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Peroneal Mononeuropathy in Pediatric Hodgkin's Disease

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A 12-year-old boy with Hodgkin's disease developed left peroneal nerve palsy during combination therapy with chemotherapy and low-dose irradiation. The palsy occurred twice; around 1–2 weeks after the second administration of vincristine in the second and third COPP (cyclophosphamide, vincristine, prednisolone, and procarbazine) regimens. Without any treatment, the peroneal neuropathy completely resolved clinically three months and electromyographically six months after the onset. He used to play television games for more than 6 hours a day with the legs crossed while sitting on the bedside. Compared to adult patients, little is known about the relationship between peroneal neuropathy and systemic malignant diseases in pediatric patients. This case shows for the first time that habitual leg crossing during potentially neurotoxic chemotherapy could induce peroneal mononeuropathy in a pediatric cancer patient.

Keywords: Hodgkin's disease, mononeuropathy, leg crossing, peroneal nerve palsy, vincristine neurotoxicity

INTRODUCTION

Nontraumatic peroneal nerve palsy in children is uncommon. Disorders of peripheral nerve may occur as a direct result and as a remote effect of underlying malignant disease.[1] Although the relationship between peroneal neuropathy and systemic malignant disorders has been extensively investigated in adult patients,[2,3] little is known about such a link among pediatric patients. To our knowledge, there has not been any association previously identified between pediatric systemic cancer and peroneal neuropathies, aside from the association with chemotherapy.[4,5] Peroneal neuropathy related to chemotherapy is usually symmetrical.[1,6] Here we described a patient with Hodgkin's disease who developed peroneal mononeuropathy probably due to a combination of the leg crossing and neurotoxic chemotherapy.

CASE REPORT

A 12-year-old boy had been healthy until 6 months before admission, when right cervical lymph node swelling had been noted. He was hospitalized because the lymph nodes had progressively enlarged. Magnetic resonance image (MRI) showed a number of enlarged lymph nodes extending from the left cervical and supraclavicular regions. Scintigraphy using Ga^{67} and Tl^{201} showed hot spots in the right axilla in addi-

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tion to the regions detected by MRI. Histologic examination of the biopsy sample from cervical lymph nodes on the 7th day after admission showed Hodgkin's disease of the nodular sclerosing subtype. We treated him with modified combination therapy based on the Stanford experience,[7] consisting of 6 cycles of chemotherapy and low-dose (15Gy) involved field radiotherapy. Six cycles of chemotherapy were administered in an alternative fashion – three of ABVD (doxorubicin 25 mg/m^2 on days 1 and 15, bleomycin 10 U/m^2 on days 1 and 15, vinblastine 6 mg/m^2 on days 1 and 15, and dacarbazine 375 mg/m^2 on days 1 and 15) and three of COPP (cyclophosphamide 500 mg/m^2 on days 1 and 8, vincristine 1.4 mg/m^2 (top dose 2 mg) on days 1 and 8, procarbazine 100 mg/m^2 on days 2 to 15, and prednisolone 40 mg/m^2 on days 2 to 15). Treatment was initiated with two cycles of chemotherapy; one each of ABVD and COPP, and was followed by irradiation in 1.5-Gy fractions.

Around two weeks after the end of the fourth regimen (COPP), he noted muscle weakness when attempting to flex the left foot. However, this symptom disappeared within a few days. One week after the cessation of the sixth regimen (COPP), he again complained of difficulties in walking. Muscle weakness was observed in the left tibialis anterior and peroneal muscles. The deep tendon reflex was absent in the bilateral knee and ankle joints. Sensation appeared intact. The left peroneal motor response, recording the extensor digitorum brevis, was reduced in amplitude (0.97 mV) compared to the right (3.4 mV), and demonstrated a delayed conduction velocity (37.9 m/sec) compared to the right (49.2 m/sec) when stimulated above the knee, but normal results when stimulated below the knee. There were no other abnormalities observed in the both sural and median nerves. MRI did not depict any abnormalities around the spinal cord in the lumbosacral regions. However the patient had a habit of playing television games keeping the left leg crossed over the right leg while sitting on the bedside. A diagnosis of left common peroneal nerve palsy at the fibular head was made. Three months after the second onset of drop foot, he spontaneously was able to walk without difficulties. Electromyographic abnormalities had recovered six months after their onset.

DISCUSSION

We present a child with Hodgkin's disease who had a unilateral peroneal neuropathy during treatment. Peroneal mononeuropathy usually occurs in elderly patients[2,3,8,9] and is uncommon in childhood. A large series of more than 1100 pediatric patients studied by electromyography identified only 15 patients with peroneal mononeuropathy.[8] In another series of 103 patients with peroneal mononeuropathy, only 7 patients were younger than 18 years of age and in over one-half of these patients, neuropathy was the result of trauma.[9] There was no indication of systemic malignant disease in any patient in either study.

Recently, a relationship between peroneal neuropathy and systemic malignant disorders has been extensively investigated in adults.[2,3] Rubin et al. found 58 patients (0.05%) with peroneal neuropathy among 115081 cancer patients over a 10-year period, and 47 were unilateral cases.[2] They showed that the associated factors included significant weight loss (60% of patients), crossing the legs (35%), recent chemotherapy (16%), cutaneous vasculitis (5%), and local invasion (3%).[2] Another large series suggested that this neuropathy is due to a combination of metabolic factors such as poor nutritional status and mechanical factors such as weight loss and prolonged bedridden status.[3]

What was the cause of the neuropathy in our case? Since the patient was well nourished and even slightly obese, weight loss was unlikely to have induced neuropathy. The first plausible cause was neurotoxic chemotherapeutic agents. The treatment regimen used for our patient has generally been tolerated without significant problems.[7] Of the agents used, vincristine is well known to be neurotoxic. Peripheral neuropathy related to vincristine is usually symmetrical and of mixed sensory-motor type.[1,6] The neurotoxicity is generally dose-related and cumulative, such that the drug should be stopped after a total dosage of 30 to 50 mg.[6] Our patient received vincristine in 2 mg doses on days 1 and 8 of each COPP regimen, amounting to a cumulative dose of 12 mg. However, in this respect it should be noted that peroneal mononeuropathy due to vincris-

tine toxicity has been reported after 4 weekly injections of 1.6-mg vincristine in 3-year-old boy with acute leukemia, whose initial symptoms appeared as unilateral leg weakness.[5] In our case, there was a temporal association of the administration of vincristine and the development of clinical findings. Furthermore, absence of deep tendon reflexes in the lower legs may indeed indicate an early vincristine neurotoxicity.[6] Thus, vincristine may have contributed to peroneal nerve palsy in our case. In addition the peroneal mononeuropathy might also have been induced by leg crossing. The left peroneal nerve was repeatedly compressed while the patient was absorbed in television games. After he was admitted to hospital he withdrew to his room where there were no other patients, and he was unwilling to participate in recreational programs in the playroom. Hospitalized children cope with the stress of illness in a variety of ways,[10] and we should have paid a more attention to his psychological problems so as to prevent this complication. Electromyographic studies in our patient showed both a delay in conduction velocity at the head of the femur and a low amplitude in the affected peroneal nerve. These results suggest that compression was a dominant cause, since vincristine neuropathy usually manifests as axonal degeneration rather than segmental demyelination, which electromyographically manifests as reduction of amplitude but little loss of nerve conduction velocity.[9,11] Taken together, our case demonstrates for the first time that habitual leg crossing during the administration of potentially neurotoxic agents can play a causal part in peroneal mononeuropathy in a pediatric patient with systemic malignancy.

A recent epidemiological study by Koehler et al. indicated that the relative risk, corrected for age and gender, for peroneal neuropathy in cancer patients compared with patients without cancer was 3.4, and referred to this complication as a paraneoplastic syndrome.[3] A large cohort study is, however, necessary to address the issue of whether peroneal neuropathy is also more likely to occur in pediatric cancer patients.

The peroneal nerve palsy in our patient resolved without any treatment. In one large study, the outcome of this complication was good; 80% of the affected patients had either improvement (42.9%) or resolution (37.1%) after a median follow-up of 6 months.[2] Since most of the patients in this study were older with a median age of 70 years,[2] the outcome of peroneal neuropathy in pediatric patients in comparison is excellent. However, severe cases may require surgical intervention in order to correct the fixed deformity.[4] A behavioral pattern predisposing to compression of the peroneal nerve should be prevented. Furthermore, proper bracing and/or physical therapy at the time of the diagnosis of the severe neurologic deficit will prevent fixed contractures and the necessity for surgery.[4]

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