-derived alkaloid, that is clinically used as an antineoplastic drug. It is usually administered in association therapy and has been reported to be effective in the treatment of a number of neoplastic diseases, such as Hodgkin's disease, lymphocytic lymphoma, histiocytic lymphoma, mycosis fungoides, advanced testicular carcinoma, Kaposi's sarcoma, and Langerhans' cell histiocytosis (LCH). The anticancer effect of this drug may be related to its colchicine-like arrest of cell mitosis at metaphase.³ With a similar mechanism, vinca alkaloids cause cytotoxic effects in neuronal axons, resulting in neurotoxicity. They bind to a specific site on tubulin and prevent the polymerization of its dimers, disrupting the formation of neurotubules: the absence of these structures impairs the axoplasmic flow in neuronal axons.⁴ Neurological injury can occur in the peripheral nervous system (paresthesias, depression of deep tendon reflexes, foot drop, seizures, difficulties in gait) and in the central-autonomic nervous system; it can also involve the cardiovascular system, inducing postural hypotension and detrusor areflexia causing atonic bladder, or the gastrointestinal tract, with colicky abdominal pain, constipation adynamic ileus, and rarely dysphagia induced by motor dysfunction of the esophagus.^{4,5} The severity of vinca alkaloid neurotoxicity is usually dose-dependent. Recovery may take weeks or months, depending on the severity of the neuropathy, and residual minor abnormalities sometimes persist. Significant neurotoxicity is less frequently observed with vinblastine than with vincristine.¹ Neurotoxicity affects the ocular system in various way. The most frequent effects reported with vincristine therapy are extraocular muscle paresis, seventh nerve palsy with lagophthalmos, corneal hyperesthesia, and bilateral ptosis; unilateral optic neuropathy rarely occurs.⁶ Recently, a case of isolated abducens nerve palsy was also described.⁷

Cases of bilateral palpebral ptosis induced by vincristine therapy are well described in the literature. In contrast, vinblastine-induced bilateral ptosis has rarely been reported: Albert *et al.*² studied a series of 20 oncology patients with ocular signs of vinca alkaloid neurotoxicity. Eighteen patients were treated with vincristine (Oncovin), while only two were administered vinblastine. Fourteen patients presented with bilateral ptosis, often associated with ophthalmoplegia and seventh nerve palsy. Vincristine therapy in addition to other

chemotherapeutic agents was given to 13 of these patients, whereas only one child received vinblastine. The other patient treated with vinblastine in the report by Albert and co-workers developed seventh nerve palsy.

120 Bilateral ptosis without pupillary or other oculomotor dysfunction was observed by Sandler and colleagues in five of 50 patients treated with vincristine therapy.⁸ No cases of unilateral palpebral ptosis have been reported in the literature among patients with vinca alkaloid-
125 induced neurotoxicity.

Langerhans' cell histiocytosis is an uncommon disease, characterized by destructive lesions that can involve both bone and soft tissue. The lesions consist of focal agglomerations of monocytic cells along
130 with other inflammatory cells, typically eosinophils. In children, the disorder most commonly affects the bones, especially those involved in hematopoiesis, and the skin. Three different forms of histiocytosis were initially described:⁹ the first, eosinophilic gran-
135 uloma, is a disease in which the lesions are confined to bones; the second, usually seen in younger patients, is a more widespread and aggressive disorder named Hand-Schuller-Christian disease; and the third, often affecting the youngest group of patients
140 with LCH (aged 2 years or less), is characterized by multisystem involvement, including cutaneous, lymph node, visceral, ocular, and orbital diseases (Letterer-Siwe disease). Orbital involvement occurs in about 20% of all LCH cases and is usually seen in children
145 with the localized form of the disease (eosinophilic granuloma).

Our patient presented with a typical multisystem LCH. The absence of any orbital involvement of the disease and the improvement of the palpebral ptosis after the discontinuation of vinblastine therapy indicated

a typical case of vinca alkaloid-induced neurotoxicity. 150
The risk of onset of other manifestations of neurotoxicity, such as ptosis in the fellow eye, caused us to discontinue the vinblastine treatment and avoid a simple lowering of the therapy.

To our knowledge, this is the first case of vinblastine- 155
induced unilateral palpebral ptosis. Since vinca alkaloid neurotoxicity is dose- and age-dependent, with a higher toxicity in older patients, it is possible that this unusual finding of unilateral ptosis is just due to the lower rate of side effects in younger patients. Our patient's young 160
age suggested a prompt treatment of the ptosis to prevent the onset of an insidious deprivation amblyopia. Because recovery usually occurs a few weeks after the discontinuation of therapy, surgical correction of the
165 ptosis is not indicated.

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