Pediatr Blood Cancer 2013;60:E163–E165

BRIEF REPORT
Ofatumumab for Refractory Opsoclonus-Myoclonus Syndrome Following Treatment of Neuroblastoma

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Opsoclonus-myoclonus syndrome (OMS) may be associated with ANNA-1 (anti-Hu) autoantibodies. The standard treatment with IVIG, steroids, and anti-CD20 monoclonal antibody may fail, and optimal therapy is unknown. A patient developed OMS with high-titer ANNA-1 following recovery from neuroblastoma. She failed standard therapy and had only transient response to rituximab. Treatment with the humanized anti-CD20 monoclonal antibody ofatumumab combined with methotrexate resulted in transient neurologic improvement and decrease of ANNA-1. This suggests that ofatumumab combined with methotrexate should further be considered OMS patients, particularly in refractory disease. Pediatr Blood Cancer 2013;60:E163–E165. © 2013 Wiley Periodicals, Inc.

Key words: ofatumumab; opsoclonus-myoclonus syndrome; neuroblastoma; rituximab

INTRODUCTION

Opsoclonus-myoclonus syndrome (OMS) is associated with neuroblastoma in 43% of the OMS cases [1]. The characteristic symptoms of OMS are rapid, dancing eye movements (opsoclonus), rhythmic jerking involving limbs or trunk (myoclonus), and/or ataxia. This paraneoplastic autoimmune disorder involves ANNA-1 (anti-Hu) antibodies amongst others. ANNA-1 is directed towards a family of RNA-binding proteins implicated in post-transcriptional regulation of RNA named ELAVL or Hu (primarily HuD) which are expressed in neurons and are highly conserved in neurons [2]. We describe a case of severe OMS, which developed following recovery from treatment of neuroblastoma without evidence of active malignancy. We further describe how the patient, who no longer responded to rituximab, had temporary neurologic improvement with ofatumumab.

CASE STUDY

An 8-month-old female presented with left-sided Horner's syndrome, and was found to have a large mass of the left lower neck/upper mediastinum. Stage IV neuroblastoma, stroma poor, morphologically nodular, and *N-Myc* non-amplified was diagnosed, with metastatic disease to the bone marrow, and bones. She was risk stratified by International Neuroblastoma Staging System (INSS) criteria as intermediate risk due to age, favorable histology and absence of *N-Myc* amplification. The tumor was determined to be unresectable and she was treated with chemotherapy on COG protocol ANBL0531. She completed chemotherapy and underwent complete surgical removal of her primary tumor, but remained tracheostomy dependent postoperatively.

Three months following completion of therapy, she developed RSV-associated respiratory failure requiring full mechanical ventilation. She recovered and was able to be weaned to previous mechanical ventilation support only while asleep. Around this time, she started to have multidirectional ocular jerks and ocular flutter. Over the next 3 months, eye movements steadily increased in frequency and were consistent with opsoclonus.

She was readmitted with diffuse weakness. Paraneoplastic antibody panel was obtained, and only ANNA-1 (anti-Hu) antibody titers were found to be elevated at 1:10,240 (Fig. 1). Repeated evaluations showed no evidence of recurrent neuroblastoma, and no other paraneoplastic autoantibodies were detected at any time. Immunosuppressive therapy with IV immune globulin G (IVIG) and high dose prednisolone followed by dexamethasone was instituted; she had a brief decrease in ANNA-1 level to 1:240 and her opsoclonus began to improve. At this time, the patient suffered from sixth and seventh nerve palsies, and diffuses mild weakness, more proximal than distal. She remained alert and retained deep tendon reflexes. Two months later, ANNA-1 level increased (Fig. 1). She developed nearly continuous opsoclonus, hyporeflexic upper extremities and flaccid, arreflexic lower extremities. Electromyelogram (EMG) and nerve conduction velocity (NCV) studies were consistent with motor neuropathy. Cerebral spinal fluid cell counts and protein level were normal and magnetic resonance imaging was normal.

Despite ongoing IVIG, corticosteroids and plasmapheresis, the patient only briefly became stronger with her best strength determined to be three of five in the right arm with no significant change in ANNA-1 titers. Five months after the onset of her neurologic symptoms, the patient was able to shrug her shoulders and had increased right arm strength, but had no movement in the lower extremities. EMG/NCV studies showed worsening motor axonopathy consistent with anterior horn cell loss.

Eight months after onset of neurologic symptoms, the patient was started on cyclosporine (CSA) and weekly rituximab (375 mg/

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Conflict of Interest: Nothing to report.

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Received 11 February 2013; Accepted 24 May 2013

DOI 10.1002/pbc.24646
Published online 29 June 2013 in Wiley Online Library (wileyonlinelibrary.com).

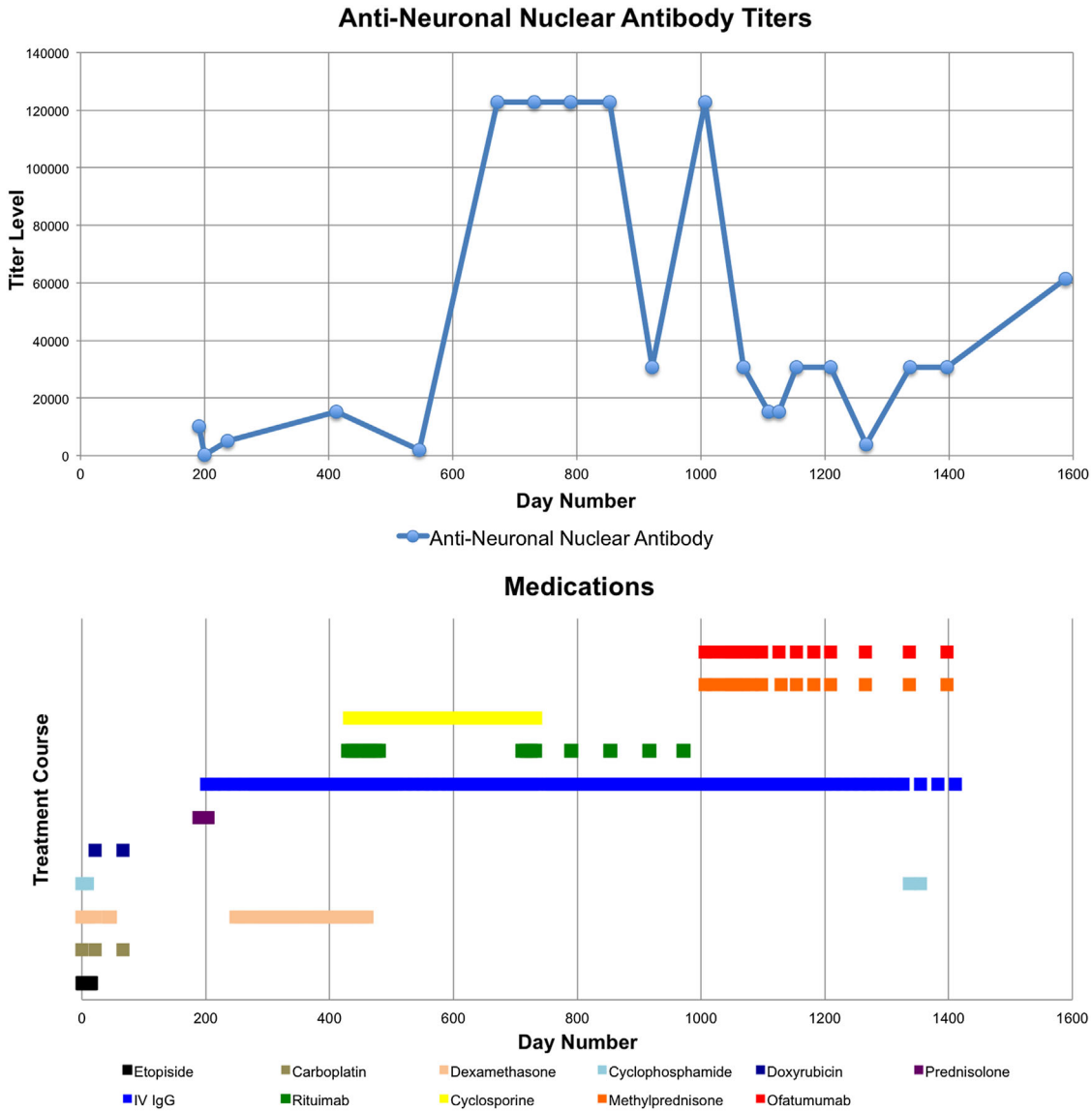

Fig. 1. Longitudinal immunotherapy and antibody titer data. **A:** Anti-Neuronal Nuclear Antibody Titer levels as compared over time. There is a clear decrease in the antibody titer in relationship to the initiation of ofatumumab. **B:** Types and duration of chemotherapy and immunotherapy.

m^2 for 8 doses), followed by monthly maintenance (375 mg/m^2). This resulted in transient improvement with improved strength, right side better than left and corresponding transient decline of ANNA-1 from a peak of 1:15,360 to 1:1,920 (Fig. 1). On rituximab and CSA, her neurologic status again worsened, with bilateral sixth nerve palsies, minimal volitional movement and a near absent blink, markedly worse EMG/NCV consistent with a profound motor axonopathy with increased ANNA-1 to 1:122,880 (Fig. 1).

Given worsening neurologic symptoms, ofatumumab was started (120 mg/m^2 initial dose, followed by 1,000 mg/m^2 weekly) and enteral (G-tube) methotrexate (15 mg/m^2/week). She tolerated treatment well without significant toxicity. She initially had improved motor function, was able to wiggle her hips and upper legs from side to side, and was able to manipulate a switch with her right knee. Neurologic improvement coincided with a significant decrease in ANNA-1 titer to 1:15,360. This was again transient, and neurologic decline was associated with increase in ANNA-1 titer to 1:30,720 (Fig. 1). Ofatumumab therapy was discontinued after 16 doses due to the development of anaphylaxis. A trial of cyclophosphamide (1,000 mg/m^2/dose IV) was instituted, but discontinued after two doses due to hematologic, and infectious toxicities and lack of clinical improvement.

DISCUSSION

The diagnosis of OMS was based on the clinical presentation of opsoclonus followed by motor axonopathy leading to severe motor regression, the association with neuroblastoma and development of high-titer ANNA-1 (anti-Hu) antibodies [1–4]. Without the classic myoclonus and ataxia typically associated with neuroblastoma, as well as the unusual association of cranial nerve palsies and hypo-reflexive neuropathy with opsoclonus, this case represents an atypical, non-classic presentation of OMS. However, unique to this case is the development of OMS following recovery from treatment

of neuroblastoma. It is possible that this represents another case of anti-HU paraneoplastic neurologic syndrome, which can be found in neuroblastoma [5], but the absence of gastrointestinal symptoms and the young age of the patient make this less likely. The presence of ANNA-1 can be found in additional conditions such as limbic encephalitis, paraneoplastic cerebellar degeneration, subacute sensory neuropathry, Lambert-Eaton myasthenic syndrome, brainstem encephalitis, encephalomyelitis, peripheral neuropathy, autonomic dysfunction, and meylopathy [6]. The patient's RSV infection prior to the onset of OMS symptoms may have triggered autoimmune dysregulation and antibody production to neuronal tissue.

Immunosuppressive therapies such as IVIG, steroids, ACTH, cyclophosphamide, and plasmapheresis have been described in the treatment of OMS with limited success [4]. The patient in this case had no appreciable improvement of neurologic symptoms with corticosteroids and IVIG. Recent literature has reported improved treatment success of OMS with anti-CD20 antibodies. Rituximab, the prototype anti-CD20 antibody, has been a successful treatment for OMS [7]. The patient in this case had transient improvement in symptoms and ANNA-1 titer. Rituximab activity depends on polymorphism of CD16 (FcγRIIIa) position 158 and CD32 (FcγRIIa) position 131 [8]. Ofatumumab is a fully humanized IgG1 anti-CD20 antibody, that binds to a different proximal membrane epitope, with greater complement-mediated cytotoxicity, and antibody-dependent cellular cytotoxicity [9,10]. It does not depend on the above-mentioned polymorphism that limits the activity of rituximab.

In our patient's case, ofatumumab was associated with improvement in neurologic symptoms and a sustained decrease in ANNA-1 titers. Successful treatment of chronic-relapsing OMS with ofatumumab was recently reported [11]. ANNA-1 is not always found in OMS, nor the levels reflect the severity of the neurologic manifestations [12,13]. However, the severity of neurologic symptoms loosely correlated with ANNA-1 titers in our patient's case. Methotrexate was added as a modulator of T- and B-cell function, based on our group's experience with use of combination methotrexate and rituximab for successful induction of tolerance to enzyme-replacement therapy in infantile Pompe disease [14,15].

The improvement of neurologic symptoms from OMS refractory to rituximab in this case, as well as the case reported by Pranzatelli et al. [11] demonstrates that a different anti-CD20 antibody agent may provide unique therapeutic advantages [11]. Since chronic and relapsing OMS can be difficult to treat and overall neurologic outcome is poor [16], ofatumumab with or without methotrexate may be promising. Larger, controlled therapeutic trials are needed to confirm these findings.

ACKNOWLEDGMENTS

The authors wish to acknowledge Cynthia L. Sawtell, R.N. for her assistance with the clinical summary of this case.

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