OPHTHALMOLOGY GRAND ROUNDS

Jordan Spindle MD

November 15th, 2012

Patient

HPI: 5 year old male brought to ER with right painless periocular swelling x 10 weeks. Mother states that the child had an unwitnessed fall at home and developed swelling around the right eye at that time. He was then brought to ER, diagnosed with a hematoma, no imaging was done. 1 month later he went to private pediatrician with continued swelling and was told that it would slowly resolve. After symptoms progressed she brought him back to ER 1 month later….

History

- POH: none
- Gtts: none
- PMH: none
- Birth History: none
- Meds: none
- All: nkda
- FH: no glaucoma/blindness

EXAM

- dVa sc: 20/20, 20/20
- Pupils: 3→2 ou, no apd
- EOMs: 10% supraduction OD, all other full
- CVFs: full ou
- Ttono: 20/18

PLE

- LLA: RUL fullness
- C/S: white and quiet ou
- K: clear ou
- A/C: formed and symm ou
- P/I: round and reactive ou
- L: clear ou

DFE

- V: clear ou
- C/D: 0.3/0.3, s and p ou
- M: flat ou, +flr ou
- V: wnl ou
- P: no holes/tears/heme seen ou

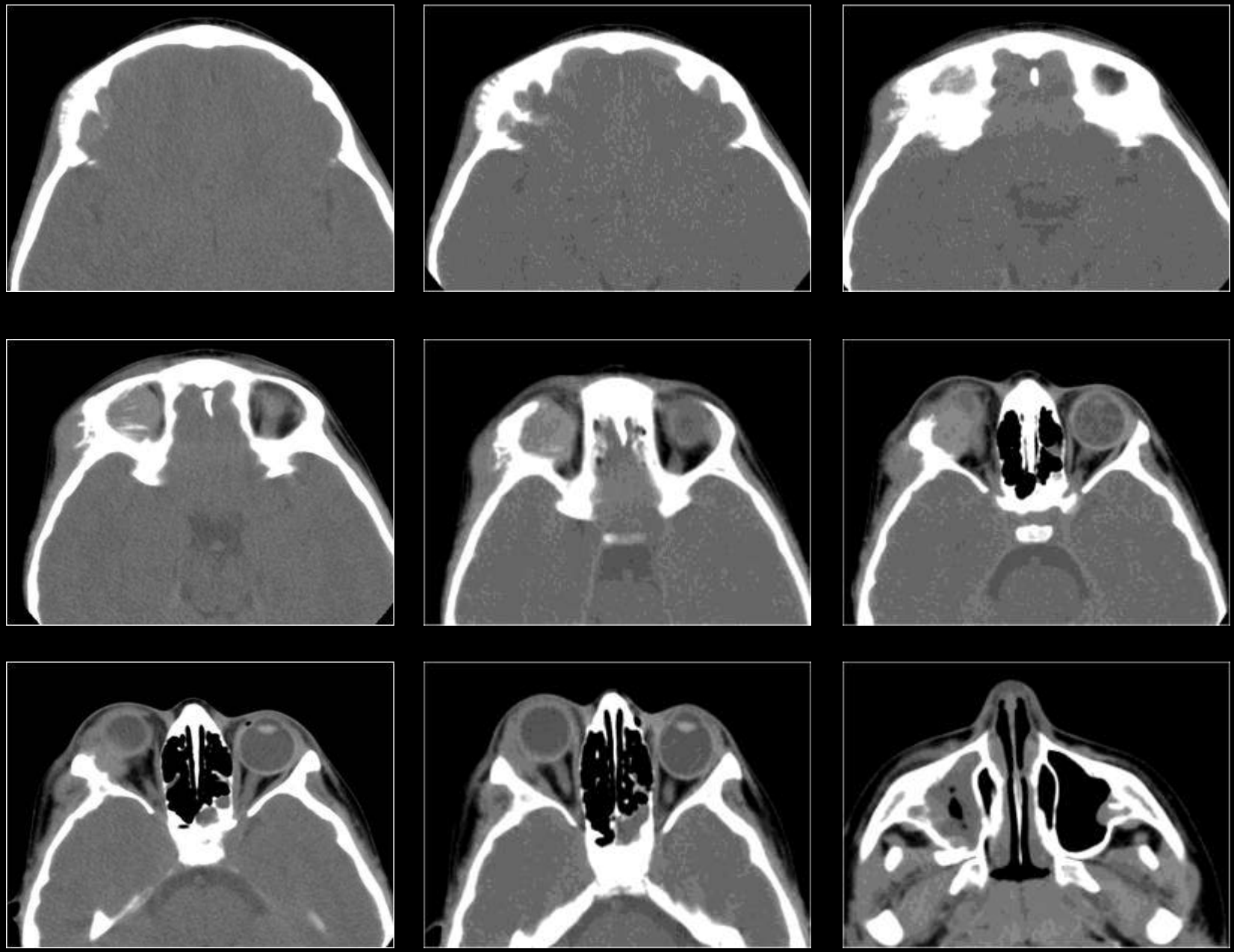
Differential Diagnosis

Differential Diagnosis

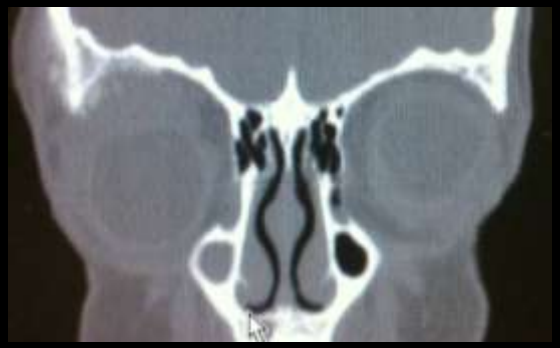
- Rhabdomyosarcoma
- Neuroblastoma
- Histiocytosis X
- Trauma
- Infectious (preseptal vs. septal)
- Orbital Varix
- Capillary hemangioma
- Ruptured dermoid cyst
- Lymphangioma
- Other mesenchymal tumor (Osteosarcoma, Ewing's sarcoma, etc).

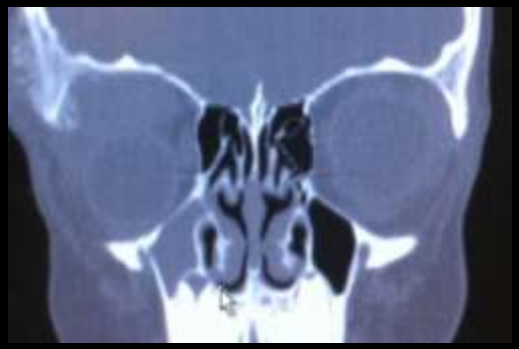
What would you do next?

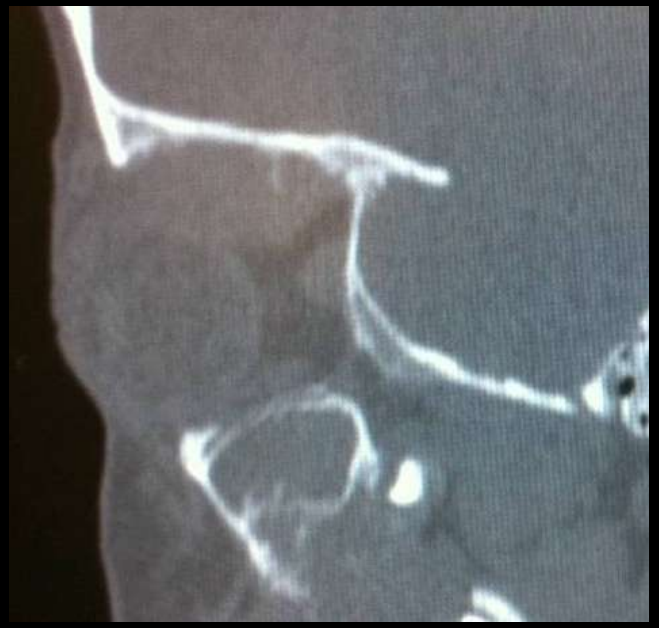
CT

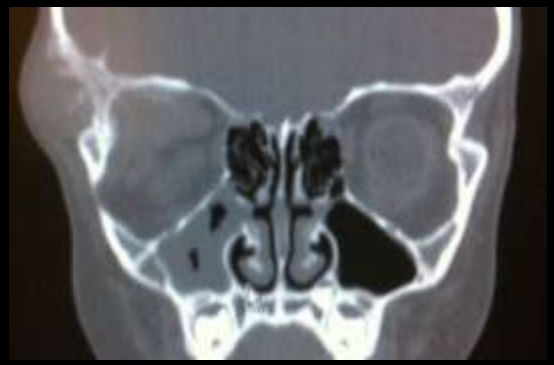


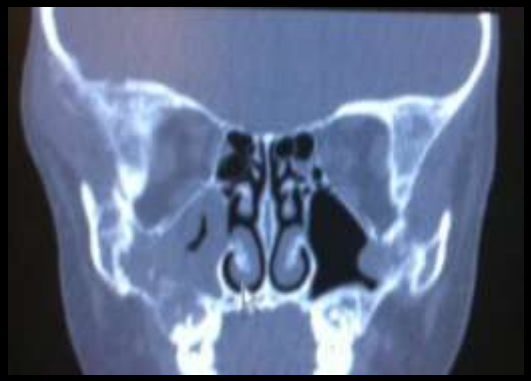
CT

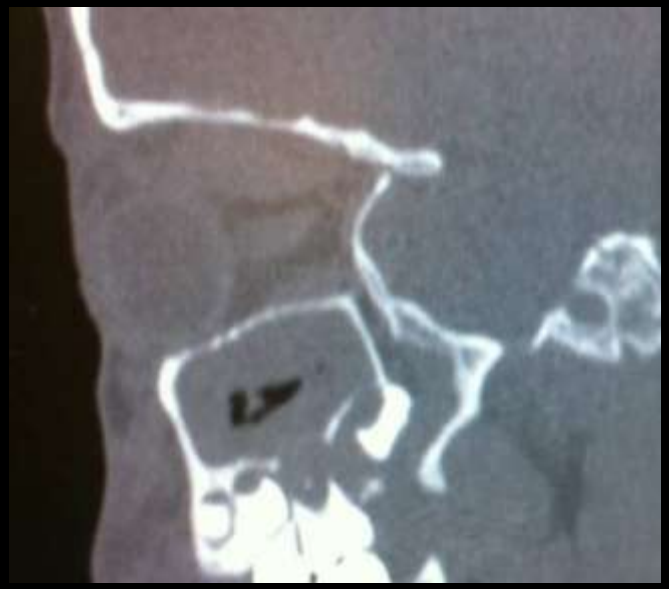












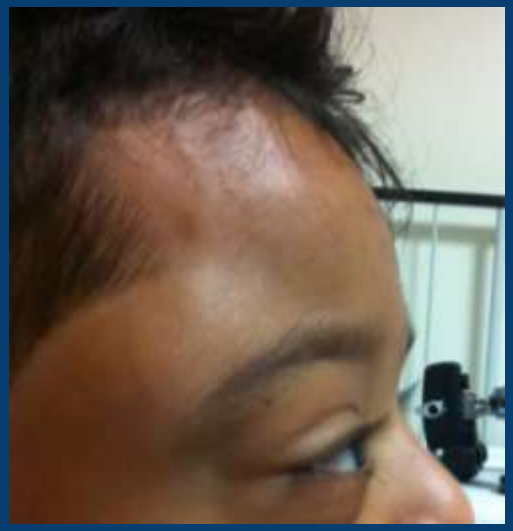
CT

- Inferonasal globe dystopia with homogenous fairly poorly circumscribed, space occupying lesion in the superotemporal orbit. Subcutaneous homogenous lesion lateral to the lateral orbital wall with lytic bony change.

Next Step

Patient Care, Medical Knowledge

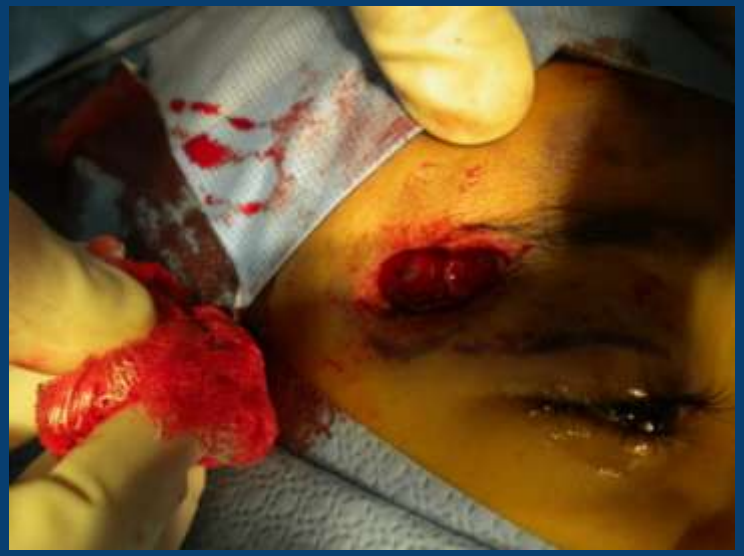

EXIT
To the OR!!



Patient Care, Interpersonal Skills and Communication Skills

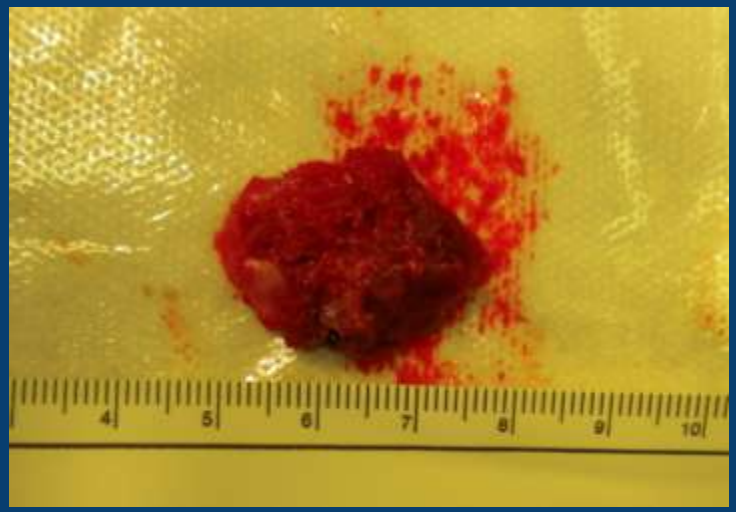
Pre Op Labs

Hgb: 10
Platelets: 100k
WBC: 5



Surgical Findings:

- vascular tumor, gross bony lytic change of lateral orbital wall



Frozen Section – inconclusive

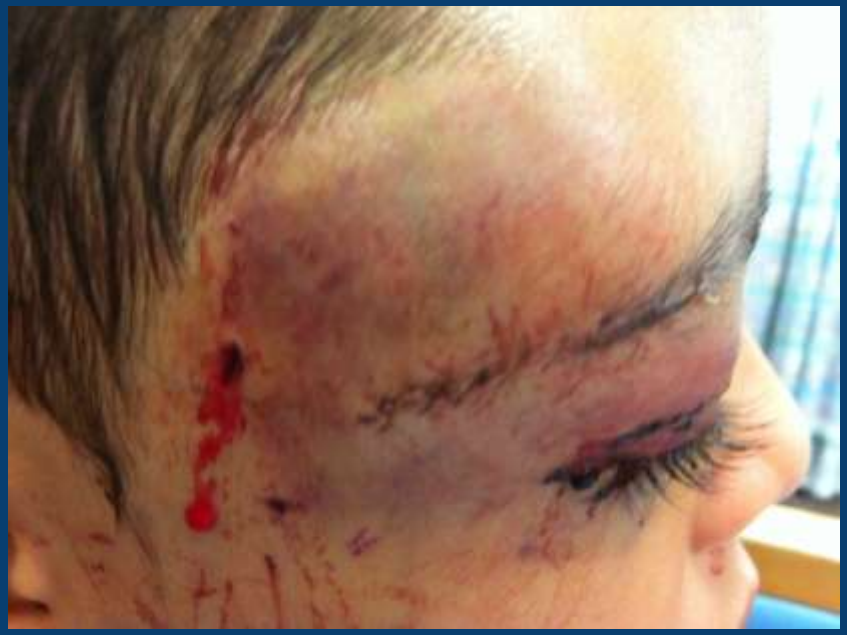
Extended lid crease incision was done and orbital biopsy was taken.

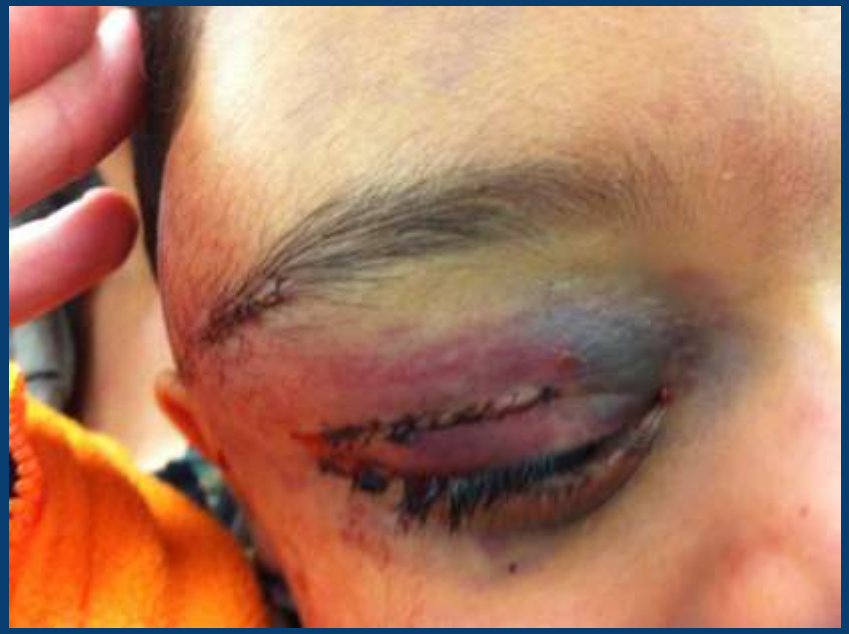
Frozen Section – inconclusive, but favoring Rhabdomyosarcoma

Intralesional steroid injection was given in case diagnosis was Histiocytosis X

The patient had excessive bleeding during the operation. Two drains were placed (one in orbit, one at brow incision site) and removed POD#2. Patient was admitted to PICU following surgery.

Pre Op Labs	Post Op Labs	Transfusion
Hgb: 10	Hgb: 4	2 units RBC's
Platelets: 100k	Platelets: 20k	1 unit of platelets
WBC: 5		

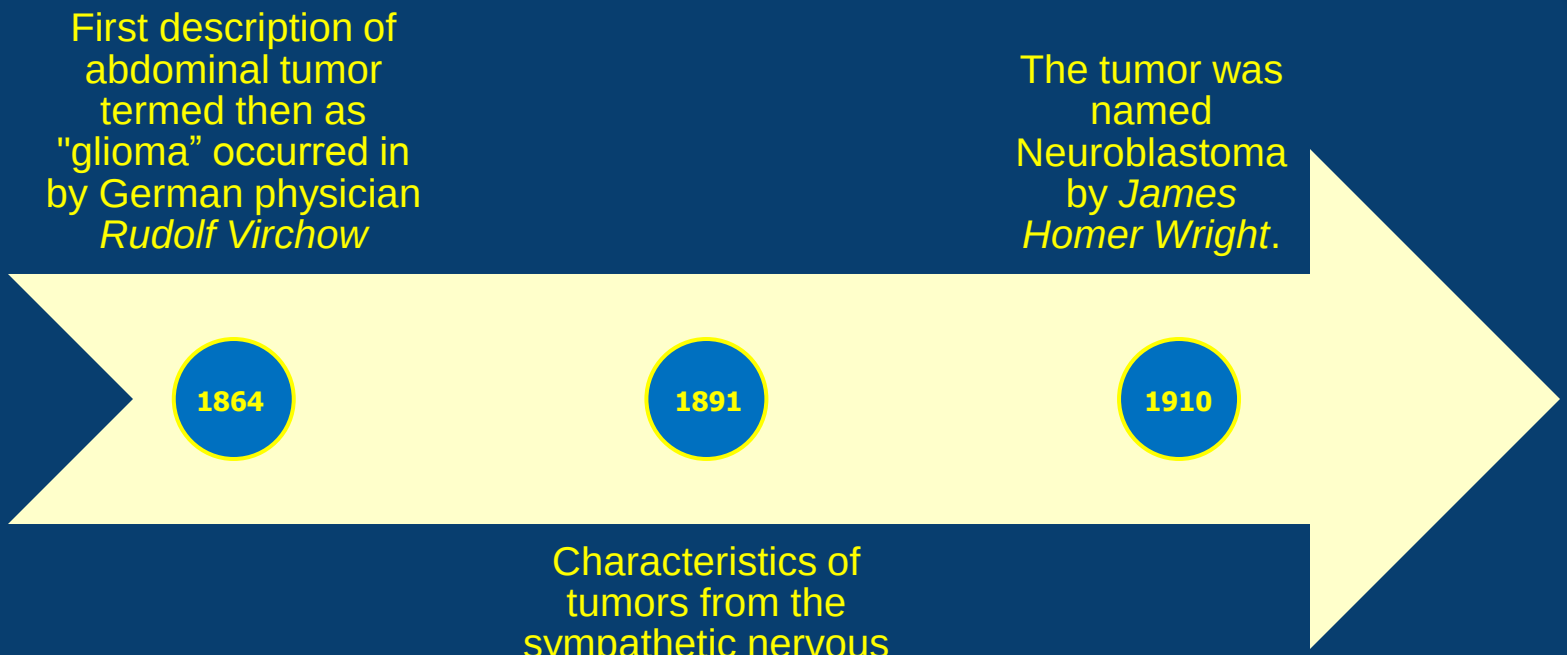




Pathology Results shortly after arriving at Memorial Sloan-Kettering:

Metastatic Neuroblastoma

Neuroblastoma



Neuroblastoma

"Metastatic Neuroblastoma typically produces an abrupt ecchymotic proptosis that may be bilateral. A deposition of blood in the eyelids may lead to the mistaken impression of injury"

"Commonly bone destruction is apparent, particularly in the lateral orbital wall or sphenoid marrow."

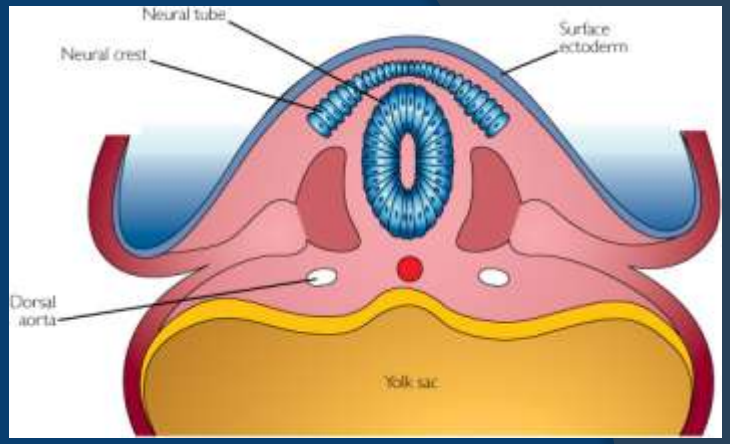
HAVE TO CONSIDER IN ANY PEDIATRIC PATIENT WITH ACUTE ORBITAL SIGNS

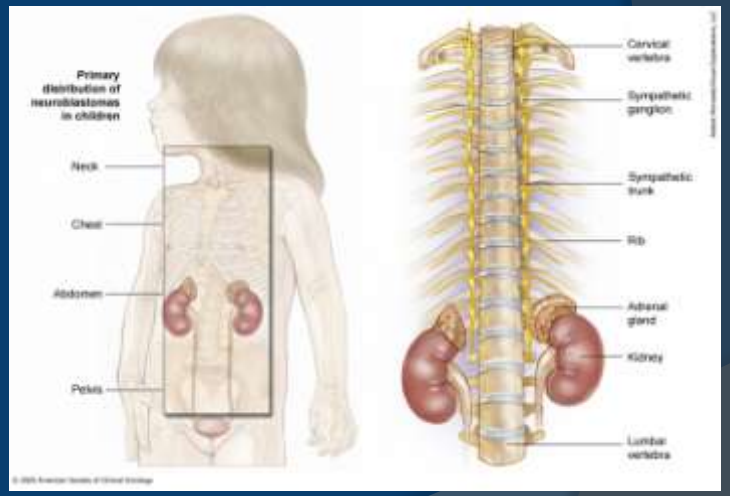
Ophthalmic Findings

Proptosis
Periorbital ecchymosis
Ptosis
Horner's syndrome
Anisocoria
Opsclonus/Myoclonus
Papilledema
Retinal striae
Other cranial nerve paralysis
Blindness

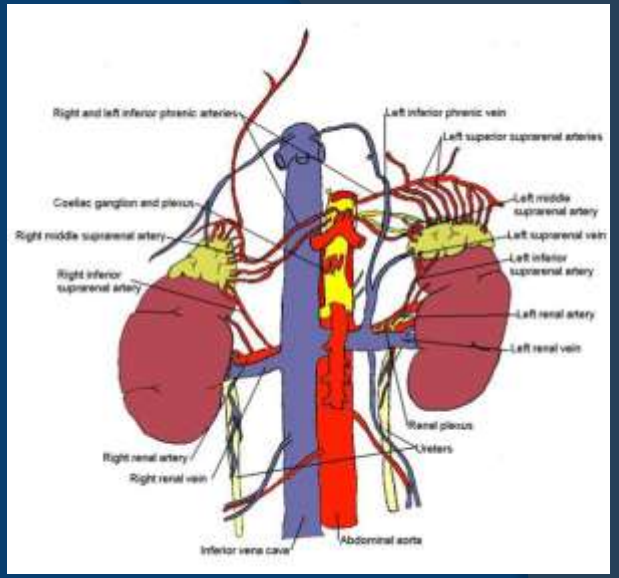
Neuroblastoma

- Embryonal tumor arising during fetal or early postnatal life from sympathetic cells derived from the neural crest.
- It is the most common solid extracranial malignancy of childhood and the most common malignant tumor in infants.
- The overall incidence of neuroblastoma is 1 case per 100,000 children in the United States, or approximately 700 newly diagnosed patients per year.





Neuroblastoma



- The median age at diagnosis is about 16 months
- 95% of cases are diagnosed by 7 years of age
- The most common sites of origin of neuroblastic tumors are the adrenal region (48%), extraadrenal retroperitoneum (25%), and chest (16%). Less common sites are the neck (3%) and the pelvis (3%) and from ciliary ganglion
- Forty-eight percent of patients have metastatic disease at diagnosis

Neuroblastoma

- Some tumors disappear spontaneously without any therapy, while others progress with a fatal outcome despite the implementation of maximal modern therapy.

- However, strong prognostic factors can accurately predict whether children have "good" or "bad" disease at diagnosis, and the clinical stage is currently the most significant and clinically relevant prognostic factor.

Table 1

Descriptions of Original INSS Tumor Stages

Tumor Stage	Description
1	Localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor microscopically. Nodes attached to and removed with the primary tumor may be positive.
2A	Localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically
2B	Localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor; enlarged contralateral lymph nodes negative microscopically
3	Unresectable unilateral tumor infiltrating across the midline (beyond the opposite side of the vertebral column) with or without regional lymph node involvement, or midline tumor with bilateral extension via infiltration (unresectable) or lymph node involvement
4	Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs (except as defined for stage 4S disease)
4S	Localized primary tumor (as defined for stage 1, 2A, or 2B disease) with dissemination limited to skin, liver, and/or bone marrow (limited to infants younger than 1 year, marrow involvement of less 10% of total nucleated cells, and MIBG scan findings negative in the marrow)

Source.—Reference 6.

International Neuroblastoma Staging System (INSS)

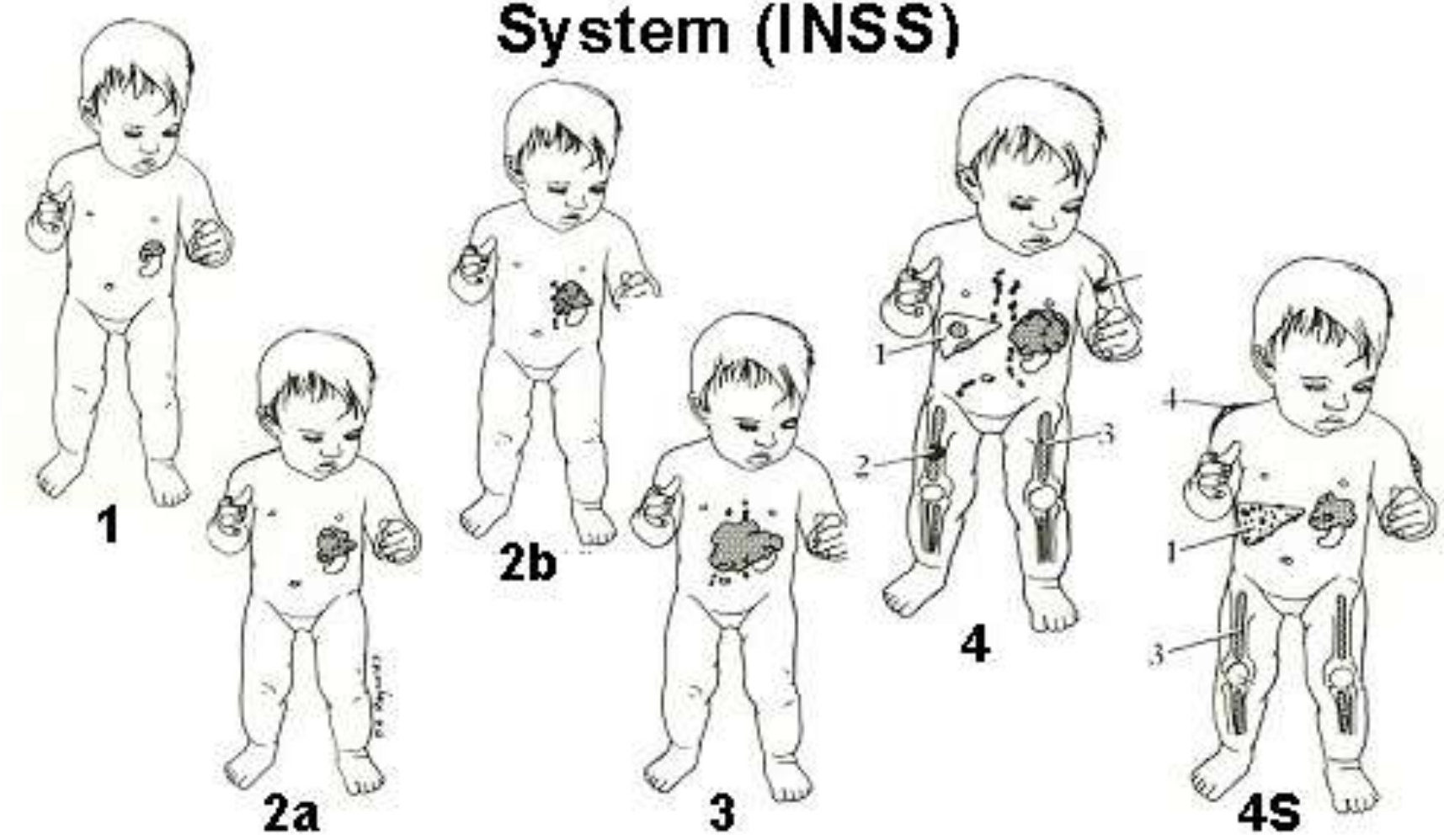


Table 3 Children's Oncology Group risk stratification for children with neuroblastoma

Risk stratification	INSS stage	Age	Biology
Low			
Group 1			
	1	Any	Any
	2A/2B (>50% resected)	Any	*MYCN*-NA, any histology/ploidy
	4S	<365 days	*MYCN*-NA, FH, DI>1
		Intermediate	
Group 2			
	2A/2B (<50% resected or Bx only)	0-12 years	*MYCN*-NA, any histology/ploidy*
	3	<365 days	*MYCN*-NA, FH, DI>1*
	3	>365 days - 12 years	*MYCN*-NA, FH*
	4S (symptomatic)	<365 days	*MYCN*-NA, FH, DI>1*
Group 3			
	3	<365 days	*MYCN*-NA, either UH or DI=1*
	4	<365 days	*MYCN*-NA, FH, DI>1*
	4S	<365 days	*MYCN*-NA, either UH or DI=1*; or unknown biology
Group 4			
	4	<365 days	*MYCN*-NA, either DI=1 or UH
	3	365 -<547 days	*MYCN*-NA, UH, any ploidy
	4	365 -<547 days	*MYCN*-NA, FH, DI>1
High			
	2A/2B, 3, 4, 4S	Any	*MYCN*-amplified, any histology/ploidy
	3	> 547 days	*MYCN*-NA, UH, any ploidy
	4	365 - >547 days	*MYCN*-NA, UH or DI=1
	4	> 547 days	Any

DI, DNA index; FH, favorable histology; MYCN-NA, *MYCN* not amplified; UH, unfavorable histology.
*If tumor contains chromosomal 1p LOH or unb11qLOH, or if data are missing, treatment assignment is upgraded to next group.

Table 2

Descriptions of New INRG Tumor Stages

Tumor Stage	Description
L1	Localized tumor not involving vital structures, as defined by the list of IDRFs, and confined to one body compartment
L2	Local-regional tumor with presence of one or more IDRFs
M	Distant metastatic disease (except stage MS tumor)
MS	Metastatic disease in children younger than 18 months, with metastases confined to skin, liver, and/or bone marrow

Source.—Reference 8. Complete definitions of these stages are cited in the text. IDRFs = image-defined risk factors.


Table 2

Descriptions of IDRFs

Anatomic Region	Description
Multiple body compartments	Ipsilateral tumor extension within two body compartments (ie, neck and chest, chest and abdomen, or abdomen and pelvis)
Neck	Tumor encasing carotid artery, vertebral artery, and/or internal jugular vein Tumor extending to skull base Tumor compressing trachea
Cervicothoracic junction	Tumor encasing brachial plexus roots Tumor encasing subclavian vessels, vertebral artery, and/or carotid artery Tumor compressing trachea
Thorax	Tumor encasing aorta and/or major branches Tumor compressing trachea and/or principal bronchi Lower mediastinal tumor infiltrating costovertebral junction between T9 and T12 vertebral levels
Thoracoabdominal junction	Tumor encasing aorta and/or vena cava
Abdomen and pelvis	Tumor infiltrating porta hepatis and/or hepatoduodenal ligament Tumor encasing branches of superior mesenteric artery at mesenteric root Tumor encasing origin of celiac axis and/or origin of superior mesenteric artery Tumor invading one or both renal pedicles Tumor encasing aorta and/or vena cava Tumor encasing iliac vessels Pelvic tumor crossing sciatic notch
Intraspinal tumor extension	Intraspinal tumor extension (whatever the location) provided that more than one-third of spinal canal in axial plane is invaded, the perimedullary leptomeningeal spaces are not visible, or the spinal cord signal intensity is abnormal
Infiltration of adjacent organs and structures	Pericardium, diaphragm, kidney, liver, duodenopancreatic block, and mesentery

Source.—Reference 8. Conditions that should be recorded but are not considered IDRFs are multifocal primary tumors, pleural effusion with or without malignant cells, and ascites with or without malignant cells.

Table 4 International Neuroblastoma Risk Group pretreatment classification

INRG Stage	Age, months	Histologic category	Grade of tumor differentiation	*MYCN*	11q Aberration	Ploidy	Pretreatment risk group
L1/ L2		GN maturing; GNB intermixed					A Very low
L1		Any, except		NA			B Very low
L1		GN maturing or GNB intermixed		Amp			K High
L2	<18	Any, except			No		D Low
		GN maturing or GNB intermixed		NA	Yes		G Intermediate
	≥18	GNB nodular; neuroblastoma	Differentiating	NA	No	E Low	
					Yes		
			Poorly differentiated or undifferentiated	NA			H Intermediate
				Amp			N High
M	<18			NA		Hyperdiploid	F Low
	<12			NA		Diploid	I Intermediate
	12 to <18			NA		Diploid	J Intermediate
	<18			Amp			O High
	≥18						P High
MS	<18			NA	No	C Very low	
					Yes		Q High
							R High

Adapted from Cohn et al.[40]
GN, ganglioneuroma; GNB, ganglioneuroblastoma.
Please define GNB + GN in the abbreviations footnote.

Prognosis

- Age at diagnosis
- Location of Tumor
- Microscopy
- Stage

Prognosis

- *Tumor Grade* – estimation of proliferative activity
- *DNA ploidy* – Hyperploidy is found in earlier stages of the disease and have better prognosis than diploid.
- *Cytogenetics* - N-MYC oncogene (amplification) tend to grow more quickly and are associated with a worse prognosis than children without the amplification.
- *Oncogene amplification* – ferritin, NSE, LDH

5 year Survival Rates

- Low Risk Disease: 95%
- Intermediate Risk Disease: 80-90%
- High Risk Disease: 10-40%

Role of the Ophthalmologist

1) Diagnosis and Staging by virtue of distant spread

2) Monitoring and Managing visual involvement
   - Decompression, strabismus, etc.

3) Monitoring response to both medical and surgical interventions
   - Stability of proptosis, vision, EOMS, fundus

4) Long term supportive treatment

Incidence, Ocular Manifestations, and Survival in Children with Neuroblastoma: A Population-Based Study

STEPHEN J. SMITH, NANCY N. DIEHL, BRIAN D. SMITH, AND BRIAN G. MOHNEY

- PURPOSE: To determine the incidence, ophthalmic manifestations, and survival among children with neuroblastoma in a defined population.
- DESIGN: Population-based retrospective cohort.
- METHODS: The medical records of all pediatric (<19 years) residents of Olmsted County, Minnesota, diagnosed with neuroblastoma from January 1, 1969, through December 31, 2008, were retrospectively reviewed.

TABLE. Historical and Clinical Characteristics of 14 Patients <19 Years Diagnosed With Neuroblastoma in Olmsted County, Minnesota, 1969–2008

Case No. (Year at Diagnosis)	Age at Diagnosis (Months)	Gender	Presenting Symptoms	Primary Site	Ophthalmic Site/Manifestations	Ophthalmic Complications	Treatment	F/U Duration (Months)	Final Outcome	Stage
1 (1969)	42.6	F	Bilateral periorbital ecchymosis	R adrenal	Bilateral orbits/painful proptosis	Scleral hemorrhage	Chemotherapy	5.2	Pt deceased	IV
2 (1970)	21.5	M	Decreased appetite, listless, afebrile, hematuria	L adrenal	Right orbit/ptosis, right subconjunctival hemorrhage secondary to right temporal mass	Sluggish pupillary response	Radiation and chemotherapy	3.1	Pt deceased	IV
3 (1971)	16.5	F	Fever, rhinorrhea, cough, swollen L inguinal nodes	L adrenal	None	N/A	Resection, L adrenal and L inguinal nodes	309.6	Remission	IV
4 (1971)	4.6	F	Fever, vomiting, palpated RUQ mass	R adrenal	None	N/A	Resection, R adrenal mass and L supraclavicular mass	454.6	Remission	IVS
5 (1976)	29.7	F	Listless, purpura, thrombocytopenia, anemia	L adrenal	Bilateral orbits/right proptosis, with ecchymosis and ptosis. Bilateral temporal tumor nodules.	Difficulty depressing and abducting the right eye	Resection of L adrenal, L metastatic lymph nodes, L nephrectomy. Radiation and chemotherapy.	3.9	Pt deceased	IV
6 (1977)	34.8	F	Irritability, dehydration, fever, lethargy	L adrenal	Bilateral orbits/left proptosis with inward and medial displacement of the left globe. Bilateral metastasis.	Left esotropia with III, IV, and VI nerve palsies	Resection of L adrenal, L kidney, and L peri-aortic lymph nodes. Radiation and chemotherapy.	8.7	Pt deceased	IV
7 (1981)	24.5	M	Fatigue, fever, poor appetite, swollen L testicle	L adrenal	Left orbit/left proptosis and ecchymosis	N/A	Radiation and chemotherapy	3.5	Pt deceased	IV
8 (1987)	29.5	M	Bilateral periorbital ecchymosis, tender abdomen, ataxic gait	R abdomen	Bilateral orbits/bilateral periorbital ecchymosis. Left eye swelling with hemorrhage.	N/A	Resection of R abdominal mass and peri-aortic lymph nodes	9.1	Pt deceased	IV
9 (1988)	37.9	M	Hydronephrosis, noted abdominal mass	R abdomen	None	N/A	Resection of abdominal mass. Chemotherapy.	245.4	Remission	III
10 (1990)	36.2	F	Decreased appetite, irritability, palpable LUQ mass	Abdomen	None	N/A	Chemotherapy	17.5	Pt deceased	IV
11 (1993)	31.3	F	Ataxia, irritability, fever, urinary incontinence	R adrenal	None	N/A	Resection of R adrenal tumor. Chemotherapy.	142.1	Remission	III

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Incidence, Ocular Manifestations, and Survival in Children with Neuroblastoma: A Population-Based Study

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RESULTS:

- 14 patients
- Average age at diagnosis: 22.5 months (0.4-42.6)

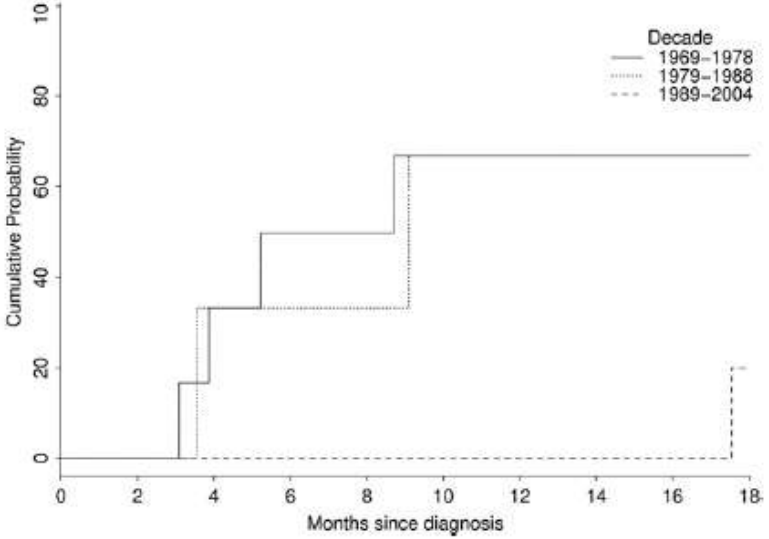

FIGURE 2. Kaplan-Meier cumulative probability of death by decade of diagnosis in pediatric patients diagnosed with neuroblastoma in Olmsted County, Minnesota, 1969–2008.

Ophthalmic Involvement:

-6 patients (43%)
* 4 bilateral, 2 unilateral
- Proptosis and Ecchymosis: 67%
- 9 month survival for those with orbital involvement was 17%

Patient update…

Currently being treated at Memorial Sloan-Kettering Cancer Center. Initial Systemic Workup revealed diffuse mets in bone marrow, multiple calvarial and skull base osseous metastases, as well as to right orbit. Primary was found thoracic paraspinal region.

He has been through a lot….

1. Bone Marrow Biopsy
2. Placement of Leukophoresis catheter
3. 3 cycles of chemotherapy
4. Posterior Thoracotomy with excision of neuroblastoma from the superior posterior mediastinum
5. Chest tube placement
6. Insertion of double lumen right sided mediport
7. 4 cycles of chemotherapy with Cyclophosphamide/Doxorubicin/Vincristine

Reflective Practice

This case demonstrated the importance of a differential diagnosis when common entities are encountered. Expedited diagnosis and treatment is also important to patient and family when dealing with the unknown.

Core Compentencies

- Patient Care: The case involved thorough patient care and attention to patient's complaints. Once diagnosed, the patient received proper management and care
- Medical Knowledge This presentation allowed us to review the presentations, proper evaluation/work up, and different treatments.
- Practice-Based Learning and Improvement: This presentation included a current literature search of developing associations and current treatment modalities
- Interpersonal and Communication Skills: The patient was treated with respect and every effort was made to communicate with the patient in a timely manner for the proper follow-up
- Professionalism: The patient was treated in the proper manner. He was also referred to the proper specialist to treat her condition.
- Systems-Based Practice: The patient was discussed in detail with pediatric oncology colleagues in regard to follow up and treatment.

References

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- Sushmita Nitin Bhatnagar & Yogesh Kumar Sarin. Neuroblastoma: A Review of Management and Outcome. Indian J Pediatr (June 2012) 79(6):787–792
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- Basic Science and Clinical Series: Orbit, Eyelids, and Lacrimal System: pages: 79-80

5 year old male with 2 month history of left periorbital edema misdiagnosed as a hematoma by emergency department and pediatrician. Urgent biopsy diagnosed as Rhabdomyosarcoma by first pathologist. Second opinion revealed final diagnosis of metastatic neuroblastoma subsequently found to be thoracic paraspinal primary. Patient is status post thoracotomy and currently undergoing chemotherapy.