Case Report

Parkinsonism reversed from treatment of pineal non-germinomatous germ cell tumor

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INTRODUCTION

Parkinsonism is a rare complication of germinomas and non-germinatous germ cell tumors (NGGCTs) arising from the pineal region. These pineal region tumors could directly cause this phenomenon by rostral-caudal extension and compression of the substantia nigra pars compacta.
in the midbrain and projections in the nigrostriatal tract to the dorsal stratum.[5] A more common etiology is likely from hydrocephalus caused by compression of the cerebral aqueduct and subsequent enlargement of the third ventricle, presumably stretching the nigrostriatal and nigropallidal tracts.[13] Hydrocephalus-induced Parkinsonism has been well-described and it is potentially reversible by relief of fluid pressure from the ventricular system.[13] Regardless, resection of the pineal region tumor is an important intervention to reverse this type of Parkinsonism.

NGGCTs are sub-classified as “secretory” and “non-secretory” based on the measurable α-fetoprotein (AFP) and β-human chorionic gonadotropin tumor markers in the cerebrospinal fluid, serum, or both.[4,9] Typical presenting symptoms include obstructive hydrocephalus and Parinaud’s syndrome, which are potentially reversible when timely intervention is administered.[4] In this case report, we describe a patient with AFP-secreting NGGCT who presented with asymmetric, bilateral Parkinsonism that was reversed by combined modality treatments consisting of tumor resection, cerebrospinal fluid shunting, multiple cytotoxic chemotherapies, and consolidative proton radiotherapy. Videos of the patient's Parkinsonian state and recovery are also presented.

CASE PRESENTATION

A 23-year-old Caucasian man with history of idiopathic hepatic abscess complicated by portal vein thrombosis developed headache, blurry vision, fatigue, and hypersomnia up to 14 hours of sleep daily. Initial neurologic examination was notable for Parinaud’s syndrome characterized by sluggish pupils, bilateral end-gaze nystagmus, and impaired upgaze. Gadolinium-enhanced head MRI revealed a pineal region mass causing 10 mm of midline shift and compressing the cerebral aqueduct, the left thalamus, and the midbrain [Figure 1], requiring an immediate ventriculoperitoneal shunt for treatment of obstructive hydrocephalus. The patient also had thrombocytopenia caused by platelet sequestration from an enlarged spleen secondary to portal vein hypertension. He was supported with romiplostim and platelet transfusion. Tissue was eventually obtained from a stereotaxic biopsy and the diagnosis was NGGCT with yolk sac component, but without embryonal tissue, choriocarcinoma, or teratoma. The tumor grew quickly and nearly doubled in size in 3 weeks [Figure 2]. He was treated with induction ifosfamide, carboplatin, and etoposide for 6 cycles resulting in partial reduction of the tumor. His serum and cerebrospinal fluid AFP dropped from a high of 1011.0 to 3.6 ng/ml and 677.9 to 0.6 ng/ml, respectively. Before initiation of cytotoxic chemotherapy, the tumor had an increase in size from 34 × 28 × 23 mm to 48 × 32 × 37 mm, but decreased after induction to 24 × 18 × 23 mm.

The patient's bilateral Parkinsonism developed after the first dose of induction carboplatin and etoposide, consisting of bradykinesia, bradyphrenia, facial hypomimia, drooling, and dysphagia requiring a gastric tube for feeding. The right side of his body was more severely affected than the left [Video 1]. His Parinaud’s syndrome and diffuse hyperreflexia also persisted during this time. Levodopa, amantadine, and methylphenidate were administered and titrated to maximal symptom improvement [Video 2]. When the tumor size was reduced by induction chemotherapies, the patient became less Parkinsonian and required fewer medications. Intensive physical and occupational therapies also helped improve his mobility.

His Parkinsonism improved further after second-look neurosurgery, which achieved near total cytoreduction [Figure 3] and revealed residual yolk sac tumor. During recovery, his AFP began to rise again to a high of 134.6 ng/ml. He received a second induction regimen of gemcitabine, paclitaxel, and oxaliplatin followed by apheresis collection of CD34+ stem cells. An autologous transplant was performed using conditioning high-dose carboplatin, thiopeta, and etoposide with concomitant colony-stimulating factor and romiplostim to support his granulocytes and platelets, respectively. His stem cells engrafted promptly in the marrow on posttransplant day 13, enabling him to discontinue growth factor support. His posttransplant head MRI showed no evidence of tumor growth and his serum AFP was within normal limits. He later received consolidative proton beam radiotherapy on posttransplant day 48 for 6 weeks to the craniospinal space. He was completely weaned off all dopaminergic drugs 5 months after his second-look surgery.

Figure 1: Initial presentation of non-germinatous germ cell tumor causing obstructive hydrocephalus. Gadolinium-enhanced T1-weighted head MRI in the axial (a), coronal (c), and sagittal (d) axes performed at presentation showed a pineal region tumor compressing the tectum and causing obstructive hydrocephalus. The FLAIR image in the axial plane (b) revealed some edema in the midbrain.

Figure 2: Initial presentation of non-germinatous germ cell tumor causing obstructive hydrocephalus. Gadolinium-enhanced T1-weighted head MRI in the axial (a), coronal (c), and sagittal (d) axes performed at presentation showed a pineal region tumor compressing the tectum and causing obstructive hydrocephalus. The FLAIR image in the axial plane (b) revealed some edema in the midbrain.
The patient remains in remission 2 years after transplant. At the time of this case report, the patient is able to perform all activities of daily living. He is able to participate in sporting activities such as jogging [Video 3], waterskiing [Video 4], and snowboarding. Consent was obtained from the patient to share videos of his Parkinsonism and subsequent recovery.

DISCUSSION

Central nervous system germ cell tumors are rare, with an incidence of 0.10/100,000 in the United States\cite{5} and belong to a spectrum of extragonadal germ cell malignancies. They are heterogeneous in histologies and are classified according to the revised 2016 WHO classification as germinomas and NGGCTs. Compared to germinomas, NGGCTs tend to be more aggressive and carry a poorer prognosis due to their resistance to treatment with chemotherapy and radiation, and there are...
no efficacy data for targeted agents or immunotherapies. Therefore, combined modality cytotoxic chemotherapies, bone marrow transplant, and consolidative craniospinal radiotherapy are still the standard treatments.

The presenting symptoms of intracranial germ cell tumors are related to their location in the midline near the pineal and suprasellar regions. For tumors arising near the vicinity of the pineal gland, as in our patient, initial symptoms are often those of obstructive hydrocephalus, such as headache, vomiting, and papilledema, as well as symptoms of Parinaud syndrome from compression of the tectum.

Dysfunction of the left substantia nigra, nigrostriatal tracts, and subsequent decreased dopaminergic input to the respective striatum is most likely the cause of our patient’s bilateral Parkinsonism. It is important to note that his motor manifestations were asymmetric and his right side was more severely affected than the left, consistent with a contralateral (left-sided) nigrostriatal localization. The pretreatment diffusion tensor imaging (DTI) revealed that the rostral-caudal fibers from the midbrain were displaced anteriorly and laterally by the portion of NGGCT located in the left thalamus [Figure 1b]. Some of these fibers could be nigrostriatal tracts. Zhang et al. performed DTI studies on patients suffering from Parkinson’s disease and found that signals from the nigrostriatal and nigropallidal tracts were decreased in quantity compared to controls. In our patient, the more severe displacement of the nigrostriatal fibers and/or direct mass effect on the left midbrain and left substantia nigra by the tumor are likely responsible for our patient’s asymmetric Parkinsonism. There could have been additional contributions from evolving ventricular dilation on the right-sided nigrostriatal fibers; however, the asymmetry of the presentation would suggest that direct tumor-related effects on the left midbrain and thalamus were the predominant inciting factor.

Levodopa treatment improved our patient’s secondary Parkinsonism. Using positron emission tomography, Racette et al. demonstrated reduced uptake of 18F dopa in the caudate and anterior putamen of a patient suffering from hydrocephalus-induced Parkinsonism. Reversal of the decreased dopaminergic input is most likely the reason behind the improvements observed in the motor functions of our patient after treatment with levodopa and, to a lesser extent, with methylphenidate and amantadine. Ultimately, the treatment needed to reverse the Parkinsonism is chemotherapy to rapidly reduce tumor size and provide relief of substantia

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**Video 2:** Marked bradykinesia in upper extremities from asymmetric Parkinsonism. This video was obtained after 6 cycles of induction ifosfamide, carboplatin, and etoposide. The non-germinatous germ cell tumor was only partially reduced in size.

**Video 3:** Resumption of activities of daily living. The patient remains healthy and was able to jog 9 months after completion of bone marrow transplant and consolidative craniospinal proton beam radiotherapy. He is able to perform all activities of daily living.

**Video 4:** Resumption of swimming and water sports. This video was obtained 2 months after bone marrow transplant and consolidative craniospinal proton beam radiotherapy. He was able to participate in sports such as waterskiing (video) and snowboarding (not shown).
Our patient’s Parkinsonism appeared after his first dose of chemotherapy. We suspect that this is related to the cytotoxic effects of the chemotherapeutic agents. Cytotoxic chemotherapy can cause abrupt tumor swelling as cells undergo apoptosis, which may have precipitated the onset of the patient’s Parkinsonism. With ongoing chemotherapy, he began to have an improvement in his Parkinsonism and this improved substantially after second-look surgery. We speculate that in his case, surgery was able to relieve pressure on the substantia nigra and nigrostriatal fibers to a greater extent than chemotherapy. This patient’s younger age and motivation to participate in rehabilitation also aided his recovery, which resulted in his ability to perform all activities of daily living and participate in sports.

There are other case reports that describe Parkinsonism associated with pineal masses\(^{[3,12]}\). Both speculate Parkinsonism as associated with compression relating to dysfunction of the nigro-striatal-pallidal system. To the best of our knowledge, there are no published case reports that include videos demonstrating the Parkinsonism associated with pineal gland tumors. The striking improvement in symptoms can be best appreciated by video and offers an example to future clinicians regarding the degree of recovery that is possible.

**CONCLUSION**

This case illustrates that aggressive treatments can reverse Parkinsonism from NGGCT, improve disease control, and restore overall quality of life. While poor functional status can be considered as a negative outcome predictor in brain tumors, this should be interpreted in the overall neurological context of the patient and can be potentially reversible.

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**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent.

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**Conflicts of interest**

There are no conflicts of interest.

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