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CASE REPORT

Treatment-induced remission of medulloblastoma using a chemotherapeutic regimen devoid of vincristine in a child with Charcot–Marie–Tooth disease

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ABSTRACT

Charcot–Marie–Tooth (CMT) disease is the most common form of inherited neuropathy. Core features include peripheral neuropathy and secondary axonal degeneration, with a noted distal predominance of limb-muscle wasting, weakness, and sensory loss. Given the significant prevalence of CMT, superimposed neoplastic disease can be encountered within this patient population. Malignancies that are treated with vincristine (a microtubule-targeting agent), even at low doses as part of standard treatment, pose a significant challenge for patients with CMT. Here, we present the case of a child with CMT who was successfully treated for medulloblastoma without vincristine, a standard drug used for treatment of that disease, to avoid the risk of severe debilitating neuropathy. This report is the first of a patient successfully treated for medulloblastoma without vincristine.

Key Words Charcot–Marie–Tooth, chemotherapy, medulloblastoma, neurotoxicity, radiotherapy, vincristine

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INTRODUCTION

Charcot–Marie–Tooth (CMT) disease is a genetically and phenotypically diverse disease affecting peripheral sensory and motor nerves alike. It occurs in up to 1 in 2500 people in the United States[1,2]. Symptoms often arise in childhood or adolescence and include gradually progressive motor neuropathy of the arms and legs, distal limb-muscle wasting, sensory loss, and reduced deep-tendon reflexes[1]. Patients with CMT can also have any or all of pes cavus, hammer toes, gait difficulties, foot drop, and muscle cramps[1].

Given the underlying pathogenesis of CMT, it is perhaps unsurprising that data have emerged to suggest that certain antineoplastic agents with neurotoxic profiles are contraindicated[3]. Chemotherapy-induced peripheral neuropathy is a recognized side effect of several antineoplastic agents, including vinca alkaloids (for example, vincristine), taxanes (for example, paclitaxel), and platinum-based compounds, and has been found to cause severe sequela in patients with CMT[4]. Unfortunately, vincristine has been part of the backbone of standard-of-care treatment regimens for patients with medulloblastoma.

Here, we report the case of a child with CMT who was subsequently diagnosed with desmoplastic nodular medulloblastoma. The clinical conundrum for this patient was weighing the historical data (which suggest the need for vincristine as a part of a multi-agent protocol) against the risk of known toxicities from vinca alkaloids in CMT. Critically, our patient's medulloblastoma was successfully treated with gross total resection, daily carboplatin during standard-dose craniospinal radiation, and 9 cycles of maintenance chemotherapy that was devoid of vincristine.

CASE DESCRIPTION

A 3.5-year-old girl previously diagnosed with CMT related to an *MPZ* mutation presented with chronic posterior neck pain, increasing difficulty ambulating, left-sided esotropia,

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and intermittent vomiting. Magnetic resonance imaging demonstrated an intra-axial non-enhancing mass located within the cerebellar vermis. The patient underwent a gross total resection of the tumour, and postoperative magnetic resonance imaging showed no evidence of residual disease. Pathology confirmed the diagnosis of a desmoplastic nodular histologic variant of medulloblastoma, *SHH*-activated and *TP53* wild-type molecular subtype (Figure 1). Spinal magnetic resonance imaging and lumbar puncture evaluating the cerebrospinal fluid were negative for disease.

Accordingly, the patient was staged as standard-risk medulloblastoma and was started on therapy based on the Children's Oncology Group protocol ACNS0331 (Table I). The radiation plan included 23.4 Gy in 13 fractions to the entire craniospinal axis, followed by a posterior fossa boost to 54 Gy total (30 fractions). The mean cochlear dose was 33 Gy bilaterally. Standard therapy on ACNS0331 for the patient's disease would have consisted of 30 doses of vincristine at 1.5 mg/m^2. However, vincristine is known to cause severe unacceptable toxicity in patients with CMT[5], and secondary to favourable outcomes with desmoplastic medulloblastoma[6], we elected to avoid vincristine and instead to substitute daily carboplatin during radiation, followed by lomustine and cisplatin alternating with cyclophosphamide for maintenance (Table I), based on previous safety and efficacy data for that approach[7]. Complete blood count and a comprehensive metabolic panel were checked weekly during radiation and before each chemotherapy administration during maintenance therapy.

That treatment regimen was relatively well tolerated. The dose of cisplatin had to be reduced by 50% for cycles 5, 7, and 8 because of the development of bilateral mild sensorineural hearing loss. Despite the reduction, the patient continued to experience progressive hearing loss. Audiometry revealed severe bilateral hearing loss at high frequencies and mild bilateral loss at lower frequencies, and she was prescribed hearing aids after treatment. The dose of lomustine was also reduced by 50% for cycle 8 because of thrombocytopenia. Motor development continued throughout treatment. At 9 months after treatment, the patient could walk and run independently; however, she did use braces and, secondary to leg pain, had a wheelchair for long distances. Her expected motor delays were

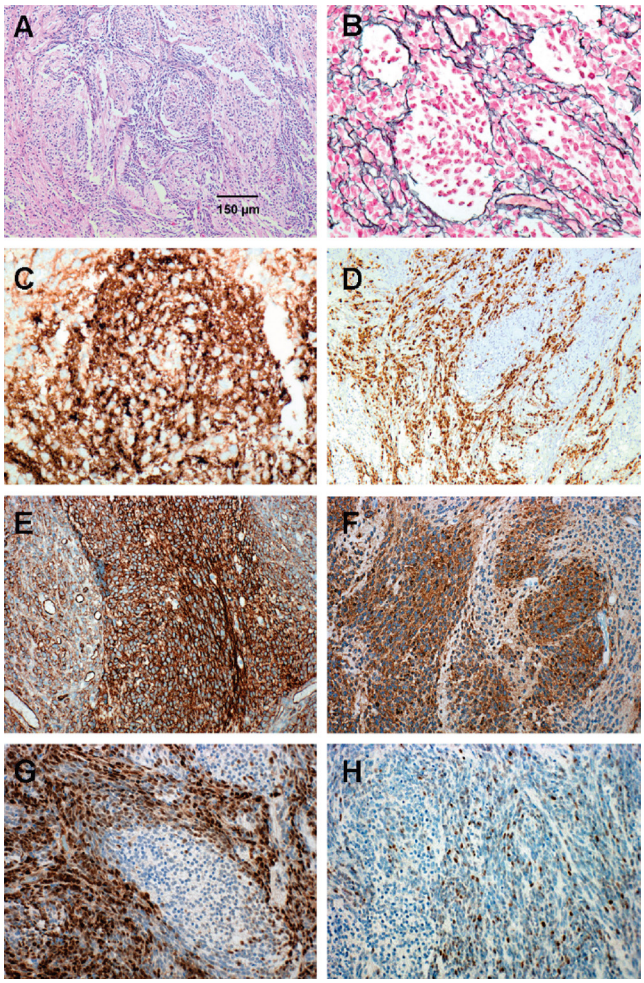

FIGURE 1 Immunohistochemistry of patient's tumour. The morphologic features and immunoprofile were consistent with the nodular desmoplastic histologic–variant, *SHH*-activated, *TP53* wild-type molecular subtype. (A) Hematoxylin and eosin stain, 10× original magnification. (B) Nodular growth pattern highlighted by reticulin silver stain, 40× original magnification. (C) Expression of synaptophysin, 40× original magnification. (D) High MIB-1 proliferation index within inter-nodular regions, 10× original magnification. (E) Beta-catenin cytoplasmic-only immunoreactivity, 20× original magnification. (F) Cytoplasmic immunoreactivity for GAB1, 20× original magnification. (G) YAP1 nuclear and cytoplasmic staining, 20× original magnification. (H) Scattered p53-positive cells, 20× original magnification.

TABLE I Treatment regimen[a] for medulloblastoma in child with Charcot–Marie–Tooth disease, adapted from Children's Oncology Group Study ACNS0331

Chemoradiotherapy
■ Craniospinal radiation, 23.4 Gy in 13 fractions
■ 54 Gy Boost to the posterior fossa in 30 fractions
■ Intravenous vincristine 1.5 mg/m^2 weekly for 6 doses **(omitted)**
■ Intravenous carboplatin 35 mg/m^2 daily during radiation therapy for 30 doses **(added)**
Maintenance
Cycles 1, 2, 4, 5, 7, 8 (42 days per cycle)
■ Intravenous cisplatin 75 mg/m^2 on day 1 of each cycle (50% dose reduction for cycles 5, 7, and 8)
■ Oral lomustine 75 mg/m^2 on day 1 of each cycle (50% dose reduction for cycle 8)
■ Intravenous vincristine 1.5 mg/m^2 on days 1, 8, 15 of each cycle **(omitted)**
Cycles 3, 6, 9 (28 days per cycle)
■ Intravenous cyclophosphamide 1000 mg/m^2 on days 1 and 2 of each cycle
■ Intravenous mesna 360 mg/m^2 given at 4 and again at 8 hours after cyclophosphamide
■ Intravenous vincristine 1.5 mg/m^2 on days 1 and 8 of each cycle **(omitted)**

[a] Boldface type indicates the adjustments made to the regimen for this patient.

attributed to CMT, and there was no clear evidence that treatment had caused any exacerbation of her neuropathy. She maintained a normal sensory exam (intact to touch and vibration) during and after treatment.

DISCUSSION

We report the case of a child with CMT subsequently diagnosed with desmoplastic nodular medulloblastoma who is currently 48 months off therapy, in remission after treatment with surgery, radiation, and a vincristine-sparing chemotherapeutic regimen. To our knowledge, this is the first report of a patient successfully treated for medulloblastoma without vincristine. It is important to note that the addition of carboplatin during radiation therapy in this patient might have contributed to both the prolonged remission and increased toxicity.

Although CMT most often presents with distal weakness and atrophy, it represents a phenotypically diverse spectrum of disorders with variation in age of onset, disease severity, and overall prognosis. Most cases of CMT are associated with mutations in either *PMP22, GJB1, MFN2,* or as in our patient, *MPZ*[8]. Patients with CMT are prone to medication-induced exacerbation of pre-existing or even subclinical neuropathy[5]. Several classes of antineoplastic agents, including vinca alkaloids, taxanes, and platinum-based compounds, have been shown to cause severe and sometimes irreversible neurologic sequela in CMT patients[3,4]. In a case review of 38 CMT patients with chemotherapy-induced peripheral neuropathy, vincristine was the agent responsible for toxicity in 92% of cases, despite the fact that cumulative doses were often below standard neurotoxic thresholds (2–6 mg/m^2)[3].

For years, the standard of care in the treatment of medulloblastoma has been surgery, radiation, and vincristine-based adjunctive chemotherapy, and the cumulative dose of vincristine for standard-risk medulloblastoma that was used in the Children's Oncology Group protocol ACNS0331[9,10] was 45 mg/m^2. Other comparable clinical trials have studied ways to lower the cumulative dose of vincristine, including PENT-5 from the International Society of Pediatric Oncology, with a cumulative dose of 18 mg/m^2, and St. Jude Medulloblastoma-96, with a cumulative dose of 12 mg/m^2. That being said, both the foregoing protocols use upwards of 2–3 times the aggregate dose of vincristine that was found still to have a major side effect profile for the CMT patient population[3]. That dose poses a significant challenge for clinicians who must decide between providing the most efficacious antitumour treatment and avoiding potentially devastating side effects.

Medulloblastoma has long been divided into subtypes based on morphologic and histologic features, and those subtypes are predictive of prognosis. New insights into genomic and molecular signatures have increased the precision and accuracy with which clinicians are able to classify and treat medulloblastoma. Current consensus opinion divides medulloblastoma into 4 molecular subgroups based on their transcriptional profile: *WNT, SHH,* group 3, and group 4. Like the histologic subtypes, those 4 subgroups are associated with distinct demographics, histology, and clinical outcomes[11,12]. An effort is being made to use histologic and genetic markers and patient age to guide trials of de-escalation therapies and to determine whether less-intensive radiation and chemotherapy regimens are able to lower the rates of therapy-associated adverse effects while maintaining a high survival rate[13].

Recent efforts have also focused on the *WNT* group (NCT02066220 and NCT02724579 at http://ClinicalTrials.gov/), which has the most favourable outcomes (10-year survival > 95%)[11]. We adopted a similar strategy of de-escalation for our patient with CMT and desmoplastic nodular medulloblastoma with *SHH* activation. Nearly all desmoplastic nodular medulloblastoma shows *SHH* activation[12]. Desmoplastic nodular tumours diagnosed before age 3 have been shown to have an excellent prognosis, with 5-year survival rates exceeding 85%[6], and in a group of older children with *SHH*-activated medulloblastoma, patients with tumours that were *TP53* wild-type had a 5-year survival rate that was nearly double that for patients with tumours that were *TP53* mutant (81% vs. 41% respectively)[14]. Because our patient was more than 3 years old and had desmoplastic nodular medulloblastoma that was *SHH*-activated and *TP53* wild-type, we decided to spare vincristine therapy based on the likelihood of response to treatment and the potential for debilitating complications if we used vincristine in the setting of CMT.

The utility of vincristine during maintenance therapy for standard-risk medulloblastoma is a subject of debate. One meta-analysis specifically evaluated the 4 most common chemotherapeutic agents used in standard protocols for medulloblastoma (cisplatin, lomustine, cyclophosphamide, and vincristine) and found that variation in the cumulative vincristine dose did not affect outcomes in children with this type of cancer[15]. In children diagnosed between the ages of 3 and 21 years with average-risk medulloblastoma, a chemotherapy regimen that reduced the cumulative vincristine dose by 75% achieved event-free survival of better than 80%[16]. That being said, standard-of-care protocols in the United States and Europe include vincristine doses that are higher than recommended for patients with CMT. All patients could benefit from the reduction in toxicities associated with reduced-vincristine regimens, but patients with CMT are still at risk for neuropathy at much lower doses than are used in standard protocols. As noted earlier, many cases of patients with CMT developing chemotherapy-induced peripheral neuropathy after treatment with low-dose vincristine (less than 2–6 mg/m^2) have been reported[3]. In this vulnerable population, complete sparing of vincristine should be considered when possible. Additionally, oncologists should assess patients for potential inherited neuropathies by taking a thorough family history and conducting a focused physical exam.

The concept of therapy regimens devoid of vincristine for patients with CMT is a generalizable theory for adult patients diagnosed with medulloblastoma as well. Although a diagnosis of CMT is rare in adults, medulloblastoma regimens are most often based on pediatric chemotherapeutic regimens, which all include doses of vincristine[17,18]. Thus, evaluating the need for vincristine in adults with a similar clinical course would be prudent to lower toxicity while maintaining an excellent outcome.

SUMMARY

Our patient experienced a complete response to therapy and has been in remission for 48 months. The increased availability of genetic and molecular diagnostic tools has made it easier to diagnose hereditary neuropathies such as CMT and to confirm medulloblastoma subgroups. It might therefore be prudent for clinicians to consider vincristine-sparing chemotherapy regimens in cases in which a patient with a hereditary neuropathy is diagnosed with a medulloblastoma of a favourable morphologic, histologic, or molecular subtype.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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