CASE REPORT

Mature teratoma of the pineal region in the paediatric age group: A case report and review of the literature

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Abstract

Introduction: Intracranial teratomas account for 0.5% of all intracranial tumours and 2-4% of intracranial tumours in children. However, in terms of tumours of the pineal area, the exact incidence is not ascertained. Although, it is noted that 50-60% of central nervous system (CNS) germ cell tumours are found in the pineal gland. The degree of difficulty in obtaining sample from lesions in the pineal gland emphasizes the importance of correlating the imaging studies, histopathologic findings, and serum and cerebrospinal fluid (CSF) tumour markers.

Case Report: This case report is that of a 9-year-old male who presented with frontal headache of eight days, associated with photophobia, nausea and vomiting, and diplopia. Biopsy with intraoperative navigation was done and the specimen was referred for histopathologic evaluation. The biopsy showed findings consistent with a mature teratoma with no histologic findings of an immature component or secondary somatic malignancy. Comparison of the pre-operative and post-operative multi-axial cranial CT scan showed findings that was consistent with a residual lesion. This was correlated with the pre-operative serum tumour markers which showed alpha-fetoprotein of 22.5 ng/mL and beta-HCG of 1.0 mIU/mL (IU/L), and the post-operative tumour markers of the cerebrospinal fluid that showed alpha-fetoprotein of 3.28 ng/mL and beta-HCG of 18.9 mIU/mL (IU/L). Conclusion: A review of the literature and comparison with current case in relation to the histopathologic, serum and CSF findings, and imaging studies was done to better understand the mechanism of this lesion.

Keywords: pineal gland, pineal region, mature teratoma, germ cell tumours, CNS, intracranial tumours

INTRODUCTION

Intracranial teratomas account for 0.5% of all intracranial tumours and 2-4% of intracranial tumours in children.¹-⁴ However, in terms of tumours of the pineal area, the exact incidence is not ascertained. Although, it is noted that 50-60% of central nervous system (CNS) germ cell tumours are found in the pineal gland.⁵-⁶ The degree of difficulty in obtaining sample from lesions in the pineal gland emphasizes the importance of correlating the imaging studies, histopathologic findings, and serum and cerebrospinal fluid (CSF) tumour markers.

CASE REPORT

This is a case report of a 9-year-old male who presented with frontal headache of eight days, associated with photophobia, nausea and vomiting, and diplopia. There was no documented history of childhood illnesses, family history of malignancy, feto-maternal complications during pregnancy and delivery, and no developmental delay documented. Multi-axial CT scan showed a midline enhancing solid mass measuring 9.9 x 12.2 x 8.0 mm in the posterior portion of the third ventricle. Biopsy with intraoperative navigation was done and a 1 x 1 x 0.2 cm tissue sample was submitted for histopathologic evaluation.

Surgical pathology findings

The specimen was submitted in a container containing formalin fixative and labelled as “pineal gland mass”, consisting of a cream white, ovoid to irregular, soft to firm tissue measuring 1
Histologic sections showed a mature teratoma comprising mostly of mature ectodermal and mesodermal components, and a few rudimentary endodermal components. A cyst wall enclosed by stratified squamous epithelium (Fig. 1 A-B) was seen adjacent to a cluster of neural tissue (Fig. 1C). These were seen adjacent to areas of blood vessels (Fig. 1D), fibrous stroma, and adipose tissues (Fig. 1E). No normal pineal gland parenchyma was appreciated. No malignant component or primitive teratomatous components were documented in the specimen submitted. The surgical pathologic report indicated that the findings were consistent with a mature teratoma with no histologic findings of an immature component or secondary somatic malignancy.

Immunohistochemistry studies were done to document the possible potential for secondary somatic malignancy of the lesion sampled. The p53 expression was noted to be less than 10% which is consistent with a wild-type expression of p53. The p16 expression was likewise negative, which indicated that there was no aberrant p16 expression that is commonly associated with malignant transformation. Although p57 expression was negative in this lesion, the lack of overt malignant histologic features may indicate presence of dysplasia since previous reports have described that p57 negative lesions in the head and neck may indicate squamous cell carcinoma or squamous epithelial dysplasia\textsuperscript{7,8} (Fig. 2 A-C).

**Neuroimaging findings**

Comparison with the post-operative imaging cranial CT scan showed findings that were representative of a residual tumour. Pre-intravenous and post-intravenous contrast enhanced multiaxial CT scan showed a midline enhancing solid mass measuring 9.9 x 12.2 x 8.0 mm in the posterior portion of the third ventricle.
Follow-up non-contrast enhanced multiaxial cranial CT scan dated January 30, 2016 and dated March 23, 2016 (S/P excision biopsy of pineal mass) showed no significant change in size (9.7 x 12.0 x 8.1 mm) of the previously reported solid mass in the posterior portion of the third ventricle (Fig. 3 D-F).

Tumour markers
Pre-operative serum tumour marker levels were taken and showed the following findings: alpha-fetoprotein of 22.5 ng/mL (normal values: 1.45-8.47 ng/mL) and beta-HCG of 1.0 mIU/mL (normal values: 0-5 mIU/mL).

An intraoperative sampling of the CSF was done and the CSF tumour marker levels showed an alpha-fetoprotein level of 3.28 ng/mL (normal values: 1.45-8.47 ng/mL) and a beta-HCG level of 18.9 mIU/mL (normal values: 0-5 mIU/mL).

The patient underwent five cycles of chemotherapy with etoposide and cisplatin. The first cycle of chemotherapy was done the day after the surgical procedure with the pre-operative serum tumour markers and the first day post-operative CSF tumour markers as baseline. Serum alpha-fetoprotein levels were taken again on the 34th post-operative day and showed a decrease from baseline with a value of 5.61 ng/mL.

A repeat serum alpha-fetoprotein level was taken on the 62nd post-operative day and showed a decrease from the previously recorded level, with the value of 2.61 ng/mL. The five cycles of chemotherapy was completed on the 110th post-operative day but the patient underwent a serum beta-HCG and serum alpha-fetoprotein testing on the 93rd post-operative day. The serum beta-HCG was stable at 1.0 mIU/mL. In contrast, a mild increased in the serum alpha-fetoprotein was observed from a previously recorded level of 2.61 ng/mL to 4.27 ng/mL. However, the serum alpha-fetoprotein level recorded at this point was still within the normal range (Fig. 4).

At this point, the serum levels were within the normal range, which may indicate that the lesion that was not within the blood brain barrier was responsive to chemotherapy. The CSF levels of the tumour markers were not taken due to the risk of brain herniation upon spinal tap due to the residual tumour. The patient was advised surgery for the excision of the tumour, given the presence of the pineal region lesion, and detection of activity in tumour because of the serum alpha-fetoprotein that showed a slight increase.

Diagnostic algorithm for malignant potential
The elevated CSF beta-HCG with a normal CSF
alpha-fetoprotein, in the context of a normal serum beta-HCG and an elevated serum alpha-fetoprotein may have been due to an unsampled focus of syncytiotrophoblastic giant cells in the region of the tumour that was within the region of the CNS that was limited by the blood-brain barrier but was not found in the other portions of the tumour that was devoid of blood-brain barrier. Furthermore, the elevated serum alpha-fetoprotein may have been due to an unsampled focus of immature alpha-fetoprotein-secreting embryonal-type intestinal tissues in the pineal region that was devoid of blood-brain barrier, but was not present in the portions of the tumour within the blood brain barrier, which caused the presentation in the serum but not in the CSF (Fig. 5).

FIG. 4: The pre- and post-operative testing of tumour markers.

FIG. 5: Correlation of the histologic findings and the serum/CSF tumour markers.
In the light of absent trophoblastic tissues and intestinal tissues in the biopsy sample provided, an immunohistochemistry panel elucidating the presence of both cannot be utilised.

An immunohistochemistry panel utilising surrogate cell cycle protein markers were used in this case to determine the possible regrowth of the tumour and the potential for malignant transformation, which is particularly important because there is residual tumour in the pineal region.

A positive p53 expression limited to less than 10% of the basal portion of the nests of squamous cells may indicate a strong likelihood of a wild-type p53 and correlates with a low potential for malignant transformation compared with a high p53 expression or an absent p53 expression on immunohistochemistry.

A negative p16 expression likewise may pertain to a low probability for malignant transformation since studies of p16 expression in squamous epithelium within teratomas showed that a diffuse p16 expression was strongly correlated with malignant tumour behaviour. However, p16 expression testing for teratomas was only documented in lesions coming from the ovary.

A negative p57 expression, although of limited use and was documented only in the head and neck tumours of squamous cell origin, was associated with dysplastic changes or malignant cellular features and tumour behaviour in malignant oral and laryngeal squamous epithelium. In comparison, a positive p57 expression was reported in normal squamous lining epithelium. As such, when interpreted within the context of being a component of a mature teratoma in the CNS, a negative p57 expression may be correlated with a behaviour more similar to dysplastic squamous epithelium rather than a normal squamous cell epithelium.

A review of published research on pineal region teratomas were done to derive an estimate of the prevalence of pineal region teratoma and identify the particular type of teratoma, whether mature, immature, with secondary somatic malignancy, or with associated non-teratomatous germ cell tumour. The systematic review included all research published in the PubMed database, EBSCO database, and Google Scholar. All duplicate articles were removed from the review pool.

Among 349 records identified in the database, articles that did not contain the classification of specific non-germinomatous germ cell tumours, and were not written in English and without English translation were excluded.

Within such records, all articles with non-paediatric patients, reports with no age group stratification, and reports describing non-teratomatous, non-germinomatous germ cell tumours were excluded to yield 46 reports containing 215 patients with the diagnosis of teratoma that was classified as mature, immature, with secondary somatic malignancy, as part of a mixed tumour, benign, malignant, and type not specified.

Mature teratoma was seen in 70 patients (32.6%), immature teratoma was noted in 83 patients (38.6%), benign teratoma was observed in 2 patients (0.9%), malignant teratoma/teratoma with secondary somatic malignancy was detected in 8 patients (3.7%), malignant mixed germ cell tumour with teratoma component was diagnosed in 26 patients (12.1%), teratoma with subsequent malignant germ cell tumour/teratoma recurrence/metachronous lesion was found in 6 patients (2.8%), teratoma type not specified was identified in 19 patients (8.8%), and malignant germ cell tumour with subsequent teratoma was documented in 1 patient (0.5%) (Fig. 6).

However, among the 215 cases of pineal region teratoma reported, there were only 16 articles that contained 18 patients with indicated serum and/or CSF tumour markers with the histologic type of the teratoma (Fig. 7). Three patients with a mixed germ cell tumour with a teratoma component and 2 patients with an immature teratoma were reported to have an elevated alpha-fetoprotein. An elevated beta-HCG and alpha-fetoprotein were reported in the following cases: mixed germ cell tumour (1 patient), immature teratoma (1 patient), mature teratoma (1 patient), primary yolk sac tumour that had a recurrence as a teratoma (1 patient), mature teratoma with recurrence as a mixed germ cell tumour (1 patient), and a teratoma that harboured a secondary malignancy (1 patient).

In comparison, one patient with a mixed germ cell tumour and one patient with a mature teratoma presented with an elevated beta-HCG; while one patient with a mixed germ cell tumour, one patient with an immature teratoma, and three patients with a mature teratoma had normal beta-HCG and AFP.

For this patient, he would fall under an elevated beta-HCG and alpha-fetoprotein,
FIG 6: Graphic representation of the teratoma of the pineal region by specific histologic type reported in public database from 1977 to 2017. Note: The use of “benign teratoma” a diagnostic entity is documented only in one report (Schmugge et al. 2000).

FIG 7: Graphic representation of the histologic type presenting with normal versus elevated alpha-fetoprotein and/or beta-HCG.
because of the elevated CSF beta-HCG that was documented pre-operatively, and the elevated serum alpha-fetoprotein that was documented in the intraoperative CSF sampling. The tumour marker findings of the patient in this report correlated with the documented patients in the reviewed documents that showed a mature teratoma in the pineal region. However, an unsampled immature teratoma component in the inaccessible region of the tumour cannot be completely excluded in this patient since an immature teratoma would also present with an elevated beta-HCG and elevated alpha-fetoprotein.

**DISCUSSION**

Pineal region teratomas are included in the broader category of germ cell tumours, which is included in the three broad categories of tumours of the pineal region. The other two categories, apart from germ cell tumours, are pineal parenchymal tumours, and other tumours of the intra-axial region and surrounding structures. A germ cell tumour is classified as mature teratoma if the lesion contains only fully differentiated, ‘adult’-type tissue elements that have little to absent mitotic activity. The ectodermal component is more commonly squamous epithelium-lined cysts with associated cutaneous adnexa, islands of glioneuronal tissue and choroid plexus; while mesodermal components would include bundles of smooth muscles, adipose tissues, hyaline cartilage, and bony trabecula. Endodermal components are more commonly cystic structures lined by miniature gut- or bronchus-like structures.  

While the ectodermal and mesodermal components are established histologically, an elevated alpha-fetoprotein indirectly correlates with an unsampled endodermal component of the intestinal-type because teratomatous glands of enteric type may cause elevation of the alpha-fetoprotein in the serum and CSF. Foci of syncytiotrophoblasts have been documented to exist as isolated cells in an immature teratoma, which, in the case of the patient being discussed here, may indicate a focus of unsampled immature component in the retained tumour areas.  

Secondary somatic malignancy has been known to occur with the most common occurrence being undifferentiated sarcomatous or rhabdomyosarcomatous transformation. Adenocarcinomas of enteric type, squamous carcinomas, leiomyosarcoma, and erythro-leukaemia have been documented. As such, aside from definitively addressing the pineal region lesion through resection and chemotherapy, surveillance for both secondary malignancy and growing teratoma syndrome was recommended.

**CONCLUSION**

Complications may occur in intracranial teratoma. These complications include recurrence, growing teratoma syndrome and the development of another type of germ cell tumour in the same area or adjacent regions. As such, understanding the nature of this lesion in terms of the clinical presentation and the associated accessible tumour markers is necessary. This report contributes to the consolidation of information and suggests possible ways to determine tumour characteristics and activity in a biopsy sample when complete excision cannot be achieved.

**Ethical approval:** This case report has no studies performed to animal or human participants. This case report includes only the specimen submitted by the patient for surgical histopathology evaluation to the section of anatomic pathology with full, informed consent of specimen evaluation.

**Conflict of interest:** The authors of this case report have no conflict of interest in relation to the conduct of this case report and the publication thereof. This study has no funding provided by the academic institution and has received no funding from any service provider related to the processing of the histopathology specimen and the ancillary immunohistochemistry of this case report.

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**REFERENCES**