"Somewhere Up There": A Case Of Pineal Gland Tumor in a 20-Year-Old Male

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Abstract

Background: Pineal region tumor is a rare and reportable case. Incidence rate adults is 0.025 in 10,000 hence there is no established guidelines among adults for diagnosis and management of this case.

Case: A case of a 20-year-old male with a two-month history of intermittent headache, occipital area with VAS 5/10, increasing in severity. Until two days prior to admission with severe headache VAS 9-10/10, occipital, and nonradiating. Patient noted episodes of projectile vomiting hence, admitted. Patient presented with non-lateralizing symptoms but noted papilledema and parinaud syndrome. Cranial MRI with contrast revealed a 2.5cm pineal gland tumor with obstructive hydrocephalus. Serum AFP (alpha-fetoprotein) and beta-HCG (beta subunit of human chorionic gonadotropin) were requested and revealed elevated levels. The patient underwent endoscopic third ventriculostomy but no biopsy was done due to high risk of bleeding. Patient underwent series of radiotherapy and was advised to undergo chemotherapy but patient refused. Patient had improved upward gaze but with residuals, no recurrence of headache or vomiting, had normalization of the serum tumor markers but noted increase in size of the tumor despite radiotherapy.

Conclusion: Case reports of pineal region tumors will help doctors in the primary hospitals diagnose such cases and differentiate it from benign causes of headache. This will aid in early referral to specialists and early intervention.

Keywords: pineal region tumor; Parinaud syndrome, Endoscopic third ventriculostomy

Introduction

Pineal region tumor is a rare and reportable case. These tumors represent three to eight percent of pediatric intracranial tumors and 0.4-1 % of adult intracranial neoplasms. Incidence rate of pineal gland tumors in adults is 0.025 in 100,000. Peak age at diagnosis is at 10-12 years old. Male to female incidence is 3:1.[1] This is the first case reported in this institution.

The pineal gland is located between the right and left cerebral hemisphere, above the superior colliculus and below the splenium of the corpus callosum and the vein of Galen. The size of the gland ranges 10-14mm and develops during the second month of gestation. Manifestations of pineal gland tumors are due to mass effect. Clinical phases of pineal region masses include: 1) headaches with nausea and vomiting; 2) blurred vision, diplopia, drowsiness, pupillary changes, ataxia, dizziness, paralysis of extraocular muscles; 3) papilledema, weakness, spasticity.[2] Median time of symptom presentation may be 20-30 months. MRI with gadolinium contrast is optimum for diagnosing pineal gland tumors. Tumor markers such as AFP (alpha-fetoprotein) and beta-HCG (beta subunit of human chorionic gonadotropin) should be routinely requested in differentiating types of pineal gland tumor. Management of pineal gland tumors in adults is still adopted from the guidelines in the management of pineal gland tumors in children. Rarity of the disease condition warrants further studies to come up with an internationally accepted guideline for the management of pineal gland tumors in adults.[3]

This case report will help doctors in the primary hospitals to diagnose such cases and differentiate it from benign causes of headache. This will aid in early referral to specialists and early intervention.

Objectives

- To present a case of pineal gland tumor in a 20 year old male
- To discuss the diagnosis and management of the case

Clinical History

This is a case of a 20-year-old male, Filipino, single,

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Roman Catholic, presently residing at San Pedro, Laguna, admitted for the first time in our institution due to headache and vomiting. Patient had two months on and off headache, pulsating in the occipital area with VAS 5/10. There was no identifiable aggravating factor and headache resolves spontaneously. Two days prior, there was increased severity of headache with pain scale 9/10 associated with projectile vomiting approximately two episodes per day hence admitted.

Patient denied any weight loss, no blurring of vision or diplopia, no gait disturbances, no weakness or numbness. There was no history of behavioral changes or changes in sensorium, no bowel habit or urinary disturbance. Sexual development was at par with age. Patient has been diagnosed with psoriasis for five years and has been taking methotrexate. No history of asthma or any allergies to food or medications. No previous surgical procedure.

Patient is a student and resides with his family. He is a non-smoker and non-alcoholic. He denies use of illicit drugs and denies exposure to chemicals or radiation. There is history of hypertension in the maternal side, no family history of diabetes, no history of cancer.

On physical examination, patient had stable vital signs. Skin was warm to touch with fair skin turgor. Palpebra was pink with anicteric sclerae, no cervical lymphadenopathies. Symmetrical chest expansion, no retractions, clear breath sounds. Adynamic precordium, PMI at fifth ICS LMCL, normal rate, regular rhythm, no murmur, no heaves, no thrills. Abdomen was soft, normoactive bowel sounds, non-tender, liver and spleen not palpable, intact traube's space. Pulses are full. Body hair distribution was normal, no areas of alopecia, Tanner staging was V.

Patient was conscious, coherent, oriented to three spheres, follows commands. Pupils were 3.0 mm, sluggishly reactive to light. Lateral and medial eye movement were intact but noted vertical gaze paralysis, and convergence palsy. Fundoscopy was done and noted bilateral papilledema. There was no facial asymmetry, hearing was intact, intact gag reflex, intact shoulder shrug, no tongue deviation. There was no dysmmetria, no motor or sensory deficit. Reflexes were normal, negative dysdiadochokinesia, finger to nose test was negative, negative pathologic reflexes.

Course in the Wards

Patient was initially admitted at ICU and cranial MRI with gadolinium was done. On MRI, there was note of a 2.5cm pineal gland mass with hydrocephalus. Mannitol was started and patient referred to neurosurgery department. acetazolamide was started and celecoxib was given for headache. Patient was advised endoscopic third ventriculostomy and transferred to a government hospital for the procedure. Serum AFP, B-HCG were noted to be elevated. (Table I) Patient underwent endoscopic third ventriculostomy but biopsy was not taken due to the depth of the tumor. Patient was then referred to an Oncologist and Radio-Oncologist. CSF level of AFP, Beta-HCG was advised but was not done. For three months, the patient underwent 30 sessions of radiotherapy, maintained on Dexamethasone and monitored by serial monitoring of AFP and Beta-HCG and repeat cranial MRI. There was note of normalization of AFP and beta-HCG levels after three months. however, noted increased size of the tumor after four months from diagnosis. Thoracolumbar spine MRI was done and there was no drop metastasis noted. There was improvement of vertical gaze but still with residual palsy. At present, patient is undergoing physical therapy, until the writing of this paper.

Differential Diagnosis

Patient presented with non-lateralizing neurologic signs and symptoms. Lesion can be localized in the midline structures. Patient's symptom of severe headache and projectile vomiting with papilledema on physical examination indicates increased intracranial pressure. Patients presenting with vertical gaze paralysis, convergence palsy and accommodation palsy, known as parinaud syndrome will localize the lesion in the quadrigeminal plate, particularly in the superior colliculus. This results from the compression of the rostral midbrain, in the superior colliculus due to mass effect.[4] Differential diagnoses for a midline tumor that would present with parinaud syndrome characterized by upward gaze, accommodation and convergence palsy, include a pineal gland tumor, a midbrain AV malformation or metastatic tumors. Other causes such as infectious, demyelinating and vascular causes can be ruled out because the course of the disease was chronic and progressive. Stroke in the midbrain can be ruled out because of its acute presentation and is common in the elderly population with risk factors such as hypertension, diabetes mellitus and smoking which are absent in the patient. Demyelinating diseases such as multiple sclerosis can be ruled out because it presents with recurrent episodes of weakness, numbness, diplopia or loss of vision, months or years apart which was not seen in the patient.

The pineal gland is located in the epithalamus behind the third ventricle which can compress the superior colliculus which is the upward gaze center hence this is highly considered. AV malformation may present with progressive headache with or without focal neurologic signs depending on the size and location of the lesion. However most commonly at the time of diagnosis the lesion has ruptured. Metastatic tumors are commonly from the lungs, breast, melanoma or kidneys. Fifteen percent are solitary commonly from the breast and kidneys and 85% are multiple brain tumors. However based on the symptoms of the patient the

Table I. Tumor markers

Before Therapy				After Therapy			
Test	Result	Unit	Reference range	Test	Result	Unit	Reference range
Serum AFP	14.07	IU/mL	Less than 5.8	Serum AFP	1.2	Ng/mL	Less than 2.00

lesion is most probably solitary. If it were a solitary metastatic tumor, the mass would have been large enough to cause increased intracranial pressure hence the course would have been more chronic.

The most common tumor presenting as Parinaud syndrome is a pineal gland tumor. It is seen in 50% of cases of pineal gland tumors[5]. Obstruction of the CSF leading to hydrocephalus and direct tumor mass effect causes impingement of the superior colliculus responsible for the upward gaze. This is compatible with the case of the patient because of the chronic, intermittent, progressive headache and signs of increased intracranial pressure such as severe headache with projectile vomiting.

Pineal gland tumors can be classified as: 1. Germ Cell tumors; 2. Pineal Parenchymal Tumors; 3. Pineal cyst. Germ cell tumors comprise more than 50% of cases of pineal gland tumor and has a favorable prognosis with good sensitivity to radiotherapy. Germ cell tumors are classified as either a Germinoma or a Nongerminomatous Germ cell tumor which can further be classified as a 1. Teratoma, 2. Choriocarcinoma, 3. Endodermal sinus tumor, 4. Mixed Germ Cell Tumor.[6]

1. **Germinomas** account for 50-65% of intracranial germ cell tumors in the pineal region. It has a good prognosis and highly responsive to radiotherapy. These tumors show negative tumor markers but may have mild elevation in Beta-HCG.

2. **Nongerminomatous germ cell tumors** are tumor marker-secreting tumors and are seen more commonly in males with a 3:1 male to female ratio. Teratomas may show elevated Alpha Fetoprotein (AFP) levels whereas Choriocarcinomas will show elevated Beta-Human Chorionic Gonadotrophin (HCG). Our patient presented with elevated serum Beta-HCG and serum AFP hence a Mixed Germ cell tumor is highly considered. Germ cell tumors may show nonspecific signs and symptoms and imaging studies don't have pathognomonic features. Presence of tumor markers is an unequivocal sign of presence of a secreting germ cell tumor.[4]

3. **Pineal parenchymal tumors** comprise one third of cases of pineal gland tumors. These tumors arise from pineocytes. Serum tumor markers are less characteristic of pineal parenchymal cell tumors. Melatonin can be elevated but are non-diagnostic.

4. **Pineal cysts** are generally asymptomatic and commonly seen in patients 40-49 years old. These lesions remain stable in size over time. They have characteristic finding on MRI showing peripheral enhancement and central hypointensity [6].

In this case, a pineal gland tumor probably nongerminomatous germ cell tumor is highly considered because of the non-lateralizing signs and symptoms, Parinaud's syndrome, and elevated serum AFP and beta-HCG.

Discussion

The patient presented with nonspecific headache but increasing in severity and with signs of increased intracranial pressure. Notable on physical examination was the presence of parinaud syndrome and work-up showed a pineal region tumor with elevated tumor markers hence a nongerminomatous pineal region germ cell tumor was highly considered. The pineal gland is a pinecone structure that is 8.0 mm long and 4.0 mm wide, located midline. It is situated above the tentorium and superior colliculus and below the splenium of the corpus callosum and the vein of Galen. It is attached to the superior aspect of posterior border of the third ventricle.[6] The function of the gland has not been previously understood but is now linked to sex hormone regulation aside from the sleep-wake cycle through the hormone melatonin. The pineal gland is composed of photoreceptor cells resembling cells in the retina which converts light perception into wavelengths. Animal studies have shown that continuous environmental illumination for weeks brought a decrease in the weight of the pineal gland and consequent increase in weight of the ovaries. Researchers have then identified a gonad-inhibiting substance in the pineal gland extract. They noted that melatonin injection in rats starting before puberty slowed the estrus cycle and caused decrease in size of the

ovaries. Removal of the pineal gland on the other hand accelerated the estrus cycle.[7]

The median time to symptom presentation for pineal region tumors is usually 20-30 months. Symptoms are usually evident when the cerebral aqueduct is obstructed.[4] By virtue of the Monroe Kelly hypothesis, intracranial pressure is constant and is determined by the brain tissue, blood vessels and the CSF. The normal intracranial pressure is 10-15mmHg. Treatment should be instituted once ICP in >20-25mmHg. Measures to reduce intracranial pressure include mannitol bolus 0.25-1 g/kg then 0.25-0.5g/kg every two to six hours. If the patient is hypotensive, hypertonic saline solution can be given. Steroids are given for brain tumors with surrounding edema. Acetazolamide on the other hand is a carbonic anhydrase inhibitor that reduces CSF production and is useful in hydrocephalus.[8]

Parinaud syndrome also called dorsal midbrain syndrome is composed of upward gaze palsy, convergence palsy and accommodation palsy. The vertical gaze center lies in close vicinity to the superior colliculus, near the pineal gland. Compression of the structures due to mass effect leads to symptoms of Parinaud syndrome.[6] Our patient was noted to have vertical gaze palsy, convergence paralysis, light accommodation palsy and a pineal gland tumor. The pineal gland tumor compressed the superior colliculus and cerebral aqueduct significant to cause Parinaud syndrome and increased intracranial pressure due to obstructive hydrocephalus.

Neurologic signs and symptoms of pineal region tumors are non-lateralizing because the gland is a midline structure. Peripheral neurologic symptoms may be evident for germ cell tumors and ependymomas with drop metastasis by spread thru the CSF. [9] Our patient presented with the typical symptoms of progressive headache and signs of increased intracranial pressure due to hydrocephalus, and Parinaud syndrome. However unlike the other case reports of pineal region tumor, there was no diplopia, no change in the sleeping pattern and no endocrinologic abnormalities.

Cranial MRI with gadolinium contrast is optimum for brain tumors. However, literature suggests that common pineal gland tumors have no pathognomonic imaging pattern. There was no significant difference in the T1 and T2 signal intensity values between the pineal parenchymal tumors and germinomas. Pineal parenchymal tumors showed isohypointensity on T1 and isohyperintensity on T2. Germinomas on the other hand showed hypointensity on T1 and isointensity on T2.[10]

Pineal region tumors are composed of Germ cell tumors, 70% of cases, Pineal parenchymal tumors 15% and other types such as Papillary tumors, gliomas and meningiomas comprising 15% of cases.

Germ cell tumors can be located both in the pineal region and the suprasellar area. Bifocal tumors comprise 13% of cases of germ cell tumors. Germ cell tumors are characterized by secreting tumor markers such as AFP and beta-HCG. Precocious puberty is more evident in pineal gland tumors secreting beta-HCG such as choriocarcinoma. Germinomas are extra-gonadal seminomas whose AFP and beta-HCG levels are not typically elevated. Germinomas have a better prognosis and good response rate to radiation compared to nongerminomatous germ cell tumors.[9] Tumor markers for Nongerminomatous germ cell tumors are evident in the serum and CSF in 80% and 20% of cases, respectively. Beta HCG for >50 IU/mL and AFP level of >25 IU/mL are associated with a worse prognosis. Presence of tumor markers is assumed to be equivocal sign of presence of secreting germ cell tumor and it is justified to start therapy without histologic confirmation. Tumor markers are useful during treatment and follow-up to monitor response to therapy.[4] The patient did not have any biopsy but had elevated tumor markers hence radiotherapy was started. Serum AFP and beta-HCG levels were monitored during the course of treatment and noted decrease in levels.

The patient presented with signs of increased intracranial pressure, Parinaud's syndrome, and a pineal gland mass on cranial MRI with elevated serum tumor markers. With the presentation of the patient and laboratory work-up, the patient has a pineal gland tumor probably nongerminomatous germ cell tumor. Final diagnosis was pineal gland tumor probably nongerminomatous germ cell tumor.

Pineal gland tumors become evident when the tumor causes mass effect such as increased intracranial pressure. In cases wherein the patient presents with increased intracranial pressure, this must be addressed first. Mannitol, an osmotic diuretic was initially given to the patient to do medical decompression. Patient was then referred for Neurosurgical intervention because the pineal region tumor was causing obstructive hydrocephalus. Surgical intervention involved in pineal region tumors include Endoscopic third ventriculostomy and VP shunting. Endoscopic third ventriculostomy, which was done to our patient, is the procedure of choice because of its advantages. This procedure avoids shunt malfunction and infection, avoids peritoneal seeding of malignant cells and this approach allows tissue biopsy and CSF collection for tumor markers. However, this procedure has risk of bleeding for vascular tumors.[11] In cases wherein a biopsy was taken, case should be reported by an accredited neuropathologist according to the NICE guidelines.[8] However, biopsy was not taken in this case due to high risk of bleeding. VP shunting is less used because of increased risk of infection and malfunction. This should be the option only if endoscopic third ventriculostomy fails.[6]

Management of pineal gland tumors have been adopted from the Pediatric guidelines due to lack of prospective studies in adults. Treatment options include radiotherapy, chemotherapy and surgical resection. There is no specific staging system uniformly accepted for germ cell tumors and investigators utilize the TM staging for medulloblastoma. Mo corresponds to No metastasis, M1 for free floating malignant cells and M2,M3 for presence of tumor cells in the spinal or subarachnoid space. T staging is not used in pineal gland tumors since it is located midline. Radiotherapy is the backbone in management of pineal gland tumors but dose to be given is not standardized. Chemotherapy has been standard in the management of ovarian and testicular germ cell tumors but has not been routinely used in intracranial germ cell tumors. The value of total or near total resection of pineal gland tumors still remain unproven.[12]

Germinomas have better prognosis than other histologic types. Germinomas have good response rate to radiation alone with tumor boost total 4500-5000 cGy. Studies have shown poorer survival rate if dose is less than 4000 cGy. Craniospinal irradiation was instituted and studies showed 96% in a three-year relapse free for patients with Germinoma. Chemotherapy and radiotherapy have been used and favored in United Kingdom but has not been practiced in France.[12]

Nongerminomatous germ cell tumors have poorer prognosis. Management utilizes radiation therapy and chemotherapy. These tumors are less radiosensitive. Dose of radiation is limited due to neurocognitive and endocrinologic sequelae. Endocrine disturbance may manifest even 10-15 years after therapy. Radiotherapy is essential but radiotherapy alone is rarely curative as single treatment modality with tumors relapsing within 18 months. One study showed improved survival with gross total resection of pineal gland tumor but this has not been extensively confirmed. Chemotherapeutic drugs used for nongerminomatous germ cell tumors are Cisplatin at 20mg/m2/day, Etoposide at 100mg/m2/day and Ifosfamide1500mg/m2/day in four courses with 21 days interval. Four cycles of chemotherapy have been instituted followed by irradiation 5400 cGy. Results of studies suggested chemotherapy can improve overall duration and survival rate when used in combination with radiotherapy. However, reports contain only few patients which further highlight rarity of these tumors and difficulty designing the best treatment approach. Five patients treated with four cycles chemotherapy then radiotherapy had median survival rate of 88 months. Future therapeutics with nongerminomatous germ cell tumors will likely include more aggressive chemotherapy and lower dose of radiation.[12]

Patients with pineal gland tumor require regular follow-up during radiotherapy and repeated evaluation of serum tumor marker, whose level indicate response to therapy. Normalization of the levels of tumor markers indicate good response to therapy. Repeat cranial MRI scan and spinal MRI should be done to monitor size and rule out drop metastasis.

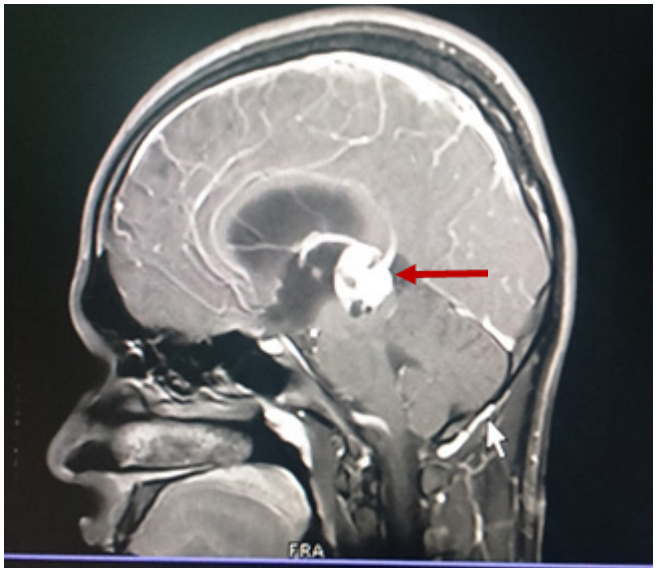

Figure 1. **Cranial MRI with contrast**

There is a soft tissue mass in the posterior aspect of the third ventricle measuring 2.5x2.7x2.9cm. Small internal cystic components are noted. There is homogenous contrast enhancement of solid portions of the mass.

Our patient underwent radiotherapy however repeat cranial MRI showed increase in size of the tumor. Chemotherapy have been previously advised but was undecided. Patient is now undergoing physical therapy and has improved upward gaze but with residual palsy. He does not experience headaches, no vomiting. He is able to support himself and can do activities of daily living on his own. He is not currently enrolled but plans to come back to school next year until writing of this paper.

Conclusion

Pineal gland tumors are rare cases and should be reported. Clinical manifestations may be non-specific and clinicians should have a high index of suspicion. There is no widely accepted guidelines for pineal gland tumors in adults and management is adopted from the guidelines in the management for the pediatric population. Prospective studies are needed through aggressive case finding since it has good cure response rate.

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