CASE REPORT

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Treatment Outcome of a β-hCG Secreting Intracranial Germ Cell Tumor in an Adult Filipino Using Definitive Chemotherapy Followed by Radiotherapy: A Case Report

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Abstract

We report a case of a 24-year-old Filipino male who complained of general weakness, polydipsia, weight loss, bitemporal headaches, loss of libido and behavioral changes. Endocrine work-up revealed neurogenic diabetes insipidus and panhypopituitarism. Brain MRI showed multiple intracranial tumors in the left frontal lobe, pineal and suprasellar region with moderate non-communicating hydrocephalus. Intracranial mass biopsy with ventriculo-peritoneal shunting was done. Histopathology of the mass and CSF revealed a germinoma. He underwent chemoradiotherapy while on maintenance hormone replacement.

Key words: Germ cell tumors (GCTs), germinoma, β-hCG, hypopituitarism, diabetes insipidus

INTRODUCTION

Primary intracranial germ cells tumors (GCT) are rare accounting for 3-5% of pediatric intracranial tumors, but only 0.4-1% of intracranial tumors in adults.[1] The comparative incidences are 14.3% in Japan,[2] 14.0% in Taiwan,[3] 11.2% in Korea,[4] 2.3% in USA,[5] and 2.5% in Germany,[6] in various reported series. Data on pineal gland tumors from a single center in the Philippines reported close to 40% (17 of 42 patients) with pineal GCT.[7]

The World Health Organization classified intracranial GCT into three groups: germinomas, non-germinomatous germ cell tumors (NGGCTs) and mixed germ cell tumors.[8] Intracranial GCTs can also be subdivided into secreting and non-secreting tumors. Classically, secreting GCTs are defined as GCTs with cerebrospinal fluid (CSF) alpha feto protein (AFP) >10 μg/L (or above the institutional normal range) and/or a CSF beta human chorionic gonadotropin (β-hCG) level >50 IU/L. Secreting GCTs are considered more aggressive and carry a poorer prognosis than non-secreting GCTs. These typically occur in children or young adults with the majority (60-70%) under 20 years of age. GCT occurs primarily in males, with a male to female ratio of 2:1 in germinoma and 3:1 ratio in NGGCT.[1] Local data also reflects a similar epidemiology among the pediatric male population.[7]

Intracranial GCTs are heterogeneous with respect to histology, biological profile, response to treatment and secretion of AFP and β-hCG into the serum and/or CSF.[9] Clinical presentation depends upon the size and the localization of the tumor. The majority of GCTs are located at the pineal region, followed by the suprasellar region.[10] Pineal gland tumors often manifest with symptoms of obstructive hydrocephalus.[11] Suprasellar tumors are often characterized as endocrinopathies due to the disruption of the hypothalamic pituitary axis.[12] However, visual disturbances may also arise if the suprasellar tumor expands dorsally and compresses the optic chiasm.[11] In some instances, the large suprasellar mass can displace the optic chiasm and expand to the third ventricle, resulting in hydrocephalus.[13] For patients with bifocal tumors at the suprasellar area and pineal gland, hypothalamic and pituitary disorders as well as compression symptoms may be seen.[13]

Hypothalamic pituitary dysfunction may include diabetes insipidus (DI), delayed pubertal development, isolated growth hormone deficiency, hypogonadotropic hypogonadism and hypopituitarism, including central hypothyroidism and adrenal insufficiency. DI is the most common and is often the first presentation. Ophthalmic abnormalities, including bilateral hemianopsia, may also develop due to chiasmic or optic nerve compression.[1,11-13]

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Delays in diagnosis, defined as an interval of more than or equal to 6 months from the onset of symptoms to the date of cranial MRI imaging[11], are common and may exceed 12 months. The symptoms are unfortunately not recognized as an endocrinopathy, hence the delay in diagnosis. As a result of the delay, these patients have a higher incidence of disseminated disease.[11-12]

Germinomas are the most common subtype of intracranial GCTs occurring in 70–80%. They are histologically identical to testicular seminoma and dysgerminoma of the ovary.[14] Patients with pure germinoma may have elevated β-hCG but AFP is never elevated. The β-hCG secreted by GCTs causes gonadotropin-independent hypergonadism with low LH/FSH and high testosterone due to the stimulating effect of β-hCG on the LH receptor in the testes. When this happens in pediatric male patients, precocious puberty will occur. On the other hand, among pediatric female patients, development of precocious puberty requires a rise in LH and FSH on top of the increase in β-hCG. Because of this, precocious puberty is more common in pediatric males than females.[15]

Local data reports endocrine dysfunction such as diabetes insipidus, hypothyroidism, and hypocortisolism in 10 patients presenting with pineal gland tumors. Among them, 6 had bifocal (pineal and suprasellar) tumors while 4 had purely pineal gland tumors.[7]

We report this rare case of an adult with an unusual initial clinical manifestation of central DI, followed by visual abnormalities and symptoms of obstructive hydrocephalus. Referral to endocrinology was made for management of DI. Other manifestations of panhypopituitarism were recognized early and appropriate hormonal treatment was started.

CASE

A 24-year-old male presented with behavioral changes. Seven months prior to consult, he had polyuria and excessive thirst for ice cold drinks taken every 2 hours. This persisted until 4 months prior to consult, together with poor work performance, lack of energy, insomnia and weight loss of 5 kg in 3 months.. He also experienced rotatory dizziness and unprovoked intermittent bitemporal headaches graded 5/10 relieved by rest. He sought consult and was assessed to have benign paroxysmal positional vertigo and prescribed with betahistine 24 mg taken twice daily which afforded no relief of dizziness or headache. Subsequently, he had unstable gait necessitating assistance on ambulation.

Three months prior to consult, he was noted to have hourly oral fluid intake of at least 500 mL with daily urine output of more than 5 liters which did not decrease after fluid restriction. A month later, he developed emotional instability with behavioral changes such as irritability, forgetfulness, incoherent answers with lucid intervals. He was seen by a psychiatrist who initially gave a diagnosis of schizophrenia. However, with the acuteness of symptoms and presence of diplopia, he was referred to a neurologist and an endocrinologist. On further inquiry, he had decreased libido and lack of spontaneous erection since 7 months ago. He shaved his facial hair only once a week compared to daily a year ago. He also had cold intolerance, constipation and easy fatigability. His family history was unremarkable. Physical examination revealed an adult male, chronically ill with slow speech. He had diplopia on leftward lateral gaze. He had sparse pubic and axillary hair without gynecomastia. His testes were normal in size, without any masses or tenderness.

Cranial MRI revealed a 3.3 x 2.4 cm tumor in the pineal gland, a 1.7 x 0.9 cm mass localized in the suprasellar region and 4.5 x 2.4 cm mass located in the frontal lobe with evidence of hydrocephalus (Figure 1A).

During his hospitalization, his daily urine output was 5-6 liters. Urine osmolality was low at 164 mOsm (NV: 500-800 mOsm) with serum sodium of 155 mEq/L. This suggested neurogenic diabetes insipidus (DI). He was started on desmopressin 100 mcg/tablet, ½ tablet 3x a day. This resulted in symptomatic improvement. Further hormonal work-up revealed low cortisol, low luteinizing hormone but with normal testosterone, low free thyroxine but with normal thyroid stimulating hormone. See Table 1 for complete endocrinologic workup. A diagnosis of panhypopituitarism was made based on the cranial MRI findings, and the presence of hypogonadism, central hypoadrenalism and central hypothyroidism. He was started on hormone replacement therapy of prednisone 5 mg per day and levothyroxine 50 mcg per day.

He underwent septum pellucidotomy with ventriculoperitoneal shunting and biopsy of the cranial mass. Histopathology revealed a germinoma. The tumor cells stained positive for placental-like alkaline phosphatase (PLAP) and c-Kit (CD117). The CSF AFP and CSF β-hCG are markedly elevated (Table 1). These clinched the diagnosis of Primary Intracranial NGGCT, stage M1.

He had his first cycle of chemotherapy (100 mg/m^2 Etoposide per day for days 1-5 as a 4-h infusion in 0.9 sodium chloride in a total of 500 mL; 20 mg/m^2 Cisplatin per day for days 1-5 as a 4-h infusion with 0.9 sodium chloride in a total of 500 mL, Ifosfamide with MESNA) at the Benavides Cancer Institute of the University of Santo Tomas Hospital, Manila, Philippines. A daily dose of dexamethasone 10 mg/IV was given as pre-chemotherapy medication.

After 4-6 weeks, his hormone levels were all within normal limits. He had marked improvement in mood. There was resolution of easy fatigability. He was also able to perform activities of daily living without assistance.

After three cycles of chemotherapy, repeat cranial MRI (Figure 1B) showed interval regression of the frontal

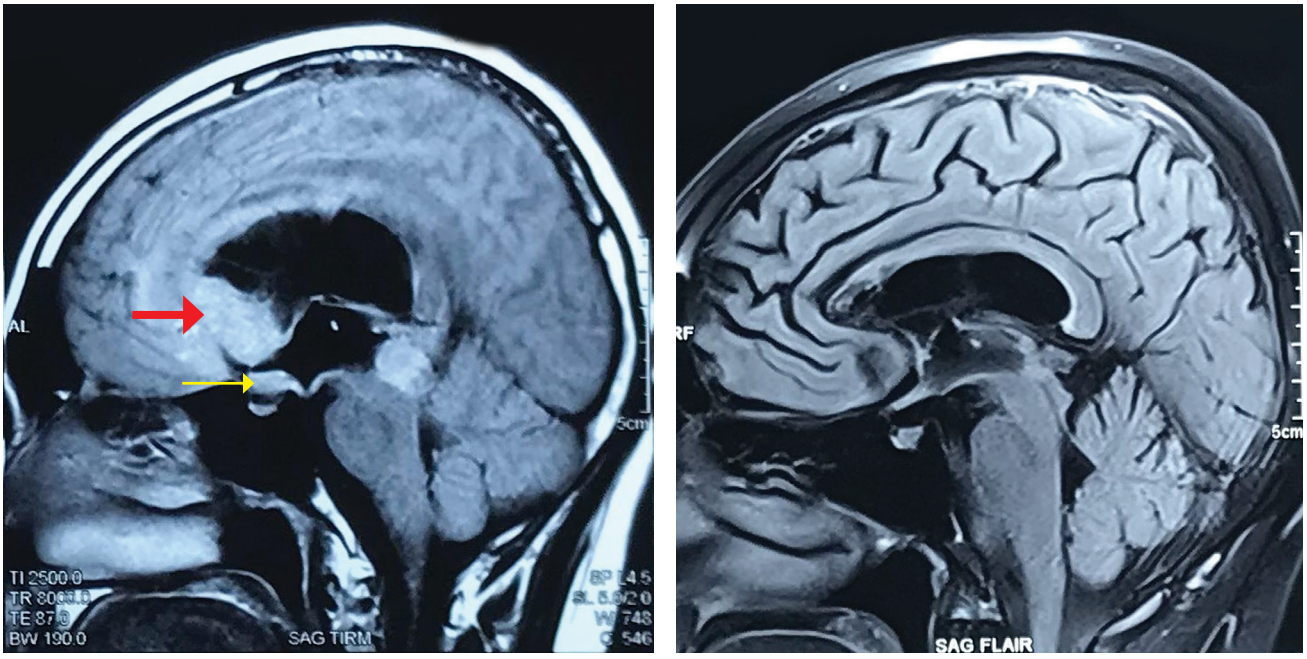

Figure 1. (A) Pretreatment cranial MRI in sagittal section. There was a 4.5 x 2.4 x 2.2 cm mixed signal predominantly isointense lobulated mass in the left frontal lobe parasagittal region extending across the midline with involvement of the anterior corpus callosum to the right frontal lobe *(thick arrow)*. The mass encroached into the left frontal horn and anterior third ventricle. Mixed signal lesions were also seen in the pineal gland about 3.3 x 2.4 x 2.2 cm and in the suprasellar region measuring about 1.7 x 0.9 cm *(thin arrow)*. There was also moderate non-communicating hydrocephalus. **(B)** Postreatment cranial MRI in sagittal section showing tumor size reduction (1.6 x 0.8 cm) in the frontal lobe and resolution of suprasellar and pineal masses.

Table 1. Summary of hormonal investigation and oncologic workup of the patient pretreatment and after treatment

Laboratory test	Normal value	Patient's result pretreatment	Patient's result after 3rd cycle of chemotherapy	Patient's result after completing chemoradiotherapy
Endocrine workup				
Urine osmolality (mOsm)	500-800	164		
Serum sodium (mEq/L)	135-145	155	139	139.3
Luteinizing hormone (mIU/mL)	1.7-8.6	<0.01		
Testosterone (ng/mL)	2.8-8.0	5.5		
Thyroid stimulating hormone (uIU/mL)	0.35-4.94	0.83	0.35	
Free thyroxine (ng/dL*) or (pmol/L**)	Variable	0.54 (NV 0.70 - 1.48*)	9.6 (NV 9 - 23.2**)	1.18 (NV 0.93 - 1.71*)
Serum 8am cortisol (mcg/dL)	>15	1.79		
Oncologic Workup				
Serum AFP (ng/mL)	≤7	6.6	3.17	
Serum β-hCG (mIU/mL)	0 – 0.6	19.97	<0.100	
CSF AFP (ng/mL)	≤1.5	2.5	<0.61	
CSF β-hCG (mIU/mL)	<1.0	516.81	1.26	
Cytology	Negative	Positive	Negative	

mass which measured 1.6 x 0.8 cm from 4.5 x 2.4 cm. The masses on the pineal gland and suprasellar region were no longer present. Repeat oncologic workup revealed marked improvement in the levels of β-hCG and AFP both in the serum and CSF (Table 1). His levothyroxine was periodically adjusted to maintain an FT4 goal at mid- to upper-limit of normal value. His desmopressin dose was adjusted based on monitoring of thirst, urine output and sodium level. Overall, he gained a total of 4 kilograms since his treatment started. He underwent another cycle of chemotherapy (total of four cycles of chemotherapy) and completed 17 fractions of craniospinal 30.6 Gy and 13 fractions of 23.4 Gy brain boost gross tumor.

DISCUSSION

We present the case of a 24-year-old male with visual abnormality, obstructive hydrocephalus, diabetes insipidus and pituitary dysfunction. Given the multifocal tumor location, patient's hormonal dysfunction and mass compression symptoms were evident. Figure 2 explains the pathophysiology for the clinical manifestation of the patient.

Our patient had low LH but with normal testosterone. Among adults, there was one reported case of a 38-year-old man with panhypopituitarism and hyperandrogenemia

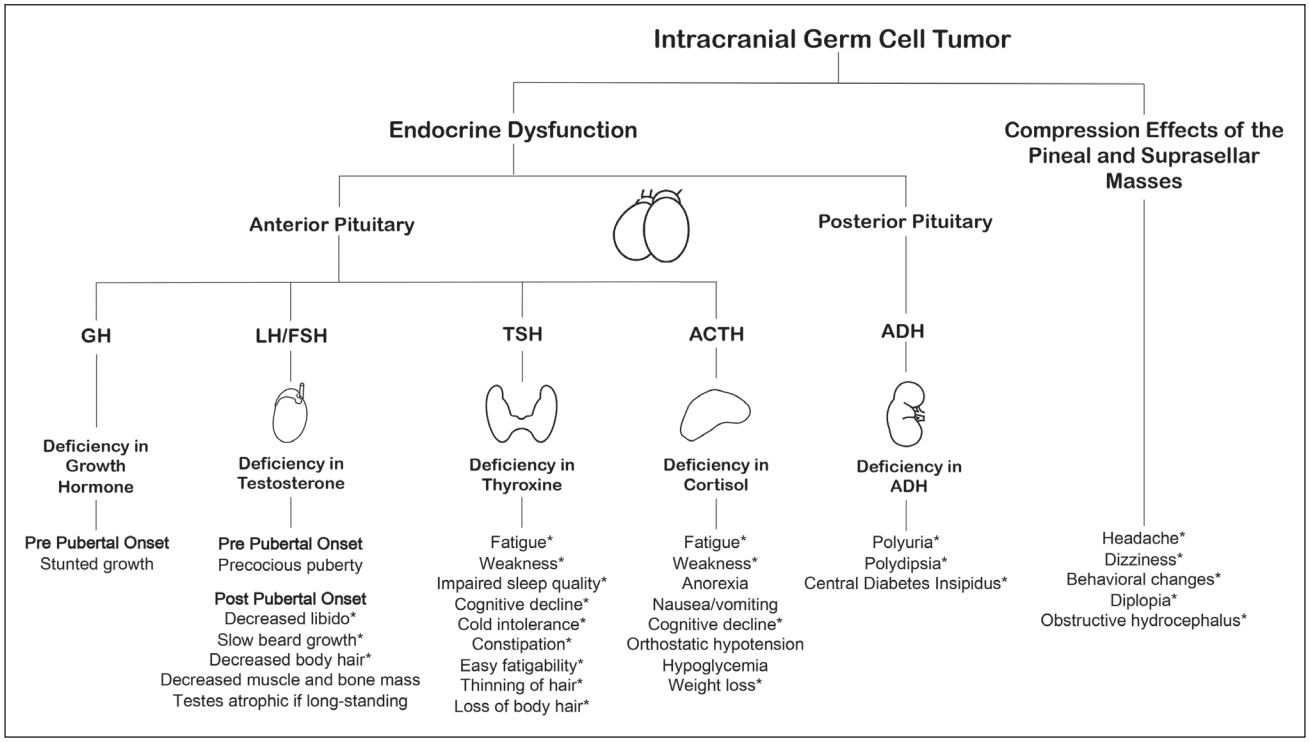

Figure 2. Pathophysiology of clinical presentation of intracranial germ cell tumor.
(*) represents signs and symptoms present in the patient.

associated with β-hCG secreting intracranial GCT. In spite of hyperandrogenemia, this patient experienced low libido, motivation and vitality.[16] A 32-year-old male was reported with testicular seminoma and increased β-hCG secretion, and hyperandrogenism that manifested as worsening acne and increasing muscle bulk.[17] Other case reports of testosterone excess by seminoma in testes or mediastinum presented with gynecomastia or male infertility in adult male patients.[18-19]

The behavioral change and visual abnormalities exhibited by the patient were attributed to structural compression secondary to the brain tumors. His symptoms, including fatigue and weakness, improved following hormone replacement with levothyroxine and prednisone.

Fortunately, the definitive diagnosis of GCT was obtained through histopathology and immunostaining. The majority of GCTs demonstrate immunohistochemical staining for placenta-like alkaline phophatase and c-Kit, otherwise known as CD117, which is an important mitogen for normal germ cells.[20] CSF β-hCG assays reflect the intensity of intracranial β-hCG secretion and are more sensitive than serum β-hCG levels.[20] The levels of β-hCG and AFP can be measured in the CSF and high levels could indicate malignancy. CSF cytology helps establish tumor extension to the ventricular system and spinal subarachnoid region.

The treatment options involve radiotherapy, chemotherapy and radiosurgery. Intracranial GCTs are sensitive to chemotherapy and radiotherapy. Craniospinal irradiation (CSR) or whole ventricular radiotherapy to a dose of 25–35 Gy followed by a primary tumor boost for a total dose of 45–50 Gy is associated with a superior outcome, with a 5-year survival rate of 80–99.5% in retrospective and prospective studies.[21]

When planning the initial treatment strategy against intracranial GCT, pathological subtype and disease extent (especially spinal metastasis) are the most important factors. Traditionally, CSR is considered the gold standard of treatment against intracranial germinoma. However, concerns about late neurologic detrimental effects of CSR, especially in young patients, have led physicians to omit spinal irradiation and reduce the radiation field as much as possible in limited disease.

In this regard, the German Cooperative Prospective Trials MAKEI 83/86/89 examined the outcome after radiotherapy alone at a reduced dose. After a median follow-up of 61 months, results showed that 5-year relapse-free survival rate was 91.0% and the overall survival rate was 93.7%; thus, justifying the effectiveness of reduced radiotherapy doses.[22] However, among patients with NGGCT, only 20-40% of the patients respond to radiotherapy alone; hence the need for chemotherapy as well.[23]

Based on previous reports about chemotherapy against intracranial GCT, methotrexate, ACNU, vinblastine, vincristine, bleomycin, ifosfamide, etoposide and carboplatin/cisplatin had been used as main chemotherapeutic agents. Chemotherapy with cyclophosphamide, ifosfamide, etoposide, cisplatin, and carboplatin were highly effective in CNS GCTs.[24] However, chemotherapy alone was proven

to be inferior compared to radiotherapy-based treatment protocols. The Second International CNS Germ Cell Study Group showed that intensive chemotherapy was effective only in one-third of patients with 5-year event free survival and overall survival rates were 36% and 75%, respectively, and patients were salvaged through radiotherapy.[25] Likewise, the Third International CNS Germ Cell Tumor Study also confirmed that a chemotherapy only approach led to inferior survival. The 6-year event free and overall survival was 45.6% and 75.3%, respectively.[26]

In our case of metastatic intracranial NGGCT, the standard of therapy is a multimodal treatment approach with chemotherapy and craniospinal irradiation.[27] Radiation therapy remains the backbone of the treatment regimen. Administration of chemotherapy with radiotherapy led to shrinkage of tumor size and reduction of radiotherapy dose; thus, minimizing radiation-related toxicity and improving long-term survival rates.[1,27]

The decision was to treat this patient's pituitary germinoma with 4 sessions of chemotherapy followed by radiotherapy in accordance to the SIOP CNS GCT 96 trial.[28] The chemotherapeutic agents were selected primarily based on the experience in gonadal GCT treatment. Recently, many institutions have preferentially used a combination chemotherapy consisting of ifosfamide, cisplatin and etoposide as one of the mainstays of treatment.[29] The 5-year progression-free survival and overall survival were 68% and 75%, respectively.

Significant prognostic factors included serum and/or CSF AFP >1000 ng/mL and residual disease after treatment. An AFP > 1000 ng/mL led to a progression-free survival rate of 32% as compared to 76% in those with AFP <1000 ng/mL. Moreover, residual disease after completion of chemoradiotherapy resulted in a progression-free survival rate of 48% as compared to 85% in those without residual tumors.[27]

In our patient, the post-treatment cranial MRI revealed that the tumors markedly decreased in size. Both the β-hCG and AFP levels in the serum and CSF were brought down to the normal range. The patient has maintained a stable disease status. He was followed up monthly during his chemotherapy and radiotherapy sessions for a total of 6 months. Thereafter, patient should ideally follow-up every 3 months, but he only came to clinic every 6 months, for a total of 18 months.

A retrospective review of long-term toxicity effects of radiotherapy and/or chemotherapy among adolescents and young adults showed that a significant proportion of patients developed late effects after 10 years. The most common was physician-reported neurocognitive impairment. Fifteen percent of patients developed new treatment-induced hormone deficiency, more commonly, hypothyroidism followed by hypogonadism and diabetes insipidus.[30]

In a reported case, pituitary dysfunction in the form of hypogonadotropic hypogonadism occurred secondary to germ cell tumor specific therapy; hence, hormone replacement therapy was recommended.[31] Conversely, patients who developed endocrine dysfunction secondary to suprasellar involvement do not usually recover completely and are dependent on hormone replacement therapy.[13,30] Surgery or radiation therapy may increase the severity of these endocrine and hypothalamic deficiencies. Late effects from chemotherapy are drug dependent. Cisplatin use was associated with increased risk of ototoxicity.[30]

CONCLUSION

Pineal and suprasellar germinomas are rare tumors that can occur in adulthood and are characterized by the presence of endocrine dysfunctions such as central diabetes insipidus, hypogonadotropic hypogonadism and panhypopituitarism as initial clinical manifestations. Hormonal deficiency can manifest prior to mass compression symptoms, delaying neurologic evaluation and imaging; hence, early recognition and implementation of treatment are important to improve outcomes. Adult intracranial GCTs are sensitive to chemoradiotherapy, resulting to good overall prognosis. Late treatment effects of chemoradiotherapy can occur; thus, requiring long-term monitoring with hormonal replacement and follow-up.

Ethical Consideration

Upon acknowledgment from JAFES the need to seek an updated patient consent, the author reviewed his outpatient and inpatient charts for his contact information.

The first listed contact is a cellphone number that belonged to his common law partner, who accompanied the patient during his check-ups, but she did not reply when asked if she still has any contact information of the patient. She also did not answer calls.

The second contact number is a landline number but this number is “not in service.”

The third contact number did not answer to multiple attempts of text messages or calls.

The authors tried their best to reach the patient but all attempts were unsuccessful.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

The authors declared no conflict of interest.

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