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Case Report

Rituximab treatment for relapsed opsoclonus–myoclonus syndrome

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Abstract

Introduction: Opsoclonus–myoclonus syndrome (OMS) is a rare neurological disorder that is associated with paraneoplastic diseases. Because OMS can frequently relapse, patients may be inflicted with neurological problems for a long time. Recently, rituximab (RTX) was introduced as a drug to treat OMS. To assess RTX treatment, we studied a patient who experienced recurrence of OMS.

Case report: A 2-year-old Japanese boy, who had left adrenal neuroblastoma, suddenly showed OMS symptoms, including ataxia and opsoclonus. Surgical resection of the tumor and subsequent steroid therapy ameliorated his symptoms. When OMS relapsed during the time when prednisolone was reduced, he was treated with full-dose RTX therapy (375 mg/m^2/week) for 4 consecutive weeks. However, 1 year later, he presented again with OMS symptoms. This time, we only administered an additional single dose of RTX treatment (375 mg/m^2), allowing remission of OMS symptoms. During 2 years after the additional RTX treatment, OMS symptoms did not appear, even when prednisolone was reduced. He had no adverse events associated with RTX during the whole treatment period.

Conclusions: An additional single-dose RTX therapy might be effective for relapsed OMS patients who were previously treated with full-dose RTX therapy.

Keywords: Opsoclonus–myoclonus syndrome; Rituximab; Single dose; Neuroblastoma

1. Introduction

Opsoclonus–myoclonus syndrome (OMS) is a rare neurological disorder that is associated with paraneoplastic diseases. OMS is characterized by cerebellar ataxia, myoclonus, opsoclonus, and other behavioral abnormalities [1]. In Japan, the number of OMS patients was only 23 according to a nationwide survey from 2005 to 2010 [2]. The mean age at disease onset of OMS is 16.5 months [2]. Although the etiology of OMS is still unclear, OMS is considered to be associated with an autoimmune pathogenesis. OMS occasionally has a chronic clinical course. OMS patients may suffer from

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residual neurological sequelae, such as motor abnormalities, speech abnormalities, and behavioral problems [3].

OMS is treated with intravenous immunoglobulin therapy and immunosuppressive therapy with agents, such as prednisolone (PSL), methyl-PSL (mPSL), and adrenocorticotropic hormone [4]. Because OMS easily relapses with even a mild upper airway infection, patients may require long-term treatment with a high dose of PSL. Rituximab (RTX), an anti-CD20 chimeric monoclonal antibody, has recently been introduced as a drug for treatment of OMS [5,6]. However, the efficacy and safety of RTX therapy for relapsed OMS still remains to be clarified. To assess RTX therapy for relapsed OMS, we studied the clinical course of a patient with recurrent OMS, who was treated with RTX twice, with full-dose and single RTX therapies.

2. Case report

The patient was a 2-year-old Japanese boy, who was referred to our hospital because of his sudden onset of ataxic gait. He had no past history or family history of neurological disorders. He was initially diagnosed as having acute cerebellar ataxia. The ataxia spontaneously went into remission at that time. One month later, the ataxia relapsed with acute gastroenteritis. He showed multidirectional, rapid and chaotic movement in both of his eyes, and myoclonus on his extremities. Therefore, he was clinically diagnosed as having OMS. Abdominal computed tomography showed neuroblastoma at his left adrenal gland. Urinary vanillylmandelic acid and homovanillic acid levels were elevated (172.9 mg/g creatinine and 212.1 mg/g creatinine, respectively). Iodine-123-metaiodobenzylguanidine scintigraphy showed no region of uptake. The tumor was completely surgically resected. Pathological findings of the resected tumor showed differentiating cells and the Mitosis–Karyorrhexis Index was low. There was no amplification of N-myc. These results indicated that his stage of neuroblastoma was Stage I in the International Neuroblastoma Staging System category. No chemotherapy for the tumor was provided to the patient.

Although the tumor was completely resected, opsoclonus and myoclonus remained. He was treated with mPSL pulse therapy (30 mg/kg/day, 3 days a week, for 3 consecutive weeks), intravenous immunoglobulin therapy (400 mg/kg/day, 5 consecutive days), and subsequent oral PSL therapy (1 mg/kg/day). This treatment was effective for his opsoclonus and myoclonus. However, OMS relapsed at the age of 2 years and 5 months when PSL was reduced to less than 1 mg/kg/day. His OMS relapsed six times before he received RTX. He was easily angered and showed speech difficulties.

Intravenous RTX infusion therapy was started after obtaining approval from the Institutional Review Board of Kobe University Hospital and written informed consent from his parents. RTX was administered to the patient at a dose of 375 mg/m^2/week for 4 consecutive weeks (Fig. 1). To prevent adverse events from acute infusion, we administered acetaminophen (10 mg/kg), α-chlorpheniramine maleate (0.6 mg), and intravenous mPSL (1.5 mg/kg) 30 min prior to RTX infusion. The CD19+ lymphocyte count in the peripheral blood was 751.8/μl before the first RTX infusion, but it was reduced to 7.8/μl after the first RTX infusion. His walking, grasping, and speech were moderately impaired before RTX therapy; the OMS evaluation scale score [7] was 20 (moderate; score range, 0–36). These symptoms were improved after RTX therapy began. The OMS score was 8 after 4 months of therapy (he showed mild walking and standing difficulties, and moderate speech abnormalities) and 2 after 7 months of therapy (he showed only moderate speech abnormalities).

One year after the first RTX therapy ended, when oral PSL doses were reduced to 0.5 mg/kg/day, his ataxia and tremors relapsed, without an increase in CD19+ lymphocytes. His OMS score was elevated to 10 (he showed moderate walking and speech abnormalities again, and mild standing and eye movement abnormalities). To treat the relapsed OMS, additional RTX therapy was carried out. At this time, a single dose of RTX (375 mg/m^2) was administered to the patient. The OMS rapidly improved. Opsoclonus and myoclonus did not appear in the following 2 years, although the CD19+ lymphocyte count increased again 10 months after the additional RTX therapy.

Notably, there were no adverse events or side effects associated with RTX therapy. The patient's developmental quotient was 39 evaluated by Kyoto Scale of Psychological Development (11 months after the last administration of RTX), which means that he had moderate developmental delay. The patient is currently 6 years old. He still takes oral PSL, but its dose is less than 0.2 mg/kg/day. He has no OMS symptoms, except for moderate speech impairment and mild autistic features.

3. Discussion

OMS often presents as a paraneoplastic disease. Therefore, OMS patients recover after neoplastic treatment, including surgical resection [8]. However, more than half of OMS patients have residual neurological motor problems or intellectual disability [3]. Mitchell et al. reported that early aggressive immunosuppression for OMS improved the outcome of OMS patients [4]. In most cases, high-dose therapy of PSL or adrenocorticotropic hormone is effective for OMS. However, long-term administration of these drugs is harmful for physical and psychological development in childhood. Intravenous immunoglobulin is effective in some OMS patients [8], but intravenous immunoglobulin treatment