

# Intriguing Cases of Rare Malignancies of Childhood and Adolescence- A Series of Six Cases

RENA GUHA<sup>1</sup>, SANGHAMITRA MUKHERJEE<sup>2</sup>, SUCHARITA SARKAR<sup>3</sup>, PALASH KUMAR MANDAL<sup>4</sup>, MEGHADIPA MANDAL<sup>5</sup>



## ABSTRACT

Intracranial teratomas constitute the majority of congenital Central Nervous System (CNS) germ cell tumours. Pure mature or immature teratomas present with giant intracranial masses that cause irreversible brain damage and impair the quality of life. Two such cases are reported here: the first involves a four-month-old female infant with a large right hemispheric lesion, and the second involves a three-month-old female infant with a similar large right hemispheric space-occupying lesion. Both underwent craniotomy but ultimately succumbed to death within a few days after the operation. Immature teratomas of the ovaries are the second most common malignant germ cell tumour following dysgerminoma, with good prognosis and excellent overall survival rates. One such case is presented here, involving a 16-year-old adolescent female with a history of irregular and painful menstruation presenting with a large abdomino-pelvic mass that was determined to be of ovarian origin through imaging studies. Alveolar Soft Part Sarcoma (ASPS) is a rare soft-tissue sarcoma with a poor prognosis, demonstrated in a 17-year-old girl who presented with a painless left thigh mass that was clinically misdiagnosed as a benign intramuscular lipoma. Another case involves a 14-year-old boy with Ewing sarcoma of the ring finger, an extremely rare hand tumour with a high potential for misdiagnosis and delayed treatment, accompanied by a focus of pulmonary metastasis. The final case involves a poorly differentiated carcinoma of the Ileum in a 17-year-old girl who was eventually lost to follow-up checkups.

**Keywords:** Alveolar soft part sarcoma, Central Nervous System teratoma, Ewing sarcoma, Infant, Poorly differentiated carcinoma of Ileum

## INTRODUCTION

Paediatric malignancies are distinctive and comprise a smaller yet significant portion of all oncology databases. They are unique in their age-based categorisation and often diverse clinical presentations. Intracranial teratoma is an extremely rare neoplasm constituting 0.5% of all intracranial tumours [1] and 2-4% of intracranial tumours in infants [2]. These pose a diagnostic problem due to their rarity compared to other intracranial tumours seen in this age group. Germ cell tumours are rare entities with a bimodal distribution. In the first four years of life, extragonadal GCTs are common, contrasting with the predominantly gonadal presentation of adolescent cases. Here, the authors depict three cases of GCTs representing both peaks, showing a gonadal (ovarian) germ cell tumour in an adolescent female and an extragonadal (intracranial) germ cell tumour in children under one year of age.

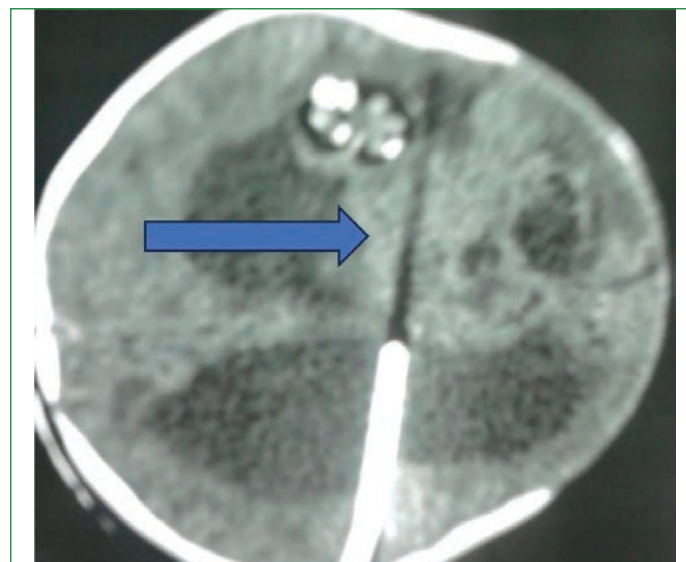
ASPS is an aggressive sarcoma of uncertain histogenesis that predominantly occurs in the extremities of both children and adolescents. They are characterised by unusual metastatic potential [3]. Ewing sarcoma is the second most common primary bone cancer in childhood and adolescence, following osteosarcoma [4]. The case presented here is distinctive as it has occurred in an extremely rare site, i.e., the digit. Small bowel malignancies are rare and present with non-specific symptoms, significantly rare in the younger population [5]. One such unique case is presented here.

## CASE SERIES

### Case 1

A four-month-old female infant of non-consanguineous parents, born at term by caesarian section, was noted to have a slightly increasing head circumference at the age of three months. She also experienced her first generalised tonic-clonic convulsion at that age, followed by eight such episodes within a week. Upon presentation at the primary

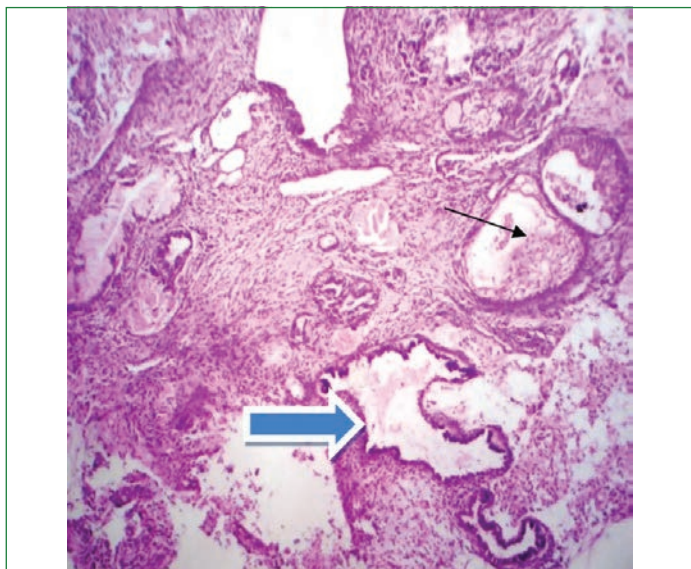
hospital, she was found to be lethargic, with left hemiparesis and a head circumference of 44cm, along with a bulging anterior fontanelle. An emergency ultrasound scan revealed a large right hemisphere tumour with gross hydrocephalus. An emergency left ventriculo-peritoneal shunt was performed. An emergency Computed Tomography (CT) scan was conducted [Table/Fig-1], confirming the presence of a left ventricular catheter with a giant right hemisphere variable attenuation lesion containing areas of cystic changes, calcification, and fat within the large lesion. A large right fronto-temporo-parietal craniotomy was performed, raising an osteoplastic flap, and the tumour was immediately visualised upon opening the dura. It appeared extremely vascular, with cystic areas as well as areas of obvious calcifications within it.



**[Table/Fig-1]:** Computed Tomography (CT) scan (non-contrast) showing large heterogeneously enhancing tumour occupying most of the hemisphere (marked by blue arrow).

There were also tufts of hair within the tumour mass. Extensive debulking was performed (approximately 80% debulking), leaving the peri-ventricular calcified part. After achieving haemostasis, the dura was closed, and the bone flap was replaced. The child was electively ventilated for 48 hours and then gradually weaned off the ventilator. She was progressing well but showed no improvement in the level of consciousness or in her hemiparesis. On the tenth post-operative day, she experienced status epilepticus and needed to be placed back on ventilator support, ultimately passing away on the 20<sup>th</sup> postoperative day.

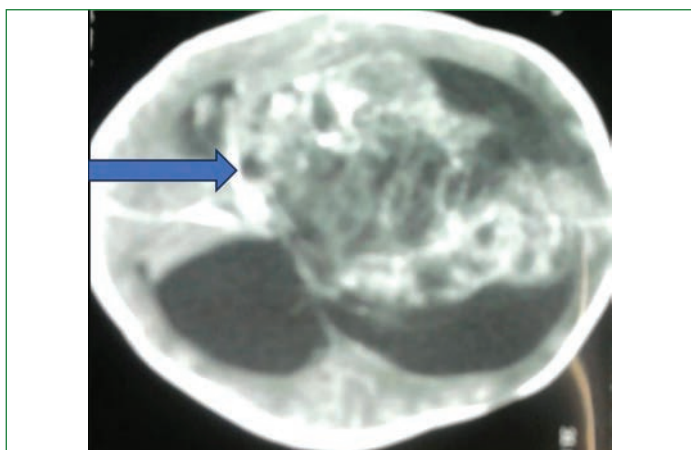
Microscopic examination of the tumour tissue revealed a mixture of different types of mature tissue. Foci of squamous epithelium, glandular epithelium, cartilage, bone, and fat were observed. Immature tissue was absent, leading to a diagnosis of Mature Teratoma [Table/Fig-2].



[Table/Fig-2]: Photomicrograph of mature teratoma showing squamous (Single arrow) and glandular element (Double arrow) (H&E, 40X magnification).

**Case 2**

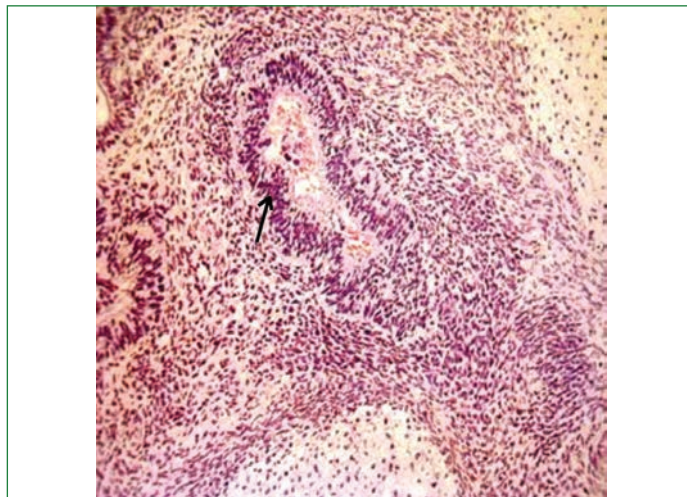
A three-month-old female infant with a history of birth asphyxia requiring resuscitation in a Neonatal Intensive Care Unit presented to a local hospital with lethargy and failure to thrive, leading to admission for investigations that revealed a large space-occupying lesion encompassing most of the right hemisphere [Table/Fig-3]. While in the hospital, the baby began to exhibit extension posturing and respiratory difficulty, requiring intubation. She scored 3 on the Glasgow Coma Scale but displayed sluggishly reacting pupils and a tense, bulging fontanelle. At this stage, the differential diagnoses included Extragonadal Germ Cell Tumour or Glioma. An attempt to perform a ventricular tap failed, and after explaining the grave prognosis to the parents, a craniotomy and debulking of the tumour were carried out.



[Table/Fig-3]: CT scan (axial section) showing mixed density tumour with calcification in the posterior part of cerebral hemisphere (marked by blue arrow).

The tumour was found to be vascular and extremely friable, allowing for a radical removal. While there was some slight improvement in the level of consciousness postoperatively, with responses to pain stimuli, respiratory efforts did not return satisfactorily. Weaning the baby off ventilator support was not possible, and she passed away on the 12<sup>th</sup> post-operative day due to renal shutdown.

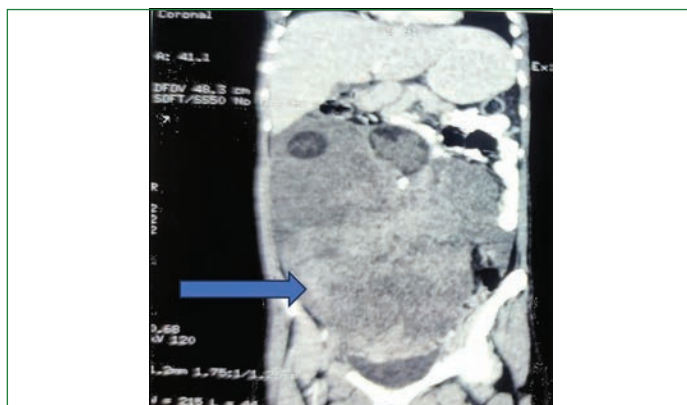
Microscopic examination once again revealed a variety of tissue types, including squamous epithelium, glandular epithelium, and foci of immature primitive neuro-ectodermal elements [Table/Fig-4]. A diagnosis of Immature Teratoma was established.



[Table/Fig-4]: Photomicrograph of Immature teratoma with primitive neuroectodermal elements (H&E, 100X magnification).

**Case 3**

A 16-year-old girl with complaints of irregular and painful menstruation for five months was found to have a huge lower abdominal mass equivalent to 24 weeks in size with restricted mobility. Ultrasonography (USG) and Contrast-Enhanced Computed Tomography (CECT) scans of the abdomen revealed a large abdomino-pelvic mass of ovarian origin with a solid-cystic appearance, along with hepatosplenomegaly and early hydronephrotic changes in both kidneys [Table/Fig-5]. Peritoneal fluid collection was scanty, and the cell block of the same was inconclusive.



[Table/Fig-5]: CT scan (contrast-enhanced) showing large abdomino-pelvic mass with solid-cystic appearance in coronal section (marked by blue arrow).

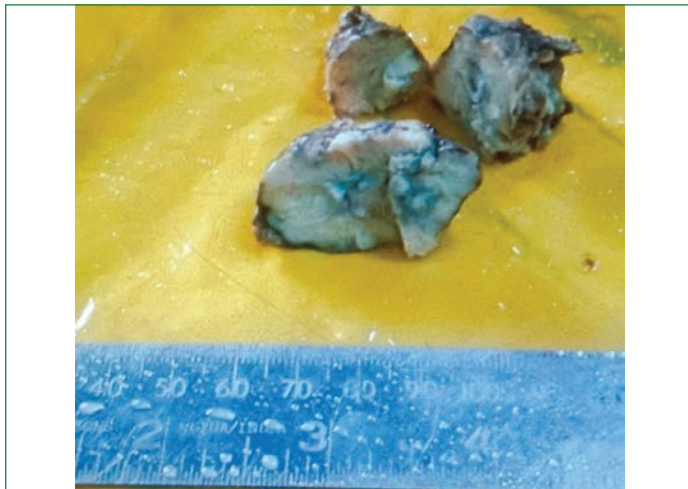
Pre-operative investigations revealed Hb-9.8 gm/dL (normal Hb 12-15 gm/dl), Total leukocyte count- 5700/cmm (Normal Total Leucocyte Count 4000-11000/cmm), platelet- 2.4 lac/cmm (Normal 1.5-4 lacs/cmm), and tumour markers such as CA-12512.1 U/ml (Normal 0-35 U/mL), AFP 2826.0 ng/ml (Normal 5-10 ng/mL), βHCG 12.7 mIU/mL (Normal 0.02-0.8 mIU/mL), CA19-9 1.7 U/mL (Normal <37 U/mL). The clinical, radiological, and biochemical picture favored a Germ cell tumour of gonadal origin. She underwent laparotomy followed by unilateral salpingo-ophorectomy (right) with infracolic omentectomy under general anesthesia. She received three units of packed RBCs in the immediate post-operative period. Her recovery was uneventful, and she was referred to radiotherapy at a later date.

Gross examination of the specimen showed a right ovarian mass measuring 30.0×20.0×12.0 cm, with a solid cystic appearance. Multiple foci of capsular breach were noted, and normal ovarian tissue appeared to be absent. Serial sections from the omentum revealed multiple firm, fibrotic deposits, the largest measuring 2.0×2.0×1.0 cm. Microscopic examination revealed an Immature teratoma.

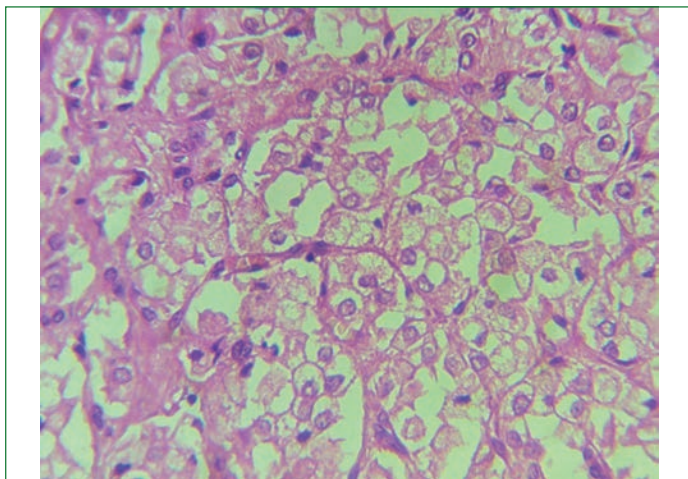
#### Case 4

A 17-year-old girl presented with a painless left thigh mass of six months duration and was provisionally diagnosed with an intramuscular lipoma. Ultrasound imaging showed a 4.5 cm hyperechoic fusiform mass with fine internal echoes that deceptively gave an impression of Intramuscular lipoma, further substantiating the provisional diagnosis. Fine Needle Aspiration Cytology (FNAC) could not be done due to the patient's apprehension. She underwent wide local excision under regional anaesthesia with sedation and had an uneventful recovery. She was eventually lost to follow-up.

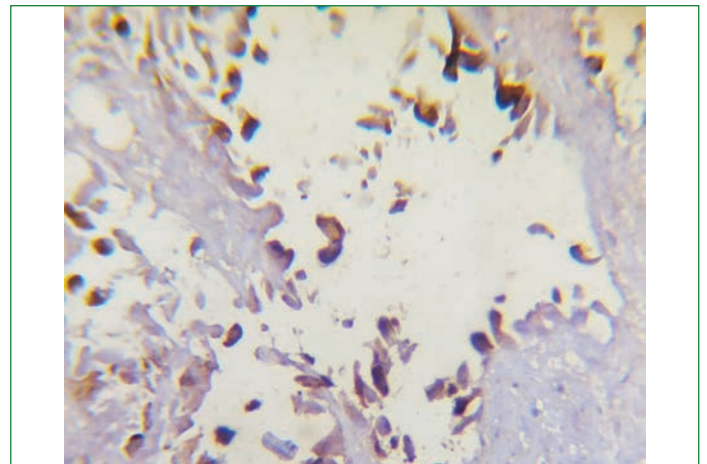
Gross findings showed a solitary, irregular, greyish-brown tissue, measuring 4.5×4.0×1.5cm, with a firm, homogenous, greyish-white cut surface with a haemorrhagic centre [Table/Fig-6]. Histopathological examination unveiled a well-delineated tumour with infiltrating margins, arranged in an alveolar pattern, comprising large cells with eccentric, hyperchromatic nuclei and densely eosinophilic cytoplasm [Table/Fig-7]. Widespread cellular pleomorphism and pseudo-glandular patterns were noted. All surgical resection margins were involved, with the presence of lympho-vascular invasion. Periodic Acid-Schiff (PAS) stain showed strong cytoplasmic staining, Immunohistochemistry (IHC) for TFE3 was positive [Table/Fig-8], whereas Myo D1 and S100 were negative. Thus, a diagnosis of Alveolar Soft Part Sarcoma (ASPS) was made.



[Table/Fig-6]: Cut surface of the tumour showing greyish-white area with haemorrhagic foci.



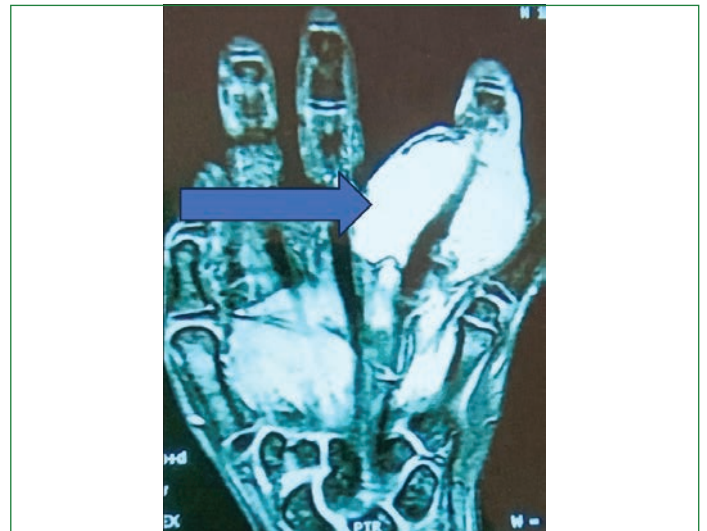
[Table/Fig-7]: Microscopic section showing tumour cells arranged in alveolar pattern (H&E, 100X magnification).



[Table/Fig-8]: Immunohistochemistry for TFE3 showing nuclear positivity (400x magnification).

#### Case 5

A 14-year-old boy who was right-hand dominant presented to the orthopaedics department with complaints of a painful swelling of the right ring finger for three months. A large soft-tissue swelling involving the proximal phalanx of the right fourth finger with surrounding soft tissue, adjacent metacarpophalangeal, and proximal interphalangeal joints measuring 4.1×3.6×4.5 cm was seen on X-ray and Magnetic Resonance Imaging (MRI) of the right hand, leading to a provisional diagnosis of Soft-tissue sarcoma [Table/Fig-9].

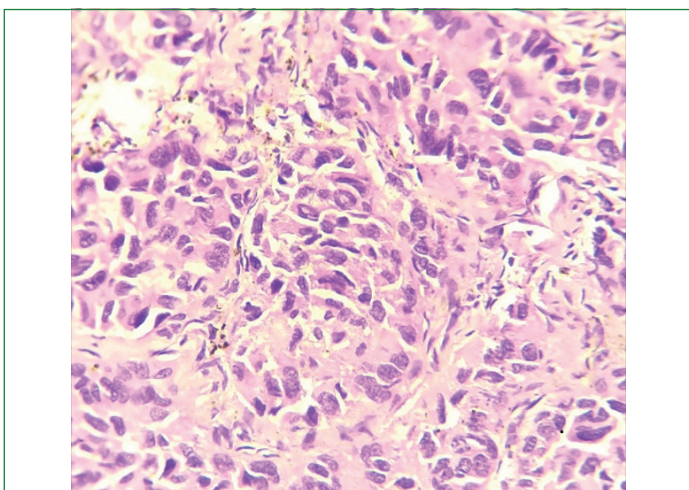


[Table/Fig-9]: T1 weighted MRI scan showing hyperechoic lesion involving the digit and adjoining soft-tissue (marked by blue arrow).

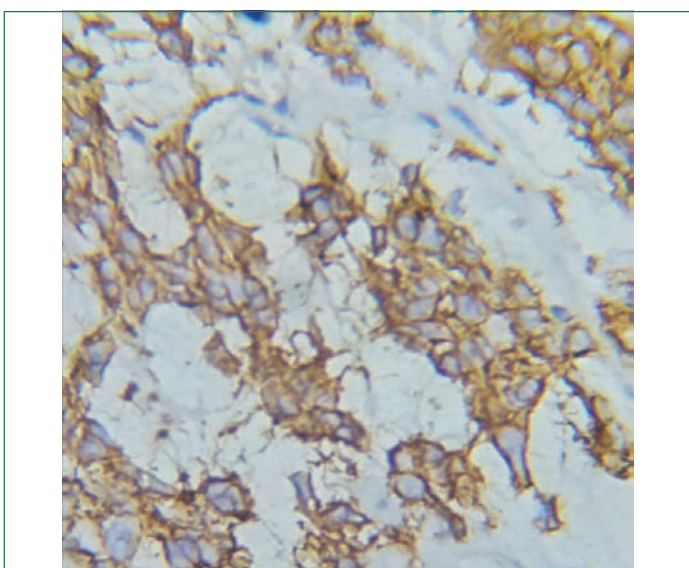
A CT scan of the thorax revealed a soft-tissue density Space-Occupying Lesion (SOL) in the right middle lobe lateral segment of the lung with adjacent consolidation. A core needle biopsy was conducted and submitted for histopathological evaluation, which included a CT-guided trucut biopsy from the lung SOL as well. The gross examination revealed four whitish tissue cores (two from the primary site in the digit and two from the lung SOL), each measuring 1.0×0.1×0.1 cm, and they were fully processed. Microscopic examination of all tissue cores revealed a small round blue cell tumour arranged in diffuse sheets with large areas of necrosis [Table/Fig-10]. The tumour cells were positive for CD99 [Table/Fig-10, 11] and vimentin, and negative for Desmin, Myogenin, S100, and EMA. A diagnosis of Ewing sarcoma with pulmonary metastasis was made. The affected finger was resected, and the patient is currently undergoing chemoradiation therapy.

#### Case 6

In another case, a 17-year-old girl presented to the surgical department with complaints of pain and discomfort in the periumbilical region, sometimes associated with vomiting for



**[Table/Fig-10]:** Microscopic section showing small blue round cells arranged in sheets (H&E, 100X magnification).



**[Table/Fig-11]:** Immunohistochemical (IHC) for CD99 showing diffuse membranous positivity.

eight months. She also had a history of a generalised tonic-clonic seizure since early childhood. Initially suspected as a case of sub-acute intestinal obstruction, she underwent laparotomy. A zone of ileal loop constriction was noted, and segmental resection with regional lymph node dissection was performed under suspicion of intestinal tuberculosis. On gross examination, an ileal segment measuring 10.0 cm in length and 3.0 cm in diameter was received. A circumferential constriction measuring 3.5×2.0×1.5 cm was noted with an irregular and congested mucosal surface [Table/Fig-12]. Microscopic examination revealed a poorly differentiated carcinoma with lymphovascular and perineural invasion, as well as radial margin involvement [Table/Fig-13]. Her immediate postoperative recovery was uneventful, but being an out-of-state patient, she was lost to follow-up, and hence, IHC wasn't conducted.

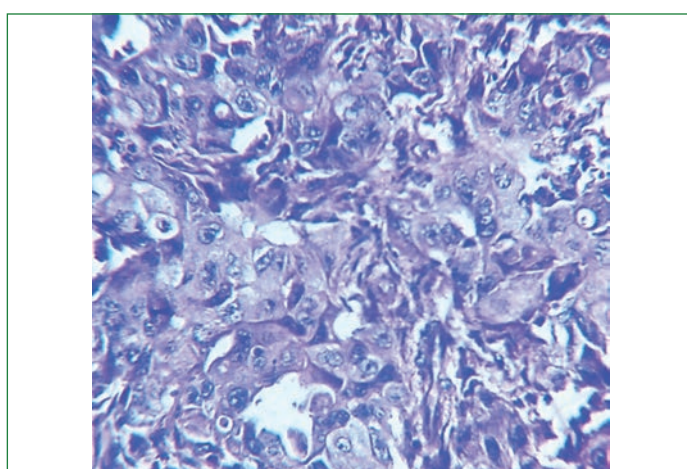
The summary of all the aforementioned cases has been tabulated below [Table/Fig-14].

## DISCUSSION

Intracranial germ cell tumours primarily affect the young, with approximately 90% occurring in individuals younger than 20 years old [6]. The incidence peaks between 10-12 years of age [7], with a male-to-female ratio of 2-2.5:1 when considering the CNS as a whole. However, the gender distribution varies with localisation, with pineal lesions more commonly affecting boys and suprasellar lesions affecting girls [7]. WHO classifies intracranial germ cell tumours into different types, including germinoma, embryonal carcinoma, yolk sac tumour, choriocarcinoma, teratoma (mature, immature,



**[Table/Fig-12]:** Gross segment of the ileum showing greyish-white constricted area.



**[Table/Fig-13]:** Microscopic section of poorly differentiated carcinoma (H&E, 400X magnification).

and teratoma with malignant transformation), and mixed germ cell tumours [7].

Radiological studies, such as CT scans and MRIs, are critical in identifying the location, size, vascularity, calcifications, necrosis, and various other changes in the neoplasm. The accurate histological identification and sub-classification of CNS germ cell tumours are crucial for current treatment and prognostication. Often, the histological diagnosis of an intracranial tumour needs to be confirmed by ancillary investigations like IHC, molecular genetic analysis, etc.

An intracranial teratoma is an uncommon intracranial neoplasm but accounts for the largest proportion of foetal intracranial neoplasms (33-50% of foetal brain tumours) [8]. Intracranial teratomas usually arise from the suprasellar region, pineal gland, quadri-geminal plate, walls of the third ventricle, or cerebellar vermis [9]. The presenting clinical manifestations of CNS germ cell tumours and their duration vary with histological type and location [6]. Tumours of the pineal region often compress and obstruct the cerebral aqueduct, resulting in progressive hydrocephalus with raised intracranial pressure, whereas suprasellar germ cell tumours typically impinge on the optic chiasma, causing visual field defects [7].

A diagnosis of teratoma should be considered for a lesion that can be shown to contain intratumoural cysts admixed with calcified regions and foci having the low signal-attenuation characteristics of fat [7]. CT scans and Magnetic Resonance Imaging (MRI) studies are of considerable value in demonstrating hydrocephalus, invasion of regional structures, and CSF-borne metastases [7]. Assays of serum and CSF for a few oncoproteins (like AFP, HCG, and PLAP) are part of the pre-operative evaluation and monitoring response of proven cases to treatment.

Sl. no.	Age	Gender	Chief complaints	Duration	Investigations	Differential diagnosis	Histopathological diagnosis	IHC /Ancillary studies	Treatment	Follow-up
1.	4 months	Female	Convulsion, lethargy, left hemiparesis	1 week	USG-Right hemispheric tumour with gross hydrocephalus; CT-variable attenuation lesion with cystic, calcific and fatty areas	1. Extragonadal germ cell tumour 2. glioma	Mature Teratoma	Not done	Initially-Emergency left ventriculo-peritoneal shunt; later-debulking surgery	Died on 20 <sup>th</sup> postoperative day
2.	3 months	Female	Birth asphyxia, lethargy, failure to thrive, respiratory difficulty leading to intubation	10 days	CT-large heterogeneously enhancing lesion in right cerebral hemisphere	1. Extragonadal germ cell tumour 2. glioma	Immature Teratoma	Not done	Debulking surgery	Died on 12 <sup>th</sup> postoperative day
3.	16 years	Female	Irregular and painful menstruation	5 months	USG & CECT-large abdominopelvic solid-cystic mass of ovarian origin, hepatosplenomegaly, bilateral hydronephrotic changes, scanty ascites; CA-125-Normal, AFP-raised	Germ cell tumour of gonadal origin	Immature Teratoma of Right Ovary with omental deposits, multiple capsular breach noted	Not done	Unilateral salpingo-oophorectomy with omentectomy followed by radiotherapy	Follow-up with clinical examination, imaging and tumour markers every 3 months and uneventful till date
4.	17 years	Female	Painless left thigh mass	6 months	USG-4.5 cm hyperechoic fusiform mass with fine internal echoes	Intramuscular lipoma	Alveolar Soft Part Sarcoma, Lymphovascular invasion-present, margins-involved	TFE3-positive, MyoD1 & S100-negative; PAS-strong cytoplasmic stain	Wide local excision followed by radiotherapy	Eventually lost to follow-up
5.	14 years	Male	Painful swelling of right ring finger	3 months	X-ray & MRI-4.5x4.1x3.6 cm soft-tissue swelling of proximal phalanx of right 4 <sup>th</sup> finger with involvement of adjacent soft-tissues, metacarpophalangeal joint and proximal interphalangeal joint; CECT Thorax-SOL in right middle lobe lateral segment	Soft-tissue sarcoma	Ewing sarcoma with pulmonary metastasis	CD99, Vimentin-Positive; Desmin, S100, Myogenin, EMA-Negative	Resection with chemoradiation	Uneventful till 11 months post-operative follow-up
6.	17 years	Female	Pain & discomfort in peri-umbilical region associated with vomiting; history of tonic-clonic seizure in early childhood	8 months	Not available	Subacute intestinal obstruction (?tubercular in origin)	Poorly Differentiated Carcinoma, Lymphovascular (LVS) & Perineural Invasion (PNI)-Present, Radial margin-involved	Not done (as patient did not turn up for follow-up visits)	Laparotomy with segmental ileal resection & regional lymph node dissection	Eventually lost to follow-up

**[Table/Fig-14]:** Summary of all six cases with respect to age, gender, chief complaints, duration, investigations, differential diagnosis, histopathological diagnosis, IHC/ancillary studies, treatment and follow-up.

USG: Ultrasonography; CT: Computed tomography; CECT: Contrast enhanced computed tomography; AFP: Alpha-fetoprotein; MRI: Magnetic resonance imaging; CA: Carcinoma; EMA: Epithelial membrane antigen; SOL: Space-occupying lesion; PAS: Periodic acid schiff

Mature teratomas are composed exclusively of fully differentiated, "adult-type" tissue elements (ectodermal, mesodermal, and endodermal) that are sometimes arranged in a pattern resembling normal tissue relationships [7]. Sometimes, the level of organisation is so advanced that it takes on a foetus-like appearance, and a diagnosis of a parasitic twin has to be considered. Immature teratoma is composed of incompletely differentiated components resembling foetal tissues [7]. This incompletely differentiated component is mainly a hypercellular and mitotically active stroma, reminiscent of embryonic mesenchyme and primitive neuroectodermal elements that may form neuroepithelial rosettes and canalicular arrays mimicking the developing neural tube [7].

Microscopically, metastatic Wilms tumour with its blastema and epithelial component can look identical to the immature teratoma, however, it occurs in a different setting and most of these patients are more than two years old. Immature intracranial teratomas have been reported to undergo spontaneous differentiation into fully mature somatic type tissues over time, which is often evident on re-resection specimen [10].

Teratoma with malignant transformation is an extremely rare teratomatous neoplasm that contains cancer of conventional somatic type as an additional malignant component [7]. The latter is most often a rhabdomyosarcoma or un-differentiated sarcoma [6] and, less commonly, a squamous cell carcinoma or enteric-type adenocarcinoma [11]. The single most predictive feature to have emerged from multivariate analyses of CNS germ cell tumour outcome is histological subtype [12]. The pure germinoma has an especially favourable prognosis owing to its remarkable radiosensitivity, a feature foreign to other germ cell tumours [7].

Patients harbouring non-germinomatous germ cell tumours are associated with poor outcome with the exception of those who can tolerate gross total resection of fully mature teratomas, which tend to be non-invasive [7]. Recent results suggest that chemotherapy can improve the overall duration and rate of survival when used in conjunction with craniospinal radiotherapy, as part of initial treatment. The most active agents include Cisplatin, Carboplatin, Etoposide, Bleomycin, Ifosfamide, and Vinblastine [13,14], but the majority of treatment reports contain information about only a few patients, which highlights the relative rarity of these tumours and the difficulty in designing the best treatment.

ASPS is characterised by indolent slow growth and high mortality risk, with metastasis occurring in the late course of the disease [15]. There are various controversies regarding its pathogenesis, with the most well-known being Alveolar Soft Part sarcoma Locus -Transcription Factor Enhancer 3 (ASPL-TFE3) transcript fusion produced by chromosomal translocation (X; 17) [16]. Histopathological examination is confirmed by strong nuclear expression of TFE3 in IHC that helps in clinching the diagnosis. Surgical resection with margins microscopically free of tumour cells remains the ASPS treatment of choice and represents a strong indicator of the treatment outcome [17]. The role of chemo- and radiotherapy is yet to be explored.

Ewing sarcoma has significant clinical and histological similarity with that of Primitive Neuroectodermal Tumour (PNET), both having small, round, undifferentiated cells [18]. The translocation t (11;22) (q24; q12) results in the production of a chimeric gene between EWS and Friend Leukaemia Integration (FLI) member of the ETS

family of transcription factors, whose transforming action has an important role in pathogenesis [19].

Cytogenetic/molecular study couldn't be done in our case. IHC study like strong diffuse membranous expression of CD99 is helpful in confirming histopathological diagnosis, as seen in this study case. Considerable improvements have been made in treatment and survival of children with small round cell tumour, with chemoradiation playing a pivotal role. The survival rate in Ewing sarcoma patient is mainly affected by factors like tumour size, tumour location, distant metastasis and response to chemotherapy [20].

The small bowel is the most common location of Neuroendocrine Neoplasms (NENs) [21]. They may histologically present as poorly differentiated carcinoma, as was seen in this case. They require further work-up in the form of IHC or molecular genetic study for exact categorisation and further management. This case in this series could not be subjected to further investigation as she was lost in the follow-up period.

## CONCLUSION(S)

Childhood malignancies present as a distinct group of neoplasms with varied and non-specific clinical presentation. They pose major diagnostic challenges due to paucity of available literature and rarity of occurrence. Histopathological diagnosis is often the major guiding tool to predict prognosis, further survival and delineate further management protocol.

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**Declaration of patient consent:** Written informed consent was obtained from the patients for publication of this manuscript and any accompanying images.

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### PARTICULARS OF CONTRIBUTORS:

1. Demonstrator, Department of Pathology, R. G. Kar Medical College and Hospital, Kolkata, West Bengal, India.
2. Associate Professor, Department of Pathology, R. G. Kar Medical College and Hospital, Kolkata, West Bengal, India.
3. Demonstrator, Department of Pathology, R. G. Kar Medical College and Hospital, Kolkata, West Bengal, India.
4. Professor, Department of Pathology, R. G. Kar Medical College and Hospital, Kolkata, West Bengal, India.
5. Senior Resident, Department of Pathology, Jhargram Government Medical College and Hospital, Jhargram, West Bengal, India.

### NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Meghadipa Mandal,  
AC1, Action Area1, Farsight Hsg Coop Soc Ltd, New Town, Rajarhat, North 24  
Parganas, Kolkata-700156, West Bengal, India.  
E-mail: meghadipa.mandal41@gmail.com

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