Yolk sac tumours of the orbit and sinonasal tract

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ABSTRACT

Purpose: The aim of this study is to report two cases of paediatric Yolk sac tumours (YST) of the orbit and sinonasal tract, with a major review on the subject.

Methods: Two case reports along with a comprehensive retrospective literature review of all English language publications between 1974 and 2021 is presented. Literature review examined the demographics, clinical presentation and diagnostic and prognostic factors of extragonadal YSTs of the orbit and sinonasal tract.

Results: Orbit and sinuses are rare sites for YST, with only 25 paediatric cases reported in the literature. Extragonadal yolk sac tumours carry a significantly worse outcome than those localised to the gonads, with the 5-year survival of 66% and 81–89%. Our review found the median age of presentation to be 18 months (18 months to 24 months for females). These are more commonly affected. The most common presentations were proptosis, facial swelling and ophthalmoplegia. Treatments and therefore outcomes varied in the cases due to the large time period. Of the cases reported in the last 10 years, all patients with data provided were alive and disease-free at follow-up.

Conclusion: Sino-orbital yolk sac tumours are rare and have variable presentations, dependent on the extent of local invasion. Early diagnosis and treatment with multimodal therapy are paramount in having improved overall survival.

Introduction

Germ cell tumours are neoplasms that arise from primordial cells of the testes and ovaries. Yolk sac tumours (YSTs), previously known as endodermal sinus tumours, are malignant germ cell tumours, which primarily occur in the gonads. Extragonadal YSTs form 10–15% of these tumours and often favour midline structures of the mediastinum, sacrococcygeal area and retroperitoneum. The exact pathogenesis of extragonadal yolk sac tumours is unclear. The widely accepted explanation is that during the migration of germ cells in the fourth to sixth week of embryogenesis, primordial germ cells are misplaced. These cells are thought to undergo local transformation and become malignant, resulting in extragonadal YST tumours of the sinonasal tract and orbit, which are particularly rare with 25 paediatric cases reported in the literature since they were first described in 1959. We describe two new cases and review the literature of paediatric sino-orbital yolk sac tumours.

Methods

A retrospective review of published data (between 1974 and 2021) on orbital and sinus yolk sac tumours and/or endodermal sinus tumours was conducted. Data were collected from each of the identified articles on the age of presentation, sex, initial presentation, tumour location, imaging, pathology and treatment. Medline, PubMed and Google Scholar were searched for case reports and reviews in the English language using keywords - yolk sac tumour, endodermal sinus tumour, sinus, paranasal sinus, nasopharynx and orbit, which were screened for relevance and included if a case was described.
Case report 1

A 12-month-old girl presented with a 1-week history of progressive left eye proptosis and conjunctival injection. Clinical examination revealed visual acuity of 6/12 in the right eye and light perception in the left eye. There were prominent left eye proptosis with conjunctival injection, prominent left relative afferent pupil defect with optic atrophy and marked impairment in adduction of the left eye.

MRI of the head (Figure 1) confirmed a left-sided sinonasal mass involving the maxillary, ethmoidal regions with involvement of posterior orbit and infra-temporal and pterygopalatine fossa as well as the cavernous sinus. There was extensive invasion into the posterior orbit with optic nerve compression.

Biopsy of the left ethmoid and maxillary sinus mass was performed via a nasal endoscopic approach, which was intraoperatively noted to be a solid mass. Histology confirmed the presence of large epithelioid cells in a reticular pattern within a myxoid background, with large tumour cells with clear cytoplasm and occasional hyaline globules, and this appearance is characteristic of yolk sac tumour (Figure 2). Immunohistochemistry showed strong positivity to cytokeratin stain as well as Glypican 3 and alpha-fetoprotein – latter two confirming the lesion to be a yolk sac tumour. No evidence of other malignant germ cell tumour elements was seen.

The child was reviewed by the paediatric oncology team, and a positron emission tomography (PET) scan confirmed enhancing sino-orbital lesion with no metastatic spread. Serum alpha fetoprotein (AFP) was markedly raised at 3700 kIU/L (normal <6 kIU/L) with a minimum level in CSF 6.9 μg/L (presumed spill over from the blood-brain barrier).

She was commenced on triple agent chemotherapy – carboplatin, bleomycin, and etoposide, 4 cycles of 4 weeks each for a total of 3 months. There was a rapid response to chemotherapy, confirmed by a rapid decline in serum AFP down to 4 kIU/L. Follow-up MRI and

Figure 1. MRI of the head. (a) and (b) MRI T2 fat-suppressed images showing minimally hyperintense mass arising from left maxillary sinus with posterior orbital invasion and optic nerve compression. (c) and (d) DWI with mild diffusion restriction with and corresponding hypointense change in ADC.
PET scan 4 months post-treatment confirmed a residual mass in left pterygopalatine fossa with no FDG uptake. Biopsy of the residual mass in the pterygopalatine fossa had the clinical appearance of scar tissue and showed no histologic evidence of residual tumour. The child is tumour-free 6 months post-treatment with chemotherapy and is being monitored with regular serum AFP and PET scans.

Case report 2

A 23-month-old boy presented with a one-week history of right-sided epistaxis, facial swelling and right eye squint. On examination, visual acuity in the right eye was 6/18 and the left eye was 6/9 with no relative afferent pupil defect. There was a global reduction of right eye extraocular movements with normal movement in the left eye.

MRI scan showed a large mass arising from right infratemporal fossa and involving the nasopharynx, ethmoid sinuses, cavernous sinus, postero-medial orbit with optic nerve compression and superior extension to the middle cranial fossa without involvement of brain parenchyma. (Figure 3).

Biopsy of infratemporal fossa confirmed that the lesion also showed a microcystic reticular pattern, which is the characteristic histological feature of yolk sac tumour including large cells with eosinophilic to clear cytoplasm and prominent hyaline globules (Figure 4). Serum alpha fetoprotein was measured at 9838 µg/L (normal <16 µg/L). FDG-PET scan showed no evidence of metastatic spread of the tumour. The patient was commenced on triple therapy of cisplatin, etoposide and bleomycin. There was a good response to chemotherapy, with a rapid decline to a normal level in serum AFP.

PET scan 4 months post-treatment showed a mildly enhancing lesion in the nasopharynx region (significant reduction in the size of the tumour) with reduced SUVmax from 4.0 to 1.8. MRI scan at 12 months post-treatment showed post-treatment soft tissue changes with no residual tumour. He was regularly followed for 6 years and was tumour-free prior to discharge. His final visual acuity was equal and reduced in both eyes due to myopic astigmatism (6/12 with pinhole in both eyes) with no signs of optic neuropathy.

Discussion

Germ cell tumours (GCTs) are primordial cell neoplasms that commonly arise in the gonads. Yolk sac tumours are germ cell tumours that were first described in 1959 by Teilum. YSTs are uncommon highly malignant neoplasms, which selectively differentiate towards yolk sac structures. YSTs primarily occur in the ovaries or testes (75%) and much less frequently in extragonadal locations (25%), of which the head and neck represent 6%. Extragonadal GCTs carry a worse prognosis than those of gonadal origin, with the overall survival of 81% and 91%, respectively.
This difference in survival is particularly evident in YSTs, which have a 66% 5-year survival for extragonad tumours compared to 81–89% for their gonadal counterparts.\textsuperscript{1,6} Due to the rare nature of the tumour, we performed a literature review of the clinical presentation, imaging findings, histology, genetics of YST and long-term outcomes and summarised these findings (Table S1).

\textbf{Figure 3.} MRI of the head. (a) and (b) Coronal T1 fat suppressed with contrast images showing iso/minimally hyperintense mass arising from maxillary/ethmoid sinuses and involving posterior orbit, infratemporal, pterygopalatine fossa as well as middle cranial fossa. (c) Axial T1 fat suppressed with the contrast image. (d) Sagittal T1 fat-suppressed image.

\textbf{Figure 4.} Histopathology performed on biopsy of left ethmoid, maxillary sinus and pterygopalatine fossa mass. (a) Low power (×10) H&E-stained section showing the microcystic reticular pattern of yolk sac tumour. (b) High power (×40) H&E-stained section showing large tumour cells with eosinophilic to clear cytoplasm and prominent hyaline cytoplasmic globules (arrow).
**Demographics**

Gonadal and extragonadal YSTs together have a bimodal distribution with an increased incidence in the first 4 years of life and post-puberty in the second to fourth decades of life. They are twice as common in the second to fourth decades of life when compared to children under 4. The median age of patients included in our literature review of 25 cases with sino-orbital YSTs was 18 months (range of 2 months to 14 years). The median age was 24 months for females and 18 months for males.

YSTs (gonadal and extragonadal) overall are more common in males than females at a 3:2 ratio. Although in the subpopulation of paediatric extragonadal YSTs, females outnumber males at a 3:2 ratio. This is consistent with the literature that females are almost twice as likely to have YST of extragonadal sites pre-pubertally when compared to males.

**Clinical presentation and imaging**

Presentations of orbital and sinus YSTs were varied. The most common clinical features at presentation were proptosis (16/25 cases, 64%), facial swelling (9/25 cases, 36%) and ophthalmoplegia (7/25 cases, 28%). A mass was observed in five cases (20%), and vision loss was reported in four cases (16%), but likely to be higher as visual acuity was reported in four cases only. Other presentations include strabismus (12%), epistaxis (12%), nasal obstruction (16%), ptosis (16%), pain (12%), RAPD (8%), conjunctival injection (8%) and nasal discharge (8%). These tumours are highly invasive and tend to spread into local structures.

Both computed tomography (CT) and magnetic resonance imaging (MRI) are effective imaging modalities to determine the size, location and extent of invasion of the lesion. Of the 25 reported cases, imaging information was available for 17 cases (63%). CT was used in 10 cases (59%), MRI was used in 10 cases (59%), and X-ray was used in two early reported cases and colour Doppler ultrasound was used in one case. Common imaging findings include heterogenous soft tissue mass in at least 13 of the 17 cases (76%), and bone destruction or erosion was reported in six cases (35%). The mass was described as well-defined in three cases (18%) and poor or ill-defined margins in eight cases (47%), and contrast enhancement was reported in only four cases (24%).

**Histopathology and immunohistochemistry**

Histological features of YST cells show large cells with cytoplasmic atypia including prominent nucleoli, mitotic activity and typically intracellular hyaline globules although these may vary in number. YST may be associated with other germ cell tumours such as teratoma, germinoma or embryonal carcinoma, although mixed germ cell tumour is more common in older age groups. The most common described pattern is reticular/microcystic, featuring tissue that resembles the magnum reticulare with a network of microcysts. Tubulopapillary pattern, also previously known as endodermal sinus pattern, may contain Schiller-Duval bodies, which are pathognomonic for YST, occur in 20 to 75% of tumours and are not required for the diagnosis. Other patterns include papillary, solid, festoon, glandular, palesecular, parietal, hepatoid and mesenchyme-like patterns, and many YSTs show a mix of patterns. The pattern of YST has no bearing on behaviour or prognosis.

Since 1975, immunohistochemical staining for alpha fetoprotein (AFP) has been the gold standard in diagnosis of YSTs and is positive in >75% of all YSTs, although staining may be weak or focal. More recently, Glypican-3 has become a more sensitive marker with strong positive staining in >95% of YSTs and is a more sensitive marker for YST but less specific than AFP. Cytokeratin is a non-specific marker of YSTs, which is present in close to all cases and in conjunction with glypican 3 and AFP can be used to support a diagnosis of YST. Measurement of alpha fetoprotein in the blood/serum is a highly sensitive (90%) but not specific tumour marker, which can aid in diagnosis of YST and monitoring treatment. Serum alpha fetoprotein acts as a prognostic marker with levels >1000 μg/L associated with worse prognosis.

**Genetics**

The pathophysiology of YST is not well understood although the RUNX3 gene hypermethylation and GATA-4 overexpression have been implicated in development of YSTs. RUNX3 is thought to act as a tumour suppressor gene, and hypermethylation of the promoter region is evident in 75–80% of paediatric YSTs. Recently, genomic analysis identified potential somatic driver genes including significant mutations in KRAS, TP53 and KIT. As well as copy number alteration drivers such as ARID1A and PARK2 gene deletions and amplification of ZNF217, CDKN1B and KRAS genes. Additionally, OVOL2 overexpression has been identified to play a role in chemo-resistance of YSTs to cisplatin.

**Treatment**

The treatment of most extragonadal YSTs requires a multimodal treatment approach, combining chemotherapy in conjunction with surgery. Uncommonly,
radiotherapy forms part of the treatment. Of the 25 cases, chemotherapy was used in 22 cases (88%) and radiotherapy was used in five cases (20%). Surgical management was chosen in 16 cases (64%) which can be further categorised into biopsy which was used eight cases (32%) and surgical debulking, exenteration or enucleation in eight cases (32%). Common chemotherapy included cisplatin, carboplatin, vincristine, bleomycin, actinomycin D, etoposide and 5-fluorouracil. Recently, cisplatin, bleomycin and etoposide have been more widely used, reflective of the changing treatment guidelines for YSTs.

Monitoring response to treatment requires follow-up MRI or CT imaging, in addition to serial AFP levels.

Studies looking at gene expression in YSTs have found activation of the Wnt/β-catenin pathway. Activation of this pathway is common among many cancers, and there are currently trials for inhibitors and modulators of this pathway, which may show some effect for relapsed and refractory disease.

**Outcomes**

Overall, the 5-year survival for extragonadal YST is reported to be 67% and varies significantly with sex. Males have a 5-year survival of 62%, and females have a survival of 73%. The follow-up data of the cases included in our literature search are varied, with an average follow-up duration of 20 months (4 months – 15 years 3 months). Of the 25 reported cases, six patients died (24%), 16 were alive at follow-up (64%) and three did not have any data provided (12%). However, all six of the patients who died were treated over 20 years ago and these are not representative of modern day outcomes. Of the seven cases reported in the last 10 years, six were alive and disease-free at follow-up (86%) and one did not have data provided (14%).

**Conclusion**

Due to the rare nature of yolk sac tumours, particularly those involving the orbit and sinonasal tract, they present a challenging clinical diagnosis with variable clinical presentation. Immunohistochemistry and serum AFP are essential in diagnosis, and serum AFP is monitored for treatment progress. The multimodal treatment approach demonstrated the best outcomes in patients with sino-orbital YST, and further tumour genetic studies will assist in novel treatments and improved outcomes.

**Disclosure statement**

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

**Funding**

The author(s) reported that there is no funding associated with the work featured in this article.

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