Tumores testiculares pediátricos: actualización del 2021 WHO PAED5 “Blue Book”

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Conflict of interest

- Expert Editor, WHO Classification of Paediatric Tumours (PAED5).

Pediatric Germ Cell Tumors

- Relatively rare, representing only 1-3% of childhood tumors.
- Remarkably diverse group, with significant variability in age and site of presentation, clinical behavior, and histology.
- They share a common origin from progenitor germ cells.
- Markedly different types may develop due to variations from normal differentiation (i.e. gonadal GCTs) and/or aberrant migration (i.e. extragonadal GCTs).
- Most common in midline locations (mediastinal, retroperitoneal, sacrococcygeal, genital, or cranial).

Pediatric Germ Cell Tumors

- The three major types include:
  - Teratoma
  - Embryonal carcinoma/yolk sac tumor
  - Seminoma/dysgerminoma.
- Common extragonadal locations are consistent with migratory pathways of primitive germ cells during the embryo-fetal development and tend to predominate in younger patients.
- Their appearance in ovaries and testes, occurring across the pediatric age spectrum, reflects the abundance of germ cells in those organs.
- Their fascinating and large morphologic spectrum reveals the wide potentiality characteristic of germinal cells.

Zambrano, De Stefano and Reyes-Múgica, 2017

Epidemiology

- GCTs may occur at any age but have a bimodal age distribution:
  - First peak between birth and 4 years of age.
  - Second one beginning with the onset of puberty and continuing through the third and fourth decades.
- In children, extragonadal sites predominate (50% of cases vs. 10% in adults).
- The majority of pediatric GCTs are benign:
  - mature teratomas are the most common.
- Approximately 20% of pediatric GCTs are malignant:
  - Approximately 3% of all pediatric cancers
  - Rate of malignancy varies by age of presentation and anatomical site.
  - The majority of malignant GCTs in children are yolk sac tumor.

Epidemiology II

- GCTs are the most common neoplasm in the newborn; 35-40% of all tumors in the first month of life.
- Most GCTs in the fetal and neonatal periods are teratomas.
- Only ≈ 5% of neonatal GCTs contain a malignant component, usually yolk sac tumor.
- Sacrococcygeal tumors (SCT) are the most common perinatal GCTs, accounting for 40% of the total.
- GCTs are 4^{th} or 5^{th} most frequent malignant neoplasm below 14 years of age, after neuroblastoma, rhabdomyosarcoma, Wilms tumor and retinoblastoma.

Most frequent GCTs in the pediatric population by age group, anatomical site and histologic type.

Age Group	Anatomical Site	Usual Histology Type	Comments
NB/Infancy	Sacrococcygeal (40%) Ovary Mediastinal>Abdominal (15-2-% vs. 5%) Cervicofacial (rare, <5%)	Teratoma	CGT: most common neoplasm in NBs (35-40% of tumors in 1st month of life); only 5% are malignant (most com. YST)
Childhood	Testis Ovary Mediastinal	Mostly YST with low (5%) metastatic rate Teratoma (40%) Mature cystic teratoma Approximately 15% are malignant. Most common malignant histology is YST in girls and younger boys, and mixed histology in older boys	Usually benign/ indolent behaviors when presenting in gonadal sites Gonadal seminoma and dysgerminoma are rare and frequently associated with gonadal dysgenesis
Puberty/ adolescence	Testis Ovary	Post-pubertal teratomas have higher metastatic potential than pre-pubertal Higher incidence of embryonal carcinoma and mixed non-seminomatous tumors Mature cystic teratoma	GCTs are the most common solid tumor in adolescent males

Zambrano E, De Stefano DV, Reyes-Múgica M. In: F.F. Nogales, R.E. Jimenez (eds.), Pathology and Biology of Human Germ Cell Tumors. ©Springer-Verlag GmbH Germany 2017

"If you don't know the names of things, the knowledge of them is lost too."

Carl Linnaeus, *Philosophia Botanica*, 1751

Ever since Carl Linnaeus in the mid 1700s developed a system to consistently classify living species, scientists in the biological disciplines… have continued classifying phenomena using a reproducible system.

Since 1956, the WHO has applied this taxonomic approach to classify tumors in all organs and systems. However, and despite the more than 6 decades of WHO volumes published, this is the inaugural WHO Volume dedicated to Paediatric Tumours.

This is explained, in part, by the fact that the subspecialty dedicated to the formal study of Paediatric Pathology is also relatively new.

But there are other reasons… compared with adults, cancer in children is much less frequent… making paediatric cancer a relatively rare disease as only 1-5% of all cancers occur before the age of 20 years.

… the study of Paediatric Pathology [is] demanding, if only by the simple reality of studying multiple organs and systems that are still in the process of acquiring their full development.

… the first question a Paediatric Pathologist asks when confronting a specimen is ***"how old is the patient?"***.

… in Paediatric Pathology, the stage of ***development is the key***.

International Agency for Research on Cancer

World Health Organization

Paediatric tumours

0.1: WHO Classification of Tumours: Editorial Board

0.2: How to cite this volume

0.3: Foreword with changes from the book, including corrigenda

0.4: ICD-O coding of paediatric tumours

1: Introduction

2: Haematolymphoid disorders
- 2.1.0.0: Introduction: Haematolymphoid disorders

2.2: Myeloid neoplasms
- 2.2.1: Myeloproliferative neoplasms
  - 2.2.1.2: Chronic myeloid leukemia (CML), BCR-ABL1
- 2.2.3: Myelodysplastic/myeloproliferative neoplasms
  - 2.2.3.1: Juvenile myelomonocytic leukaemia
- 2.2.4: Myelodysplastic syndromes
  - 2.2.4.2: Refractory cytopenia of childhood
  - 2.2.4.1: Myelodysplastic syndrome with excess blasts
  - 2.2.4.3: Myeloid neoplasms with germ line predisposition
  - 2.2.1.1: Myeloid proliferations associated with Down syndrome
- 2.2.5: Acute myeloid leukemia (AML) and related neoplasms
  - 2.2.5.2: Acute myeloid leukaemia (AML), NOS
  - 2.2.5.1: Acute myeloid leukaemia (AML) with recurrent genetic abnormalities

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- 2.2.7.1: Mastocytosis

2.3: Lymphoid neoplasms
- 2.3.1: Precursor lymphoid neoplasms
  - 2.3.1.1: B-cell lymphoblastic leukaemia/lymphomas
  - 2.3.1.2: T-cell and NK-cell lymphoblastic leukaemia/lymphoma
- 2.3.2: Mature B-cell neoplasms
  - 2.3.2.1: Primary mediastinal (thymic) large B-cell lymphoma
  - 2.3.2.2: Diffuse large B-cell lymphoma, NOS
  - 2.3.2.11: EBV-positive diffuse large B-cell lymphoma, NOS
  - 2.3.2.3: Large B-cell lymphoma with IRF4 rearrangement
  - 2.3.2.4: Paediatric-type follicular lymphoma
  - 2.3.2.5: Paediatric nodal marginal zone lymphoma
  - 2.3.2.6: ALK-positive large B-cell lymphoma
  - 2.3.2.7: Lymphomatoid granulomatosis
  - 2.3.2.8: Plasmablastic lymphoma
  - 2.3.2.9: Grey-zone lymphoma
  - 2.3.2.10: Burkitt lymphoma
  - 2.3.2.12: Burkitt-like lymphoma with 11q aberration
- 2.3.3: Mature T/NK cell neoplasms
  - 2.3.3.10: Peripheral T cell lymphoma
  - 2.3.3.1: Aggressive NK-cell leukaemia
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  - 2.3.3.3: Anaplastic large cell lymphoma, ALK-positive
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  - 2.3.3.6: Systemic EBV-positive T-cell lymphoma of childhood
  - 2.3.3.7: Hydroa vacciniforme lymphoproliferative disorder (formerly: Hydroa vacciniforme-like lymphoproliferative disorder)
  - 2.3.3.8: Subcutaneous panniculitis-like T-cell lymphoma

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- 2.3.4.1: Classic Hodgkin lymphoma
- 2.3.4.2: Nodular lymphocyte predominant Hodgkin lymphoma

2.3.5: Histiocytic and dendritic cell neoplasms
- 2.3.5.1: Langerhans cell histiocytosis and related disorders

2.3.6: Immunodeficiency-associated lymphoproliferative disorders
- 2.3.6.1: Primary immunodeficiency associated lymphoproliferative disorders
- 2.3.6.2: Post-transplant lymphoproliferative disorders
- 2.3.6.3: HIV-associated lymphoproliferative disorders

3: CNS tumours

3.1: Introduction: CNS tumours

3.2: Gliomas, glioneuronal & neuronal tumours
- 3.2.0.0: Introduction: Gliomas, glioneuronal & neuronal tumours
- 3.2.0: Paediatric-type diffuse low-grade gliomas
  - 3.2.3.10: Diffuse astrocytoma, MYB or MYBL1-altered
  - 3.4.2.7: Angiocentric glioma
  - 3.5.5.2: Polymorphous low-grade neuroepithelial tumour of the young
  - 3.2.0.2: Diffuse low-grade glioma, MAPK pathway-altered
- 3.2.1: Paediatric-type diffuse high-grade gliomas defined by H3 status
  - 3.2.1.1: Diffuse midline glioma, H3 K27-altered
  - 3.2.1.2: Diffuse hemispheric glioma, H3 G34-mutant
  - 3.2.1.3: Diffuse paediatric-type high-grade glioma, H3-wildtype and IDH-wildtype
  - 3.2.1.4: Infant-type hemispheric glioma
- 3.2.3: Circumscribed astrocytic gliomas
  - 3.2.3.1: Pilocytic astrocytoma
  - 3.2.0.4: High-grade astrocytoma with piloid features
  - 3.2.3.2: Pleomorphic xanthoastrocytoma
  - 3.2.4.2: Subependymal giant cell astrocytoma
  - 3.2.4.1: Astroblastoma, MN1-altered
- 3.2.4: Glioneuronal and neuronal tumours
  - 3.2.3.3: Ganglioglioma
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  - 2.3.1.3: Multinodular and vacuolating neuronal tumour
- 3.2.4: Ependymal tumours
  - 3.2.4.0: Introduction: Ependymal tumours
  - 3.2.4.1: Supratentorial ependymoma
  - 3.2.4.3: Supratentorial ependymoma, ZFTA fusion-positive
  - 3.2.4.5: Supratentorial ependymoma, YAP1 fusion-positive
  - 3.2.4.2: Posterior fossa ependymoma
  - 3.2.3.8: Posterior fossa ependymoma, Group PFA
  - 3.2.3.9: Posterior fossa ependymoma, Group PFB
  - 3.2.3.10: Spinal ependymoma, MYCN-amplified
  - 3.2.4.11: Myxopapillary ependymoma

3.3: Choroid plexus tumours
- 3.3.1.1: Choroid plexus papilloma
- 3.3.1.2: Atypical choroid plexus papilloma
- 3.3.1.3: Choroid plexus carcinoma

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- 3.2.0.3: Introduction: Medulloblastomas
- 3.4.1.1: Medulloblastomas, molecularly defined
  - 3.4.1.1.1: Medulloblastoma, WNT-activated
  - 3.4.1.1.2: Medulloblastoma, SHH-activated & TP53-wildtype
  - 3.4.1.1.3: Medulloblastoma, SHH-activated & TP53-mutant
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  - 3.4.2.1.1: Medulloblastoma, histologically defined
- 3.4.3.1: Other CNS embryonal tumours
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  - 3.4.3.1.8: Cribriform neuroepithelial tumour (provisional entity)
  - 3.4.3.1.2: Embryonal tumour with multilayered rosettes
  - 3.4.3.1.5: CNS neuroblastoma, FOXR2-activated
  - 3.4.3.1.6: CNS tumour with BCOR internal tandem duplication
  - 3.4.3.1.3: CNS embryonal tumour NOS

3.5: Pineal region tumours
- 3.5.1: Pineal region tumours
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  - 3.5.1.1: Pineoblastoma

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- 3.6.0.1: Meningeal melanocytosis and melanomatosis

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- 11.2.0.0: Introduction: tumours of the sellar region
- 11.2.1: Pituitary endocrine tumours
  - 11.2.1.1: Pituitary adenoma / PitNET
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- 3.7.1: Craniopharyngiomas
  - 3.7.1.1: Adamantinomatous craniopharyngioma

16: Peripheral neuroblastic tumours
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- 16.0.0.5: Ganglioneuroma
- 16.0.0.3: Ganglioneuroblastoma, intermixed
- 16.0.0.2: Neuroblastoma
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- 4.1: Introduction: Eye tumours

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  - 4.2.2.1: Conjunctival junctional, compound, and subepithelial naevi
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- 4.4.1.2: Retinoblastoma
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  - 5.2.9.10: Liposarcoma
- 5.2.2: Fibroblastic and myofibroblastic tumours
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  - 5.2.2.2.1: Fibrous hamartoma of infancy
  - 5.2.2.2.6: Lipofibromatosis
  - 5.2.2.2.2: Inclusion body infantile digital fibromatosis
  - 5.2.2.2.3: Juvenile hyaline fibromatosis (Hyaline fibromatosis syndrome)
  - 5.2.2.2.4: Fibromatosis colli
  - 5.2.2.2.5: Calcifying aponeurotic fibroma
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  - 5.2.2.4: Plantar/palmar fibromatoses
  - 2.2.2.13: Desmoid fibromatosis
  - 5.2.2.5: EWSR1-SMAD3 positive fibroblastic tumour
  - 5.2.2.12: Infantile fibrosarcoma
  - 5.2.2.7: Paediatric NTRK-rearranged spindle cell neoplasm (Provisional entity)
  - 5.2.2.8: Low-grade fibromyxoid sarcoma/Sclerosing epithelioid fibrosarcoma
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  - 5.2.3.2: Tufted angioma and kaposiform haemangioendothelioma
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  - 5.2.9.1: Schwannoma
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  - 5.4.2.7: Mesenchymal chondrosarcoma
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  - 5.4.3.4: Simple bone cyst
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  - 8.2.2.1: Gonadoblastoma
- 6.2.1: Germinoma family
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- 7.2.1.6: Metanephric tumours
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- 7.2.2: Mesenchymal renal tumours
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  - 7.2.2.1: Mesoblastic nephroma
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- 7.3.1.2: Juvenile granulosa cell tumour of the testis

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- 9.1.0.0: Introduction: breast tumours

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  - 10.2.2.4: Embryonal sarcoma of the liver
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- 11.3.1: Thyroid epithelial tumours
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  - 11.3.1.2: Papillary thyroid carcinoma
  - 11.3.1.3: Medullary thyroid carcinoma
  - 11.3.1.4: Spindle epithelial tumour with thymus-like elements

11.4: Parathyroid
- 11.4.1: Parathyroid endocrine tumours
  - 11.4.1.1: Parathyroid adenoma

11.5: Adrenal
- 11.5.1: Adrenocortical tumours
  - 11.5.1.1: Adrenal cortical tumours

11.7: Tumours of the adrenal medulla and extra-adrenal paraganglia
- 11.5.2.1: Sympathetic paraganglioma
- 11.5.2.4: Parasympathetic paraganglioma (H&N paraganglioma)
- 11.5.2.2: Pheochromocytoma
- 11.5.2.3: Composite pheochromocytoma / paraganglioma

11.6: Neuroendocrine neoplasms
- 11.6.1: Neuroendocrine tumours
  - 11.6.1.1: Other neuroendocrine tumours

12: Head and neck tumours
- 12.1.0.0: Introduction: Head and neck tumours
- 12.3.1: Benign
  - 12.3.1.1: Squamous cell papilloma and papillomatosis
  - 12.3.1.2: White sponge naevus
  - 12.3.1.3: Congenital granular cell epulis
  - 12.3.1.9: Central giant cell granuloma
  - 12.3.1.4: Odontogenic tumours
  - 12.3.1.10: Ossifying fibroma
  - 12.3.1.11: Sinonasal tract myxoma
  - 12.3.1.6: Nasal dermoid cyst
  - 12.3.1.7: Nasopharyngeal dermoid
  - 10.3.1: Epithelial tur
    - 10.3.1.1: Pan
    - 10.3.1.2: Pan
    - 10.4.1.3: Soli

10.4: Gastrointestinal
- 10.4.1: Epithelial tur
  - 10.4.1.1: Gas
  - 10.4.1.2: App

11: Endocrine tumours
- 11.1.0.0: Intro

11.3: Thyroid
- 11.3.1: Thyroid epith
  - 11.3.1.1: Foll
  - 11.3.1.2: Pap
  - 11.3.1.3: Med
  - 11.3.1.4: Spi

11.4: Parathyroid
- 11.4.1: Parathyroid
  - 11.4.1.1: Par

11.5: Adrenal
- 11.5.1: Adrenocortic
  - 11.5.1.1: Adr

11.7: Tumours of the a
- 11.5.2.1: Syn
- 11.5.2.4: Par
- 11.5.2.2: Phe
- 11.5.2.3: Cor

11.6: Neuroendocrine
- 11.6.1: Neuroendoc
  - 11.6.1.1: Oth

12: Head and neck tumours
- 12.1.0.0: Intro
- 12.3.1: Benign
  - 12.3.1.1: Squ
  - 12.3.1.2: Whi
  - 12.3.1.3: Con
  - 12.3.1.9: Cen
  - 12.3.1.4: Odo
  - 12.3.1.10: Oss
  - 12.3.1.11: Sin
  - 12.3.1.6: Nas
  - 12.3.1.7: Nas
  - 12.3.1.8: Nas
  - 12.3.1.8: Ple
- 12.3.2: Malignant
  - 12.3.2.1: Muc
  - 12.3.2.1.2: Acir
  - 12.3.2.3: Sial
  - 12.3.2.4: Nas
  - 12.3.2.6: NUT
  - 12.3.2.5: Mel

13: Thoracic tumours

13.2: Lung
- 13.2.1.2: Fetu
- 13.2.1.3: Con
- 13.2.0.1: Ple

13.3.0.2: Heart
- 13.3.0.3: Car

14: Skin tumours
- 14.1.0.0: Intro
- 14.2.0.0: Han

14.3: Epithelial Neopla
- 14.3.1: Squamous
  - 14.3.1.1: Ang
  - 14.3.1.2: Epi
  - 14.3.1.3: Pilo

14.5: Melanocytic neo
- 14.5.1: Naevi
  - 14.5.1.1: Con
  - 14.5.1.2: Jun
  - 14.5.1.3: Blu
  - 14.5.1.4: Spit
  - 14.5.1.5: Pigr
- 14.5.2: Melanoma
  - 14.5.2.1: Mel

15: Genetic tumour syndro
- 15.0.0.1: Intro
- 15.1.1: Phakomatos
  - 15.1.1.7: Neu
  - 15.1.1.8: Neu
  - 15.1.1.1: Tub
  - 15.1.1.6: Nae
  - 15.1.1.16: Von
  - 15.1.1.16: WA
  - 15.1.1.15: Bec
- 15.1.2: Familial colo
  - 15.1.1.5: Fan
  - 15.1.1.14: Lyn
  - 15.1.1.4: Cor
- 15.1.3: Other CNS
  - 15.1.1.13: Xer
  - 15.1.1.12: Rot
  - 15.1.1.10: Fan
  - 15.1.1.2: Li F
  - 15.1.1.9: Ret
  - 15.1.1.11: DIC
  - 15.1.1.3: BAF
  - 15.1.1.3: Rha

99: Inhouse scanned slides

The WHO *PAED5* Update on Pediatric Germ Cell Tumors

6: Germ cell tumours

6.1.0.0: Introduction: Germ cell tumours

6.2: Germ Cell

6.1.1: Non-invasive germ cell neoplasia

6.2.1.1: Intratubular germ cell neoplasia (Male gonadal)

8.2.2.1: Gonadoblastoma

6.2.1: Germinoma family

6.2.1.2: Germinoma/Dysgerminoma/Seminoma

6.2.2: Non-germinomatous germ cell tumours

6.2.2.0: Introduction

6.2.2.1: Mature cystic teratoma

3.4.2.1.3: Extra-gonadal teratoma

6.2.2.2: Monodermal teratomas (Female gonadal)

6.2.2.3: Immature teratoma (Female gonadal)

6.2.1.3: Prepubertal type testicular teratoma

6.2.2.4: Post-pubertal type teratoma

6.2.3.1: Embryonal carcinoma

6.2.3.2: Yolk sac tumour

5.2.9.3: Fetus in fetu

6.2.3.3: Choriocarcinoma (non-gestational)

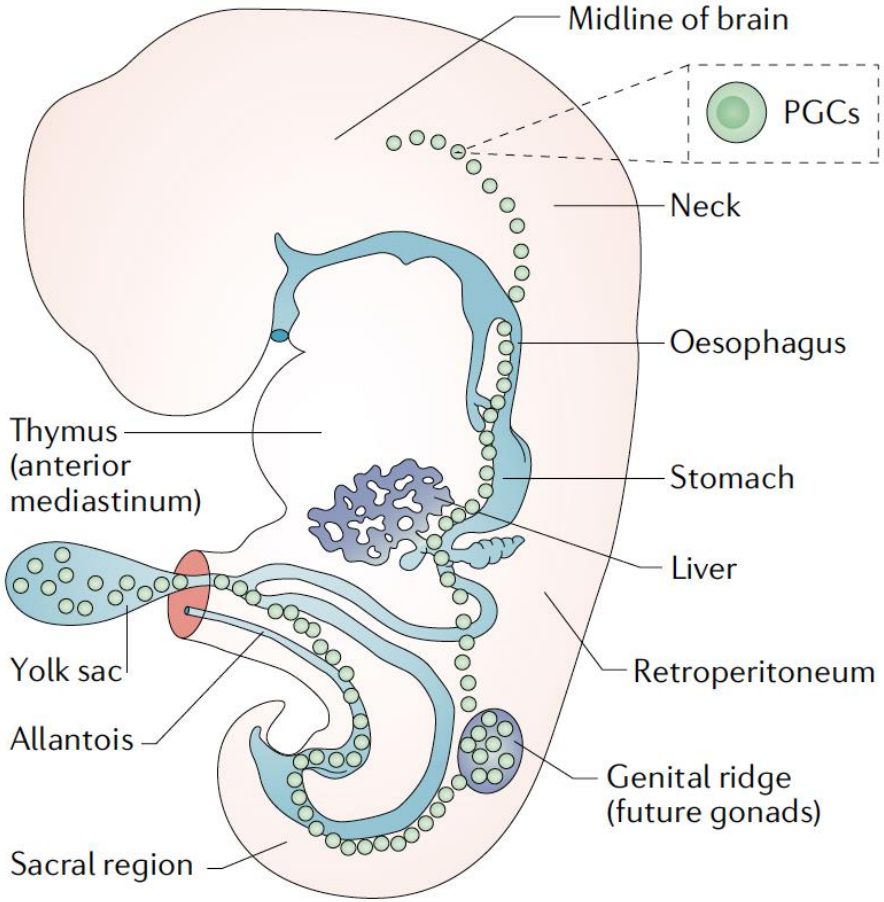
6.2.3.4: Malignant mixed germ cell tumours

Germ cell tumours (GCTs)

- Heterogeneous group occurring at various anatomical localizations; in females and males; in neonates, infants, adolescents and (young) adults.
- Developmental perspective: a continuum derived from early embryonic cells to progressively maturing germ cells.
- Predominantly gonadal but also at extra-gonadal locations usually along the midline (<6 YO) due to the migration pathway of primordial germ cells (PGC) during embryogenesis.
- Pathogenesis: “illicit” activation (reprogramming) of latent developmental program of non-neoplastic germ cells. Migrating PGCs may escape their normal fate of apoptosis. This explains why most GCTs are benign. Due to genomic instability, they are prone to progression, most often to yolk sac tumor and/or somatic type malignancy.
- GCTs malignant *per se:* germinoma-family and derived nonseminomas (rarely initiated by driver mutations) due to the ability of late PGC, from which they are derived, to survive in the gonadal and defined extragonadal ‘surrogate’ niches (thymus and brain midline). From there, they may progress to known germinoma-family precursors: germ cell neoplasia *in situ* (GCNIS) of testis; gonadoblastoma in dysgenetic gonad/ovary, and similar lesions in the thymus.
- Progression by default along the germinoma-family lineage, which upon reprogramming, may give rise to nonseminomas.
- The different identity of teratomas with similar morphology poses a diagnostic challenge, particularly in the ovary and testis. When in doubt, a germinoma-family-derived malignant teratoma must be ruled out by molecular means.

GCT type	0	I	II	III	IV	V	VI
Cell of origin	Blastomere	Early PGC	Late PGC → Transformed late PGC (seminomatous cell)	Spermatogonium	Primary oocyte	Empty ovum	Somatic cell
Reprogrammed cell of origin	Twin embryo	Primed ESC	Transformed naive ESC (EC cell)	Not reprogrammed	Gynogenote	Androgenote	Primed or naive iPSC
Mechanism of reprogramming	Fission of embryo and reprogramming of blastomere	Lack of maintenance of phenotype by SOX17, BLIMP1, OCT4 and SOX2 in migrating PGCs; reversal of germ line specification due to BMP inhibition induced by the microenvironment	Inadequate niche → delayed maturation; co-expression of OCT4 and TSPY and transformation of late PGC; reprogrammed to EC cell by BMP inhibition → reversal of germline specification	Meiosis blocked by overexpression of GDNF in niche and DMRT1 in spermatogonia	Partheno-genetic activation of primary oocyte after escape from meiotic arrest → uncontrolled meiosis	Fertilization of empty ovum	Activation of pluripotency genes by translocations; cancer progression; therapeutic use of iPSCs
Developmental potential	Included and parasitic twin	Immature teratoma (yolk sac tumour)	• Seminoma • Non-seminoma	Spermatocytic tumour	Dermoid cyst	Hydatidiform mole	• Immature teratoma (yolk sac tumour) • Non-seminoma
Intermediate types	0–I: Amorphous twin or teratoma I–II: I by phenotype, II by genotype II–III: Intermediate phenotype and genotype I–IV combination of immature teratoma and dermoid cyst 0–IV dermoid cyst with fetiform structures						

Omnipotent | Totipotent | Pluripotent | Latent pluripotent | Latent totipotent

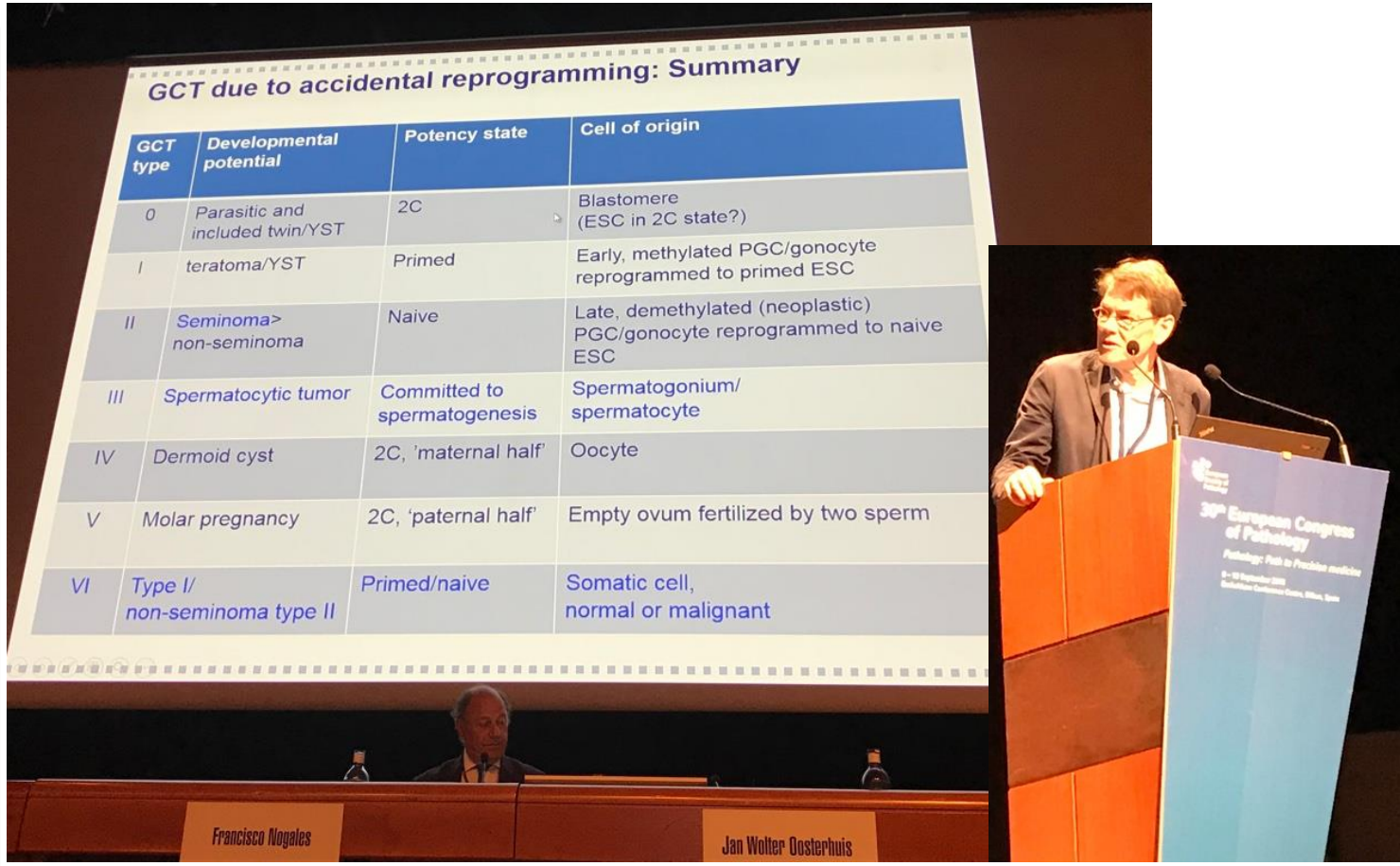


Oosterhuis JW, Looijenga LHJ. Human germ cell tumours from a developmental perspective. Nat Rev Cancer. 2019 Sep;19(9):522-537.

Table 1 | **Characteristics of seven defined types of germ cell tumour**

GCT type	Developmental potential	Age	Incidence per 100,000	Sex	Anatomical site	Familial, bilateral or multiple	Karyotype	Animal model
0	Parasitic twin; included twin; occasionally, on aneuploidization, YST and STM	Prenatally or at birth	<0.1	F:M is 3:1	Sites where conjoined twins are attached: sacral region, retroperitoneum, abdomen, neck, face, orbit and other rare sites	Family history of monozygotic multiple pregnancies in 15% of cases	Diploid; YST component near-diploid with gain of 1q, 12p13 and 20q and/or loss of 1p, 4 and 6q	9-Banded armadillo[60]
I	(Immature) teratoma; on aneuploidization, YST; rare cases of STM	Neonates and children <6 years; rarely beyond childhood; a broad age range only when occurring in the ovary	1–1.5	F > M; at attachment sites of conjoined twins ratio is 3:1	Sacral region, retroperitoneum, abdomen, anterior mediastinum (thymus), neck, midline brain, testis, ovary and other rare sites	Family history of monozygotic multiple pregnancies in 15% of cases; occasionally occurs with type 0	Teratoma diploid; YST near diploid with gain of 1q, 12p13, and 20q and/or loss of 1p, 4, and 6q; in intermediate types between type I and type II, rare cases with i(12p)[5,18,19]	Mouse teratoma; prevalence of EC more like that of type II
II	By default seminoma, dysgerminoma or germinoma reprogrammed to non-seminoma, non-dysgerminoma or non-germinoma, respectively (EC, teratoma, YST, choriocarcinoma); occasionally STM	After start of puberty; mean age 35 years; in DSD, Klinefelter syndrome and Down syndrome rarely before puberty	Gonadal dysgenesis, rare; testicular, 0.5 in Africa and Asia and 12 in northern and western Europe (and rising); ovarian, <0.5; in the mediastinum and midline brain, <0.5	DSD with Y; M > F (for type II GCTs of the thymus and midline brain)	Dysgenetic gonad, testis, ovary, anterior mediastinum (thymus) and midline of the brain (mainly in pineal gland)	Dysgenetic gonad: familial[a], 40% bilateral. Testicular type II GCTs: 40% familial, 5% bilateral. Ovarian type II GCTs: rarely familial, 6% bilateral. All type II GCTs: ovarian and extragonadal occur rarely with type II of testis, type II sporadically occur with type I	Aneuploid (± triploid) with gain of X, 7, 8, 12p, and 21 and/or loss of Y, 1p, 11, 13 and 18; in mediastinum and midline of the brain also (near) diploid and (near) tetraploid with gain of 12p	Seminoma-like tumour in zebrafish[126], possibly intermediate between type II seminoma and type III
III	Spermatocytic tumour; rare cases of STM	Older men, with peaks at 40 years and 55 years	<0.1	M	Testis	9% Bilateral	Tetraploid, triploid or near diploid with gain of 9 and 20 and/or loss of 7	Canine seminoma; mouse models
IV	Dermoid cyst, sporadically with fetiform structures; occasionally, on aneuploidization, YST and STM	Reproductive age; mean age 30 years	15	F	Ovary	Occasionally, familial; 11% bilateral; occasionally combined with type I; rarely occurs in women who have had multiple pregnancies	Diploid; rarely near diploid, tetraploid or peritriploid with gain of X, 7, 8, 12 and 15	Mouse gynogenote
V	Complete hydatidiform mole; occasionally choriocarcinoma	Reproductive age; strong increase of incidence with age	1–3 per 1000 live births (declining); highest in Asia	F	Placenta, usually in the uterus	Familial, when maternal mutations of *NLRP7* or *C6orf221* are present	Diploid (90% XX and 10% XY), rarely tetraploid	Mouse androgenote
VI	Resembling type I or non-seminoma components of type II; no seminoma	Older age, usually >60 years	Unknown	F and M	Atypical sites for GCTs, such as the soft tissues of the extremities	NA	Dependent on precursor cell	Xenograft derived from iPSCs

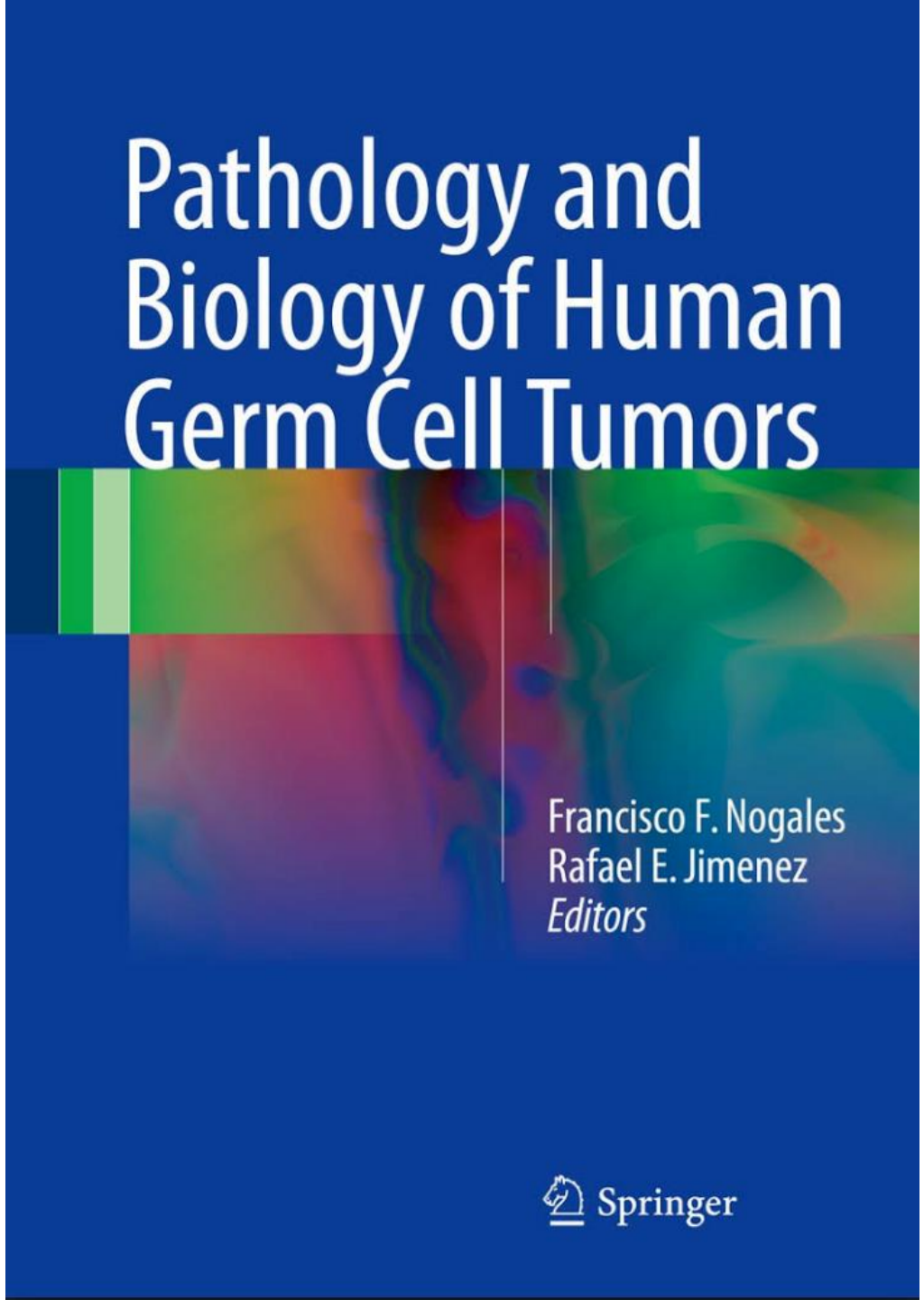
DSD, disorders of sex differentiation; EC, embryonal carcinoma; F, female; GCT, germ cell tumour; i(12p), isochromosome 12p; iPSCs, induced pluripotent stem cells; M, male; NA, not applicable; *NLRP7*, NLR family pyrin domain-containing 7; STM, somatic type malignancy; YST, yolk sac tumour. [a]Rare cases of complete and partial androgen insensitivity syndrome. Adapted from REF.[5], Springer Nature Limited.



Human germ cell tumours from a developmental perspective

J. Wolter Oosterhuis[1] and Leendert H. J. Looijenga[1,2]*

Abstract | Human germ cell tumours (GCTs) are derived from stem cells of the early embryo and the germ line. They occur in the gonads (ovaries and testes) and also in extragonadal sites, where migrating primordial germ cells are located during embryogenesis. This group of heterogeneous neoplasms is unique in that their developmental potential is in effect determined by the latent potency state of their cells of origin, which are reprogrammed to omnipotent, totipotent or pluripotent stem cells. Seven GCT types, defined according to their developmental potential, have been identified, each with distinct epidemiological and (epi)genomic features. Heritable predisposition factors affecting the cells of origin and their niches likely explain bilateral, multiple and familial occurrences of the different types of GCTs. Unlike most other tumour types, GCTs are rarely caused by somatic driver mutations, but arise through failure to control the latent developmental potential of their cells of origin, resulting in their reprogramming. Consistent with their non-mutational origin, even the malignant tumours of the group are characterized by wild-type *TP53* and high sensitivity for DNA damage. However, tumour progression and the rare occurrence of treatment resistance are driven by embryonic epigenetic state, specific (sub) chromosomal imbalances and somatic mutations. Thus, recent progress in understanding GCT biology supports a comprehensive developmental pathogenetic model for the origin of all GCTs, and provides new biomarkers, as well as potential targets for treatment of resistant disease.



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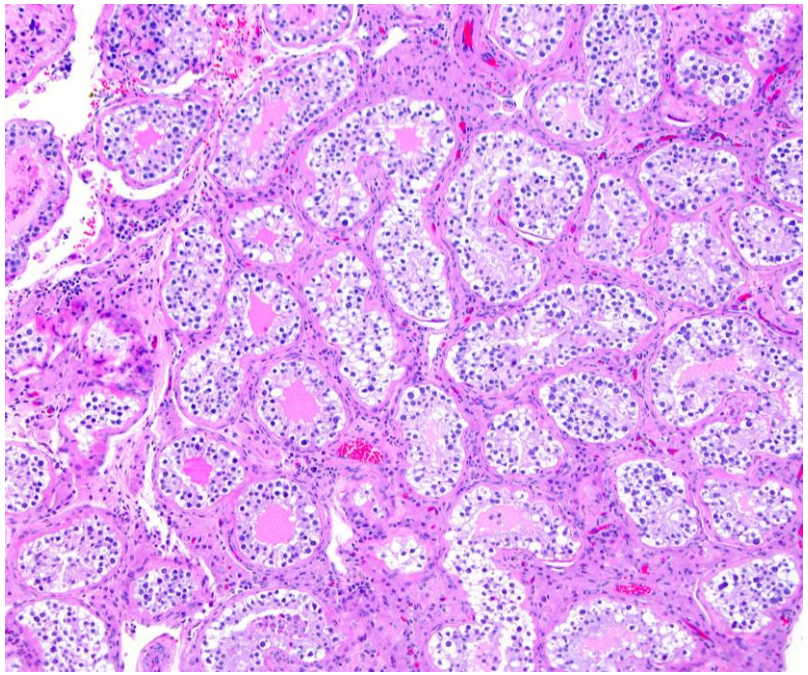
6.2: Germ Cell

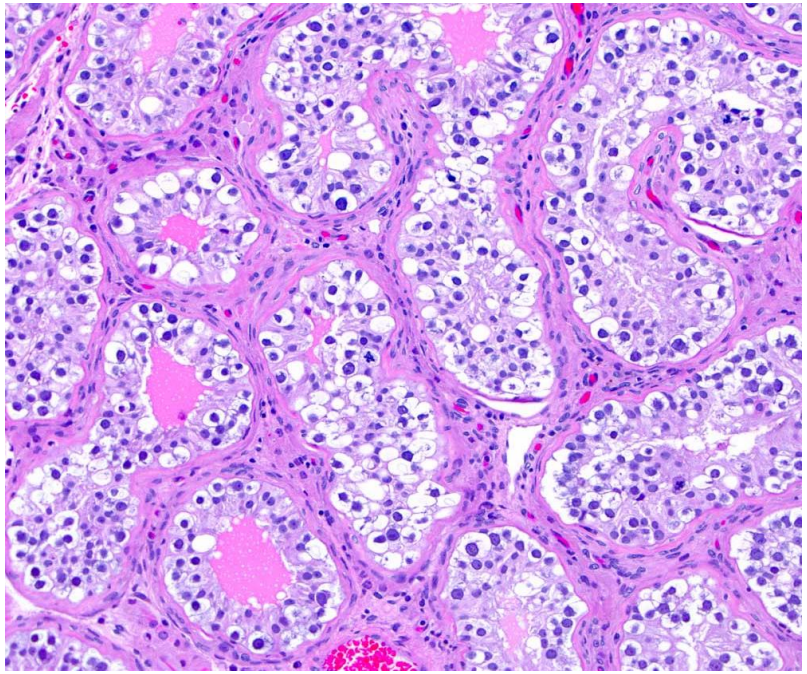
6.1.1: Non-invasive germ cell neoplasia

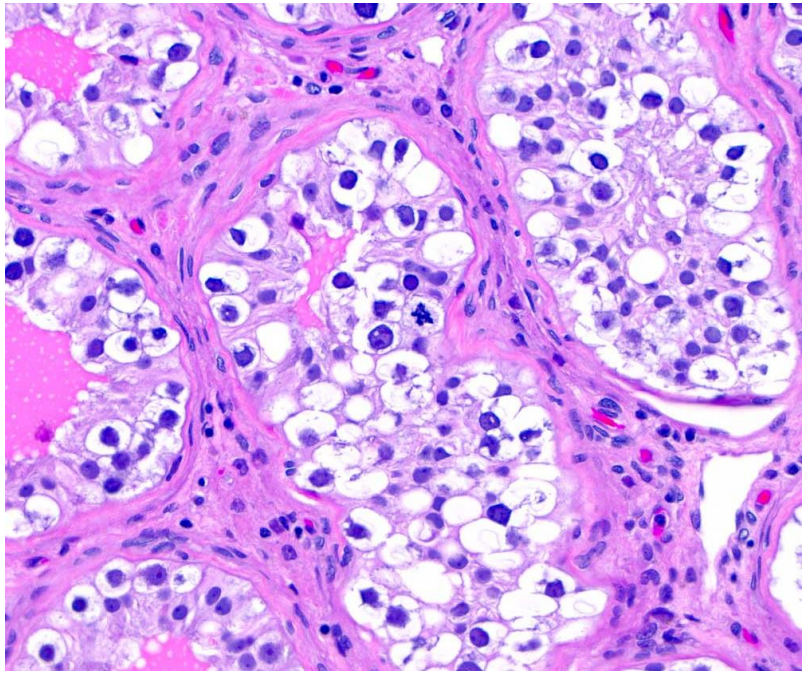
6.2.1.1: Intratubular germ cell neoplasia (Male gonadal)

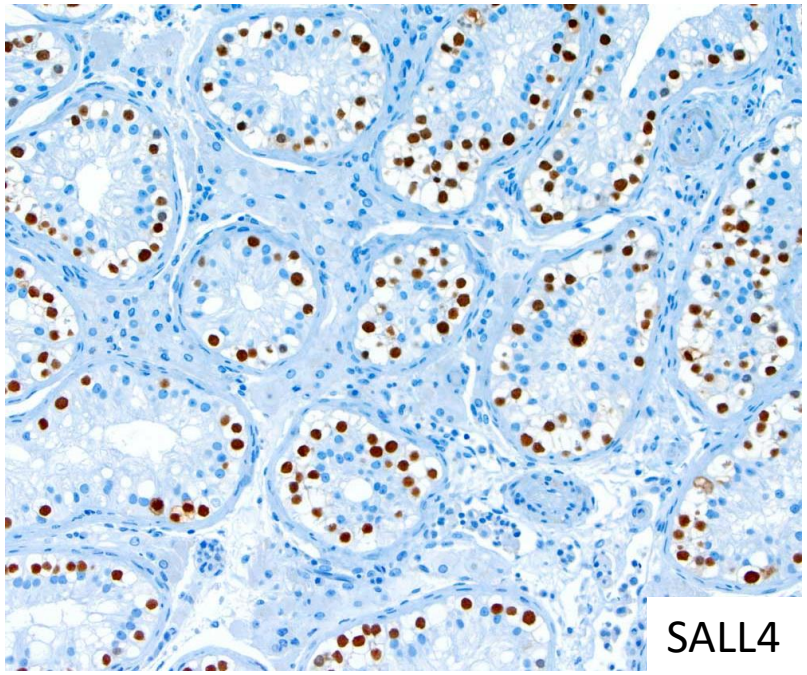
8.2.2.1: Gonadoblastoma

- Germ Cell Neoplasia in Situ (GCNIS):
  - Precursor of seminoma and non-seminoma, type II germ cell tumors of the testis.
  - Neoplastic gonocytes with latent totipotent (naïve) developmental potential, located as “strings of beads” in the spermatogonial niches of seminiferous cords/ tubules.
  - Trophoblastic giant cells in about 20%. Bilateral in 4-5%. Frequently associated with microlithiasis.
  - Risk is increased in DSDs: gonocytes fail to differentiate into spermatogonia and become the source of GCNIS cells.
  - Highest risk in DSDs, in which the gonadoblastoma region on the Y chromosome (GBY), containing the testis specific Y-encoded protein (*TSPY)*, is involved. In those conditions GCNIS can reach 70%.
  - Risk also increased up to 5%, in the so-called testicular dysgenesis syndrome: overlapping anomalies such as cryptorchidism, hypospadias, and some forms of infertility, and in the contralateral testis of patients with unilateral type II GCT.
  - 90% of GCNIS will progress to an overt TGCT within seven years (up to 15-20 years).









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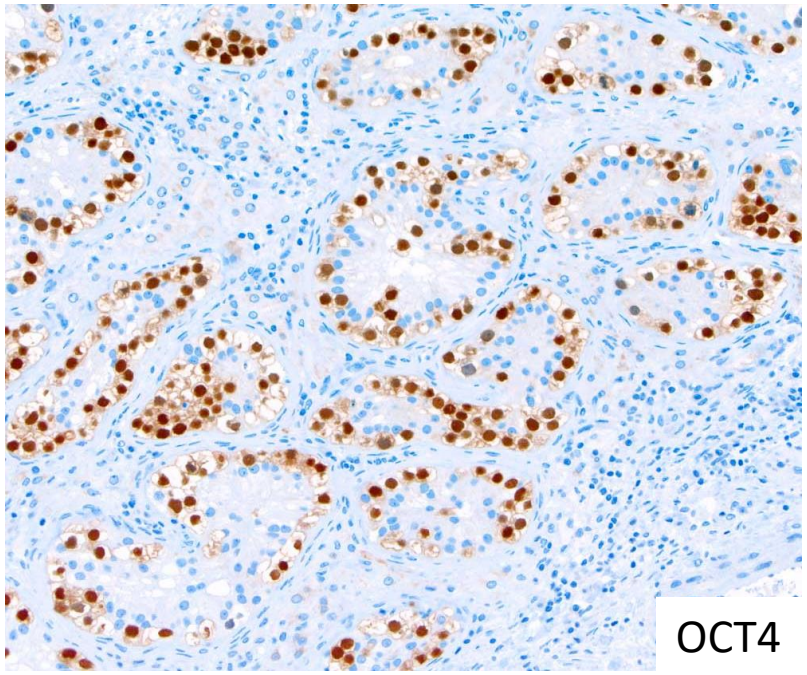

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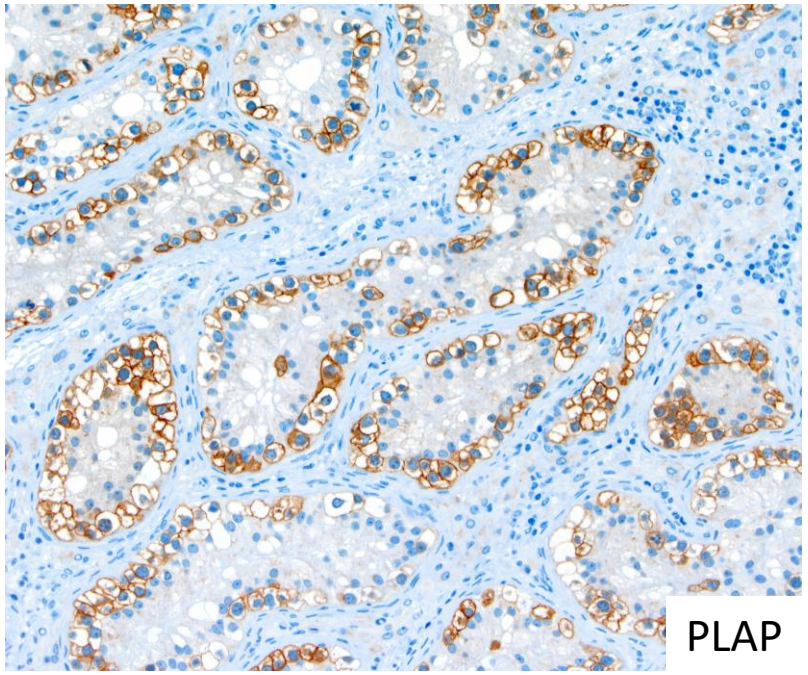


PLAP

6.2: Germ Cell

6.1.1: Non-invasive germ cell neoplasia

6.2.1.1: Intratubular germ cell neoplasia (Male gonadal)

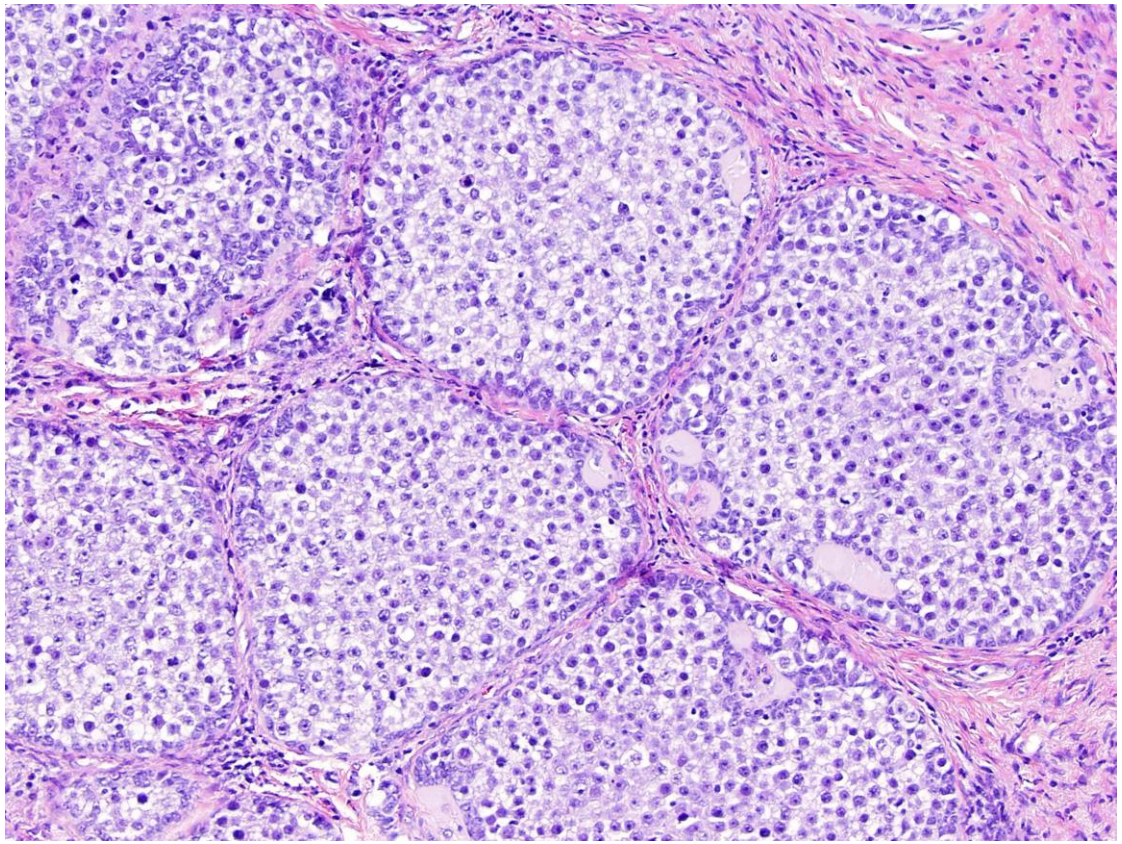
8.2.2.1: Gonadoblastoma

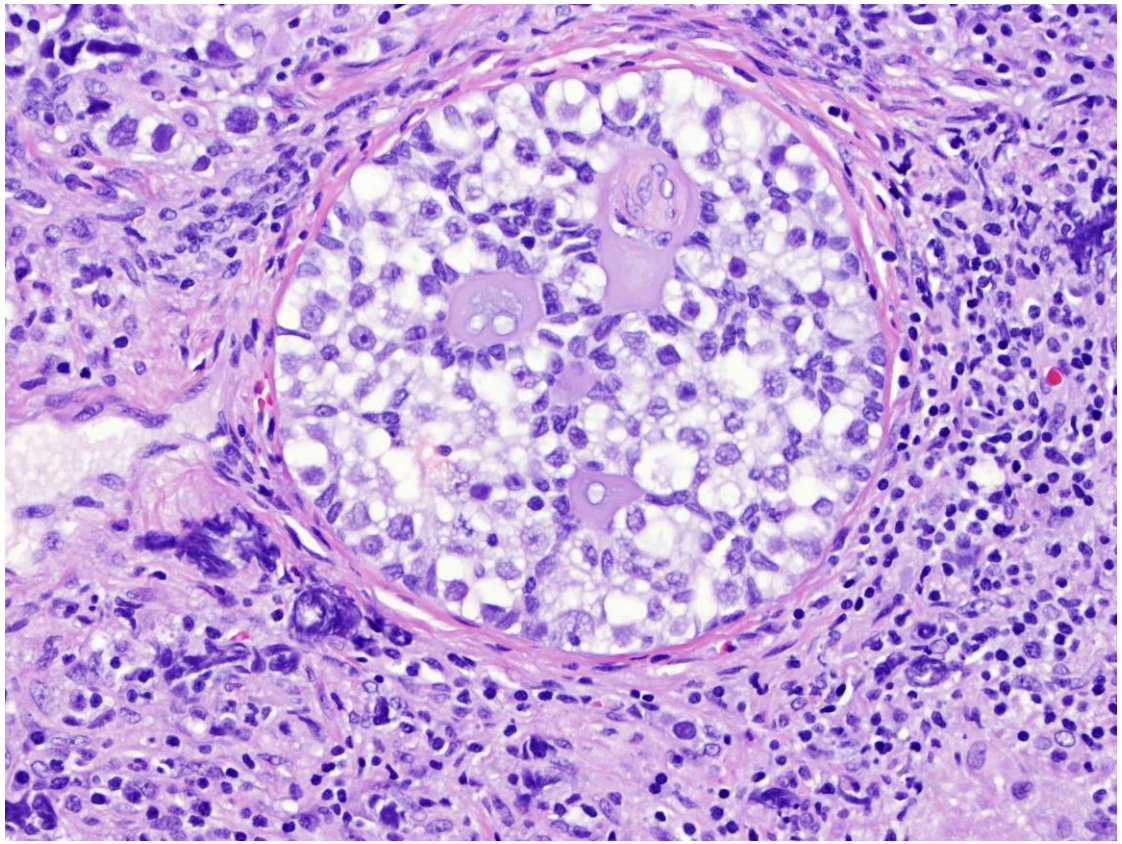
- Gonadoblastoma: *in situ* form of malignant germ cell tumor consisting of GCNIS/seminoma/dysgerminoma cells, and incompletely differentiated sex cord cells reminiscent of Sertoli/granulosa cells.
- Most patients present as neonates with ambiguous genitalia in the setting of disorders of sex development (DSD).
- Occasionally presents until the 4th decade.
- Half appear in virilized females, 30% in non-virilized females, and 20% in males with hypospadias and an empty scrotum.
- Primary amenorrhea is a common initial presentation in young females.
- Almost always associated with DSDs. A subset occurs in patients with no DSD and normal peripheral blood karyotypes.
- Up to 60% of dysgenetic gonads develop gonadoblastoma.
- Frequently associated with gonadoblastoma:
  - 46,XY pure gonadal dysgenesis (bilateral streak gonads)
  - mixed gonadal dysgenesis
  - ovotesticular disorder of sex development
  - Turner syndrome
  - androgen insensitivity syndrome
  - Gonadoblastoma is bilateral in between 1/3 and 40% of cases

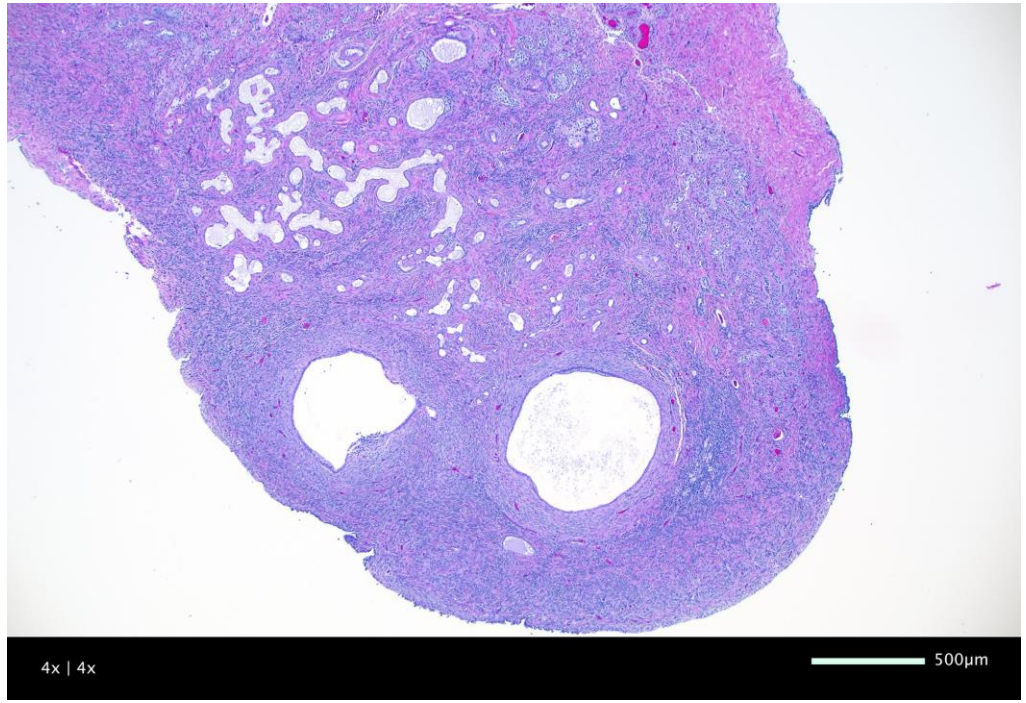
- Germline or somatic mutations in WTI (Denys-Drash and Frasier syndromes) or SRY genes (Swyer syndrome) feature dysgenetic gonads and gonadoblastomas.

- Up to 35% of Turner syndrome patients with Y-chromosomal material (which may be cryptic) develop gonadoblastomas, as do about 5% with the androgen insensitivity syndrome

Gonadoblastoma



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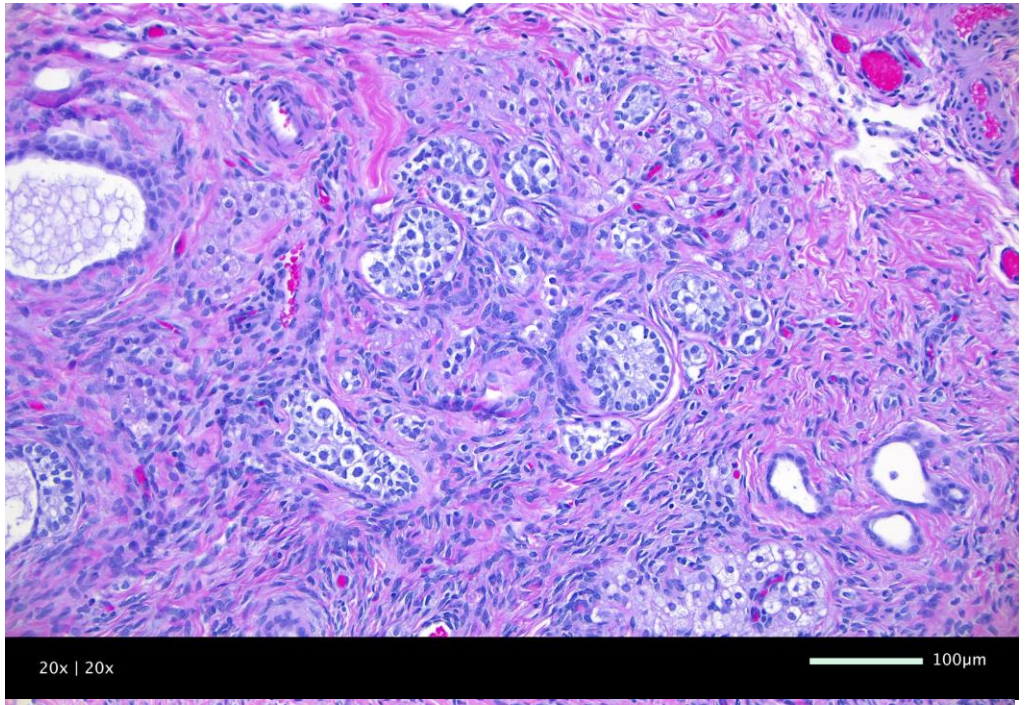
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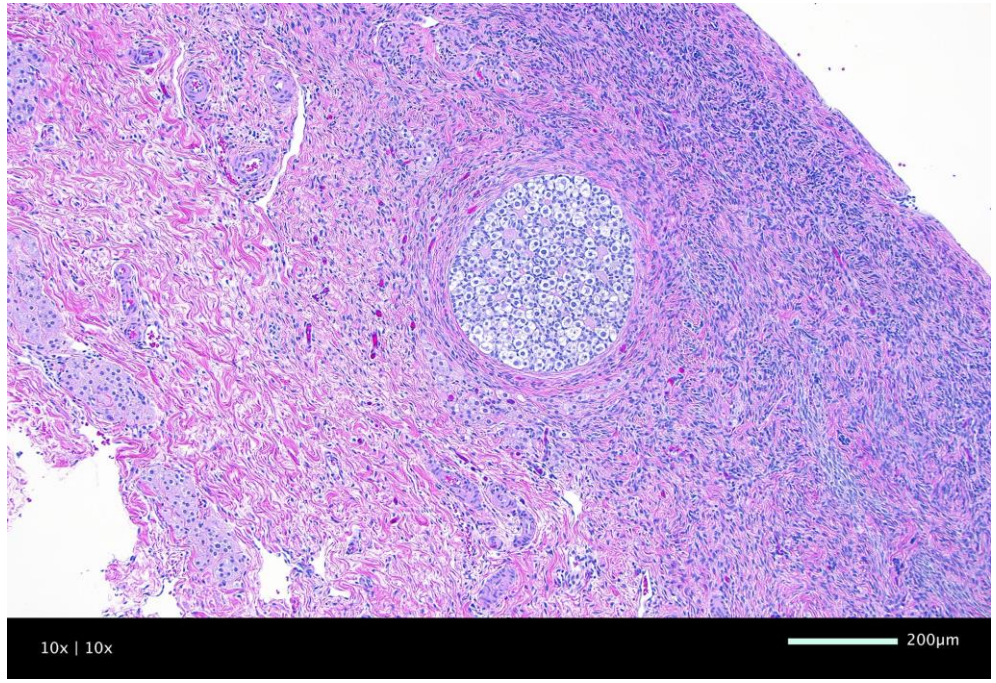
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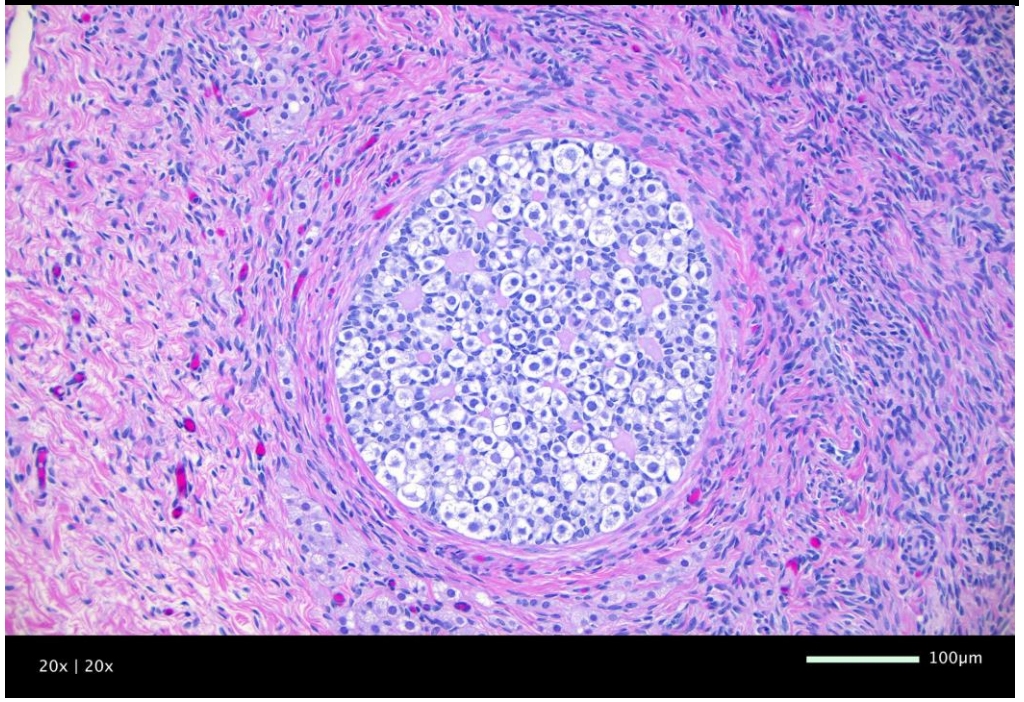
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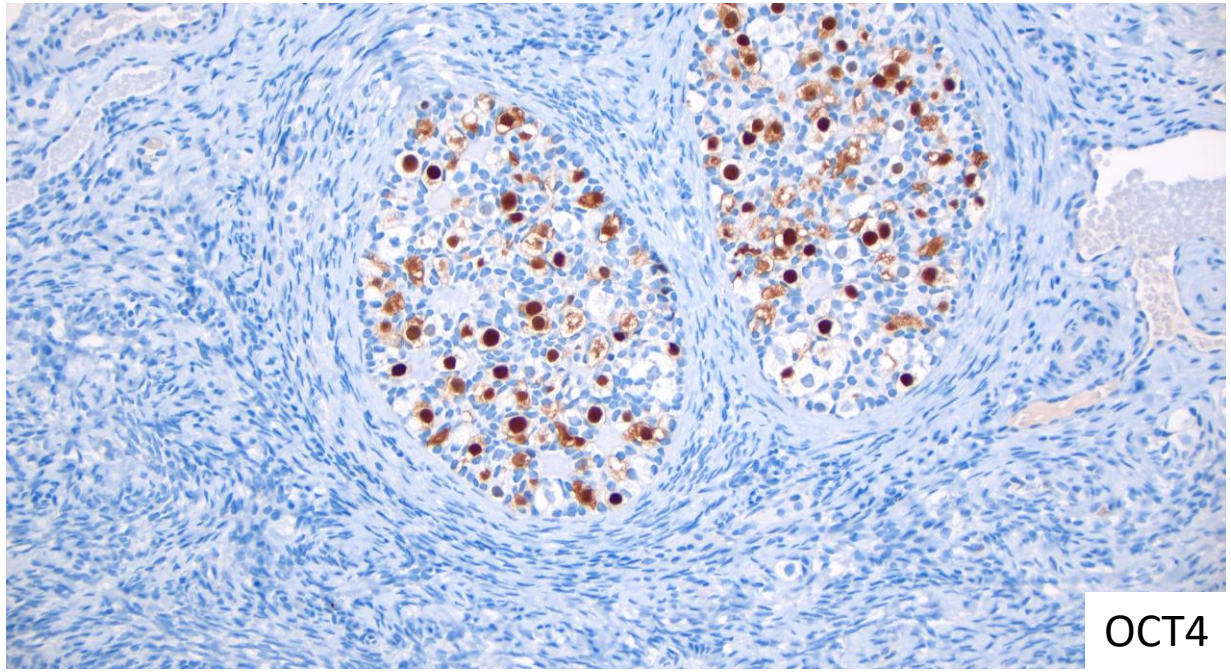
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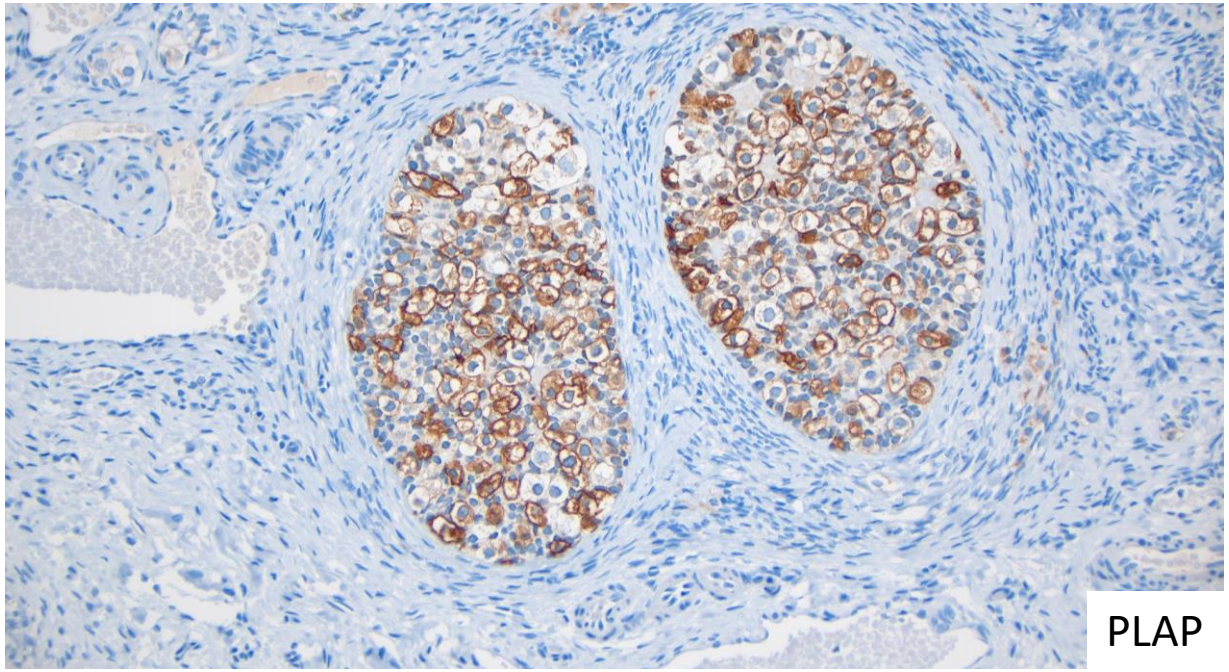
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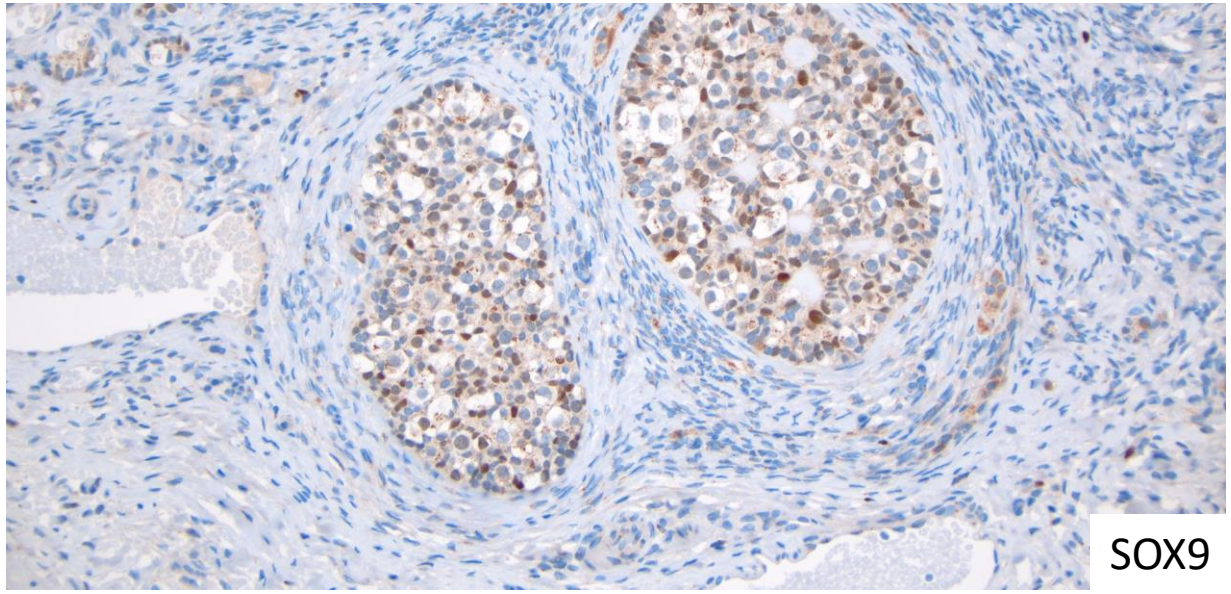
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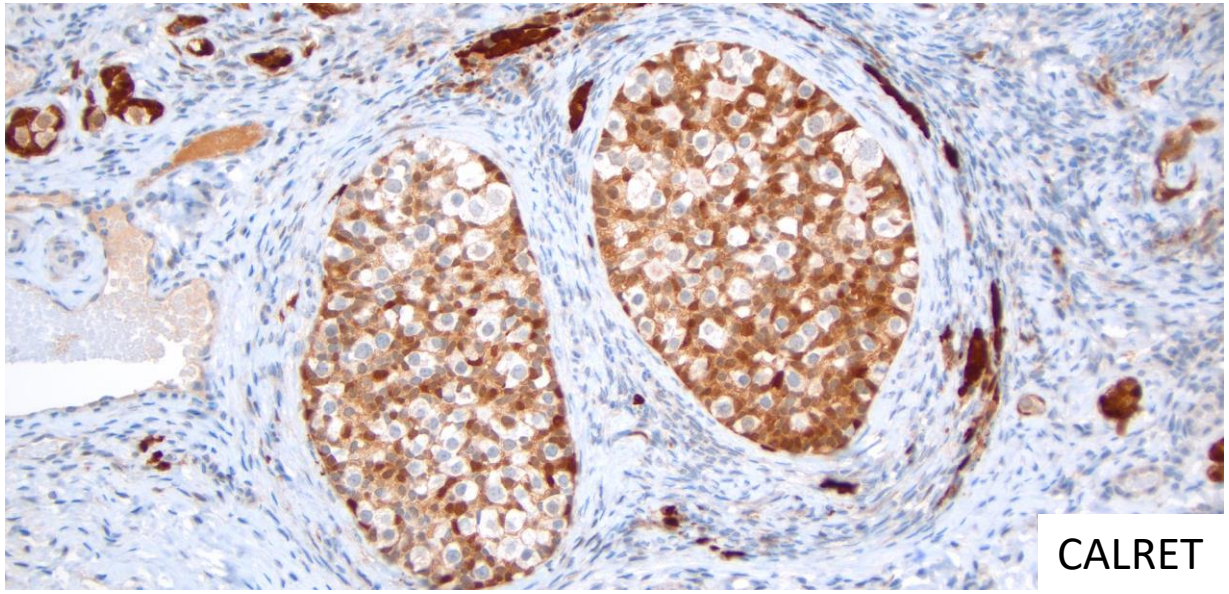
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Case Report

Early Bilateral Gonadoblastoma Associated With 45,X/46,XY Mosaicism: The Spectrum of Undifferentiated Gonadal Tissue and Gonadoblastoma in the First Months of Life

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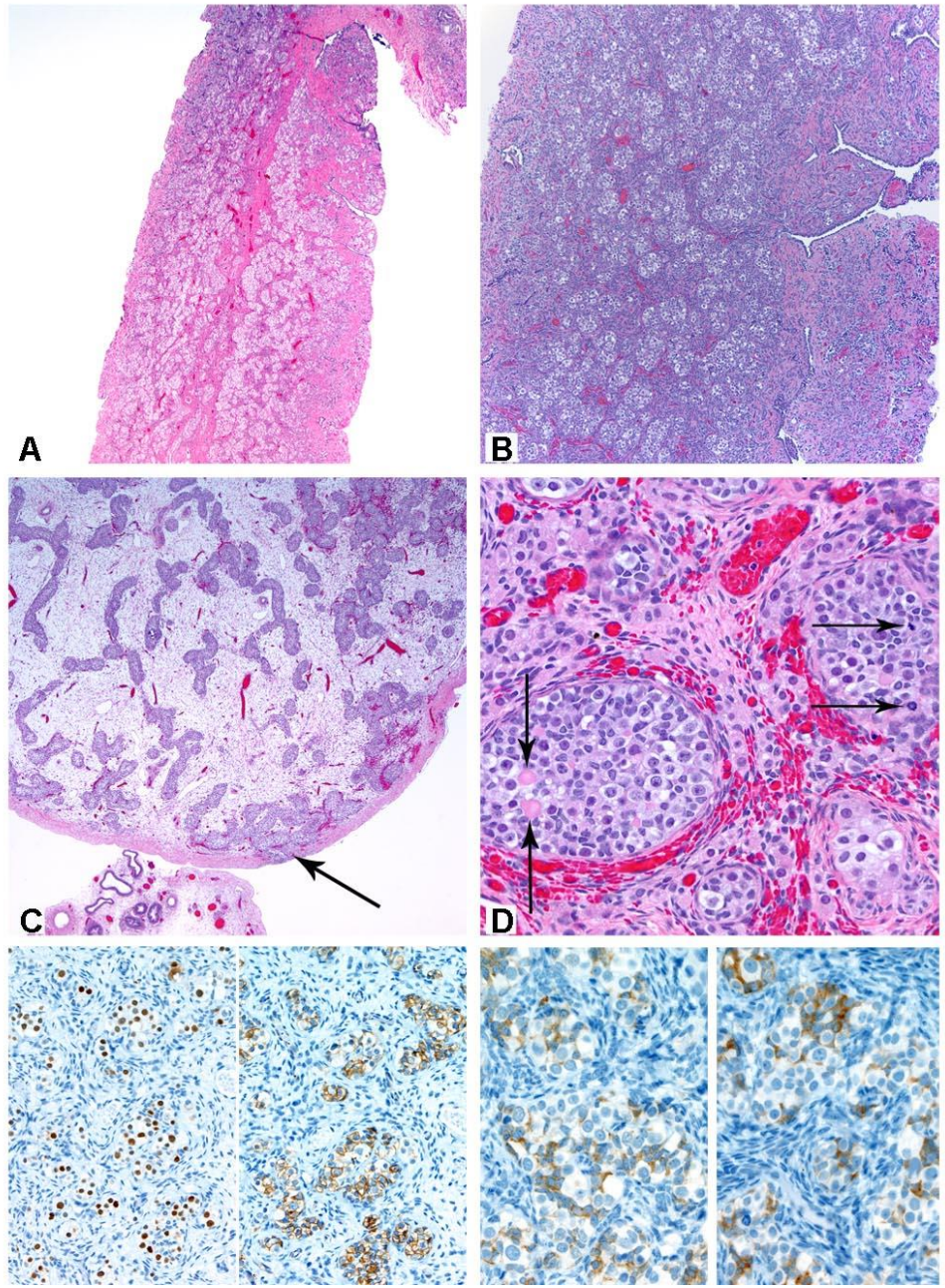
Lara Berklite[1], Selma F Witchel[2], Svetlana A Yatsenko[3], Francis X Schneck[2], and Miguel Reyes-Múgica[2]

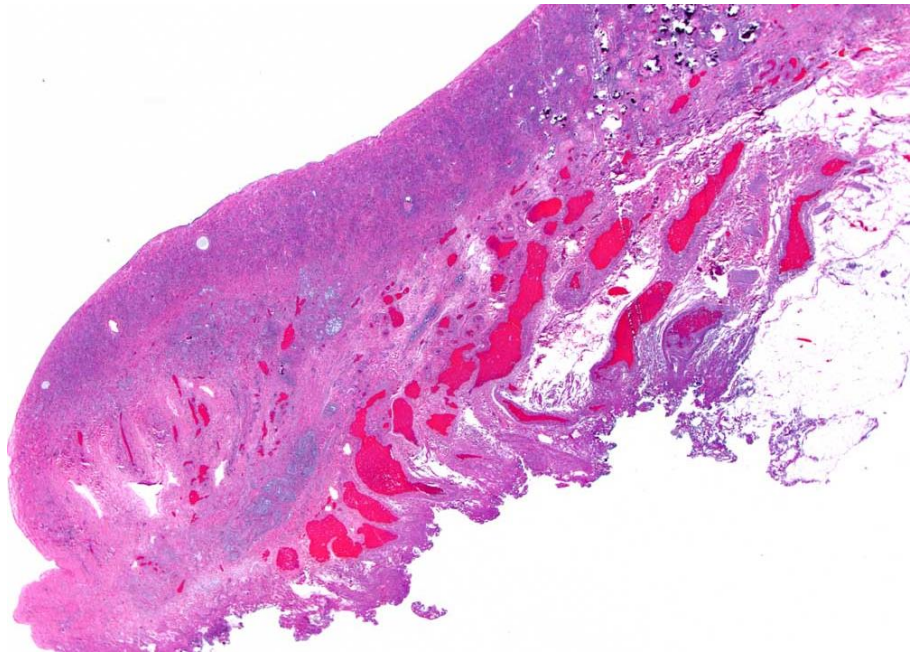
Abstract

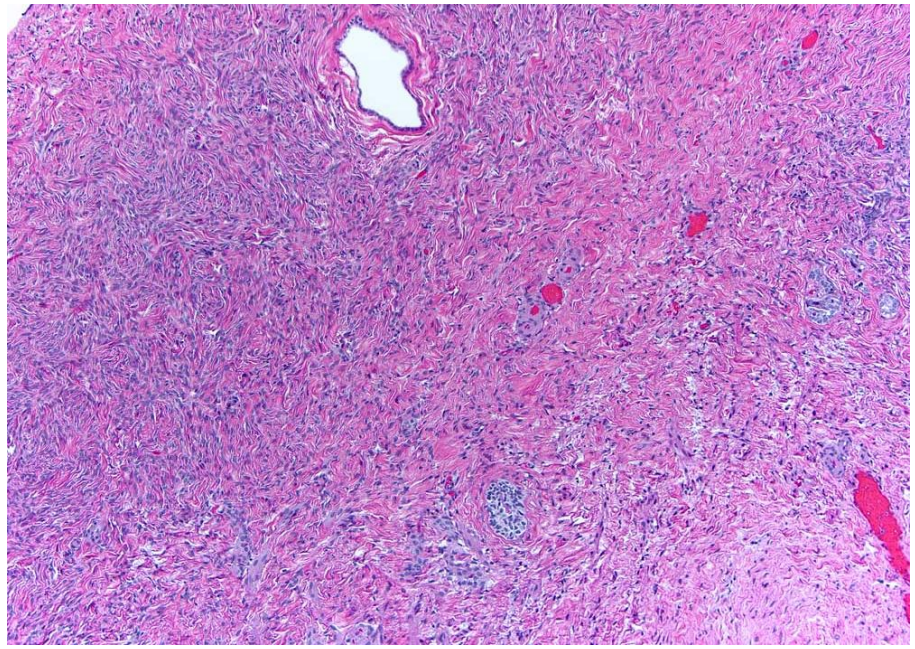
45,X/46,XY mosaicism is one of a heterogenous group of congenital conditions known as differences (disorders) of sex development (DSD) that results in abnormal development of internal and external genitalia. Patients with DSD, particularly those with segments of the Y chromosome, are at increased risk for germ cell tumors including gonadoblastoma. Gonadoblastoma is a neoplasm comprised of a mixture of germ cells and elements resembling immature granulosa or Sertoli cells with or without Leydig cells or lutein-type cells in an ovarian type stroma. Gonadoblastoma has an increased prevalence of 15% to 40% in patients with 45,X/46,XY mosaicism and has been previously reported in patients as young as 5 months of age with that karyotype. Herein, we describe a 3-month-old child with 45,X/46,XY karyotype who was referred for the evaluation of asymmetric labia majora. Additional evaluation revealed left streak gonad and right dysplastic/dysgenetic testis. Both gonads contained foci of cells typical for gonadoblastoma as well as undifferentiated gonadal tissue, underscoring the potential for very early infantile gonadoblastoma and the spectrum of developmental anomalies associated with this karyotype.

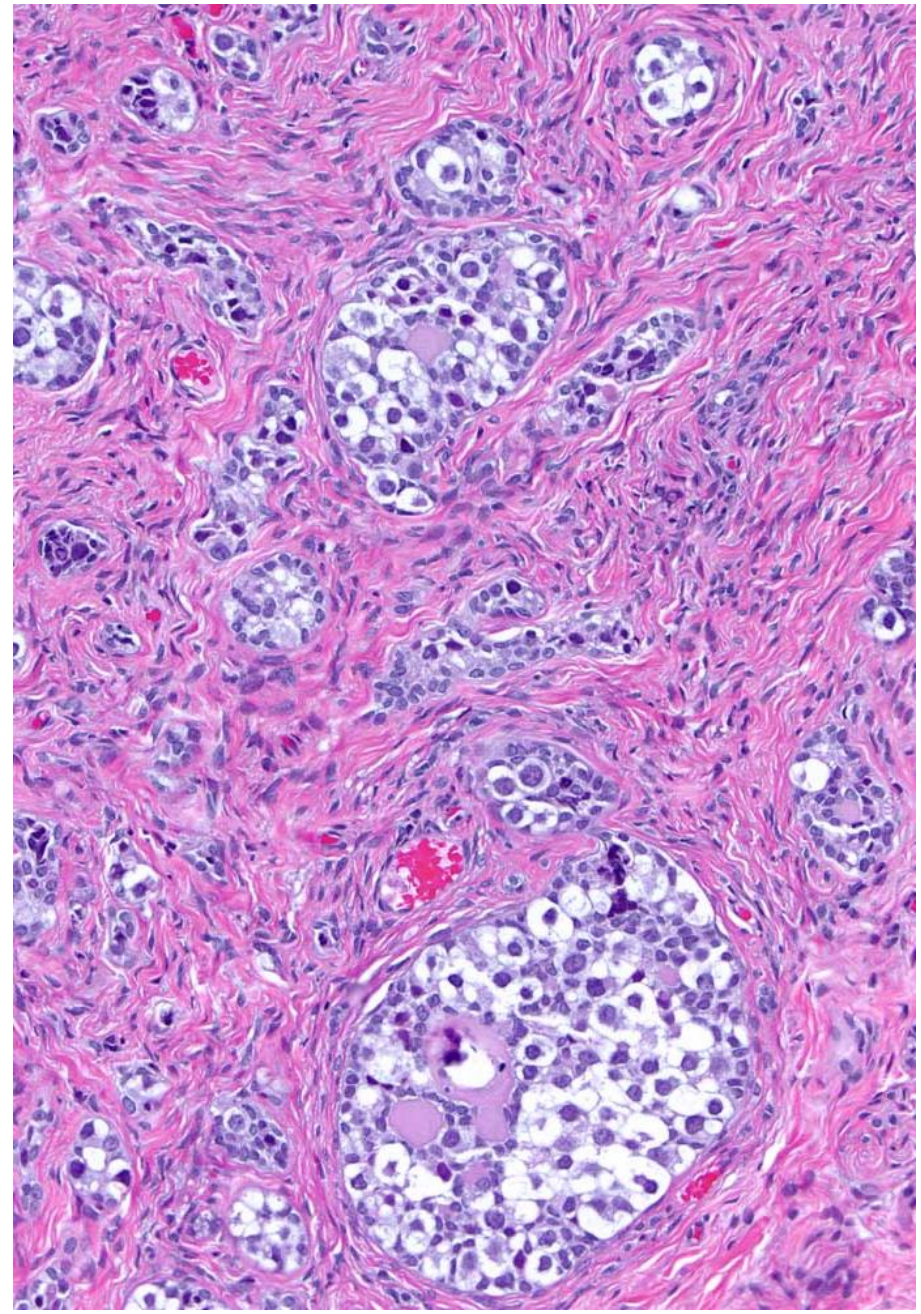
Keywords

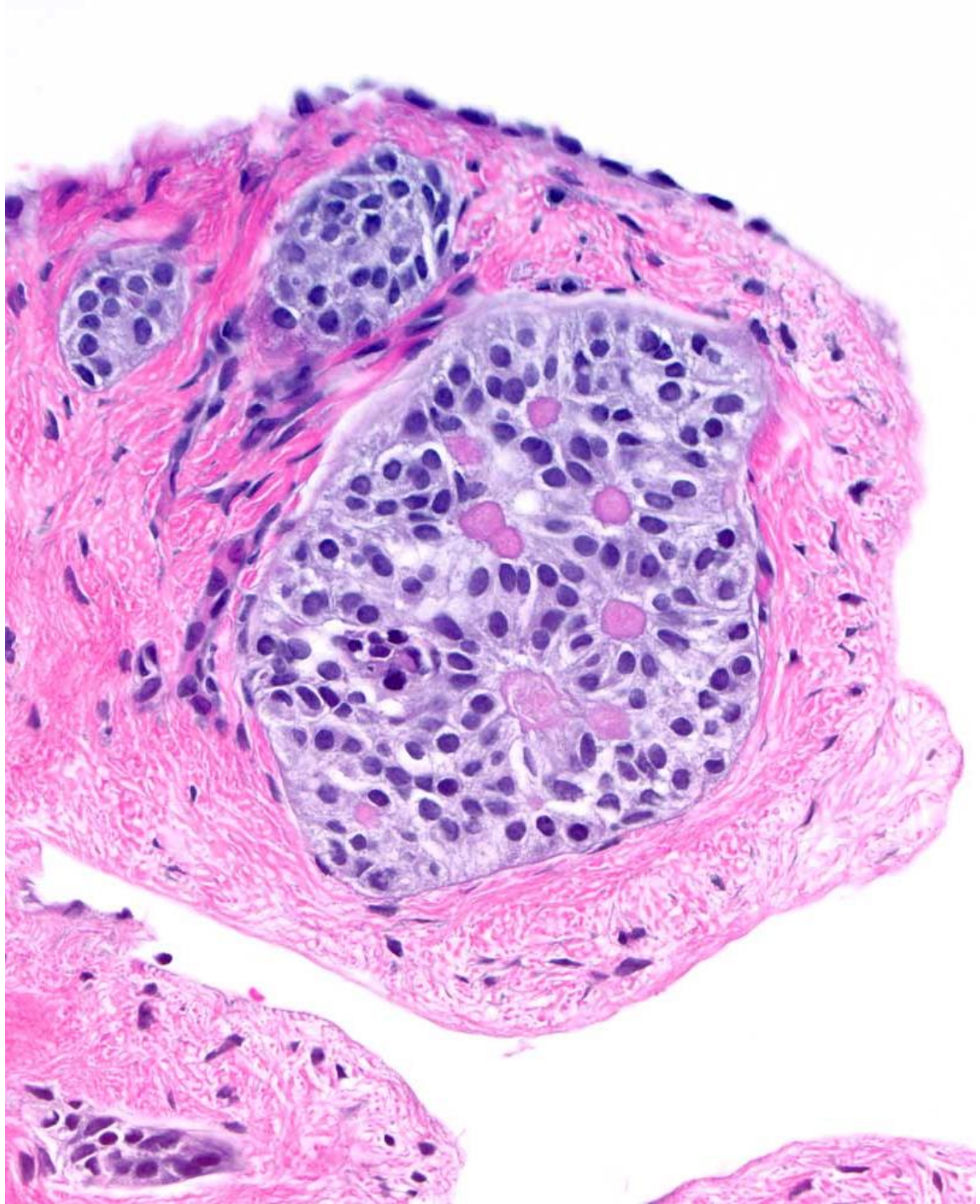
gonadoblastoma, 45,X/46,XY mosaicism, undifferentiated gonadal tissue, gonadal dysgenesis, streak gonad, differences of sex development

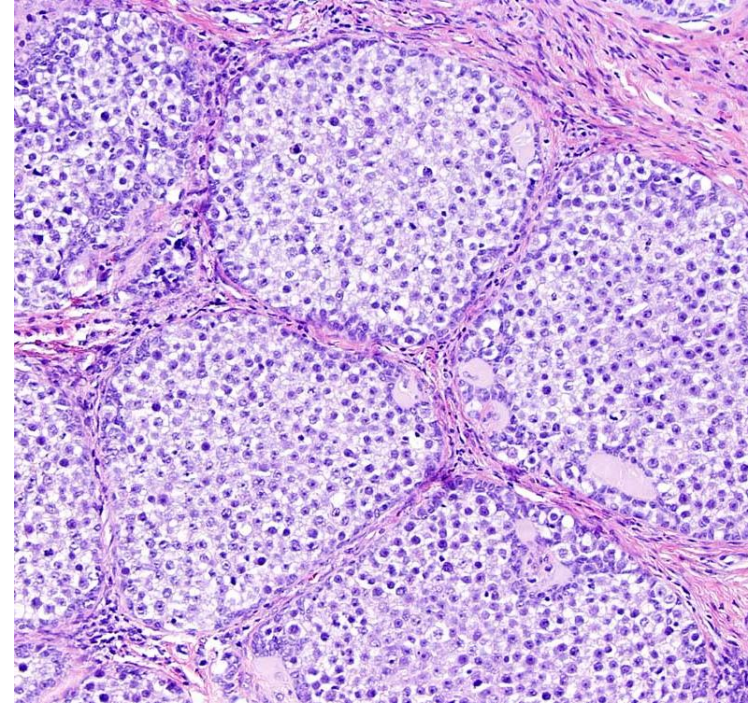


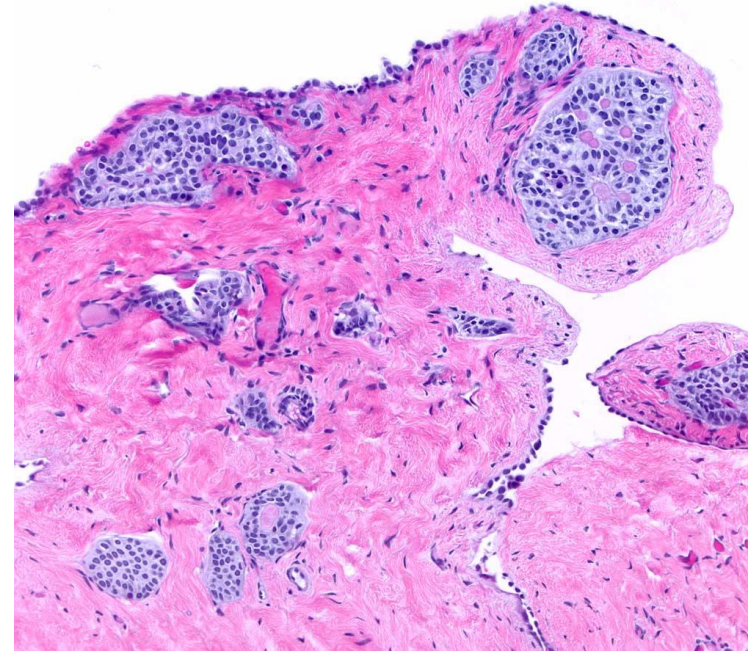




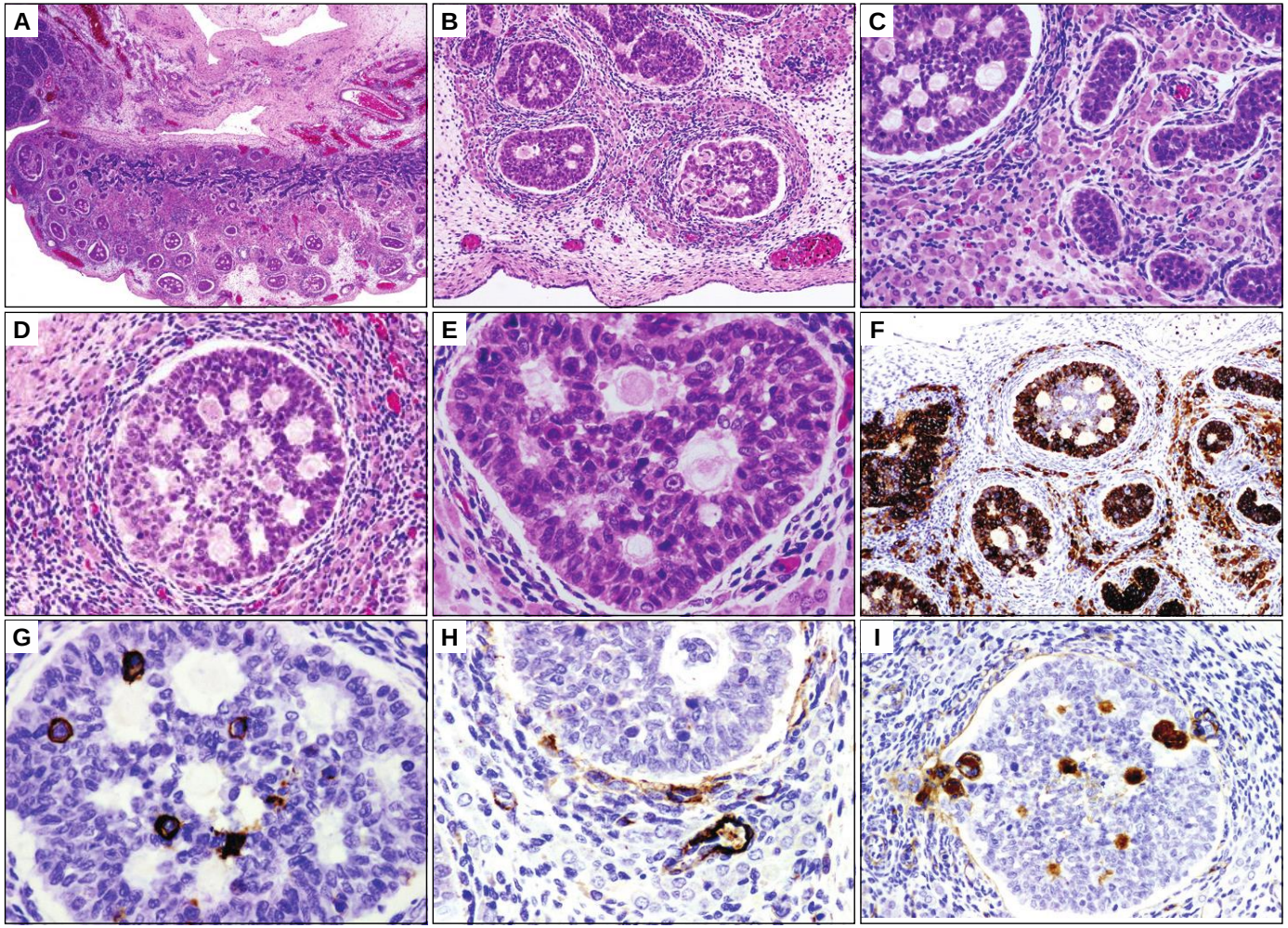








Fetal Gonadoblastoid Dysplasia



Pediatric and Developmental Pathology 10, 274–281, 2007
DOI: 10.2350/06-09-0158.1

Fetal Gonadoblastoid Testicular Dysplasia: A Focal Failure of Testicular Development

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ABSTRACT

Fetal gonadoblastoid testicular dysplasia (FGTD) is an extremely rare lesion, which, in its original description, appeared in association with *hydrops fetalis* and other malformations. Its phenotype strongly resembles gonadoblastoma, although in contrast with that rare tumor, FGTD is not associated with the intersexual states or gonadal dysgenesis that accompany such neoplasm. Two reports described an association of FGTD and a morphologically similar lesion with Walker-Warburg syndrome. However, we have not confirmed such an observation, although a nonspecific muscle disorder was found in one of the examples we describe in this article. Here we study 2 additional cases, providing a detailed topographical, histomorphological, and immunophenotypical analysis. A review of all 5 previously described cases is conducted. The features of this lesion support the notion that a focal defect in testicular development is its most likely pathogenesis.

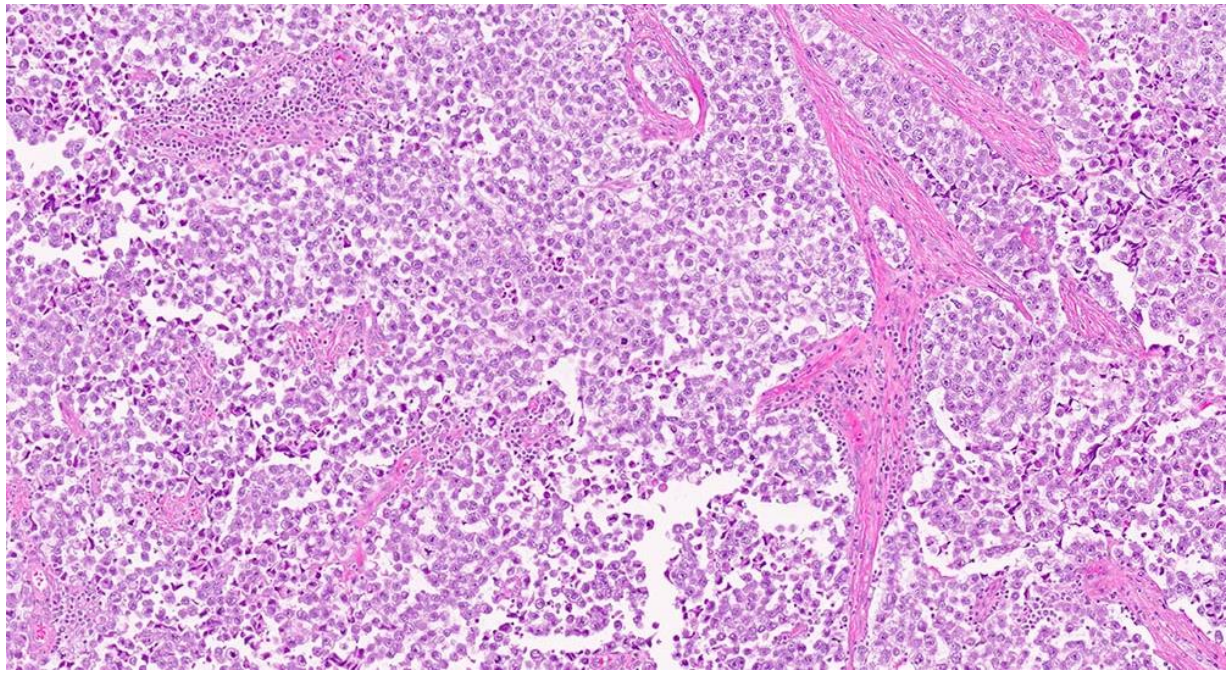
Key words: gonadoblastoid, gonadoblastoma, *hydrops fetalis*, testicular development, testicular dysgenesis, Walker-Warburg syndrome

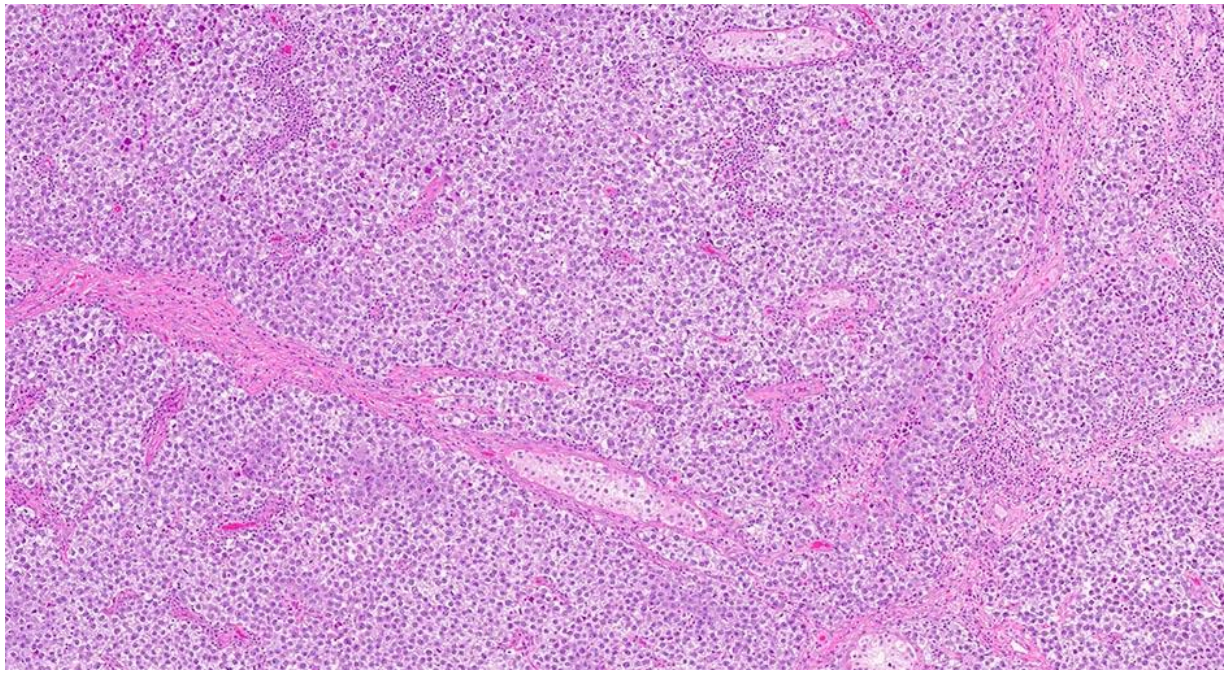
which give rise each, to the adrenal cortex, the rete testis, and the testicular parenchyma proper. These blastemal tissues arrange themselves into a craniocaudal chain, which will undergo further remodeling following the growth and involution of the metanephros and of the mesonephros, respectively, resulting in the final formation of peripheral (testicular cords) or centrally located (rete testis) structures. Following a topographical approach, the best-known example of a testicular malformation involving centrally located structures is cystic testicular dysplasia, also known as cystic dysplasia of the rete testis, the most likely etiology of which is an excessive incorporation of mesonephric duct elements into the gonadal ridge [2–4].

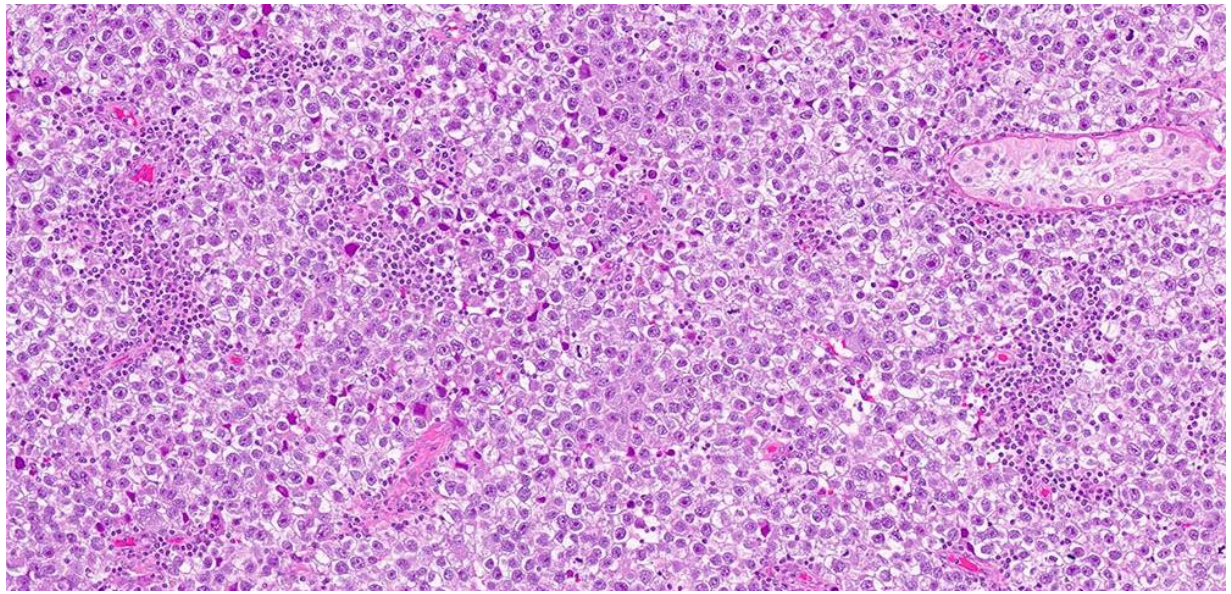
With regard to malformations involving the peripheral testicular parenchyma, the better-studied examples are those associated with defects involving the antimüllerian hormone (AMH), which lead to a characteristic testicular lesion, namely gonadal dysgenesis (GD). GD features

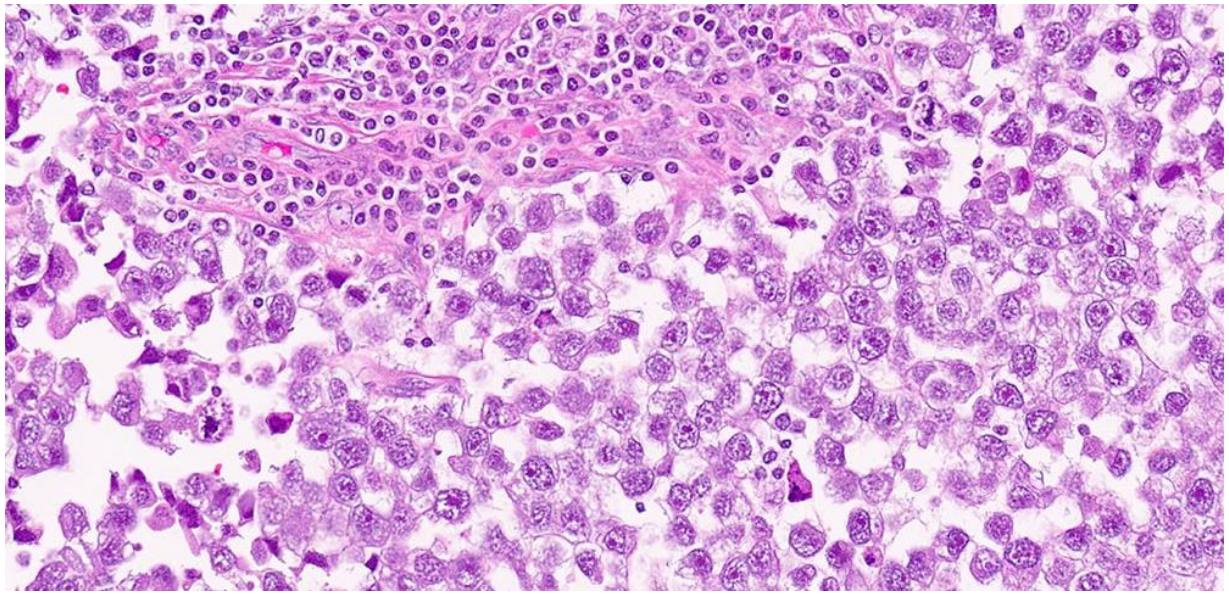
6.2.1.2: Germinoma/Dysgerminoma/Seminoma

- Malignant germ cell tumors (GCT) whose cells are considered the neoplastic counterparts of primordial germ cells (PGCs). Despite different clinical manifestations and anatomic localization, they share the same morphology, immunophenotype and molecular phenotype.
- In gonads: dysgerminoma (ovary); seminoma (testis).
- At extragonadal sites, the term germinoma is preferred.
- Pure GDS are the second most common GCT in the mediastinum after teratomas.
- They typically affect males, between 11 and 79 years of age, but most are diagnosed in the 3rd and 4th decade.
- Positive OCT3/4, KIT, D2-40; negative CD30 or AFP; no diffuse staining with cytokeratins.





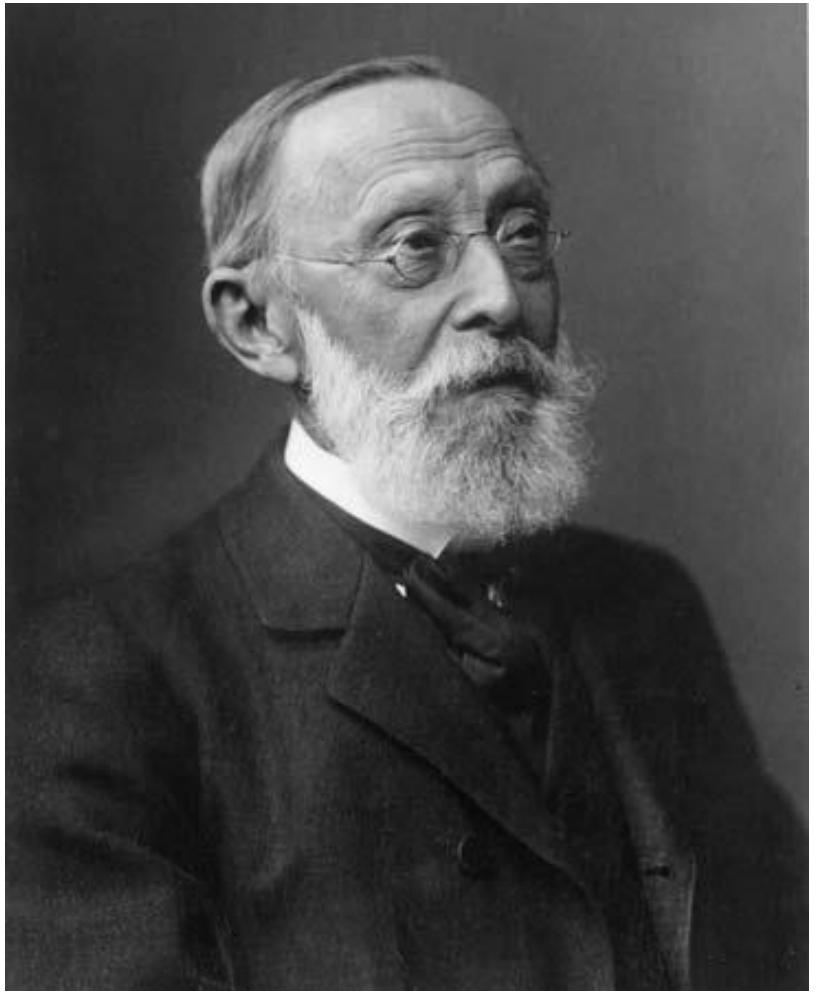




Teratomas

- Rudolf Virchow: from the Greek **τερατος** (monster), and a suffix denoting a tumor.

Bulic-Jakus et al. WIREs Dev Biol 2016, 5:186–209. doi: 10.1002/wdev.219



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6.2.2.2 Non-germinomatous germ cell tumours

- Within the Germ cell tumors, the Teratoma family represents a special group.
- In contrast with the other non-seminomatous tumors, their clinical characteristics are variable, although they all are composed of one or multiple histological elements of the three blastodermal layers: ectoderm, mesoderm and endoderm.
- The classification is predominantly determined by their anatomical localization, including various extragonadal sites, as well as the ovary and testis.
- Overarching patterns can be recognized, related to their specific maturation stage of the cell of origin.
- Based on their different developmental programs and respective timing of female and male (embryonic) germ cells, the repertoire of variants of teratomas diagnosed in the ovary and testis differ, in which an overall benign behavior is identified in the first, and a dual pattern in the last, related to the prepubertal versus postpubertal diagnosis.
- Most of the extragonadal teratomas represent the (overall benign) prepubertal type.

Teratomas - History

- First reference (to a sacrococcygeal teratoma) appears to be on a clay tablet dating from 600 to 900 BC from the Chaldean Royal Library of Nineveh, presumably a sacrococcygeal teratoma

Bulic-Jakus et al. WIREs Dev Biol 2016, 5:186–209. doi: 10.1002/wdev.219

Johann Sholz (*Scultetus*) reported the first fully documented case of an ovarian teratoma in 1658
Saint Donat reported the first teratoid tumor of the testis in 1696
J. A. Gordon reported the first mediastinal dermoid cyst in 1823
Maier reported a cerebral dermoid in a 2 week-old, and
Wiegert showed histologic evidence of a pineal teratoma

Damjanov I. 2017

Teratomas

- A GCT type I (Oosterhuis and Looijenga), is the most common germ cell tumor in the pediatric population.
- Arising from pluripotent cells, it usually contains elements from the three blastoderm layers (ectoderm, mesoderm, endoderm) although mono and bidermal teratomas exist.
- Grading based in amount of neuropetihelial tissue present. But the distinction between “mature teratoma” and “immature teratoma” is irrelevant in children. Its clinical behavior in prepubertal ages always is benign, in contrast with the adult counterparts.
- A Pediatric Oncology Group study concluded that surgery alone was curative in children and adolescents with stage I immature teratomas of any grade, and that chemotherapy should be reserved for cases of relapse.
- However, an association between grade III immature teratoma and microscopic foci of yolk sac tumor (83%) has been demonstrated, emphasizing the need for thorough histologic evaluation of tumors

6.2.2.1 Mature cystic teratoma

- A tumor composed exclusively of mature tissue derived from two or three germ layers (ectoderm, mesoderm, and/or endoderm).
- In the testis, mature cystic teratoma is a subtype of prepubertal-type teratoma.
- Extragonadal sites (including sacrococcygeal region, mediastinum, head and neck region, retroperitoneum, central nervous system, and various sites within the abdominal cavity), ovary, and testis.
- In the testis, mature cystic teratoma is within the group of Type I germ cell tumours.
- Sacrococcygeal teratoma is the most common germ cell tumor in children, and the ovary is the 2nd most common site in this age group.
- The majority of pediatric germ cell tumors are mature cystic teratomas.
- In testicular sites, there is lack of the genetic abnormalities seen in the germ cell neoplasia *in situ* (GCNIS)-derived teratomas, including isochromosome 12p.
- All elements in testicular sites lack significant atypia, and the surrounding parenchyma lacks GCNIS as well as the “dysgenetic” features seen in GCNIS-derived/postpubertal-type teratoma.

Ovarian Teratomas

- 75% of ovarian tumors in patients under the age of 15 years and are benign.
- Arise from a single germ cell after the first meiotic division, which then develops a diploid karyotype.
- Mature teratomas: typically cystic, with skin-like elements, including adnexa, hair and sebum; may show thickening of the wall with calcification (Rokitansky protuberance).
  - Ectodermal derivatives: mature neuroepithelium, ocular structures, such as retinal pigmented epithelium.
  - Mesoderm: mature cartilage, fat, smooth and skeletal muscle.
  - Endoderm: respiratory or intestinal epithelium.
- Malignancy arising in mature components is extremely rare in childhood

Gwin K, Singh N, Cavallo A and Reyes-Múgica M, 2015

Ovarian Teratoma Subtypes

- Monodermal teratomas are teratomas composed exclusively or predominantly of a single type of tissue derived from one embryonic layer, which includes struma ovarii, carcinoid, neuroectodermal-type tumours, and monodermal cystic teratoma.
- The most common monodermal teratoma is struma ovarii, which consists entirely of normal or hyperplastic thyroid tissue and is rare in children and adolescents.
- Differential diagnosis: *Struma ovarii* exhibiting a prominent microfollicular adenoma pattern can be confused with a granulosa-cell tumor.

Gwin K, Singh N, Cavallo A and Reyes-Múgica M, 2015

Ovarian Teratoma Subtypes

- Immature teratoma (IT) is a teratoma containing immature and variable amounts of mature tissue.
- Occurs either purely or as part of a malignant germ-cell tumor (MGCT).
- Typically present in the first 2 decades as a unilateral palpable mass and are the 3rd most common germ GCT in adolescence.
- Peritoneal implants are present in 30% of patients at the time of surgery.
- IT usually presents as a pelvic mass. Serum **α** -fetoprotein (AFP) can be elevated in IMT, but AFP levels over 1000 ng/ml (33) should raise concerns for a YST component as part of an MGCT, but ITs with hepatoid components may have elevated AFP.
- In addition to tumor grade, complete surgical excision is the most important prognostic indicator.
- Gliomatosis peritonei, teratoma-induced metaplasia of the submesothelial cells of the peritoneum, can be present.
- IMT can range in size from 9**–** 28 cm and reveals solid, gray-white, hemorrhagic cut surfaces with cystic changes.
- In addition to mature elements, IMTs contain immature neuroepithelium and mitotically active glial tissue

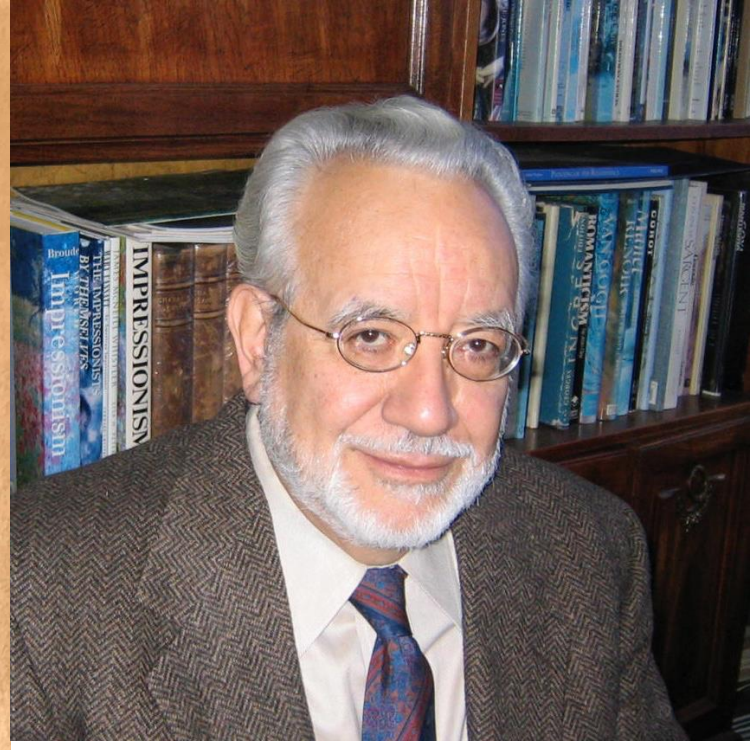
Gwin K, Singh N, Cavallo A and Reyes-Múgica M, 2015

EXTRAGONADAL TERATOMAS

by

F. GONZALEZ-CRUSSI, M.D.

AFIP



Teratomas are neoplasms that originate in pluripotent cells, and are composed of a wide diversity of tissues foreign to the organ or anatomic site in which they arise.

It is customary to add, as a prerequisite for the application of the term, that the presence of tissued derived from the three germ layers must be confirmed.

Dual nature: malformative and tumoral.

Published in 1982

Extragonadal Teratomas

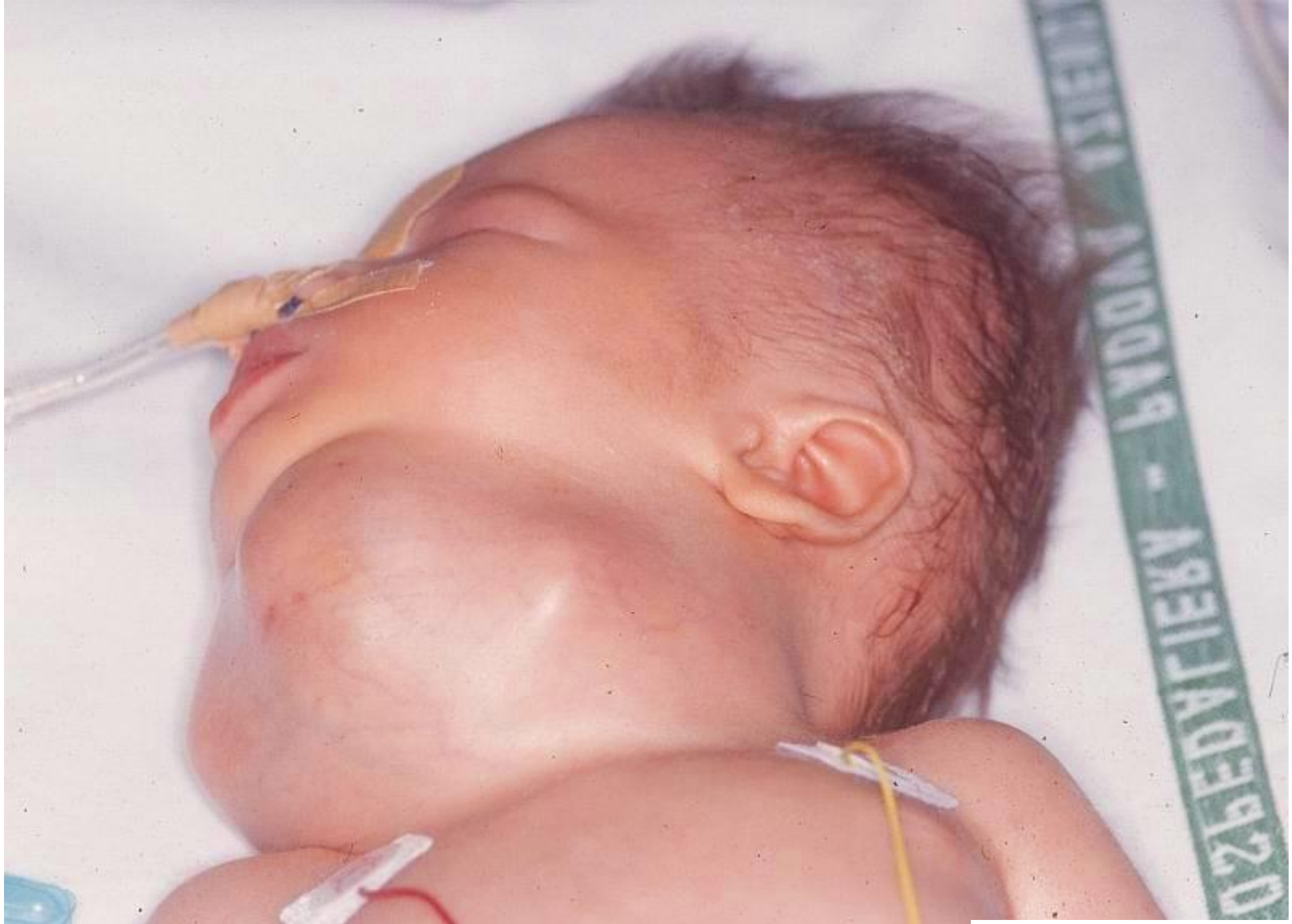
- Predominantly in neonates and infants. They arise along the migratory path of primordial germ cells.
- Sacrococcygeal teratomas (SCTs) are the most common extra-gonadal GCTs in the pediatric population.
- They are the most common germ cell tumor in newborns and infants, occurring in approximately 1:35,000 live births.
- Four types according to the degree of their external vs. intra-pelvic/intra-abdominal extension.
- SCTs usually fit one of two distinct scenarios:
  - Those presenting with large predominantly external and benign (>90%) lesions in the neonatal period
  - Those presenting between birth and 4 years that typically have more intra-pelvic/intra-abdominal tumor involvement.
- The latter group of tumors are much more likely to be malignant (60–90%). It has been theorized that the absence of visible external tumor leads to a delay in diagnosis and therefore a higher incidence of cancer due to malignant degeneration.
- Symptoms in these patients are often the result of pelvic enlargement with compression of the bladder or rectum.

Zambrano, De Stefano and Reyes-Múgica, 2017

Cervicofacial Teratomas

- GCTs of the cervical and facial regions represent 5% of all GCTs during childhood.
- GCTs in this site most commonly present during the prenatal or perinatal period.
- Nearly all are mature or immature teratomas.
- Approximately one-third present with airway obstruction.
- Giant fetal tumors have been noted with hydrops, which may lead to fetal demise

Zambrano, De Stefano and Reyes-Múgica, 2017



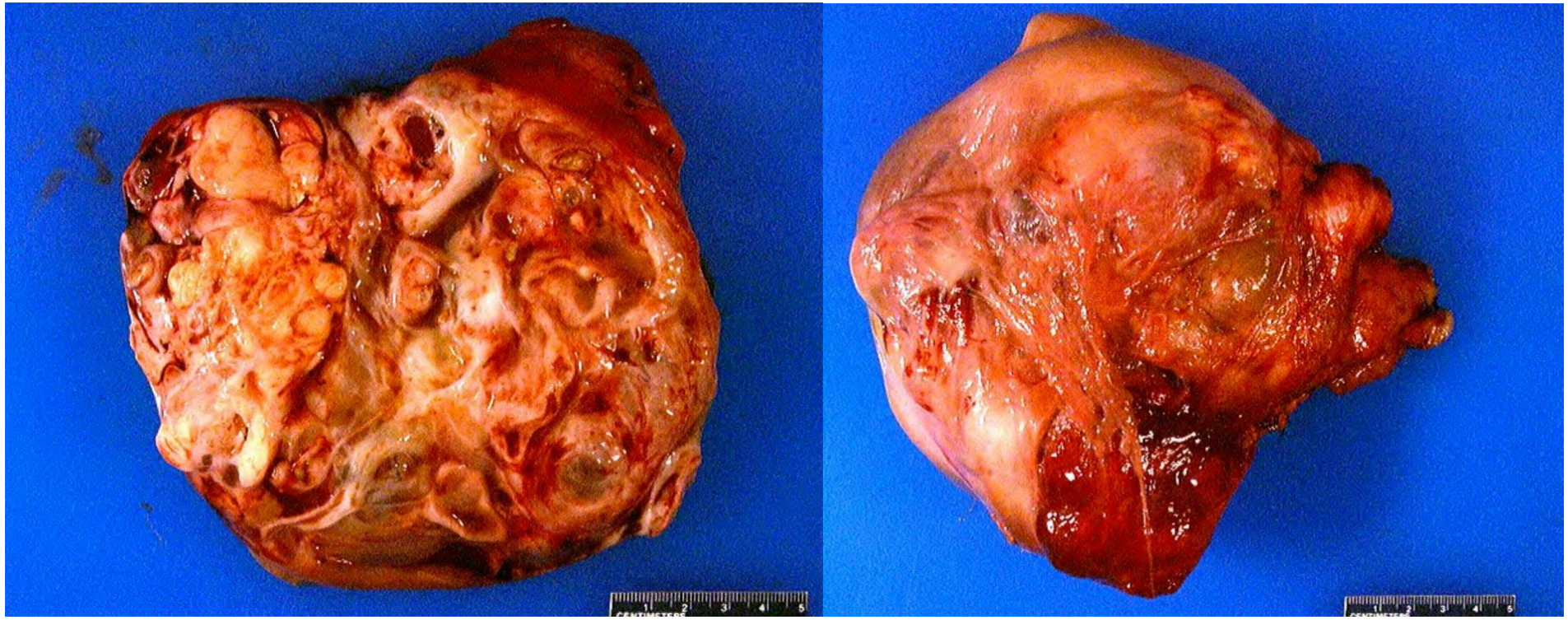
Courtesy of Dr. Rita Alaggio

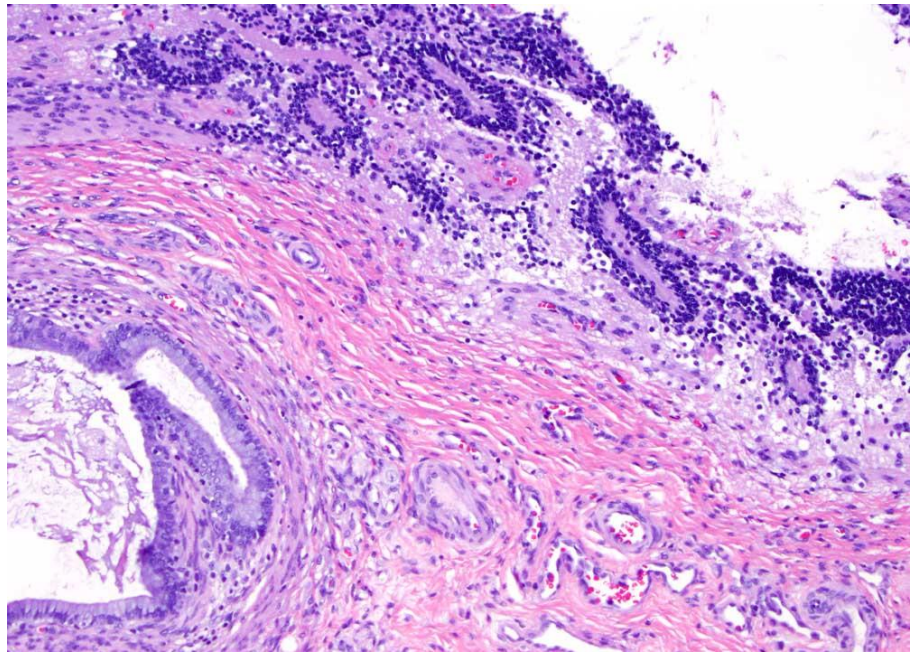
Thoracic & Mediastinal GCT

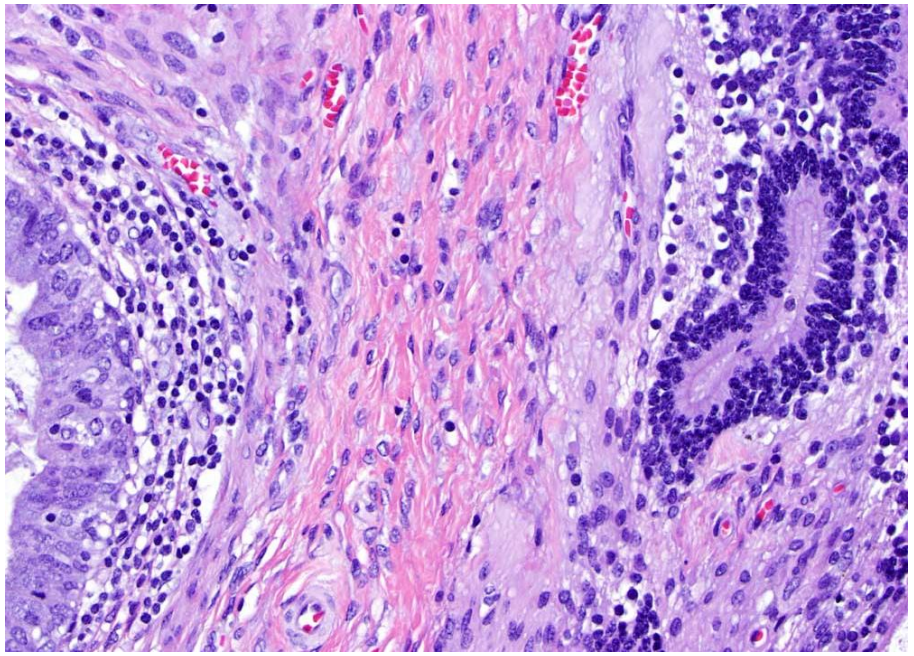
- Mediastinal pediatric GCTs are extremely rare, representing 5% of all GCTs and 6–18% of all pediatric mediastinal tumors.
- Thoracic GCTs are more common than abdominal GCTs in the newborn period (15-20% vs. 5%).
- The majority of these tumors are located in the anterior mediastinum and originate in the thymus, though they can be found to rise from the posterior mediastinum, heart or epicardial structures.
- Approximately 15% of pediatric mediastinal GCTs are malignant and carry the worst prognosis of all germ cell tumors.
- Yolk sac is the predominant histology in girls as well as younger boys, whereas older boys have mixed histology in over 50%.
- An association with Klinefelter syndrome and certain hematologic disorders has been described.

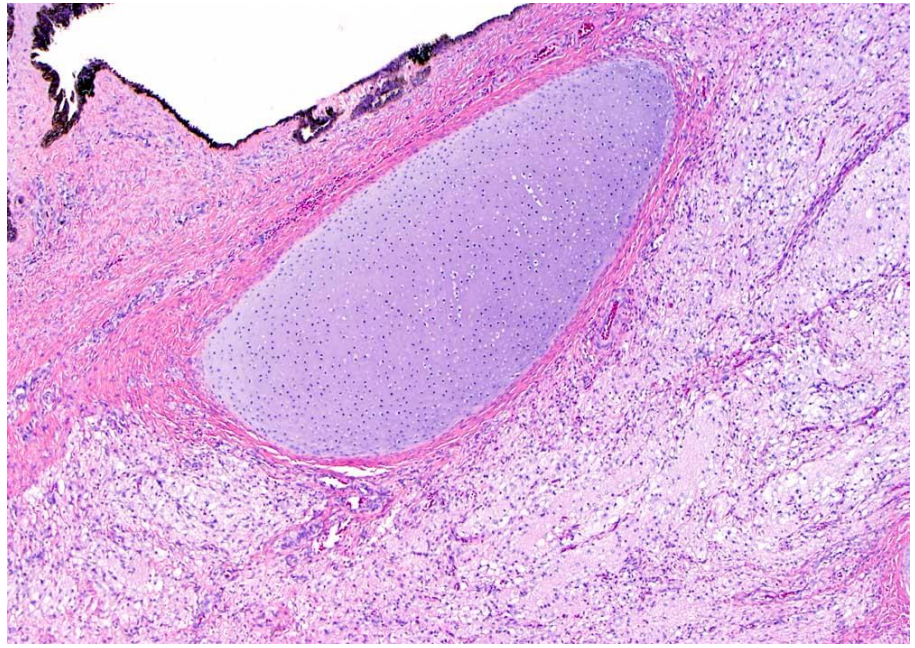
Zambrano, De Stefano and Reyes-Múgica, 2017

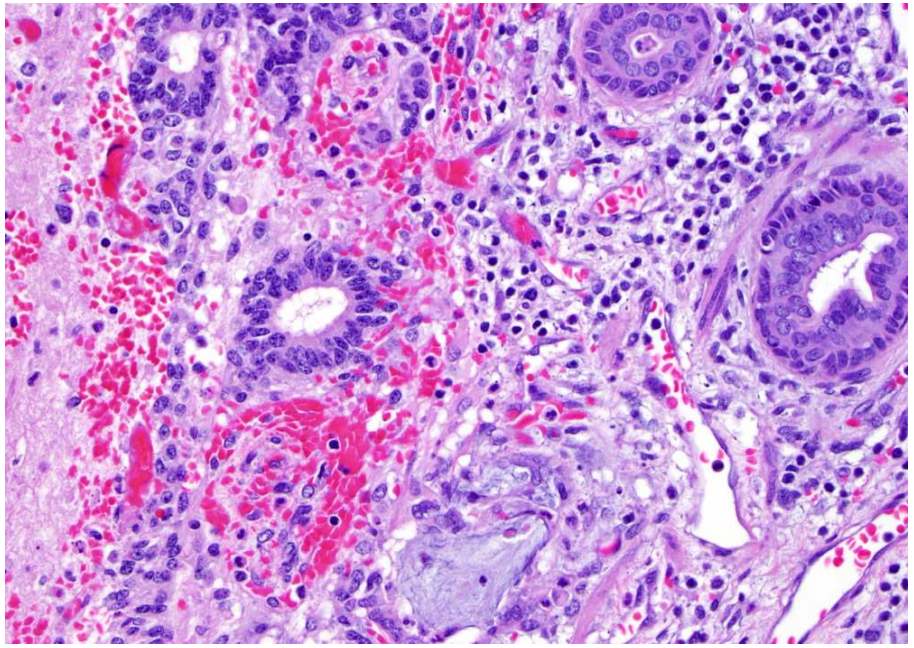
Mediastinal teratoma







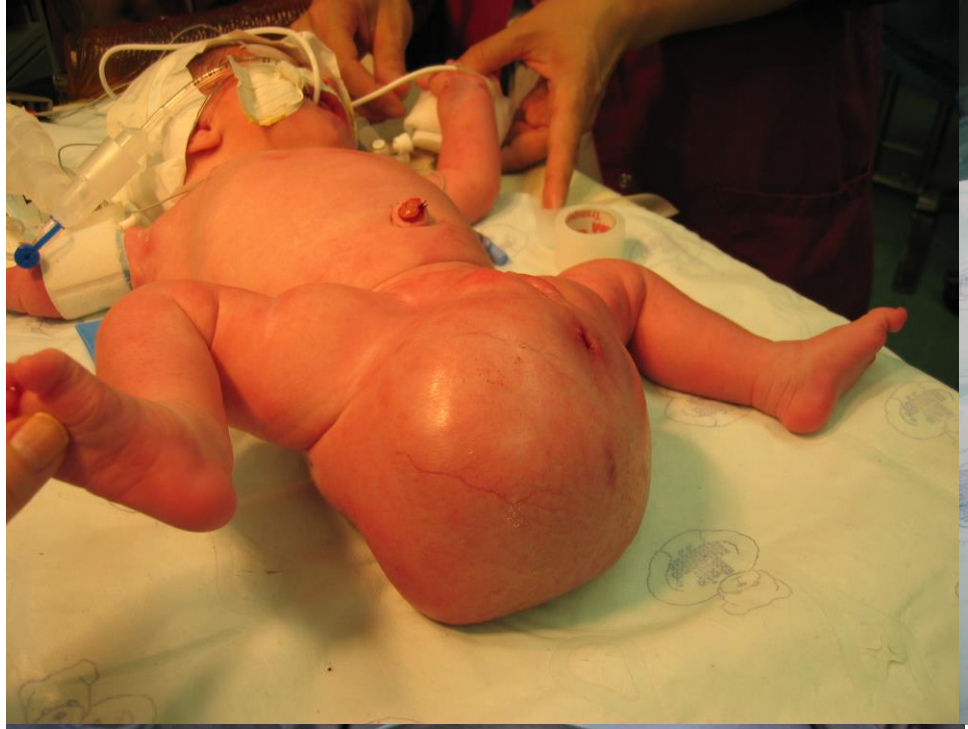


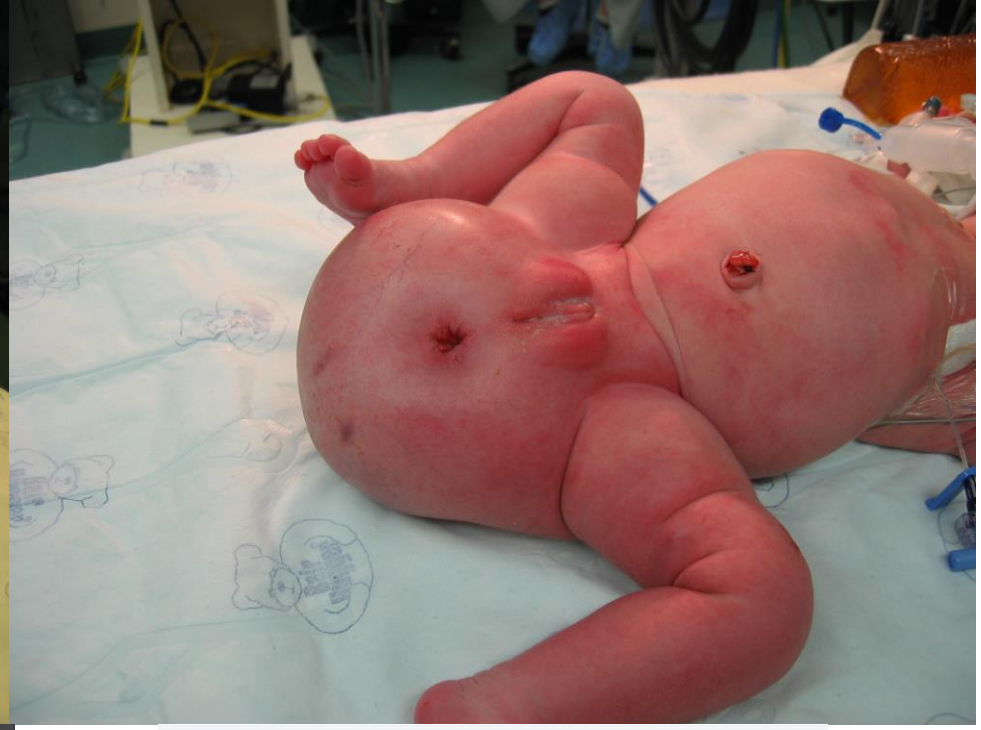


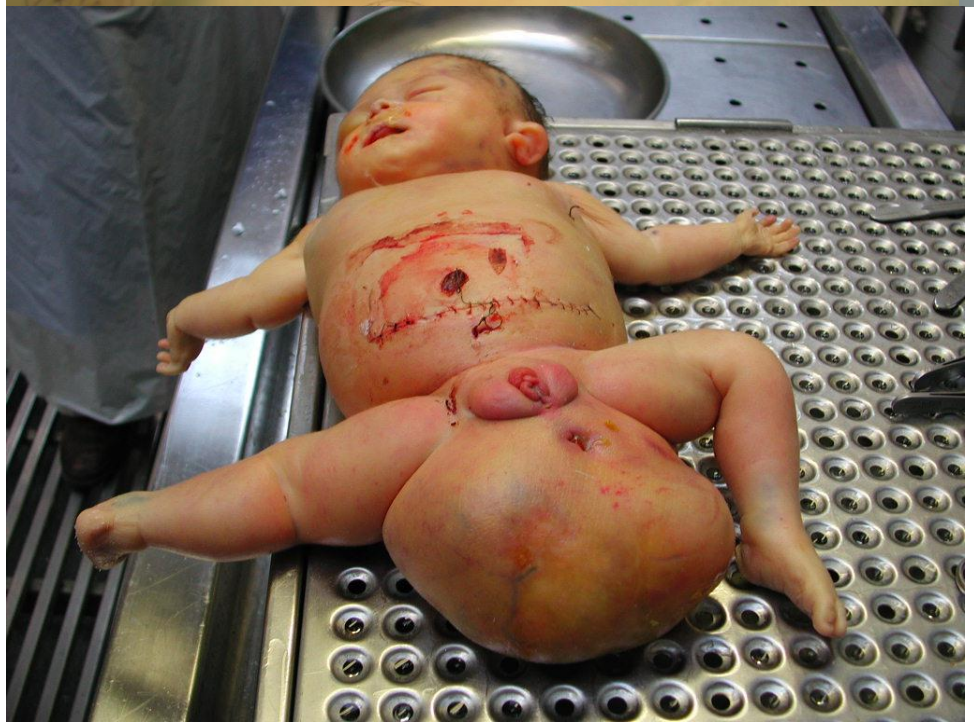
Sacrococcygeal Teratomas

- Most common extragonadal GCT in children.
- Most common germ cell tumor in newborns and infants; approximately 1:35,000 live births.
- Anatomically: four types according to degree of external vs. intra-pelvic/intra-abdominal extension.
- Usually: one of two scenarios:
  - Large predominantly external and benign (>90%) lesions.
  - Between birth and 4 years; typically more intra-pelvic/intra-abdominal tumor involvement.
- The latter group of tumors are more likely to be malignant (60–90%).
- Association of presacral teratoma with anal stenosis/anorectal malformation and sacral defects is known as the Currarino triad, an autosomal-dominant disorder secondary to mutations in the HLXB9 homeobox gene.
- Recurrence occurs between 2 and 35% (12.5% av.). Around 50% of recurrent teratomas have a malignant component at recurrence. Rec. is more likely in immature T (33%). Grade of immaturity correlates with risk of recurrence: G0: 20%; G1: 14%; G2:21%; G3: 31%.

Courtesy of Dr. Milissa McKee, Yale.

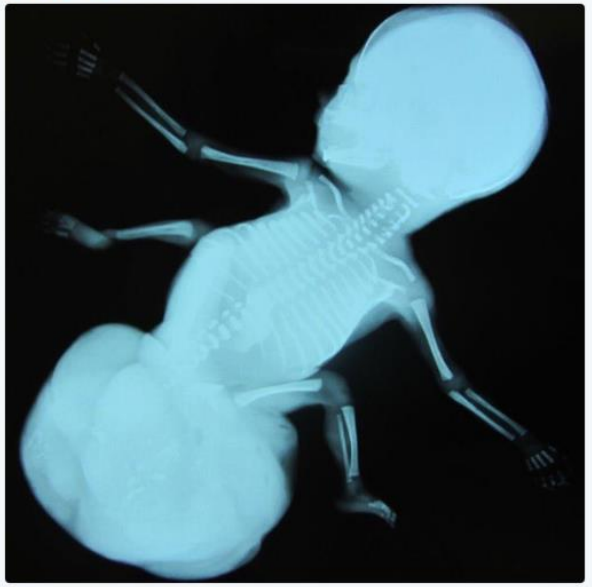






Srinivas Rao @sranna86 · Sep 7

Babygram of a Sacrococcygeal teratoma @mreyesm @DrFNA #PediPath #pps @SocPediPath



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Currarino syndrome

- Triad consisting of partial sacral agenesis with intact first sacral vertebra (‘sickle-shaped sacrum’), a presacral mass, and anorectal malformation.
- Other congenital malformations/developmental delay have been described.
- Caused by haploinsufficiency of the motor neuron and pancreas homeobox 1 (MNX1)gene on chromosome 7q36.3 that encodes a nuclear protein, homeodomain-containing transcription factor.
- Various loss-of-function intragenic mutations, as well as deletions of the 7q36 region, have been reported.
- Gold standard for these (micro) deletions is chromosomal microarray analysis.

Hodge CG, et al. 2015

Currarino syndrome

- Mutations in MNX1 result in complex phenotypes including:
  - (i) hemisacrum or bifid sacrum with neurogenic bladder, recurrent urinary infections, or incontinence
  - (ii) presacral masses such as anterior meningocele, enteric cyst, or **presacral teratoma**
  - (iii) anorectal malformations including atresia, stenosis, and fistula frequently complicated with chronic constipation or incontinence

Hodge CG, et al. 2015

CLINICAL GENETICS An International Journal of Genetics, Molecular and Personalized Medicine

Clin Genet 2016: 89: 109–114

CLINICAL GENETICS
doi: 10.1111/cge.12572

Short Report

Phenotype analysis impacts testing strategy in patients with Currarino syndrome

Cuturilo G., Hodge J.C., Runke C.K., Thorland E.C., Al-Owain M.A., Ellison J.W., Babovic-Vuksanovic D. Phenotype analysis impacts testing strategy in patients with Currarino syndrome.
Clin Genet 2016: 89: 109–114. © John Wiley & Sons A/S. Published by John Wiley & Sons Ltd, 2015

Currarino syndrome (OMIM 175450) presents with sacral, anorectal, and intraspinal anomalies and presacral meningocele or teratoma. Autosomal dominant loss-of-function mutations in the *MNX1* gene cause nearly all familial and 30% of sporadic cases. Less frequently, a complex phenotype of Currarino syndrome can be caused by microdeletions of 7q containing *MNX1*. Here, we report one familial and three sporadic cases of Currarino syndrome. To determine the most efficient genetic testing approach for these patients, we have compared results from *MNX1* sequencing, chromosomal microarray, and performed a literature search with analysis of genotype–phenotype correlation. Based on the relationship between the type of mutation (intragenic *MNX1* mutations *vs* 7q microdeletion) and the presence of intellectual disability, growth retardation, facial dysmorphism, and associated malformations, we propose a testing algorithm. Patients with the classic Currarino triad of malformations but normal growth, intellect, and facial appearance should have *MNX1* sequencing first, and only in the event of a normal result should the clinician proceed with chromosomal microarray testing. In contrast, if growth delay and/or facial dysmorphy

G. Cuturilo[a,b], J.C. Hodge[c,d], C.K. Runke[c], E.C. Thorland[c], M.A. Al-Owain[e,f], J.W. Ellison[g] and D. Babovic-Vuksanovic[c,h]

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Key words: chromosomal microarray –

Risk Factors for GCTs

- GCTs lack familial distribution.
- Thought to arise from sporadic genetic mutations.
- Several common chromosomal mutations; probably random occurrences.
- Maternal exposure to various chemicals and solvents may increase risk of GCT in the offspring; but not proven.
- **Cryptorchidism** is associated with 3- to 9-fold increased risk of GCTs (most com. seminoma).
- Early orchiopexy is associated with a lower incidence of GCT in testes.
- Certain DSDs: up to 30% in gonadal dysgenesis; 5-10% in under-virilization syndromes. This risk increases with age → prophylactic gonadectomy is recommended.

Neoplastic risk in DSDs

- The risk in each group of DSD is difficult to evaluate.
- Reported prevalence per diagnostic group varies considerably.
- Data based on gonadectomies performed during the previous decades, mainly prophylactically in early childhood; therefore, the real incidence of GCTs may be higher.
- In addition:
  - Confusing terminology and classification systems.
  - Several synonyms and eponyms are used in literature.
  - Definitions of terminology are often lacking from bibliographical sources.
- **There are no-well established criteria for identifying malignant germ cells, especially in young children, due to delay maturation, resulting in overdiagnosis of GCNIS.**

Four categories of cancer risk

- High (15 to 60%):
  - Gonadal dysgenesis
  - Intra-abdominal gonads.
  - GBY region in their genome, including:
    - Frasier and Denys–Drash syndromes.
    - PAIS
- Intermediate:
  - Patients with Y+ (GBY+) Turner syndrome and those with 17b-hydroxysteroid dehydrogenase (17b-HSD) deficiency.
  - GD (Y+), or PAIS, with scrotal gonads
- Low:
  - CAIS and patients with ovotesticular DSD (in which the gonads consist mostly of well differentiated ovarian and testicular tissue).
  - Turner syndrome lacking an apparent Y chromosome.
- Unknown:
  - 5α -reductase deficiency, Leydig-cell hypoplasia, and specific gene mutations for which there are insufficient or no data for proper analysis.

Abdominal and retroperit. GCTs

- Only 5% of GCTs, intra or extraperitoneal.
- Most occur in the first 5 years of life.
- Most present in infancy with mass and pain, weight loss and constipation.
- 2:1 female predominance.
- The majority are benign: mature and immature teratomas.
- Malignancy rates up to 15-24%.
- Most frequent malignant histology is yolk sac, but choriocarcinoma and mixed tumors also occur.

Testicular GCTs in Children

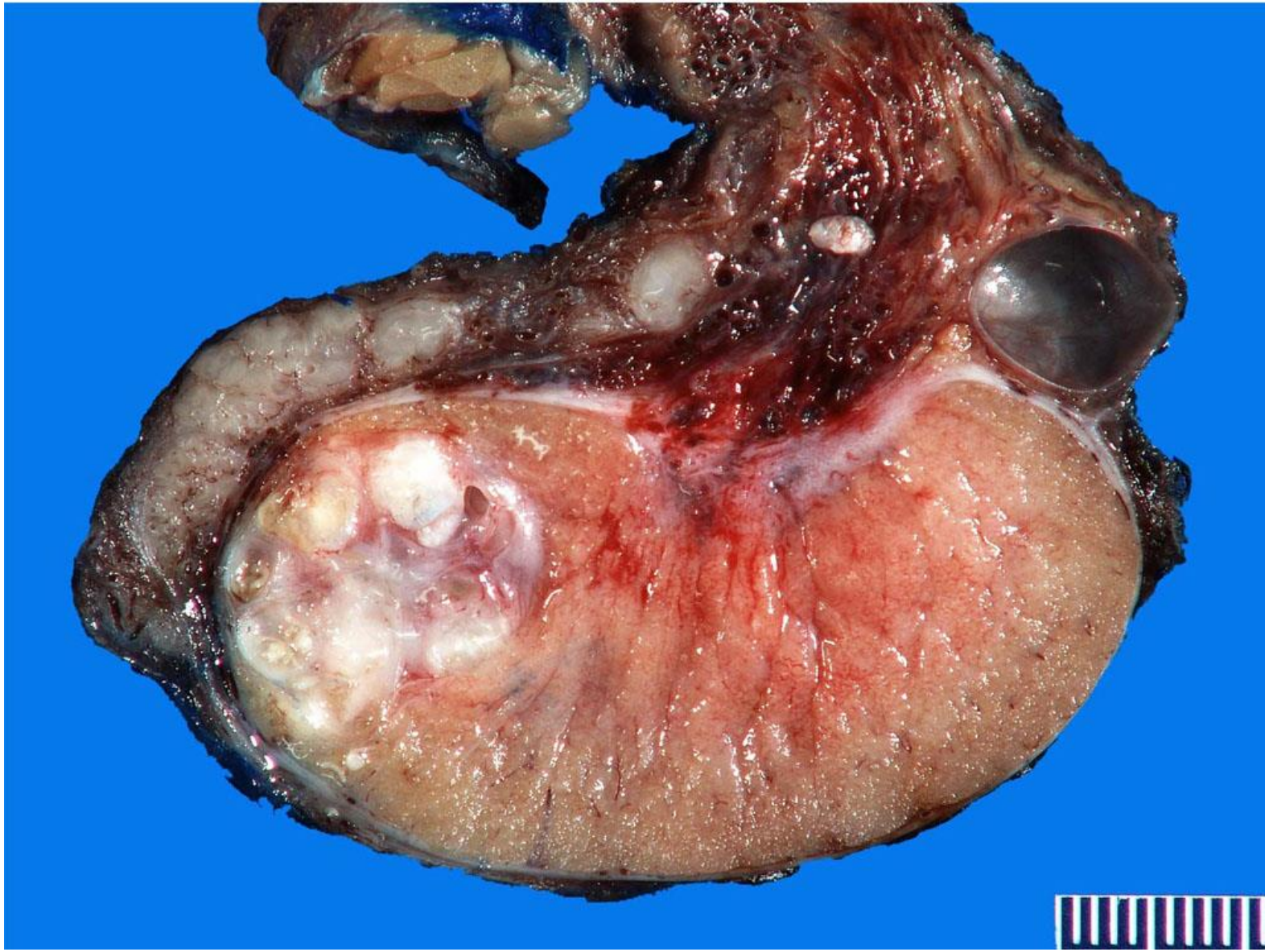
- Rare and with a bimodal distribution:
  - A small peak in the first 3 years of life
  - A larger peak in adolescence (and more aggressive)
- Most common tumor in adolescent males.
- 70-75% of prepubertal GCTs are benign, typically YST with low incidence of metastasis (≃ 5%).
- Pure teratoma ≃ 40%→ benign behavior.
- Adolescents have increased incidence of embryonal ca. and mixed non-seminomas, more aggressive that prepubertal counterparts.
- Post-pubertal teratomas are typically part of mixed GCTs., with higher potential for metastasis.
- Large surge of hormones in adolescence stimulating pre-existing GCCIS?

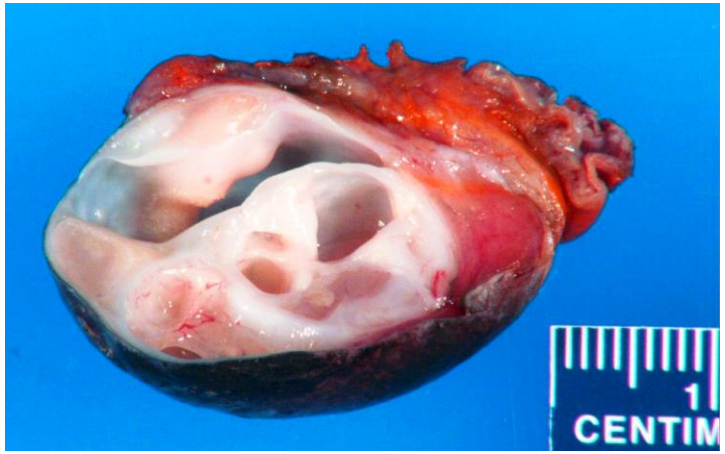
Prepubertal Testicular Teratomas

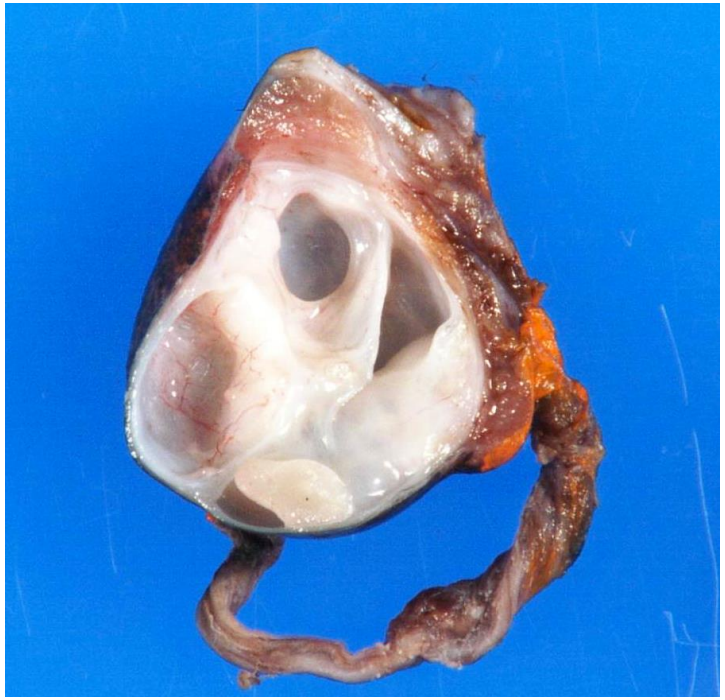
- Prepubertal-type teratoma is a germ cell tumor usually seen in the prepubertal testis, although rarely, it occurs in postpubertal patients (so-called benign postpubertal teratoma).
- Dermoid cyst, epidermoid cyst, well-differentiated neuroendocrine tumor (monodermal teratoma).
- It is composed of elements resembling somatic tissue derived from one or more of the germinal layers.
- Teratomas are the most common pediatric testicular tumor.
- From birth to approximately 18 months as solid heterogeneous masses with varying consistency and calcification.
- Prepubertal teratomas are diploid with a normal 46 XY karyotype.
- Teratomas show a haphazard, though organoid, mixture of mature tissues, such as skin, respiratory epithelium, and cartilage.
- Immature components, such as neuroepithelium, occur rarely, but their significance is uncertain.
- No germ cell neoplasia in situ (GCNIS) is present; therefore, the background testicular parenchyma should be closely examined, especially in the postpubertal setting, to exclude the possibility of a GCNIS-derived tumor. No tubular atrophy, parenchymal scars, tubular microlithiasis, necrosis, or impaired spermatogenesis ("dysgenetic features") should be observed. In difficult cases, molecular investigation for 12p gain should be considered.

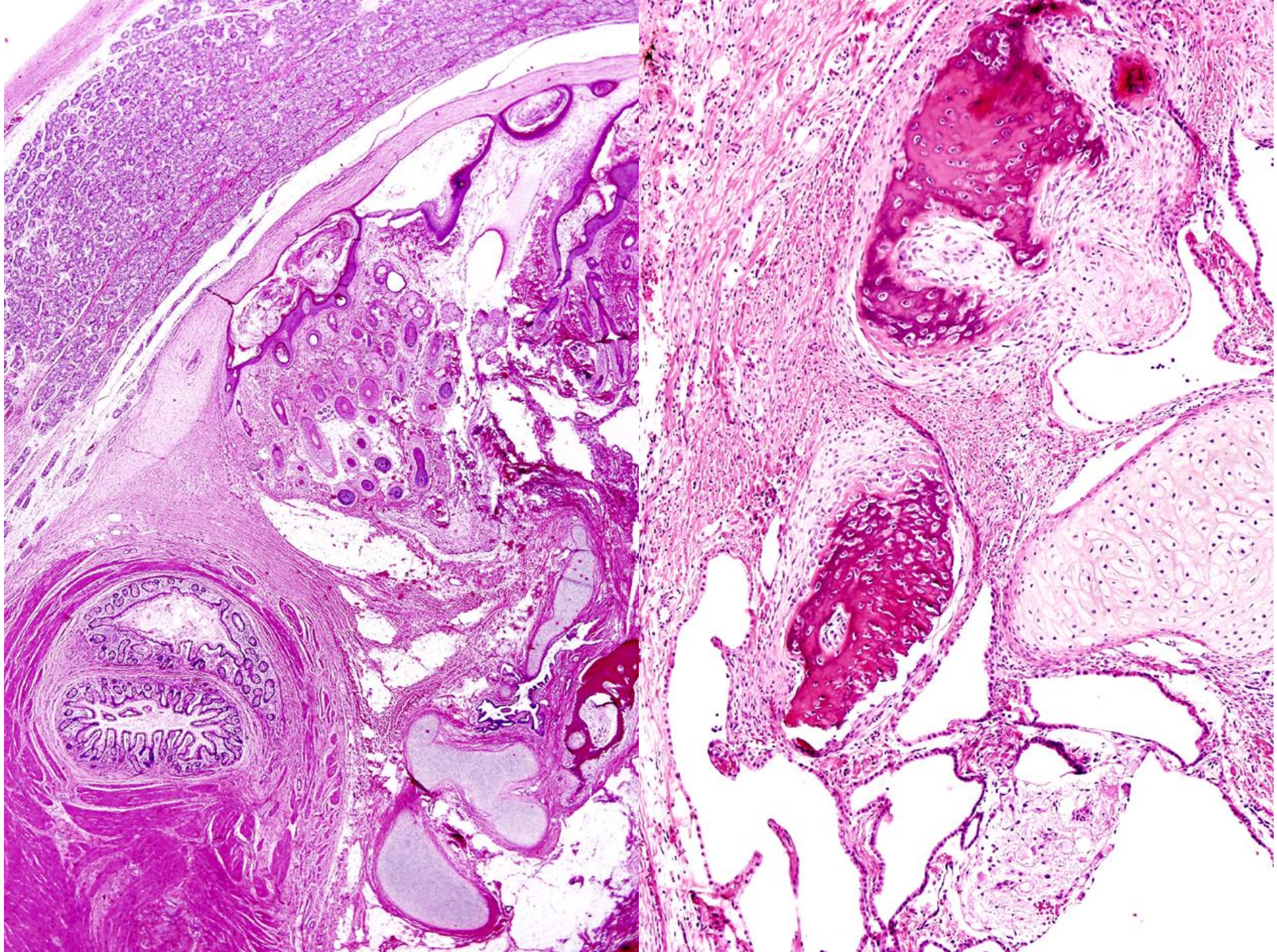
Gwin K, Singh N, Cavallo A and Reyes-Múgica M, 2015

Testicular teratoma

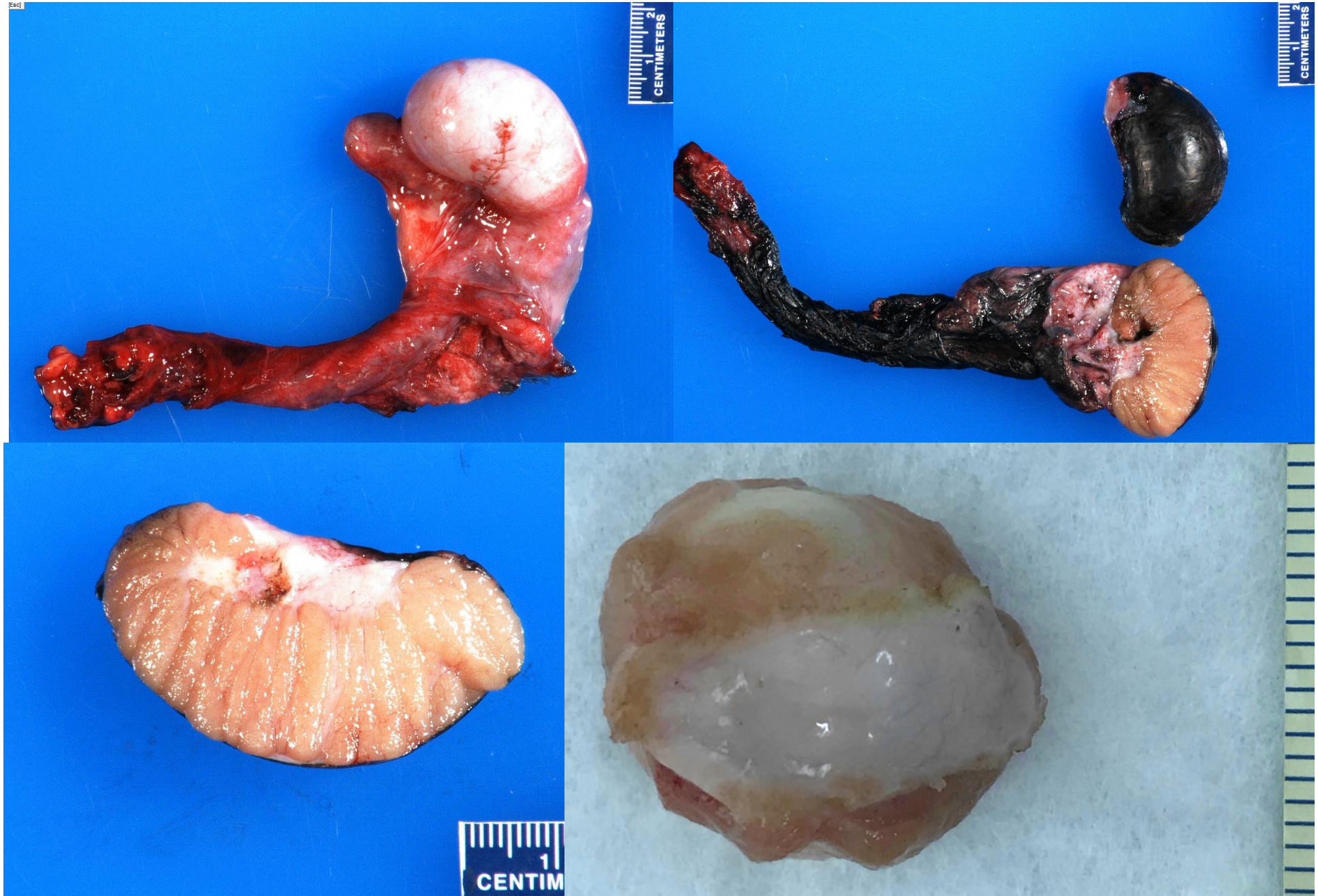


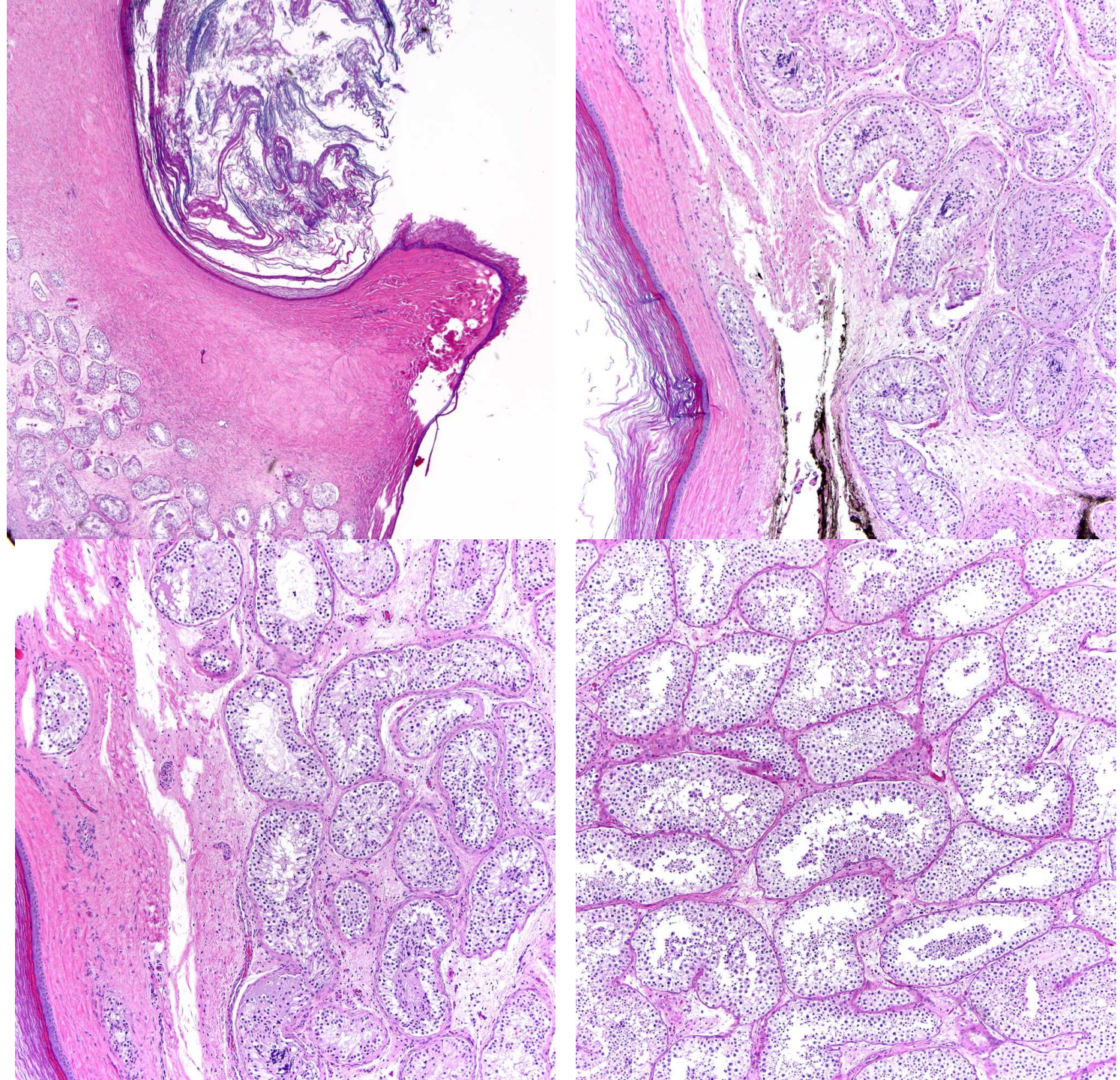






Dermoid cyst





Postbubertal Teratoma

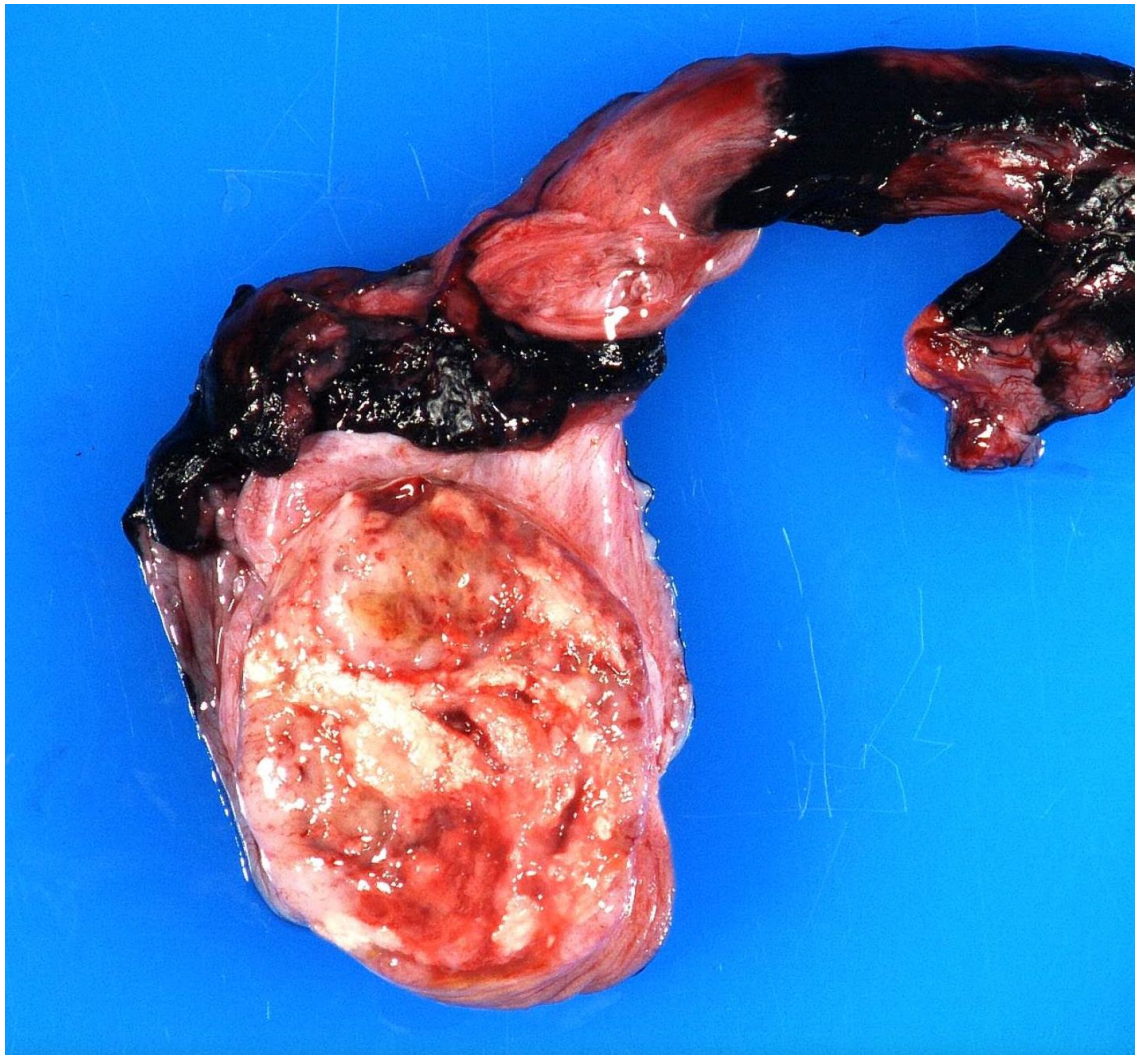
- Teratomas can be pre- (Type I) or post-(Type II) pubertal. In addition, mature teratoma, immature teratoma, and teratoma with somatic-type malignancy are recognized.
- Occur predominantly in men between 20 and 40, but sometimes occur in adolescents, usually as components of mixed GCT.
- In the testis, treatment is radical orchiectomy, retroperitoneal node dissection, and systemic chemotherapy.
- These tumors are aneuploid and show 12p amplifi cation, often as i12p.
- When mixed, the teratomatous elements share cytogenetic abnormalities with the background primitive GCT and are believed to represent differentiation into a malignant GCT.
- Solid and variegated, show variably mature mixed teratomatous elements that lack an organoid pattern, and show widespread atypia and mitotic activity.
- Adjacent seminiferous tubules show atrophy, dysgenetic changes and germ-cell neoplasia *in situ* (GCNIS).
- Immature elements may be seen, but their malignant potential is surpassed by that of the almost invariably present primitive germ-cell elements.
- Gonad, mediastinum, sacrococcygeal, head and neck. Within the CNS, pure infantile immature teratomas are most frequent in cerebral ventricles.
- After early childhood, both pure mature teratomas and immature teratomas, arise in the pineal region, followed by the suprasellar compartment, rarely basal ganglia / thalamic region, spinal and other locations.
- Teratomas with somatic-type malignancy are rare.

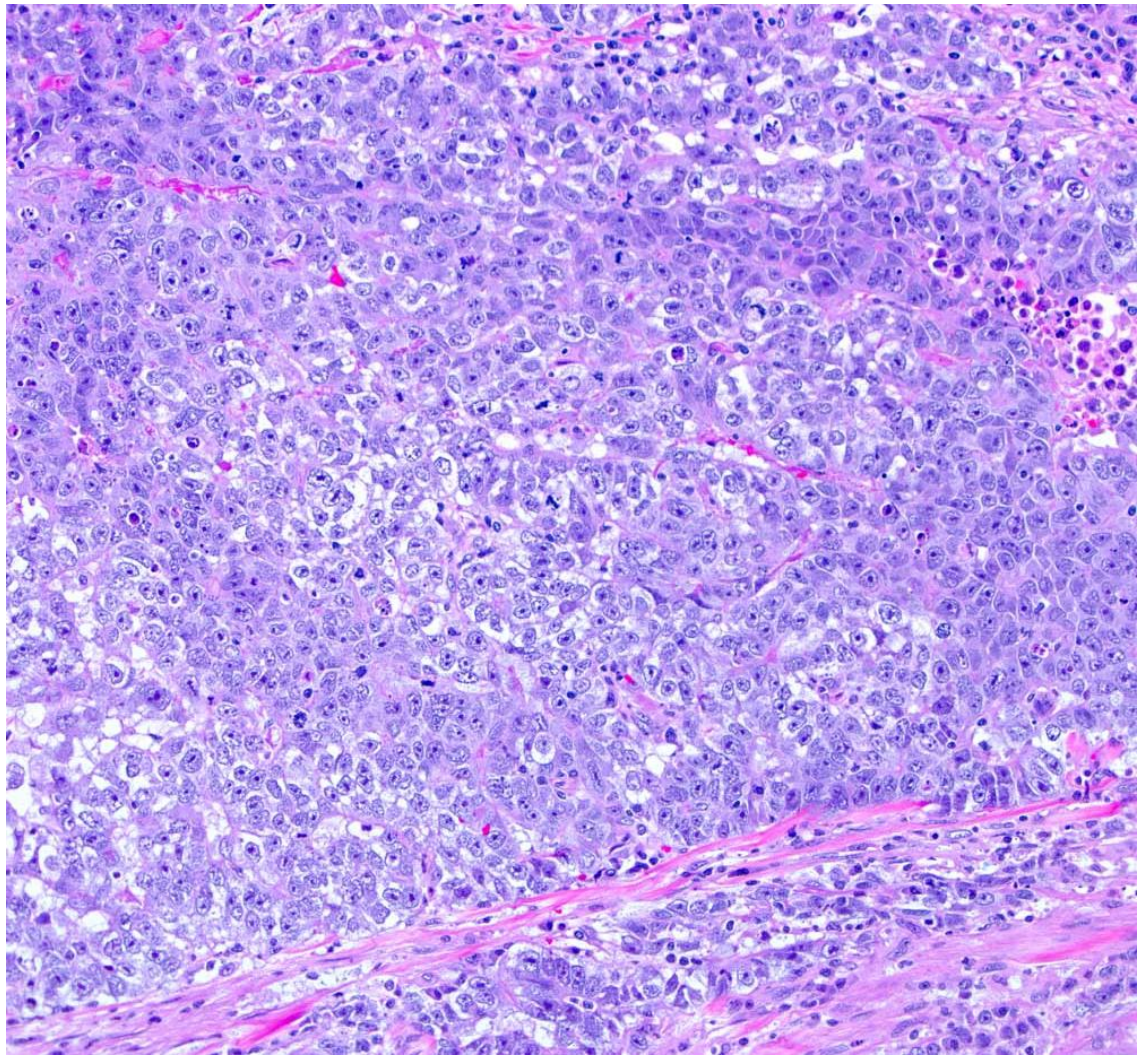
Gwin K, Singh N, Cavallo A and Reyes-Múgica M, 2015

6.2.3.1: Embryonal carcinoma

- EC is composed of cells resembling embryonic stem cells with ovoid to columnar profiles, clear to granular or amphophilic cytoplasm, markedly pleomorphic nuclei with diverse morphological patterns.
- Gonads, mediastinum, and CNS (mostly pineal region or suprasellar compartment; fewer in basal ganglia/thalami and other locations).
- After seminoma, EC is the most prevalent testicular Germ Cell Tumor (GCT).
- Present in 87% of non-seminomatous tumors.
- Rare in childhood, except in patients with disorders of sex development (DSD).
- Most testicular examples present with a mass, 10% showing metastatic disease.
- Serum βHCG is generally not elevated, although LDH and PLAP can be.
- IHC: positive for CD30 (possibly lost after chemotherapy), OCT3/4 and SOX2, LIN28A, cytokeratin AE1/AE3, and SALL4.
- Isochromosome 12p and increased gains of 12p in most ECs, are helpful diagnostic findings to differentiate from non–germ cell, poorly differentiated malignancies. EC has a lower DNA index than seminoma.

Embryonal carcinoma

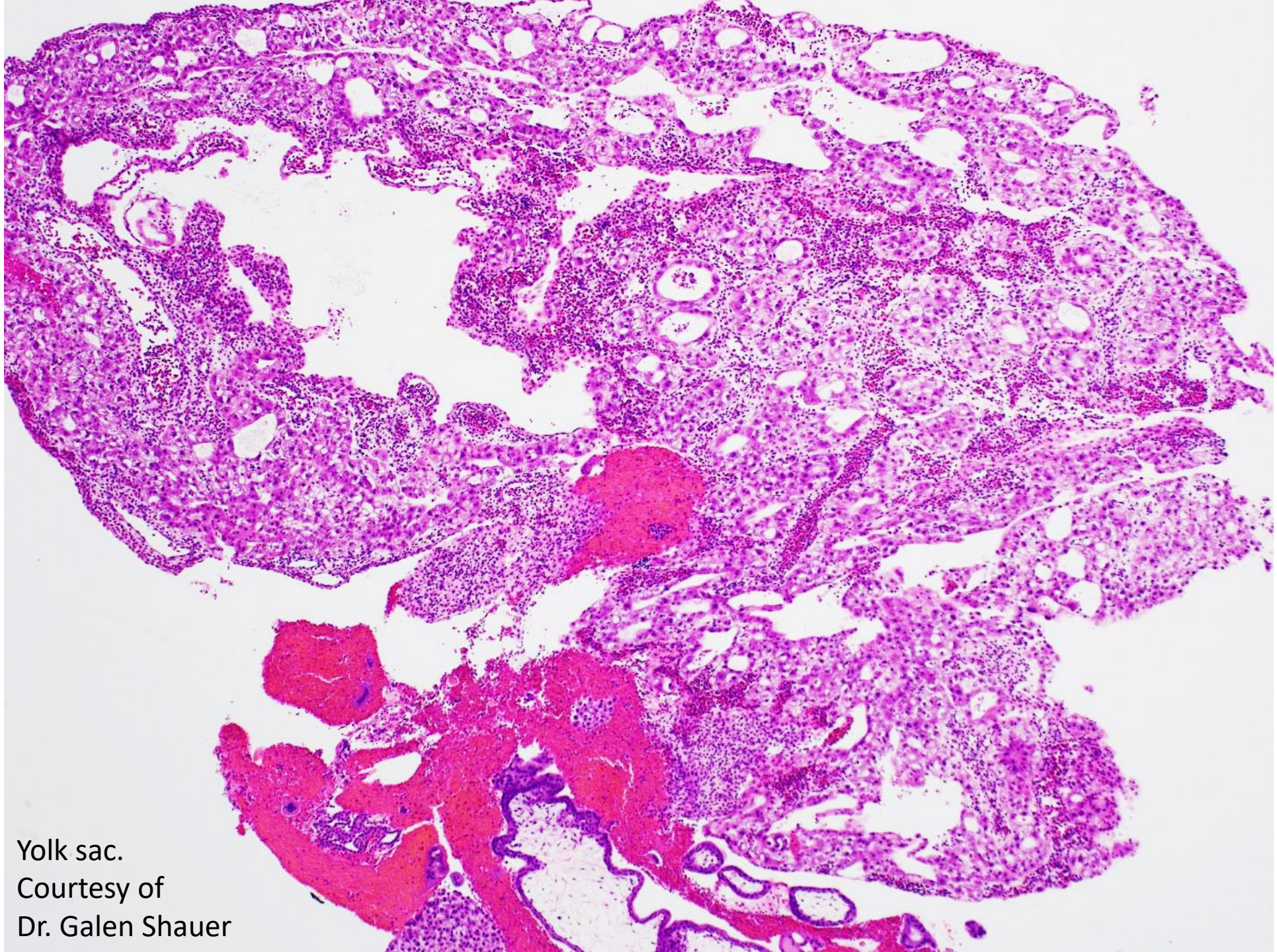




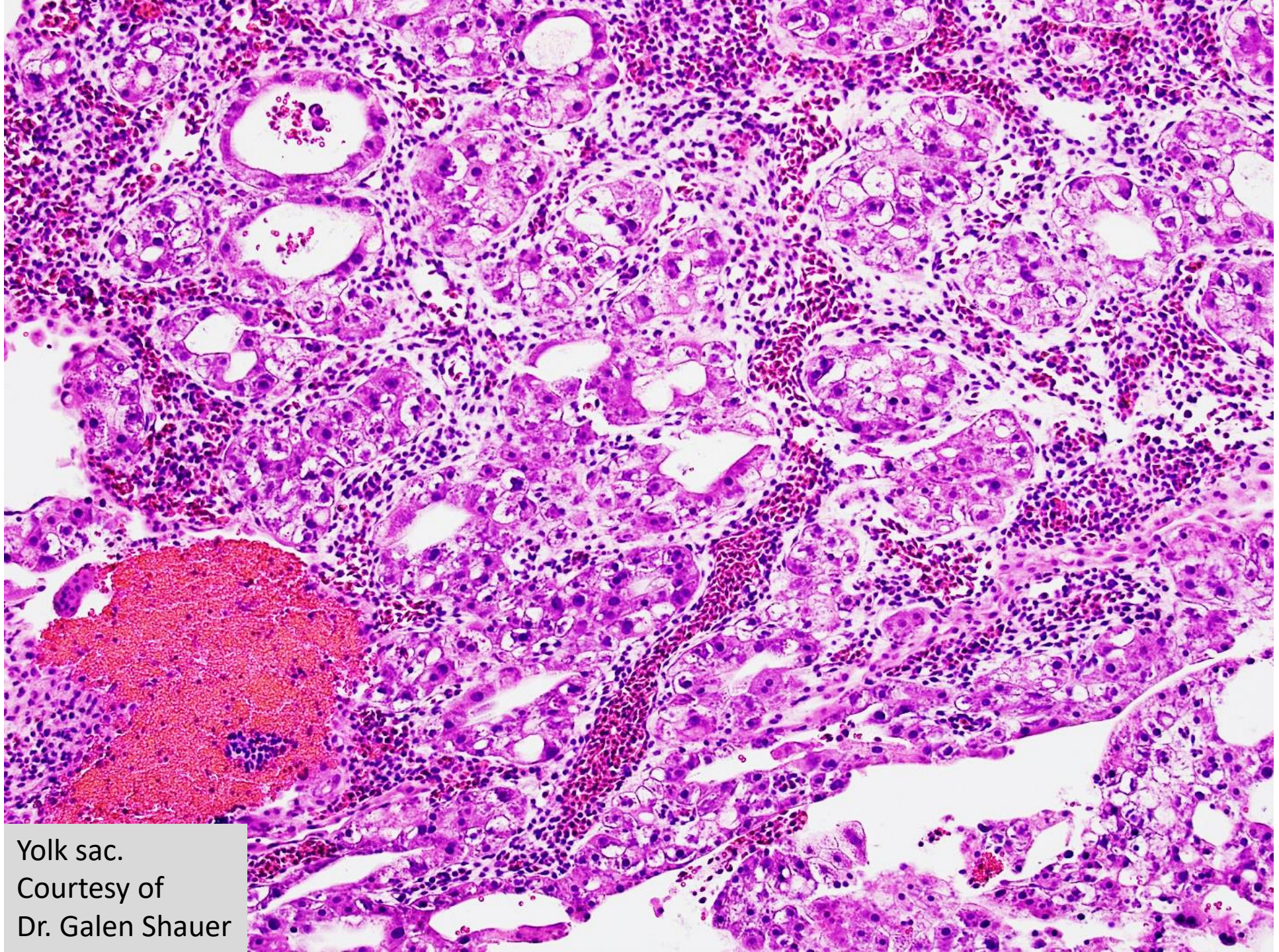
6.2.3.2: Yolk sac tumour

- YST is a malignant neoplasm resembling extraembryonic structures, including yolk sac, allantois, and extraembryonic mesenchyme.
- Pre-pubertal (type I) and post-pubertal (type II); the latter GCNIS-related.
- Gonads, mediastinum, and many other sites for pre-pubertal type.
- Within the CNS (Type I and II) more frequently in the pineal and suprasellar compartment, followed by basal ganglia/thalami, spinal cord and other locations.
- During the first two years of age the most common germ cell tumor in the vagina is a yolk sac tumor.
- Pre-pubertal YST develops at a median age of 16–20 months (ranges from 3 months to 8 years); rarely beyond 6 years.
- Postpubertal-type is rarely pure (0.6%).
- Although AFP is positive in most (95%) cases, neonates have high AFP (≥ 100 ng/mL at ≥ 6 months) normally, limiting its significance.
- About 80% of pediatric patients are clinical stage I, and only 6% relapse during surveillance (retroperitoneal and pulmonary).
- In contrast, 33% of post-pubertal YST show occult retroperitoneal metastases.
- Prepubertal-type YST is a type I GCT, likely progressed from a pure (type I) teratoma, showing recurrent gains of 1q, 12(p13), 20q, and 22, and losses of 1p, 4, and 6q.
- IHC: expression of AFP (potentially also found in glandular components of teratomas), characterize YST, in addition to cytokeratins, SALL4, glypican-3, LIN28A, possibly CD117 and PLAP.

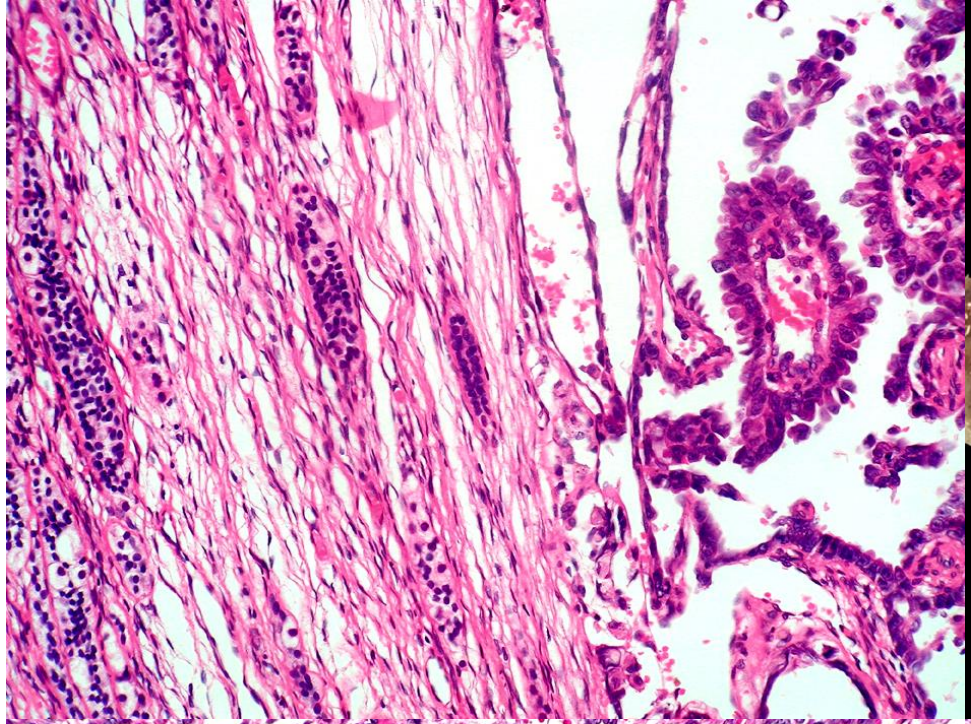
Courtesy of Dr. Robert Bendon

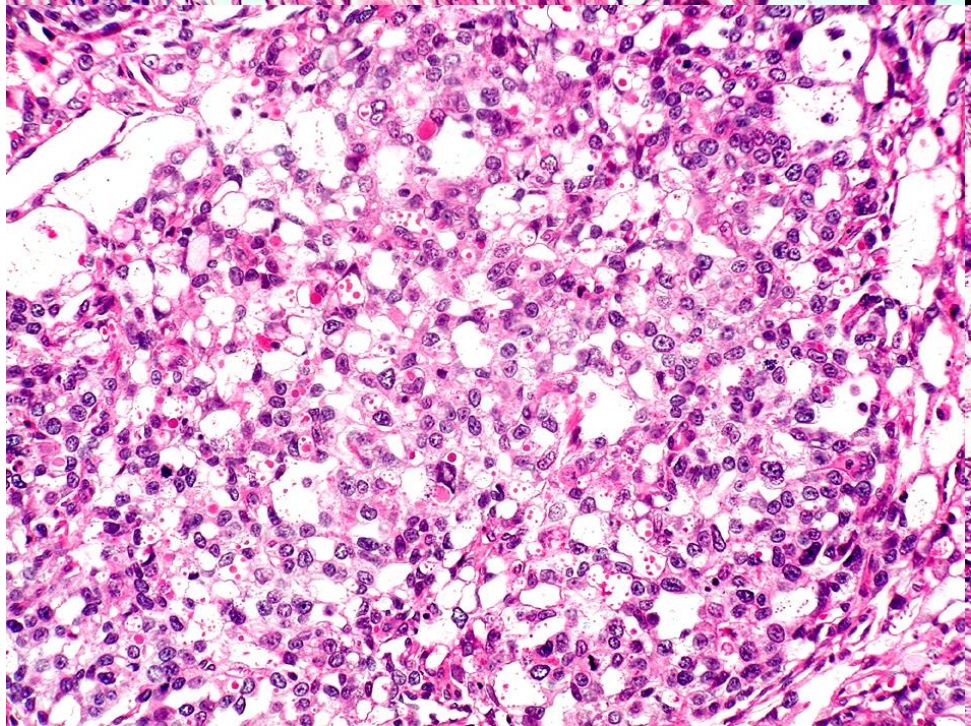


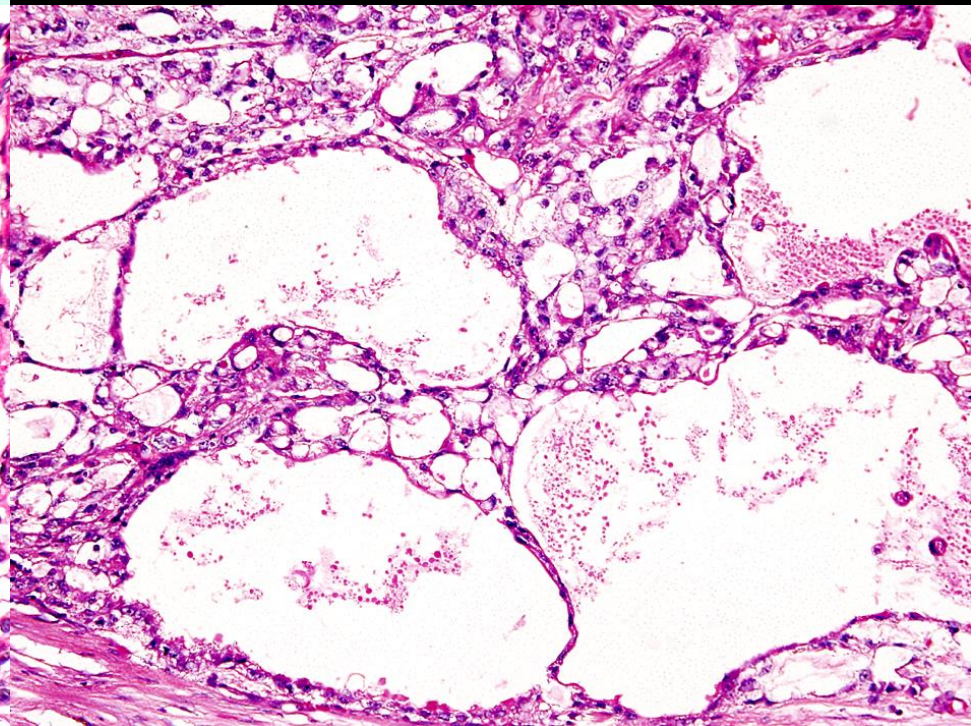
Yolk sac.
Courtesy of
Dr. Galen Shauer

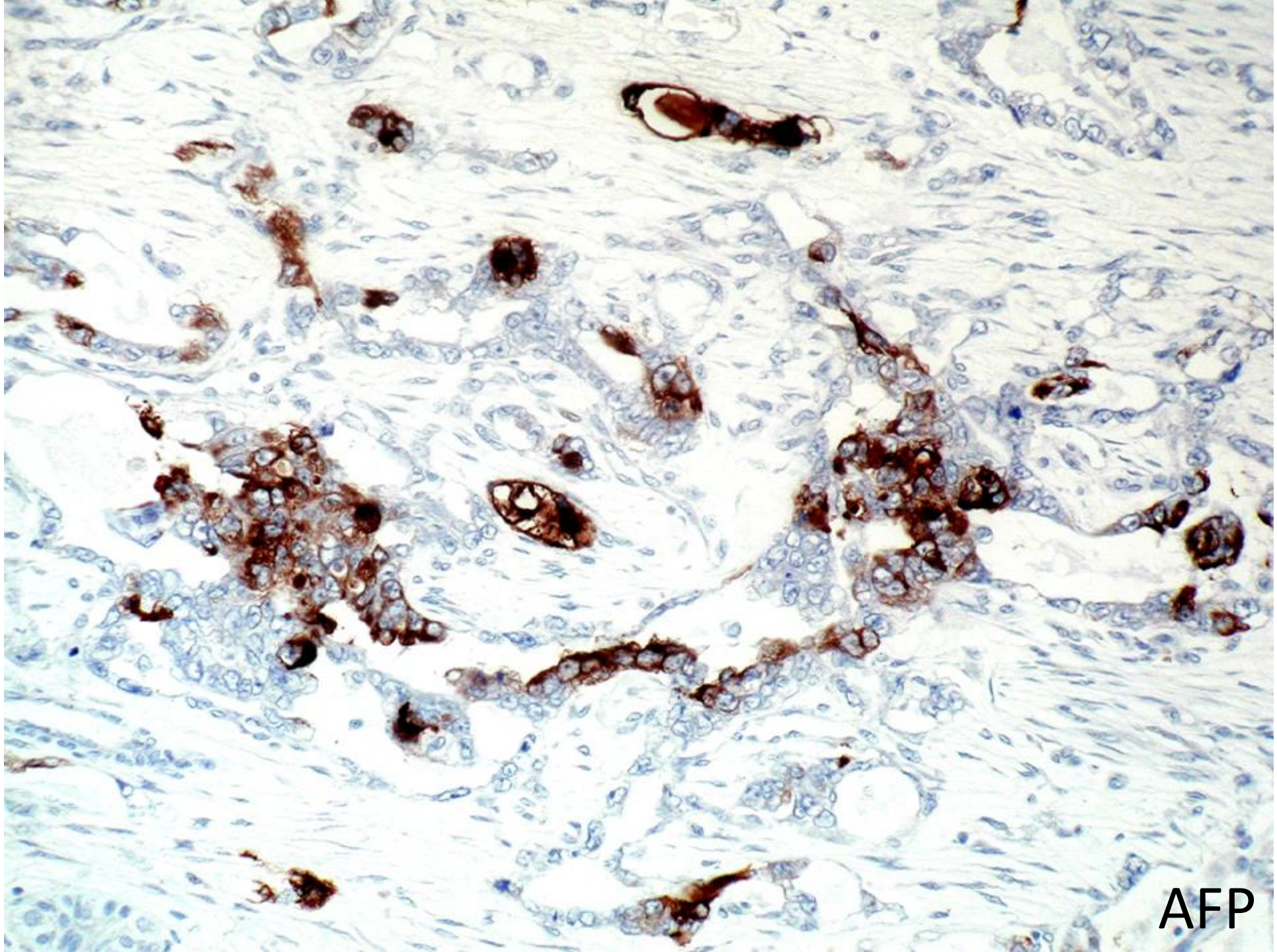


Yolk sac.
Courtesy of
Dr. Galen Shauer

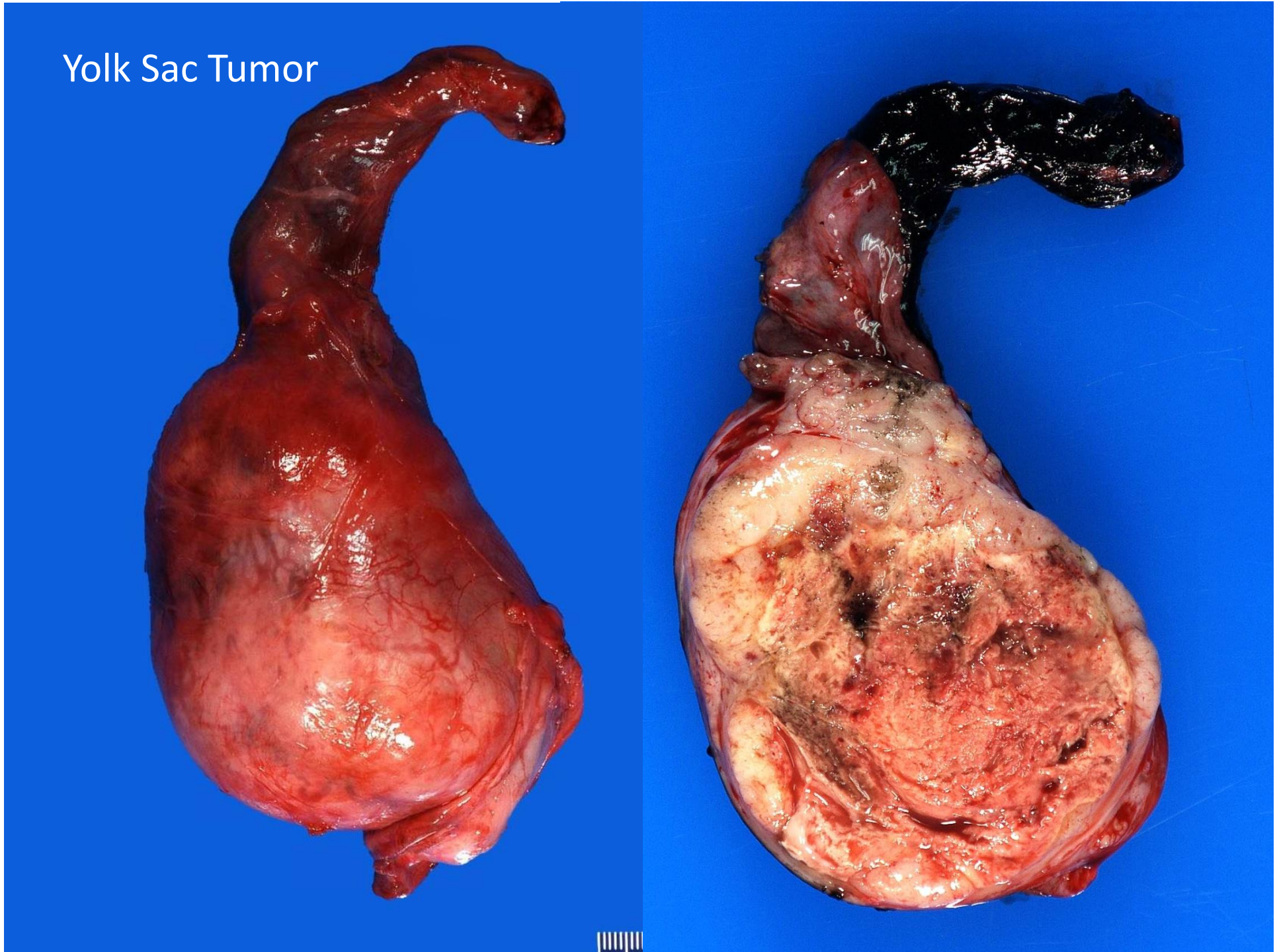


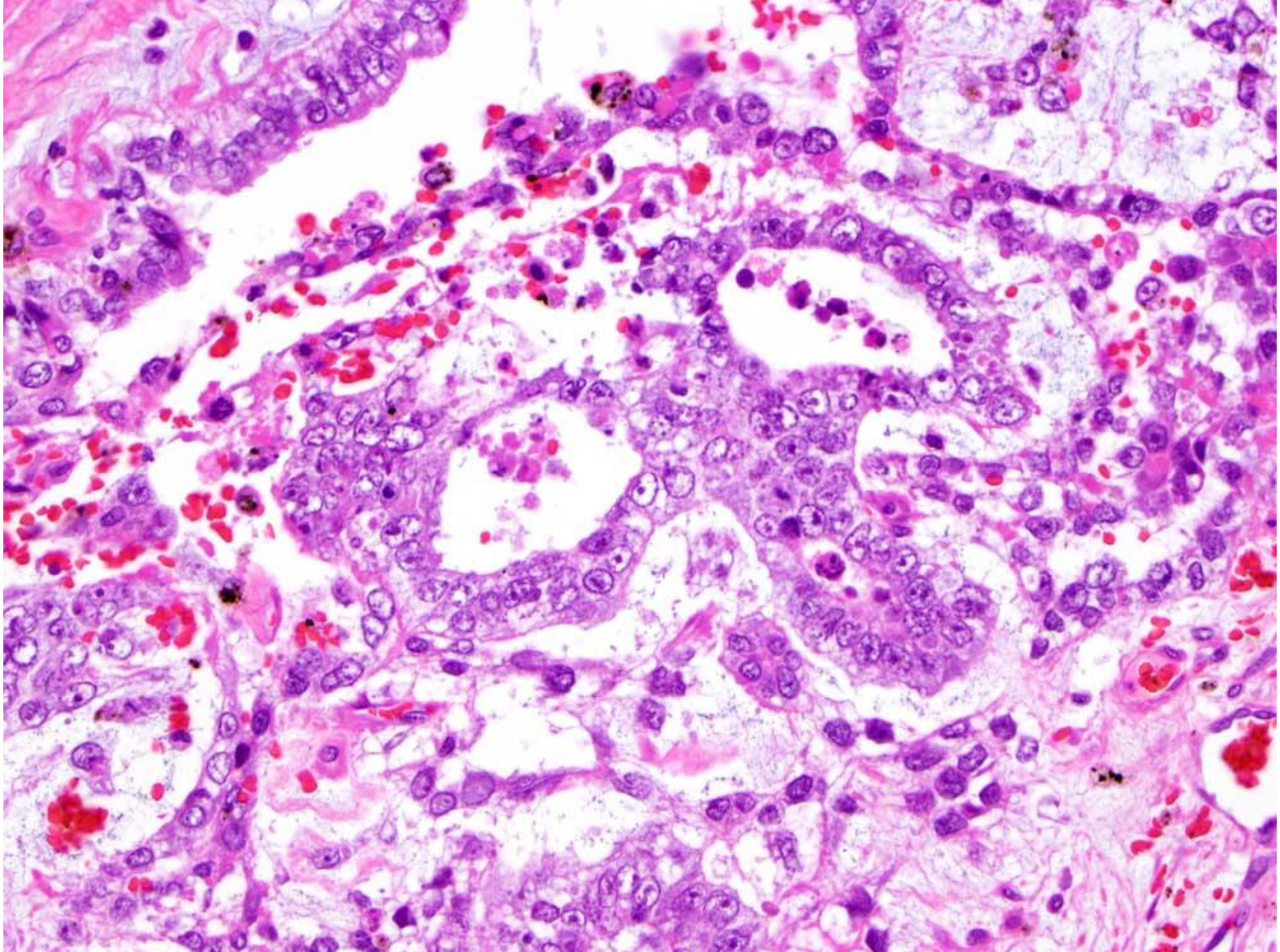





AFP

Yolk Sac Tumor





Fetus in fetu

- The term '*fetus-in-fetu*' (FIF) is attributed to Meckel in 1800 and describes the inclusion of one fetus inside of another. There are ≃ 200 cases reported.
- Unclear embryologic origin, probably from bastomere cells (type 0 of GCT).
- Monochorionic, monozygotic twin vs. well-diff. teratoma (fetiform T).
- Spencer: FIF must have:
  - Be enclosed within a distinct sac
  - Be partly or completely covered by normal skin
  - Have grossly recognizable anatomica parts
  - Be attached to host by a few relatively large blood vessels
  - Be located immediately adjacent to a site of attachment of conjoined twins or be associated with the neural tube or GI syst.

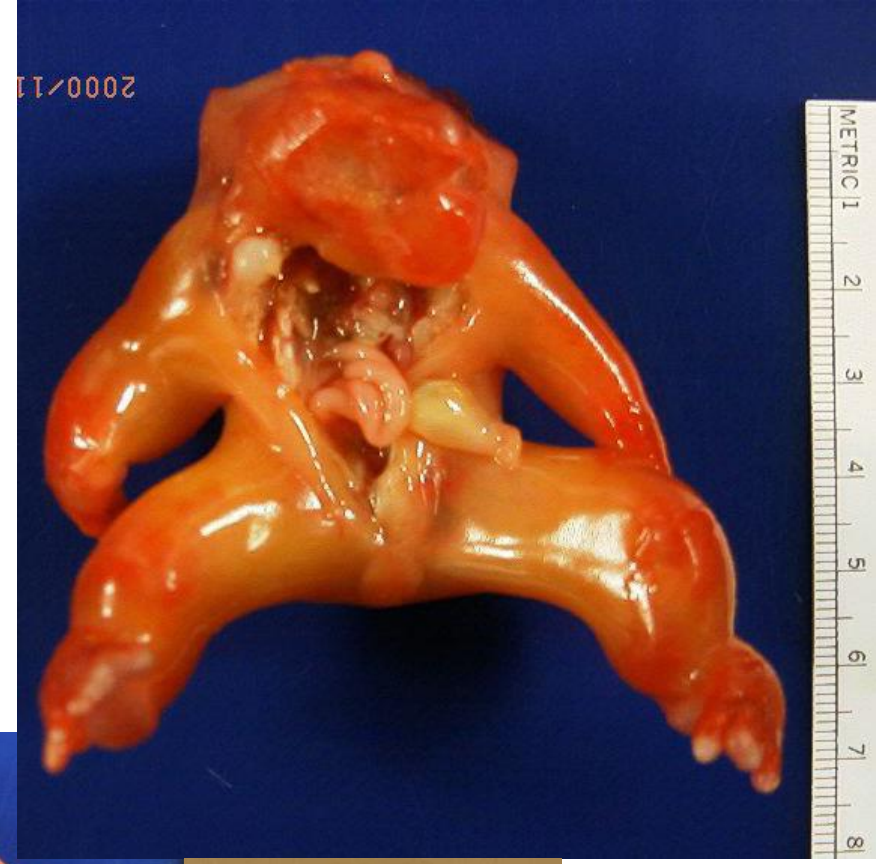
Fetus in fetu

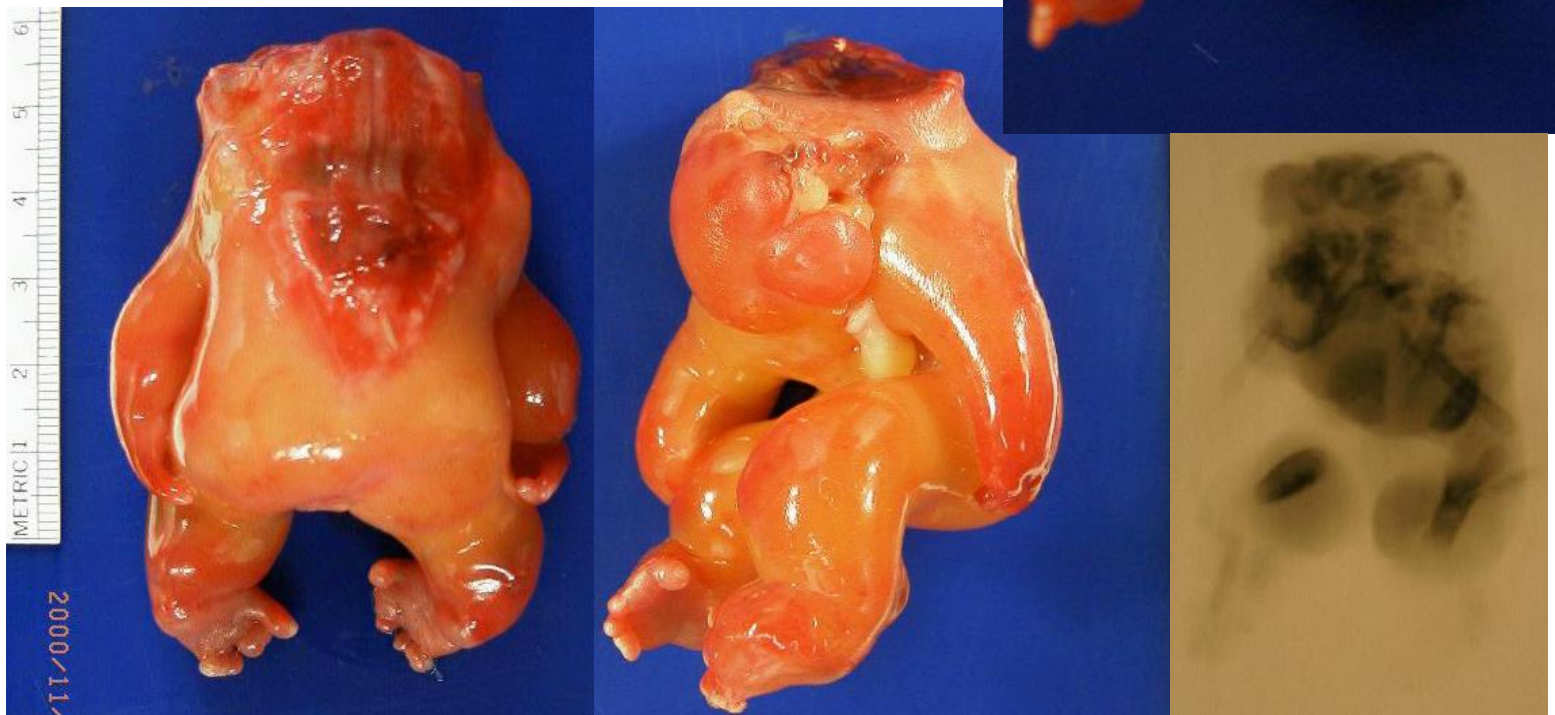
- Most are asymptomatic abdominal masses in infants.
- 80% in retroperitoneum.
- Reported in liver, sacrum, pelvis, scrotum, external genitalia, mediastinum and oropharynx.
- Treatment is surgical resection.

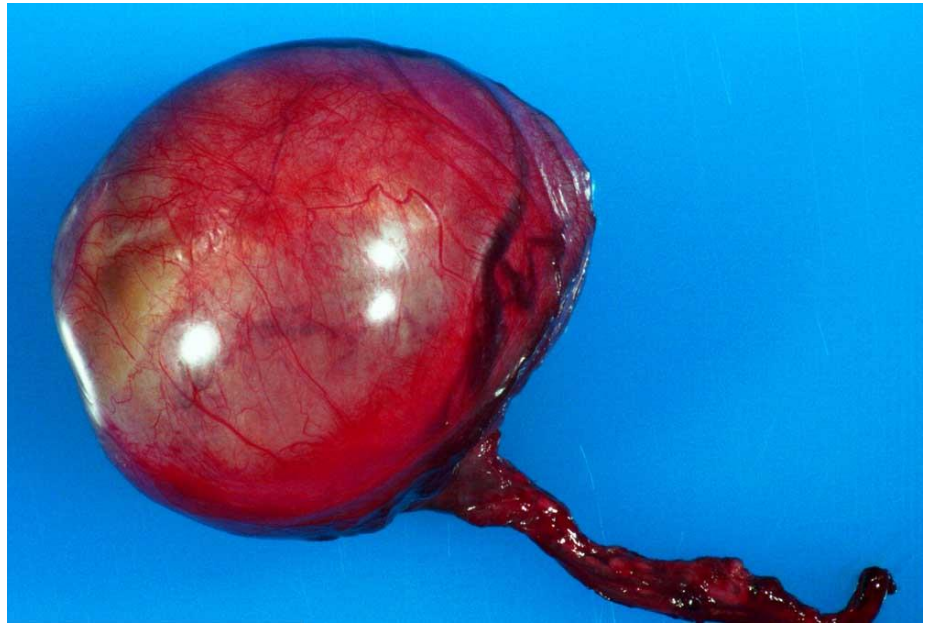
Three-dimensional Sonographic Imaging of a Highly Developed Fetus In Fetu With Spontaneous Movement of the Extremities

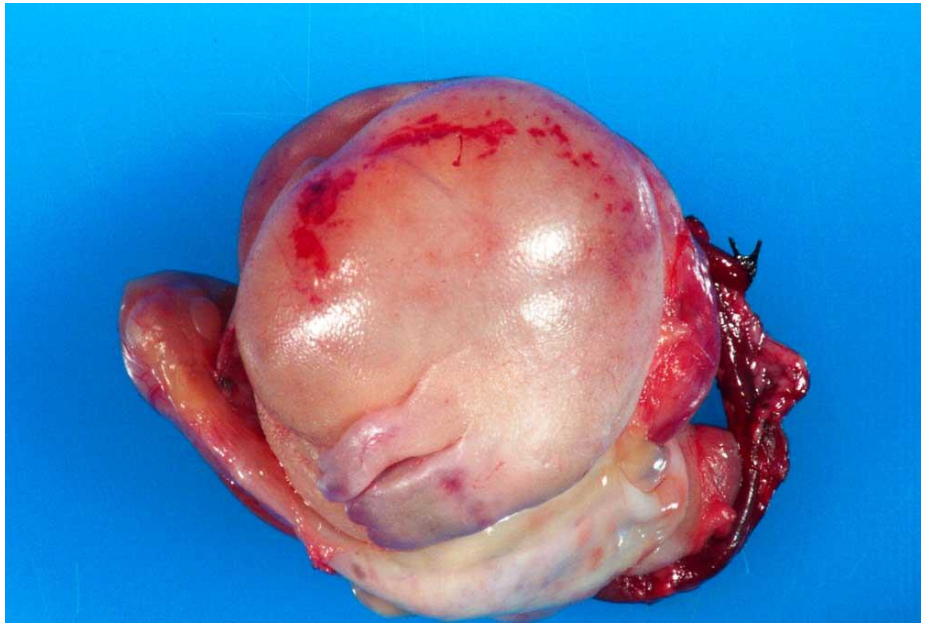
David C. Jones, MD, Miguel Reyes-Múgica, MD, Patrick G. Gallagher, MD, Peggy Fricks, RDMS, Robert J. Touloukian, MD, Joshua A. Copel, MD

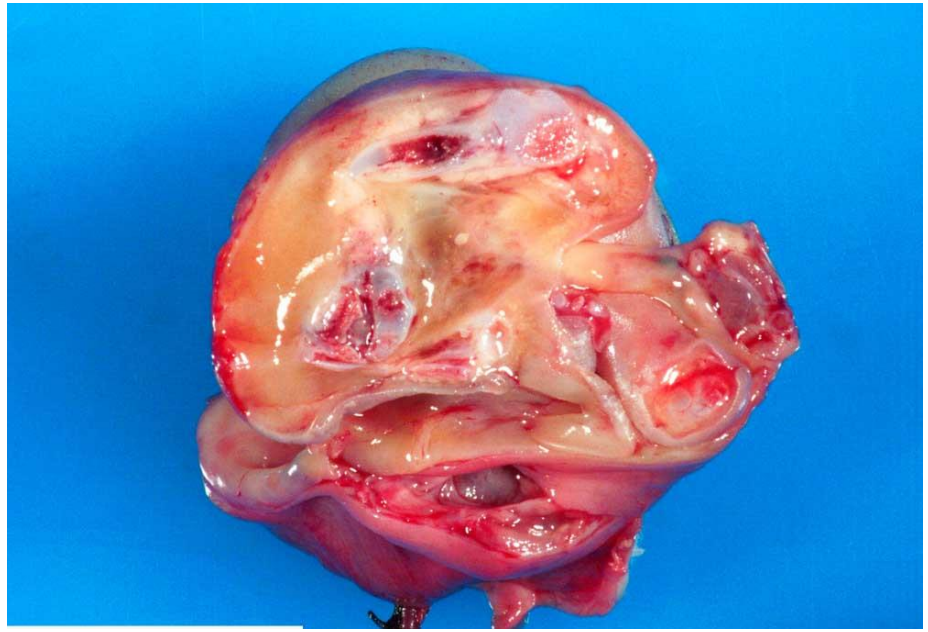
A fetus in fetu (FIF) is a rare anomaly of fetal development in which a pedunculated, fetiform mass develops inside a more mature fetus.[1,2] Minimal criteria for diagnosis include the presence of an axial skeleton or a fetus with metameric organization, skin coverage, encapsulation, and a 2-vessel cord.[3] In most cases that meet diagnostic criteria, the FIF is poorly developed and may be difficult to distinguish from a teratoma. The etiology of this condition is unknown. Although the diagnosis of an FIF has traditionally been made in infancy or childhood, there are an increasing number of diagnoses being made prenatally on the basis of sonography.[1,4–14] This report describes the prenatal diagnosis of an FIF with an extraordinarily high degree of differentiation using two-dimensional (2D) and three-dimensional (3D) sonographic imaging.

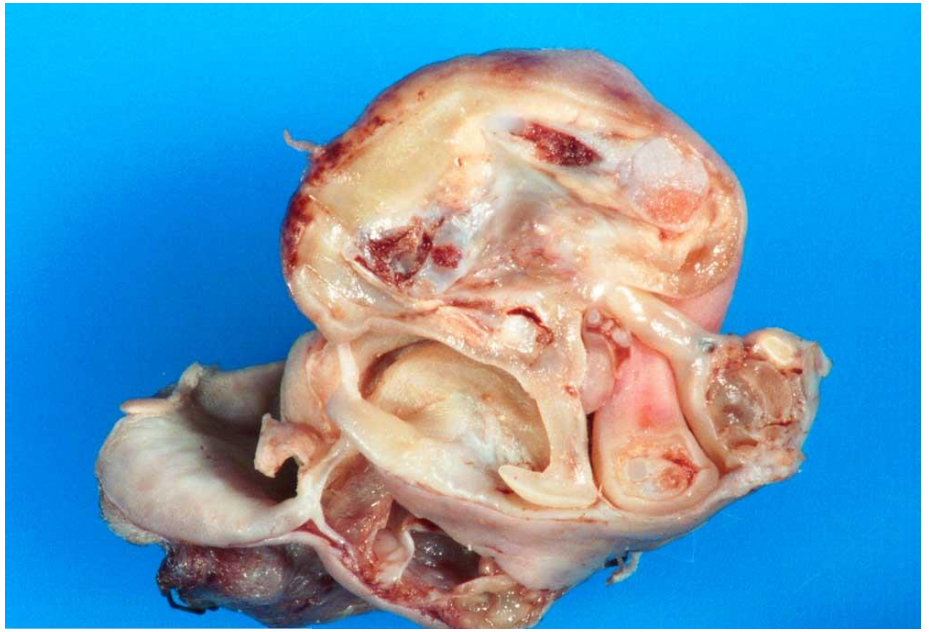


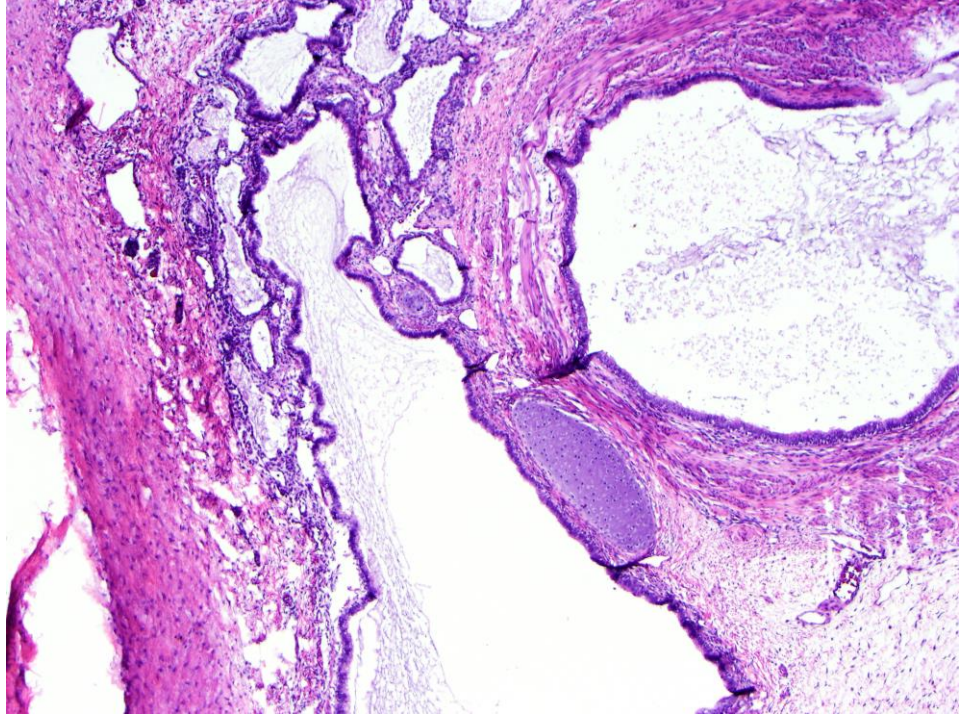


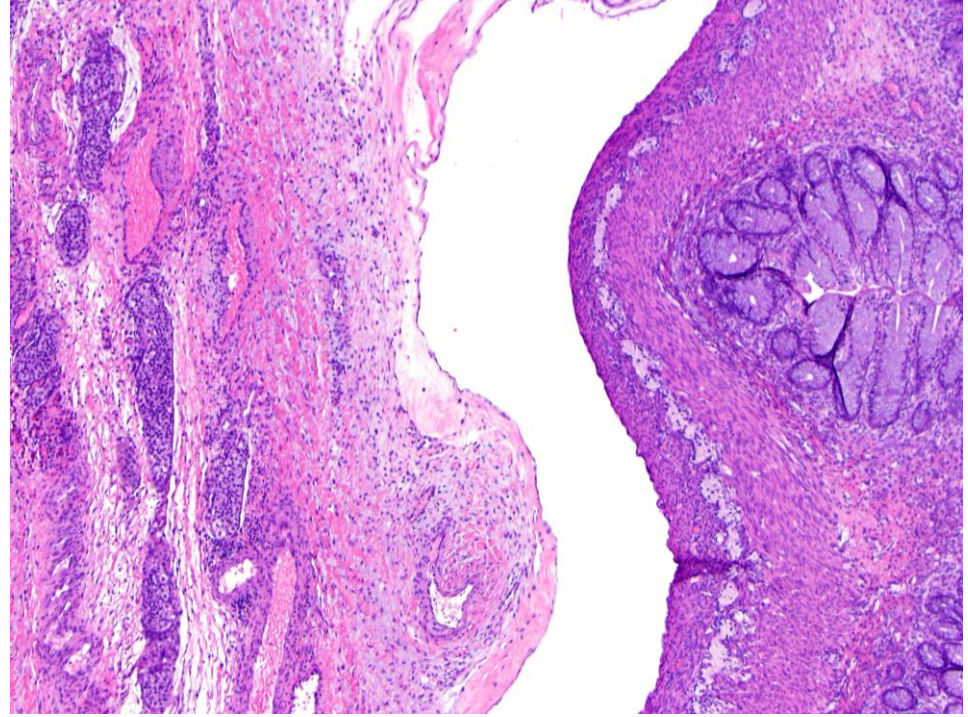


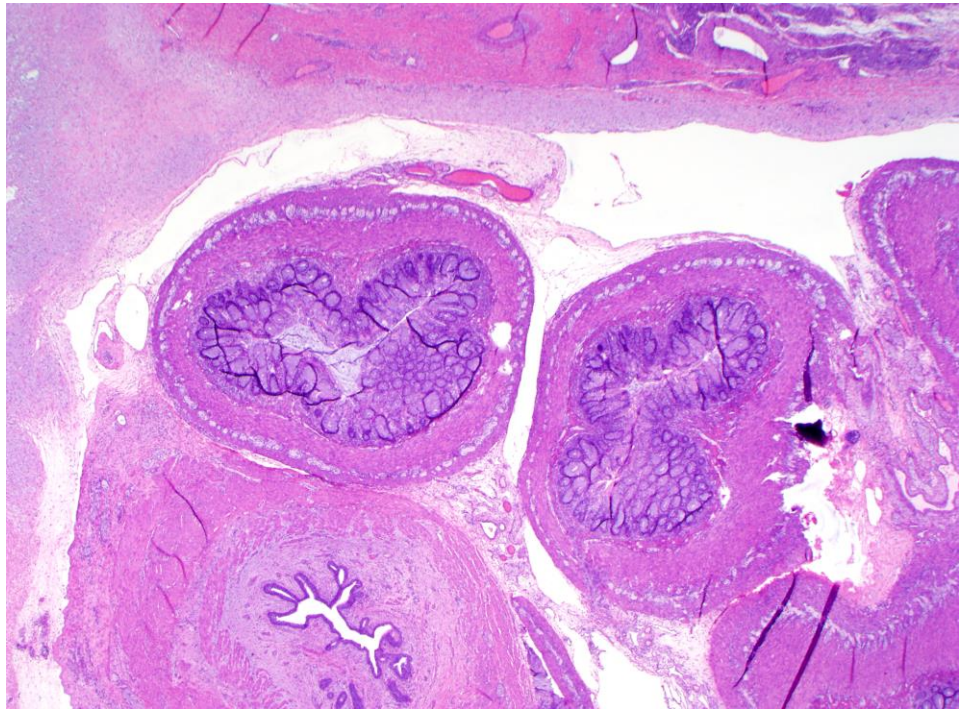


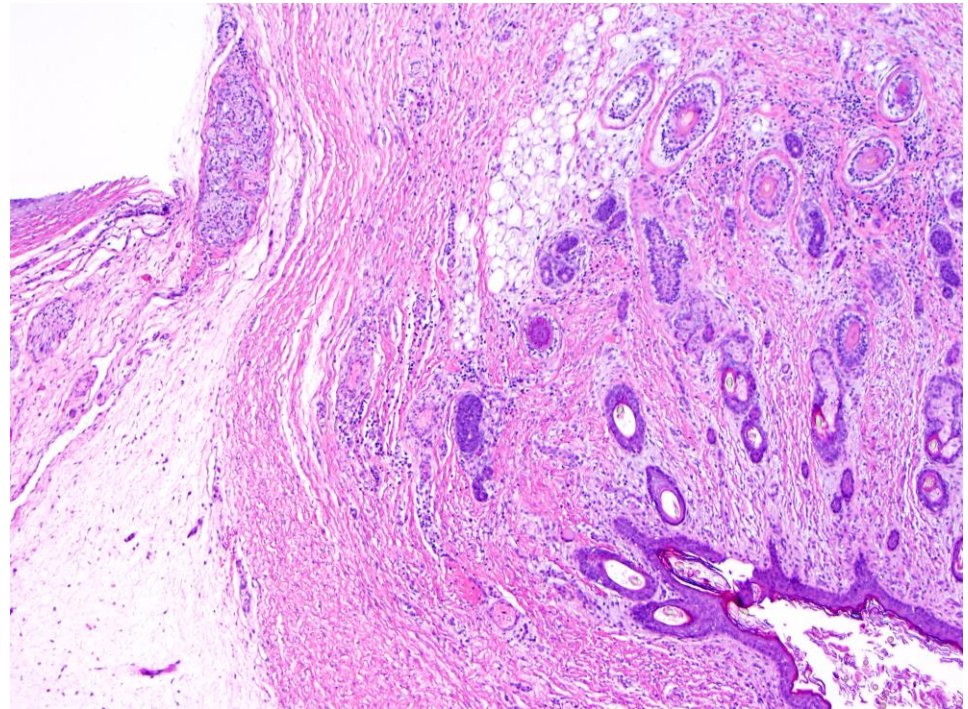












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Fetus-in-fetu presenting as a cryptorchid testis and abdominal mass: A report of a case and review of the literature

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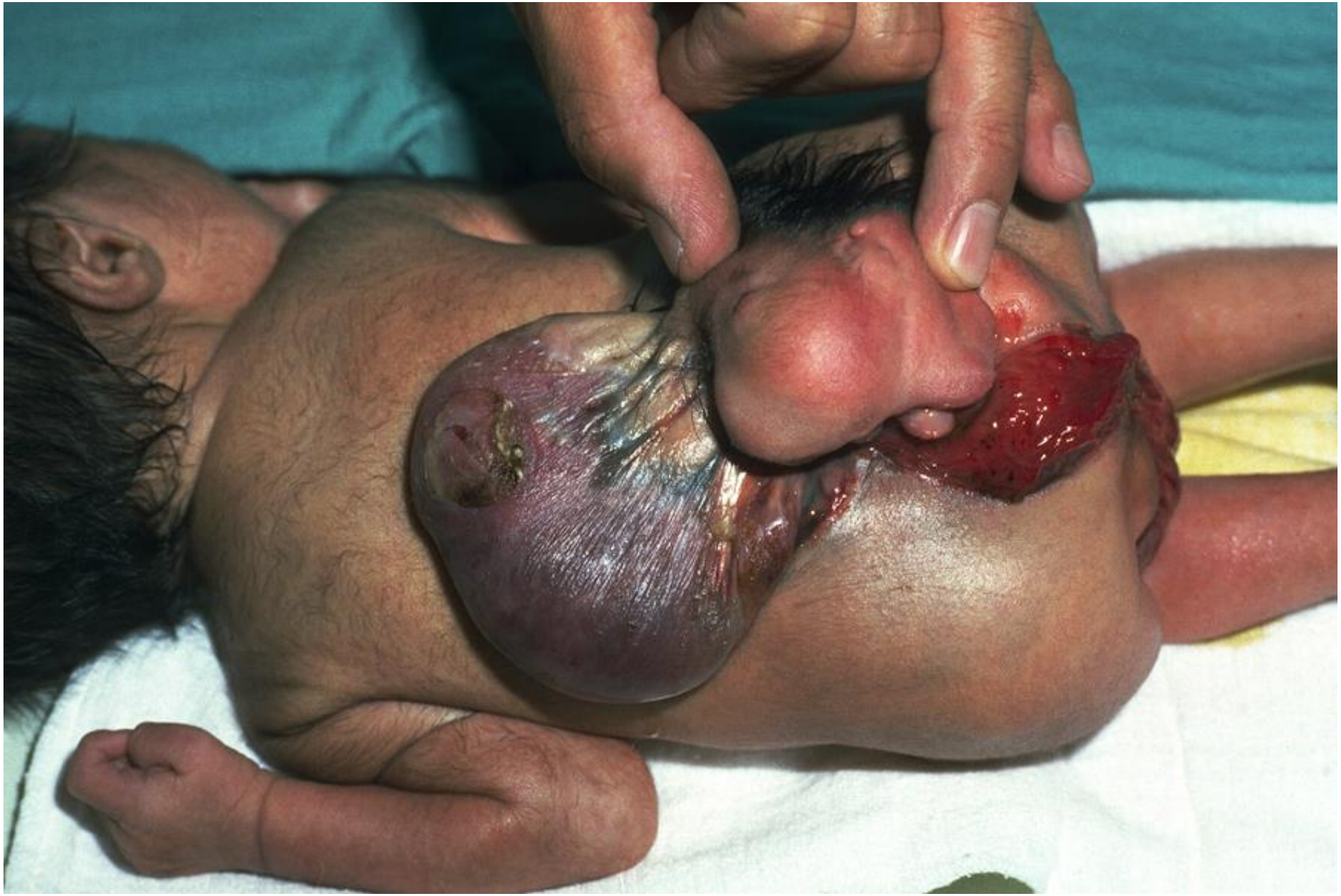
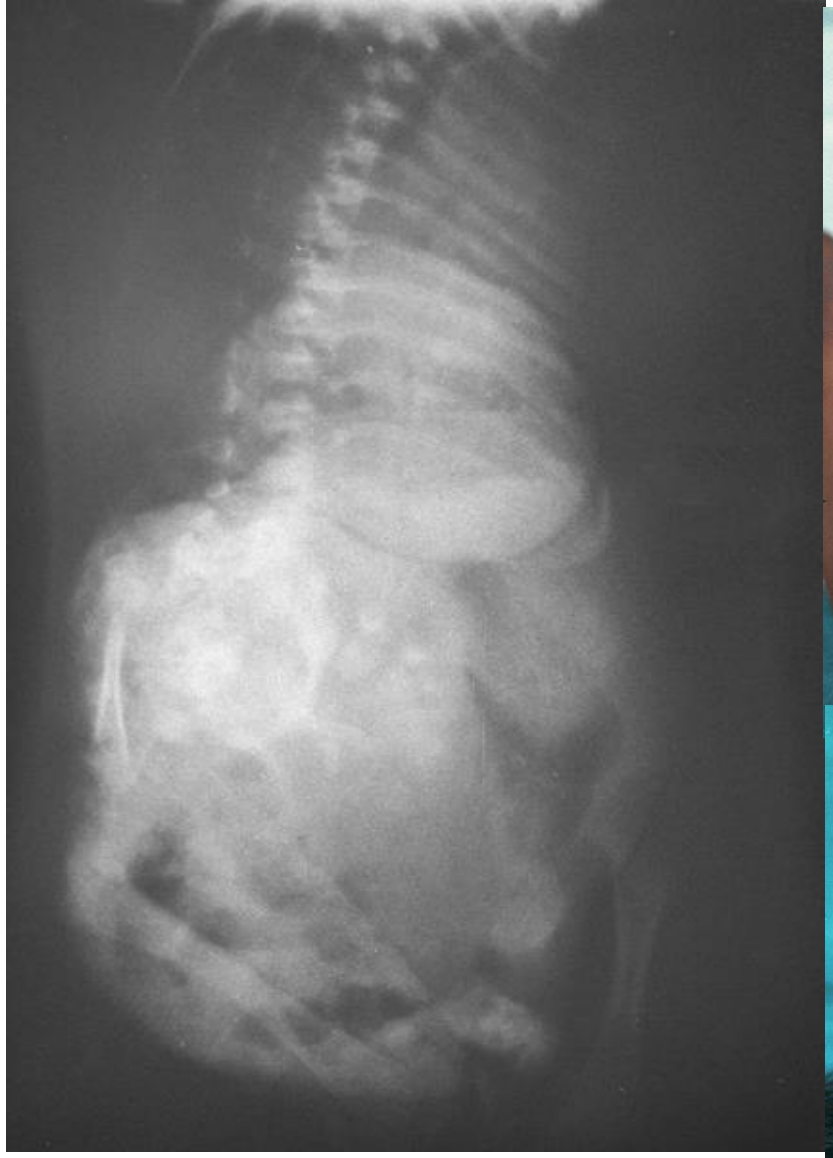
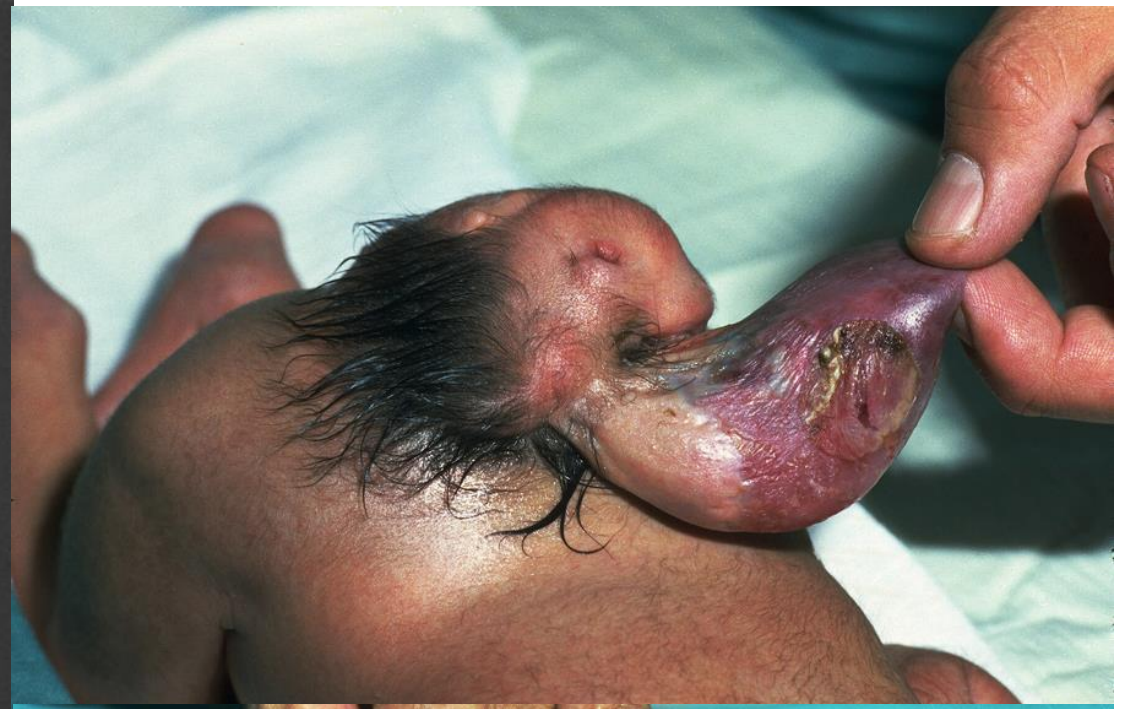
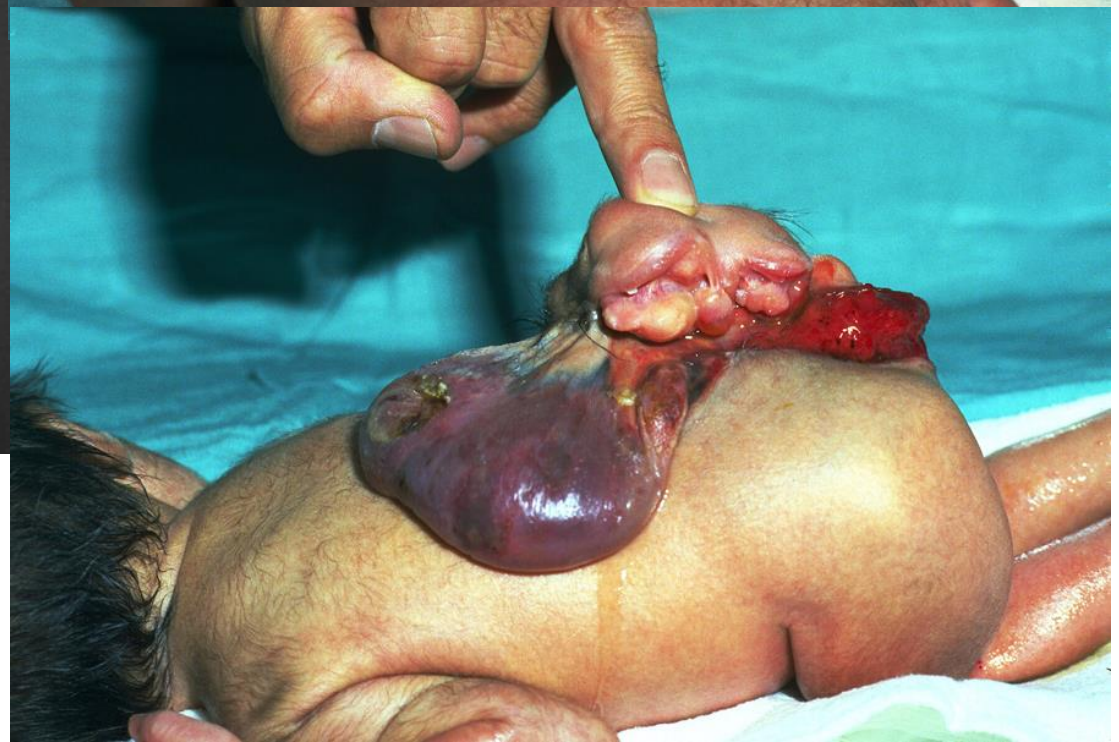
ABSTRACT

Fetus-in-fetu is a rare congenital tumor containing fetal tissue with an unclear etiology, but some believe it to arise from a parasitic monozygotic twin within the host twin. We present the case of a 3-week old term neonate found to have an abdominal mass and undescended right testicle. At laparotomy, a large, circumscribed mass was present in the right upper quadrant. It was found to be associated with the vas deferens and gonadal vessels, appearing to be closely associated with the right-sided cryptorchid testis. Pathology revealed an intratesticular fetus-in-fetu. Fetus-in-fetu is a rare condition where a well-developed mass believed to arise from a monozygotic, parasitic twin, is found within its sibling. First reported by Dr. Meckel in 1800, this is thought to occur in 1 in 500,000 live births with less than 100 cases reported in the literature. Fetus-in-fetu is differentiated from mature teratoma by the presence of an axial skeleton with metameric segmentation and well-differentiated tissues. FIF is a benign disease, however surgical excision continues to be the treatment of choice, in order to confirm diagnosis by pathology and to exclude malignant teratoma. Fetus-in-fetu is a rare of congenital lesion that can present as an abdominal mass. Due to the high prevalence of retroperitoneal location, a FIF should remain on the differential for an infant with an abdominal mass and ipsilateral cryptorchid testis.



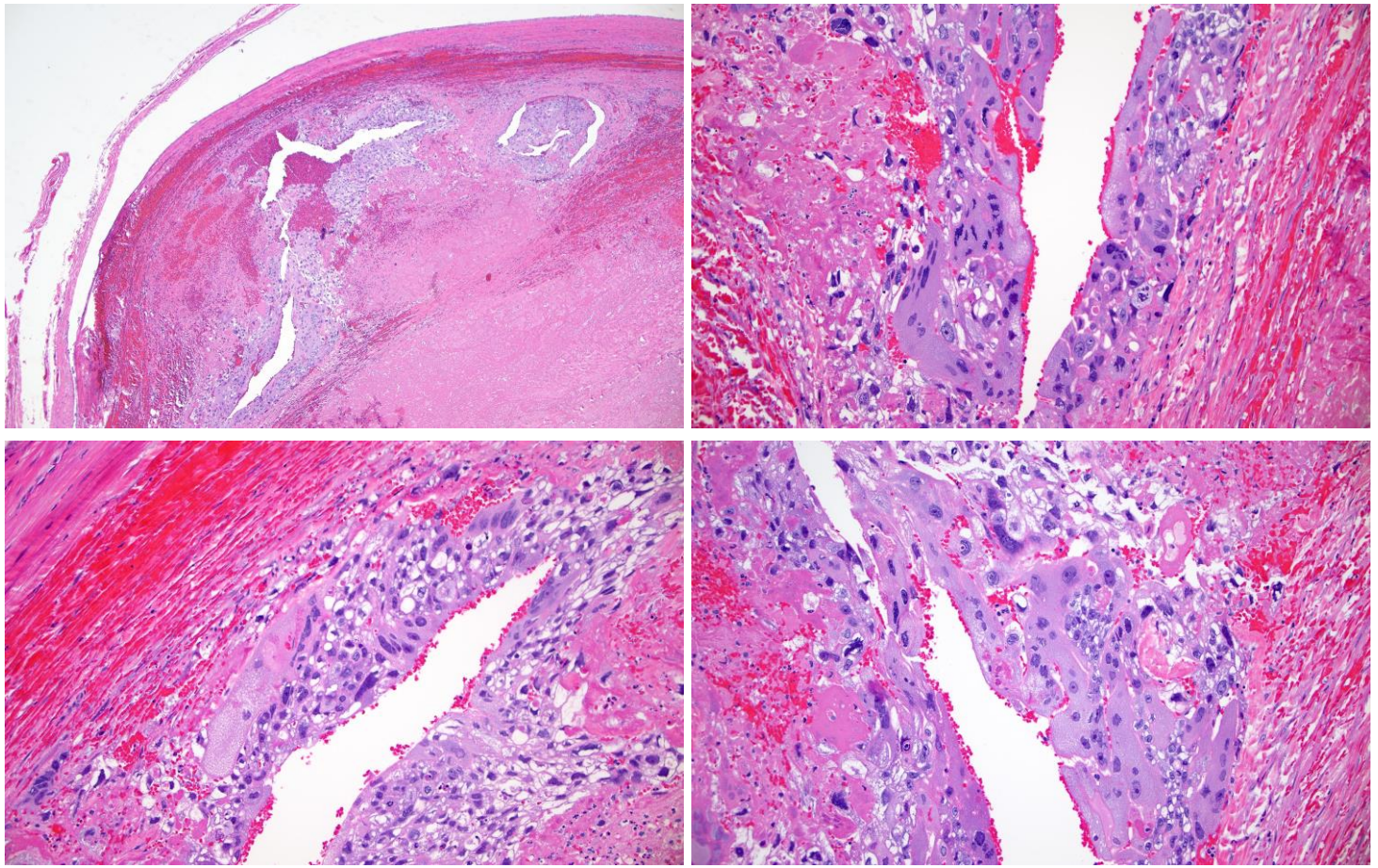






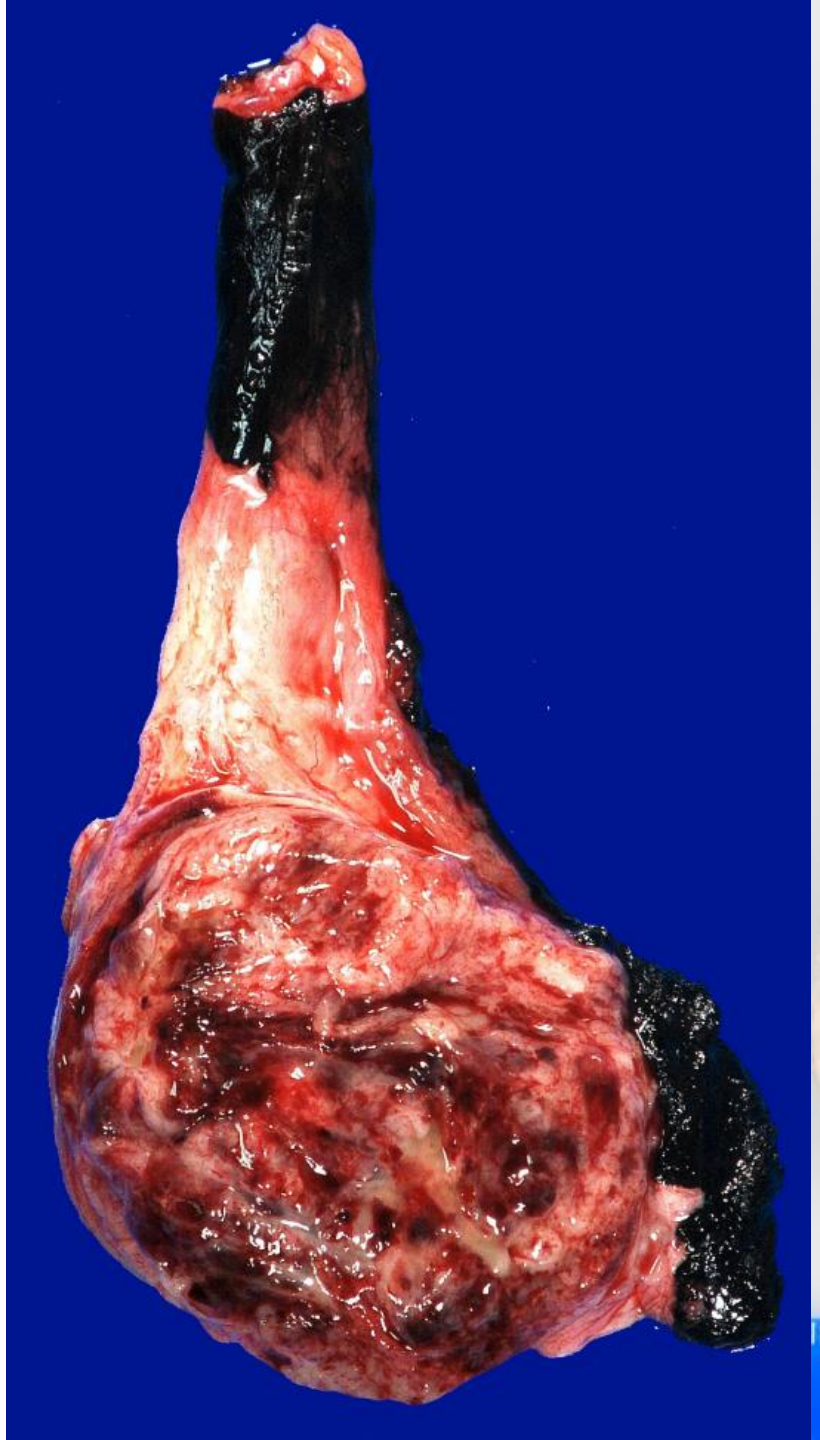
6.2.3.3: Choriocarcinoma (non-gestational)

- Choriocarcinoma is composed of cells of the extraembryonic chorion, including cytotrophoblast, intermediate trophoblast, and syncytiotrophoblast cells.
- Gonads, mediastinum, and CNS: mostly pineal region, followed by the suprasellar compartment, and basal ganglia/thalami, spine, and other locations.
- Choriocarcinoma occurs in 6.4–17.8% of mixed testicular GCTs and is pure in 0.3%.
- Rare in childhood, except in patients with a disorders of sex development (DSD).
- β-HCG is invariably elevated (often > 50 000 IU/L).
- Isochromosome 12p and increased copy numbers of 12p in most choriocarcinomas, are helpful to differentiate it from non–germ cell, poorly differentiated malignancies.
- Choriocarcinoma is highly aggressive, with early haematogenous spread, high stage, and haemorrhagic complications.



6.2.3.4: Malignant mixed germ cell tumours

- MMGCT is composed of more than one histological element.
- They are regarded as nonseminoma, despite the presence of a seminoma-like component.
- Tumours composed of teratoma and YST may either be pre- (type I) or post-pubertal (type II) GCTs.
- Gonads, mediastinum, and CNS (mostly pineal region or suprasellar compartment; fewer in basal ganglia/thalami and other locations).
- MGCTs represent the majority of non-seminomatous tumours.
- Although EC with teratoma, seminoma, or YST are frequent, any combination, often with more than two components can be seen.
- MMGCTs in pre-pubertal patients are extremely rare.
- Different components and their proportions, particularly in clinical stage I testicular GCT, may have clinical implications, requiring determination of their percentages, for which immunohistochemistry is usually helpful.
- The histopathological features of the individual components are identical to those seen in pure forms.

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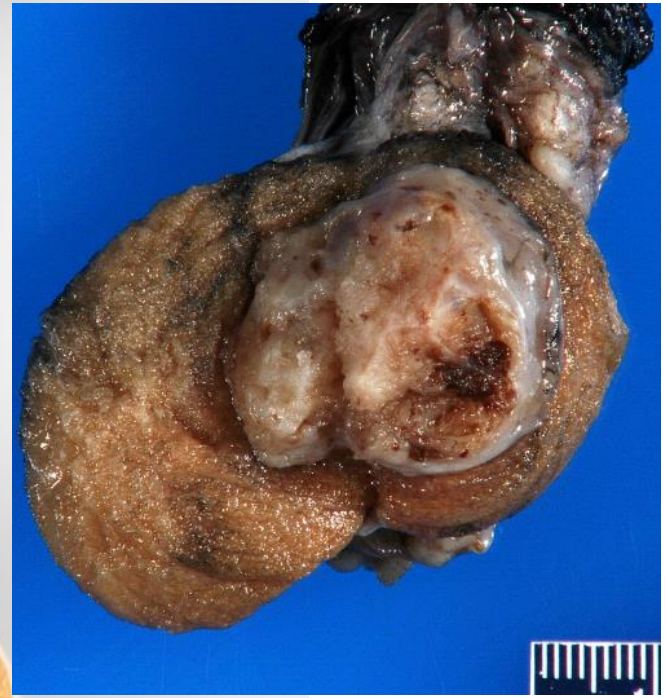

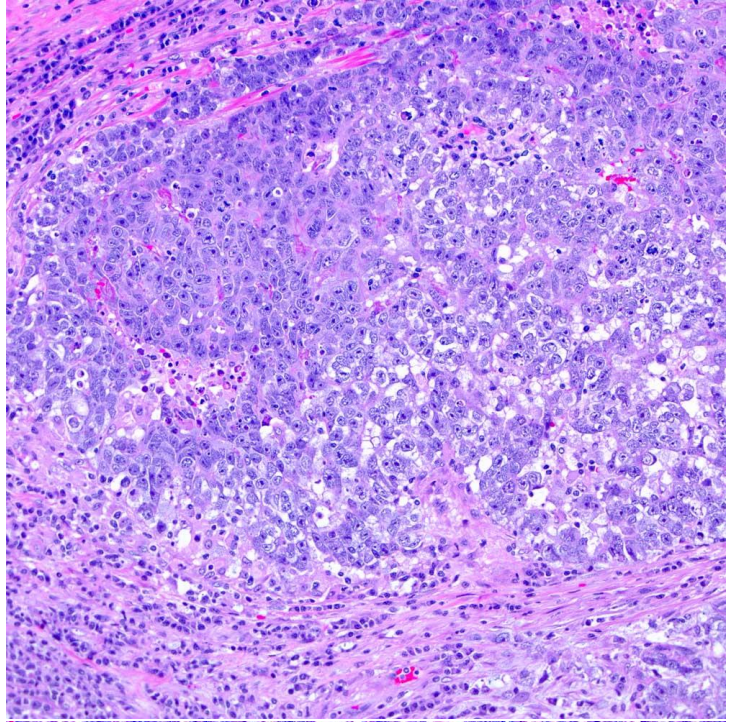

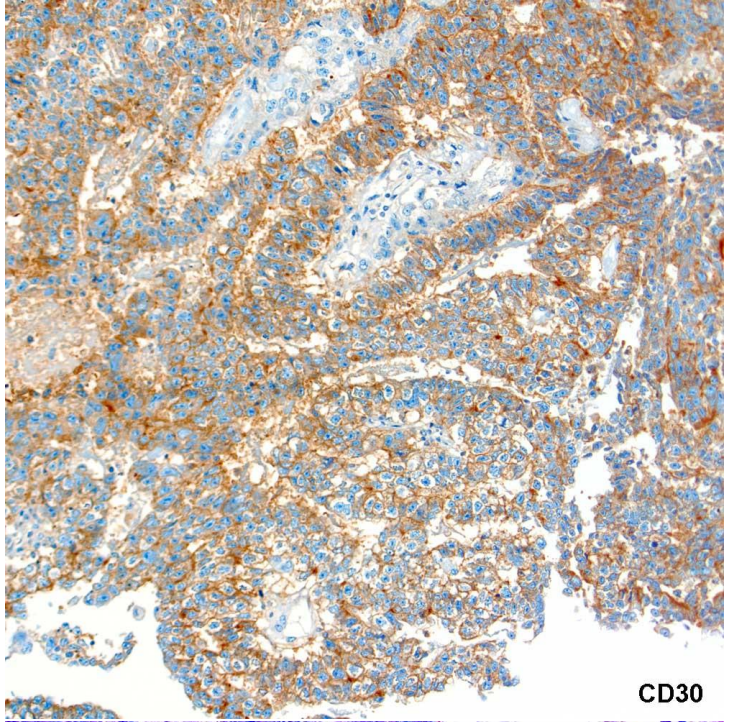
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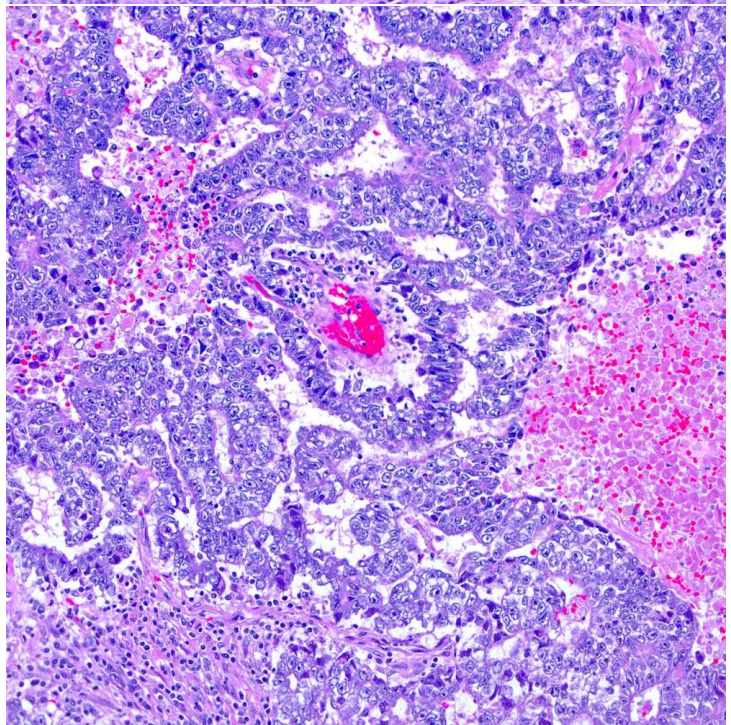

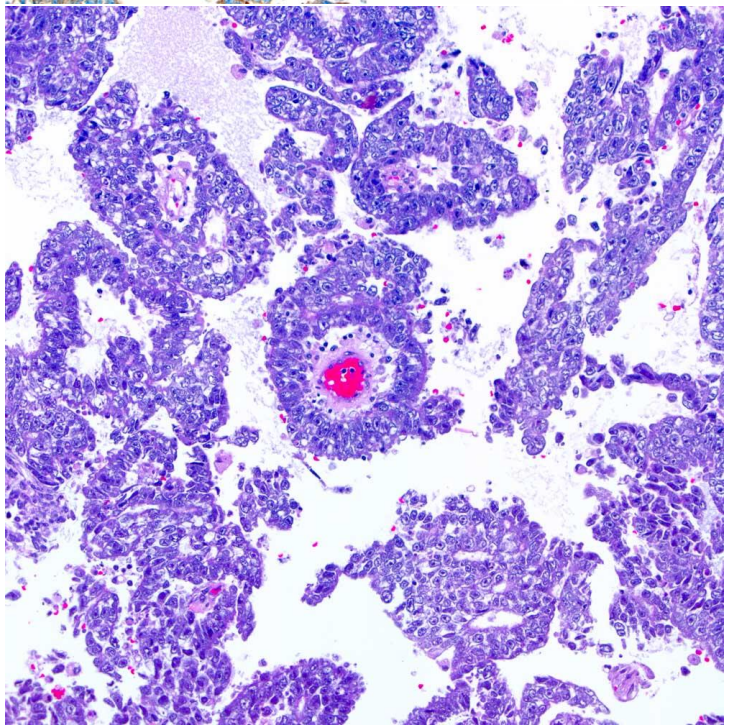

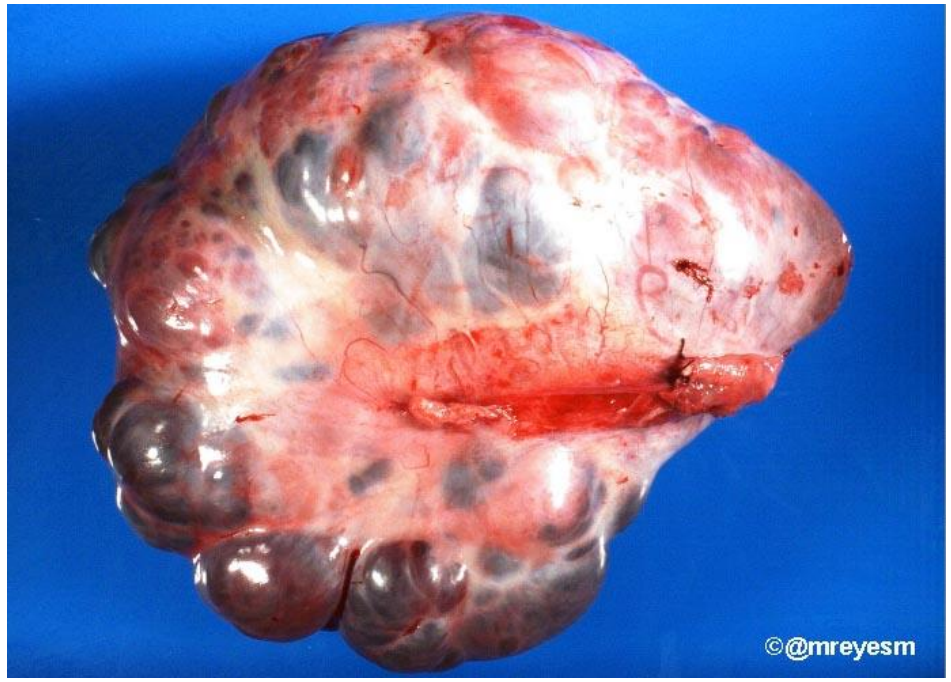
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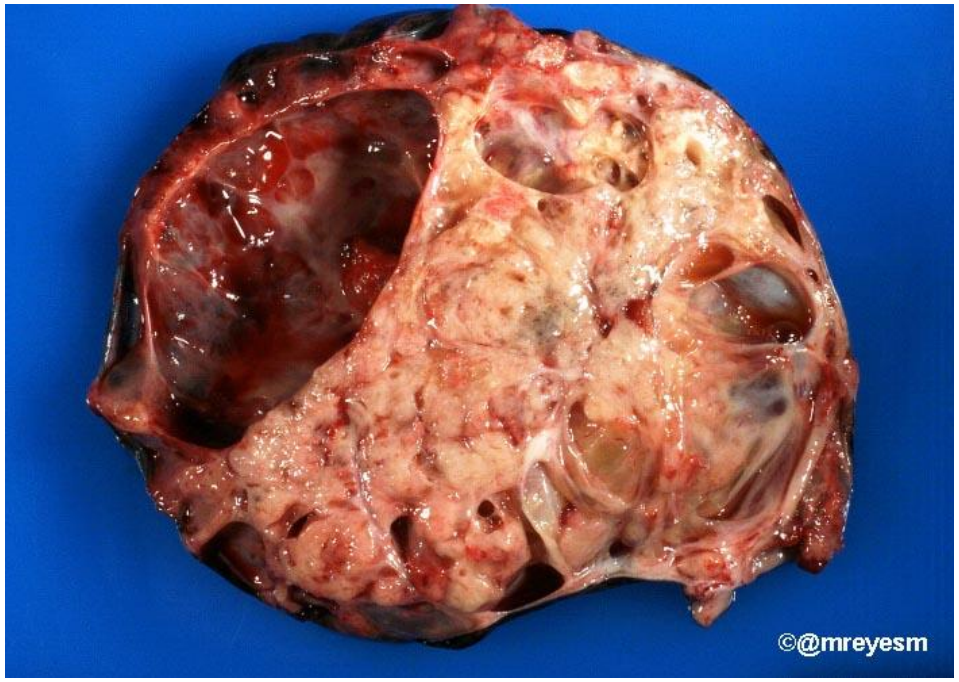
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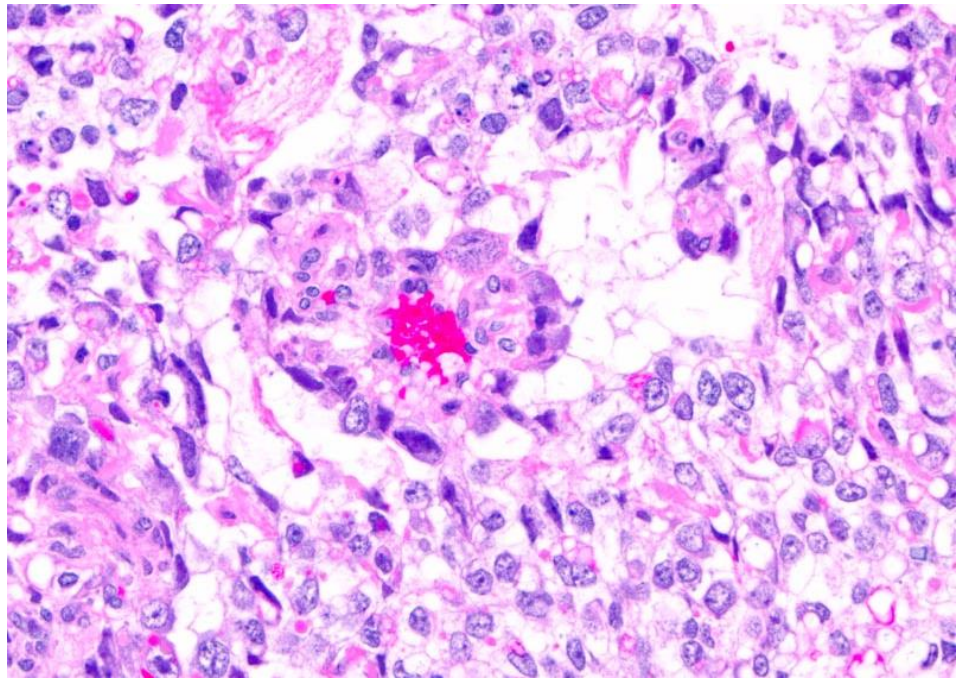

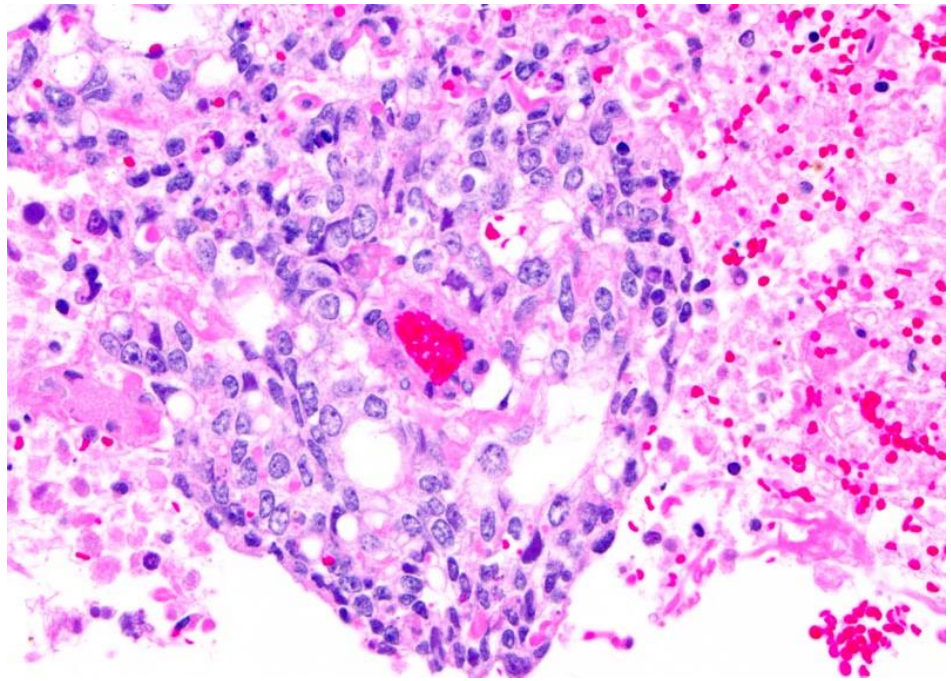

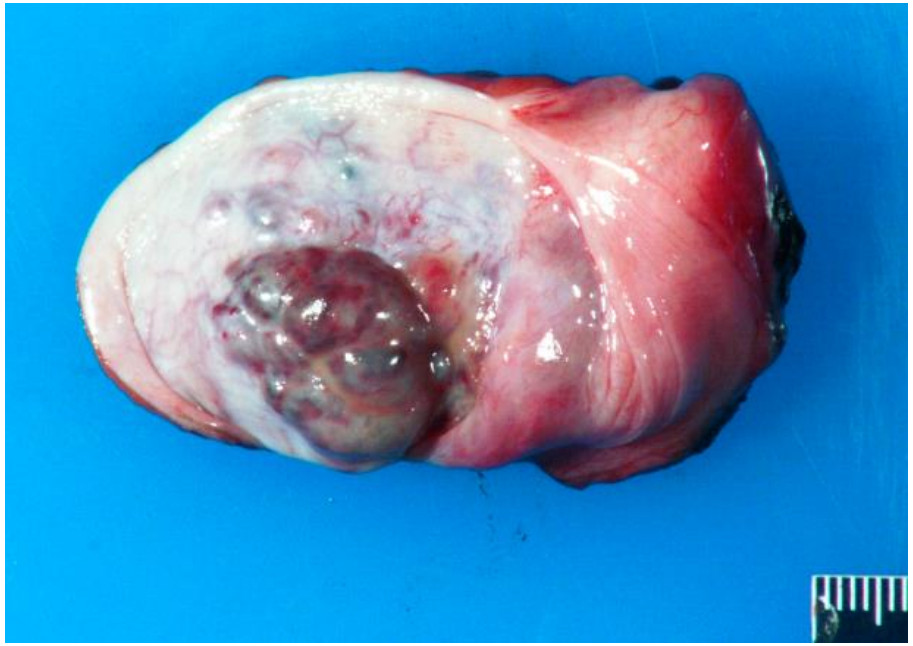

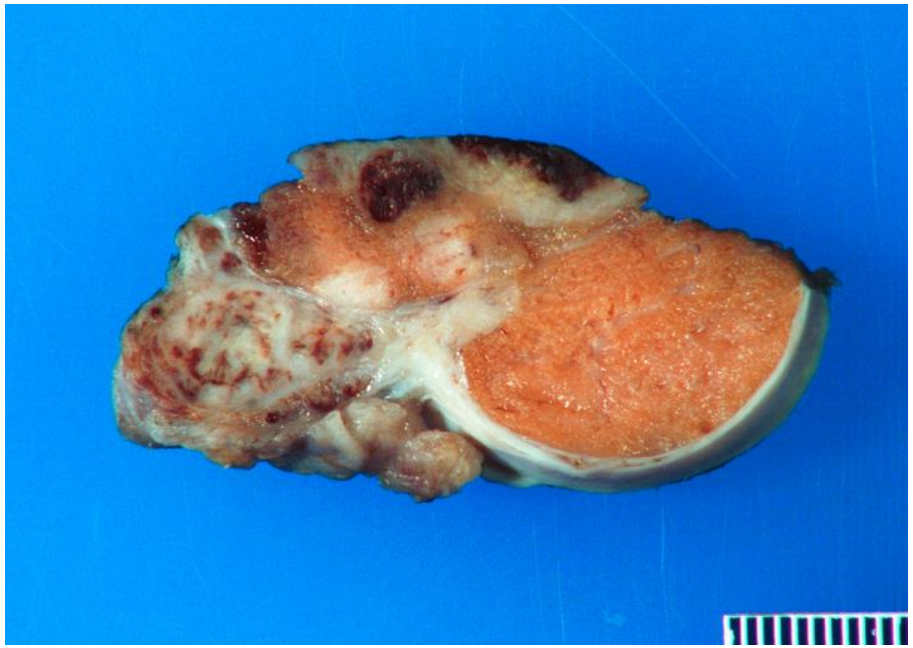

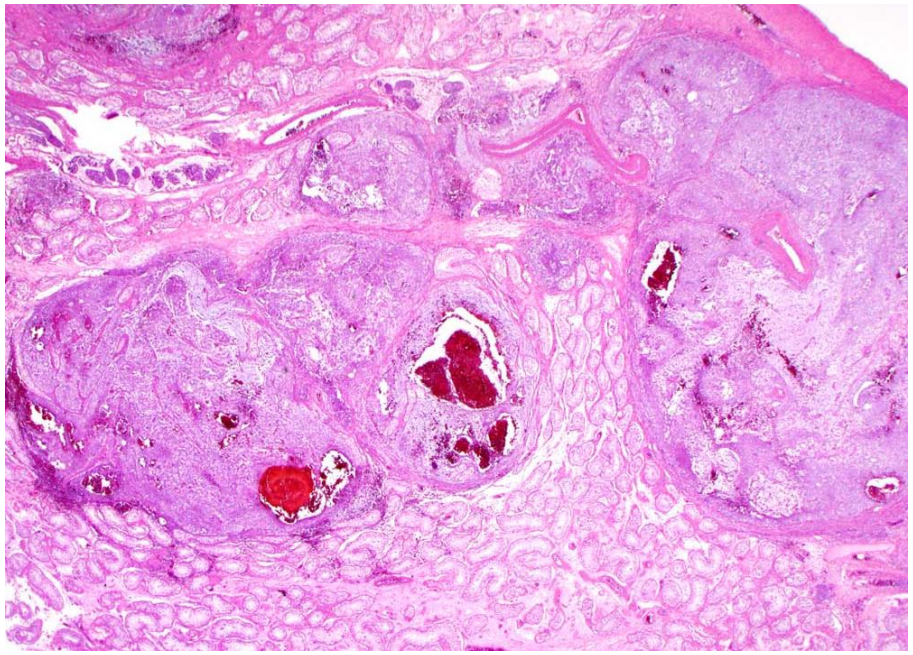

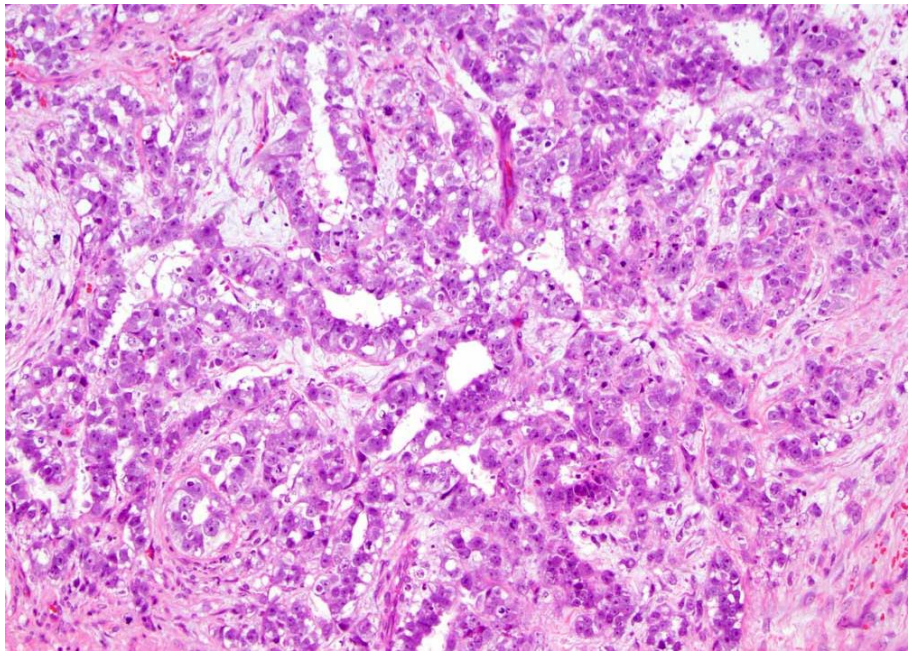

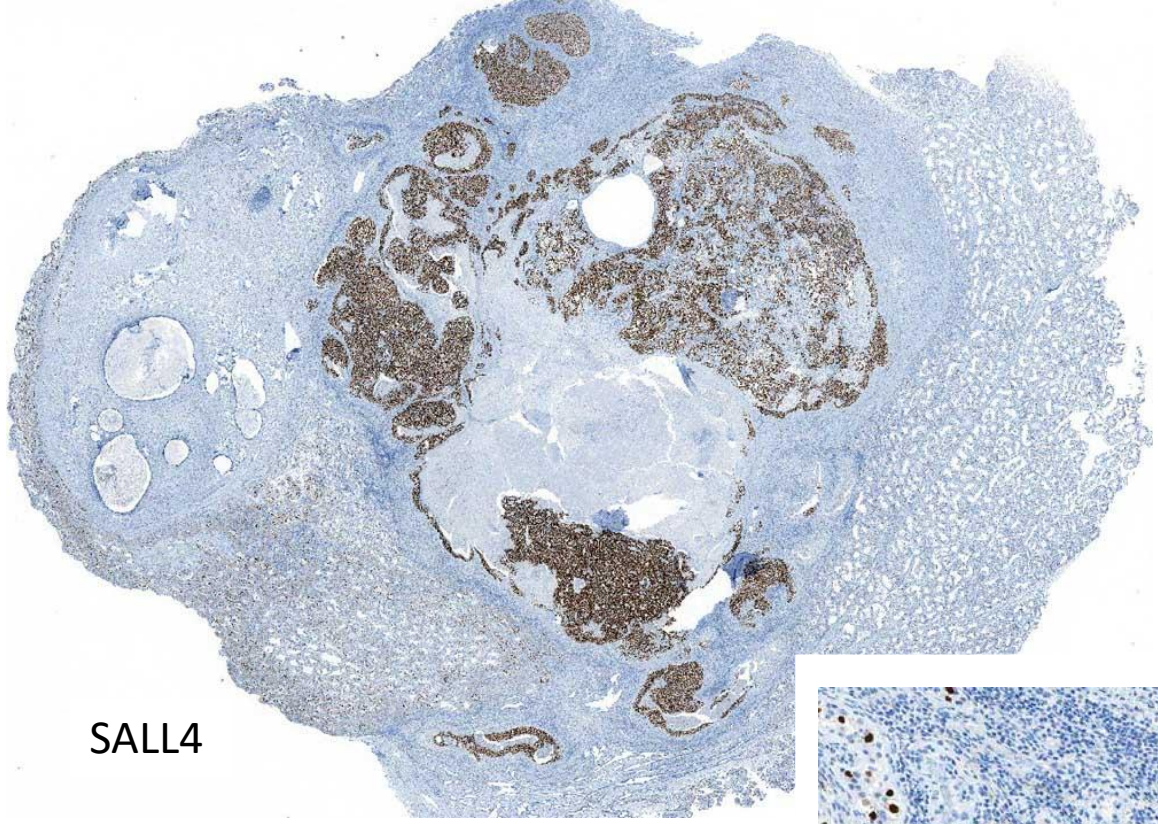

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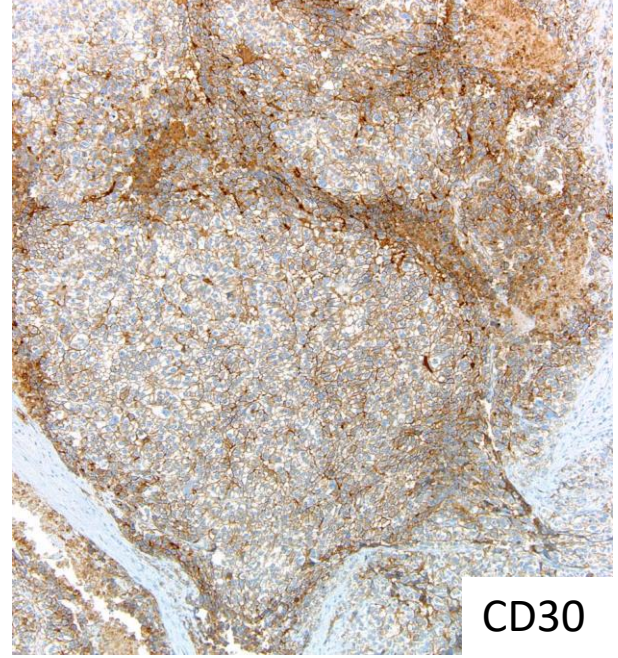

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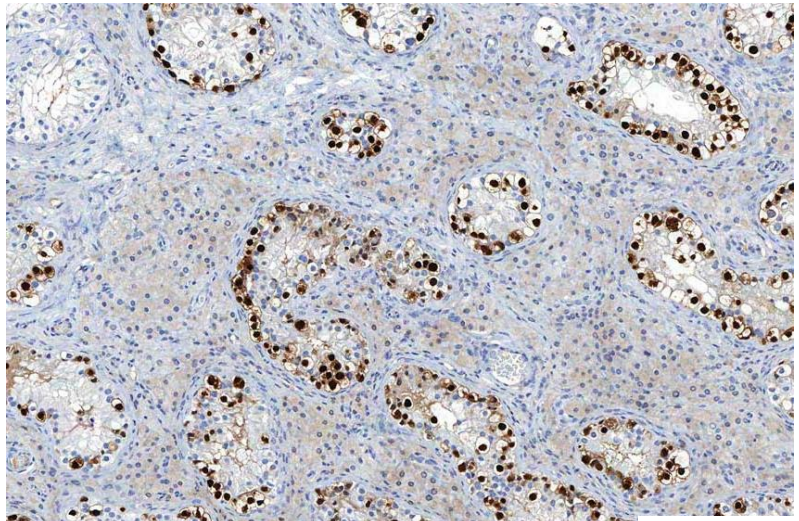

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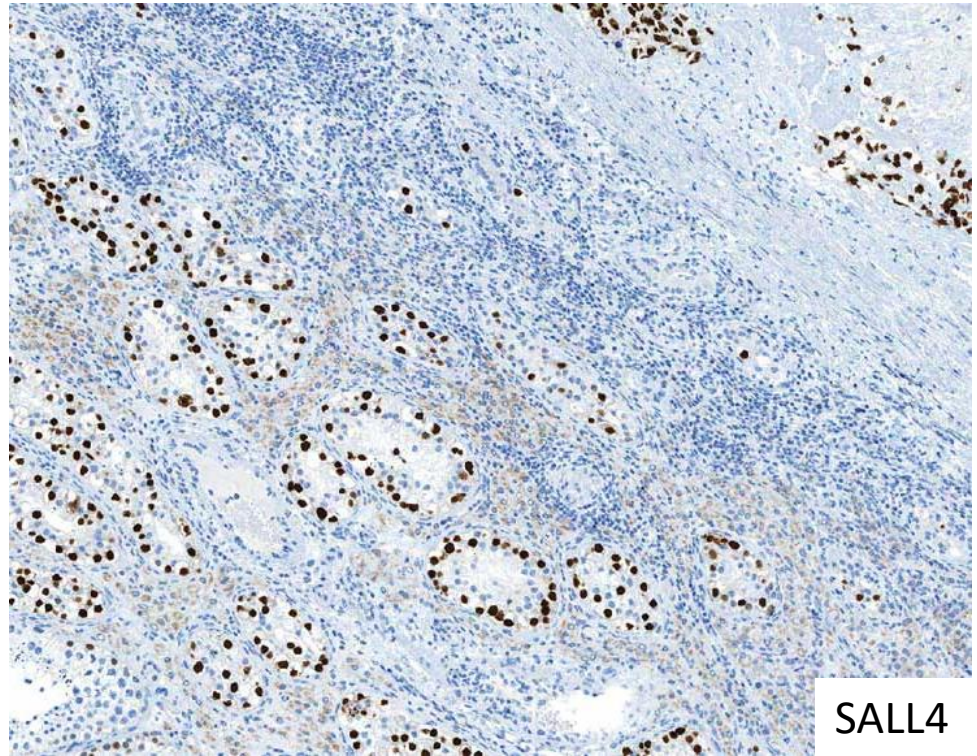

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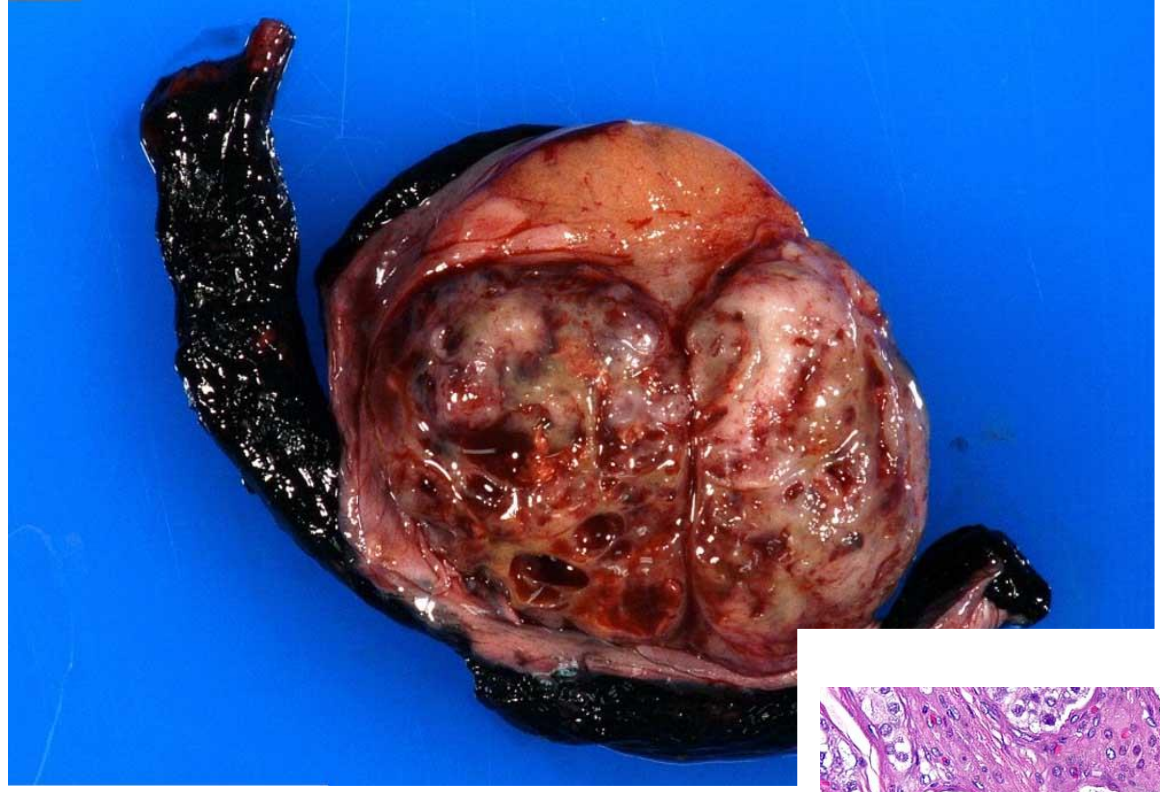

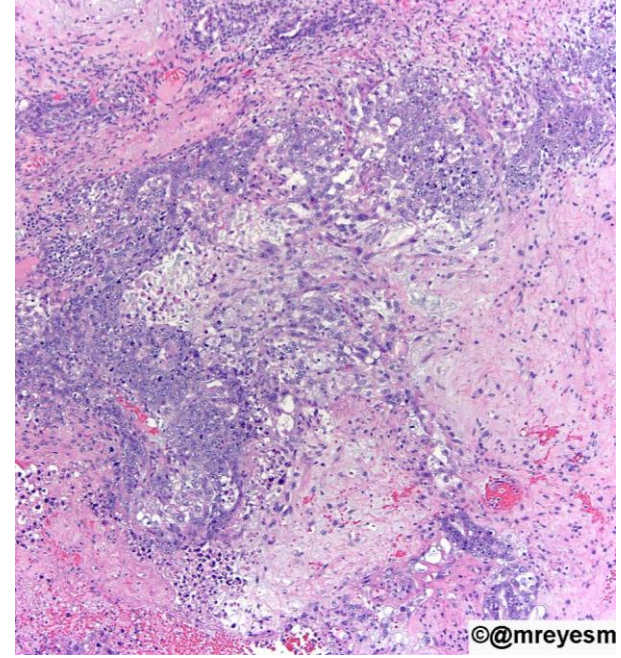
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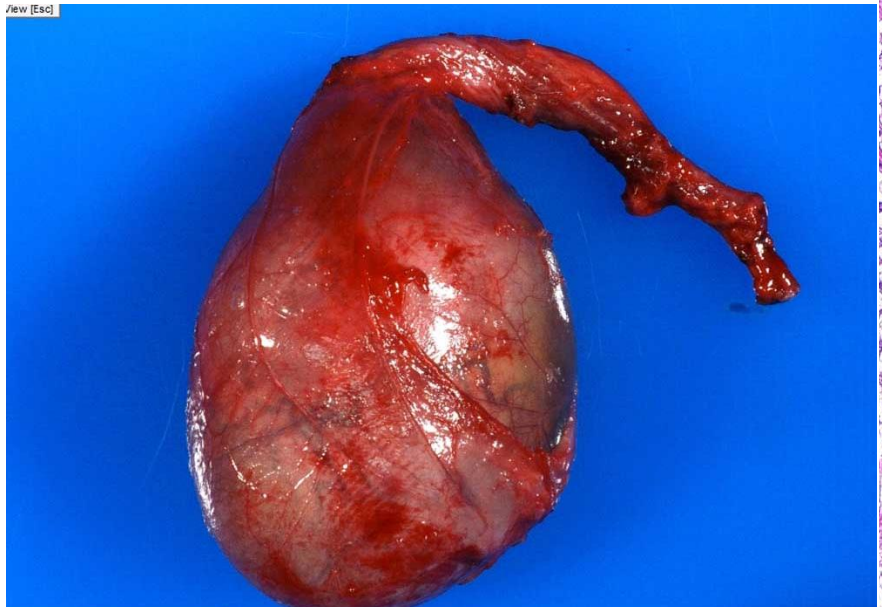
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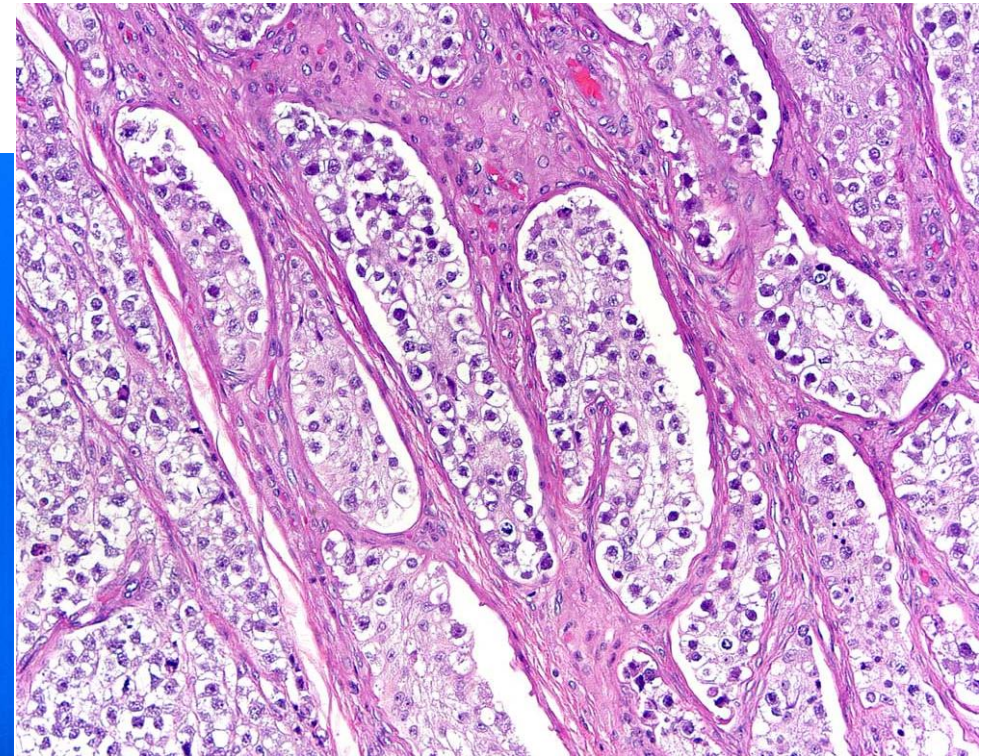

Other (Placenta and U.C.)GCTs

- Pediatric GCTs rarely may occur in the placenta and even the umbilical cord.
- Most frequent type is teratoma; Dx. Diff. with “amorphous fetus” (FIF?) by the presence in the latter of an umbilical cord and skeletal organization.
- Other forms of non-trophoblastic primary placental neoplasia include YST.
- Chorangioma and foci of hepatocellular (hepatocellular adenoma) or adrenal parenchyma, challenging differential diagnosis.

Serum Markers in Pediatric GCTs

- AFP : generally elevated in patients with YST.
- Low levels of AFP (<100 mg/l) can be seen in immature teratomas (occult YST foci).
- AFP is also normally synthesized by fetal liver, yolk sac and gastrointestinal tract.
- Interpretation of AFP levels during the neonatal period must incorporate knowledge of age-related norms.
- AFP is elevated in all infants at birth.
- It drops to normal levels over the first 2 years of life, as its synthesis in the liver ceases. The half-life of AFP varies with age during the first months of life, and stabilizes at 5-7 days by 9 months.
- HCG is a peptide hormone produced in pregnancy, which is made by the embryo soon after conception and later by the placental syncytiotrophoblast.
- The beta subunit of hCG serves as a marker of syncytiotrophoblasts (usually choriocarcinoma). Its half-life is 16 hours.

Molecular Genetics of Pediatric GCTs

- Genomic alterations are different from those seen in post-pubertal tumors.
- Prepubertal pure teratomas almost always show normal genomic profiles.
- YSTs tumors show abnormal profiles, including gains of chromosomes 1q, 3p and 20q, and loss of chromosomes 1p, 6q and 18q.
- Adolescent and adult GCTs tend to be aneuploid.
- Most consistent chromosomal aberration in adolescent/adult malignant GCTs is overrepresentation of chromosome 12p (80%).
- Abnormalities of chromosomes 7 and 8 have also been found in up to 70% of adolescent and adult testicular GCTs.

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