Neonatal cystic lung disease; How far should we proceed ?

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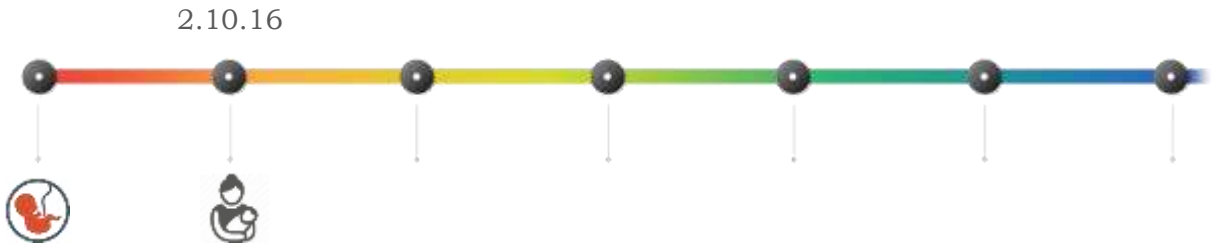
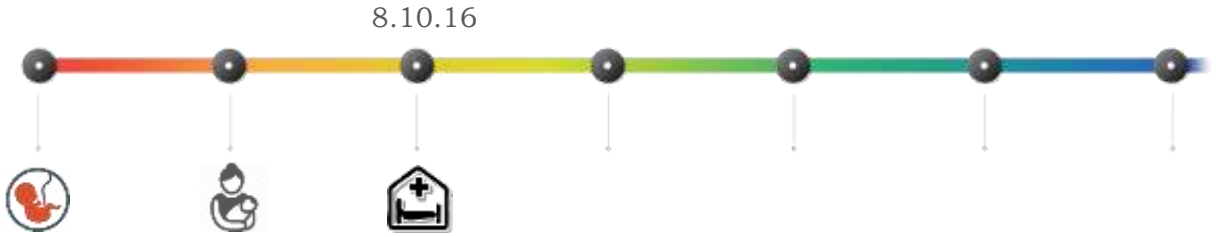
Case presentation

- Non consanguineous Christians parents
- Pregnancy
  - Abnormal Nuchal Translucency test → Amniocentesis → Chromosome 8 anomaly (father & N.) (Del. KB127 at 8P21.3)
  - Normal prenatal US
- Female, term 37 weeks, weight 3.690 Kg
- Clavicular Fracture- Bilateral

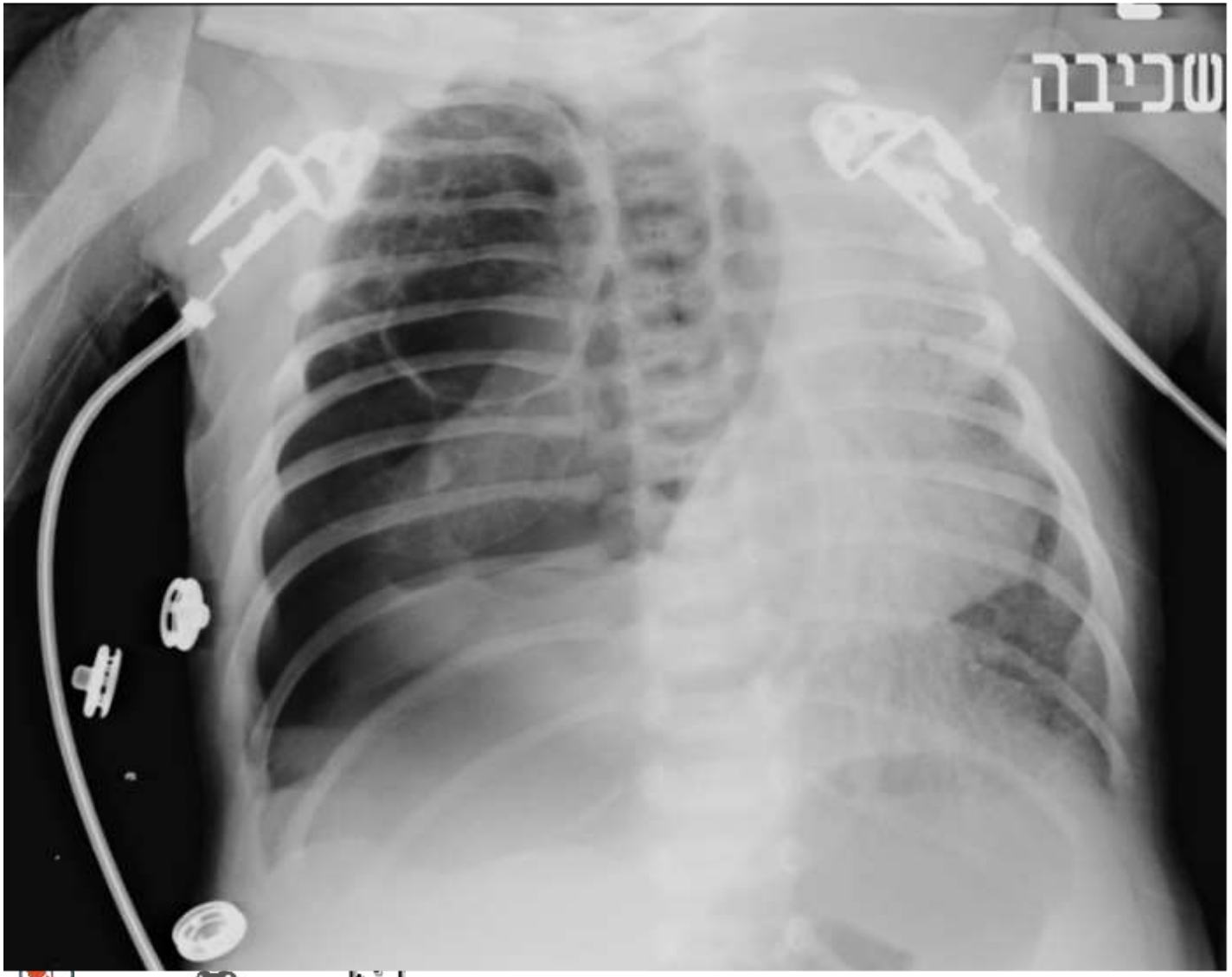


At the age of 6 days

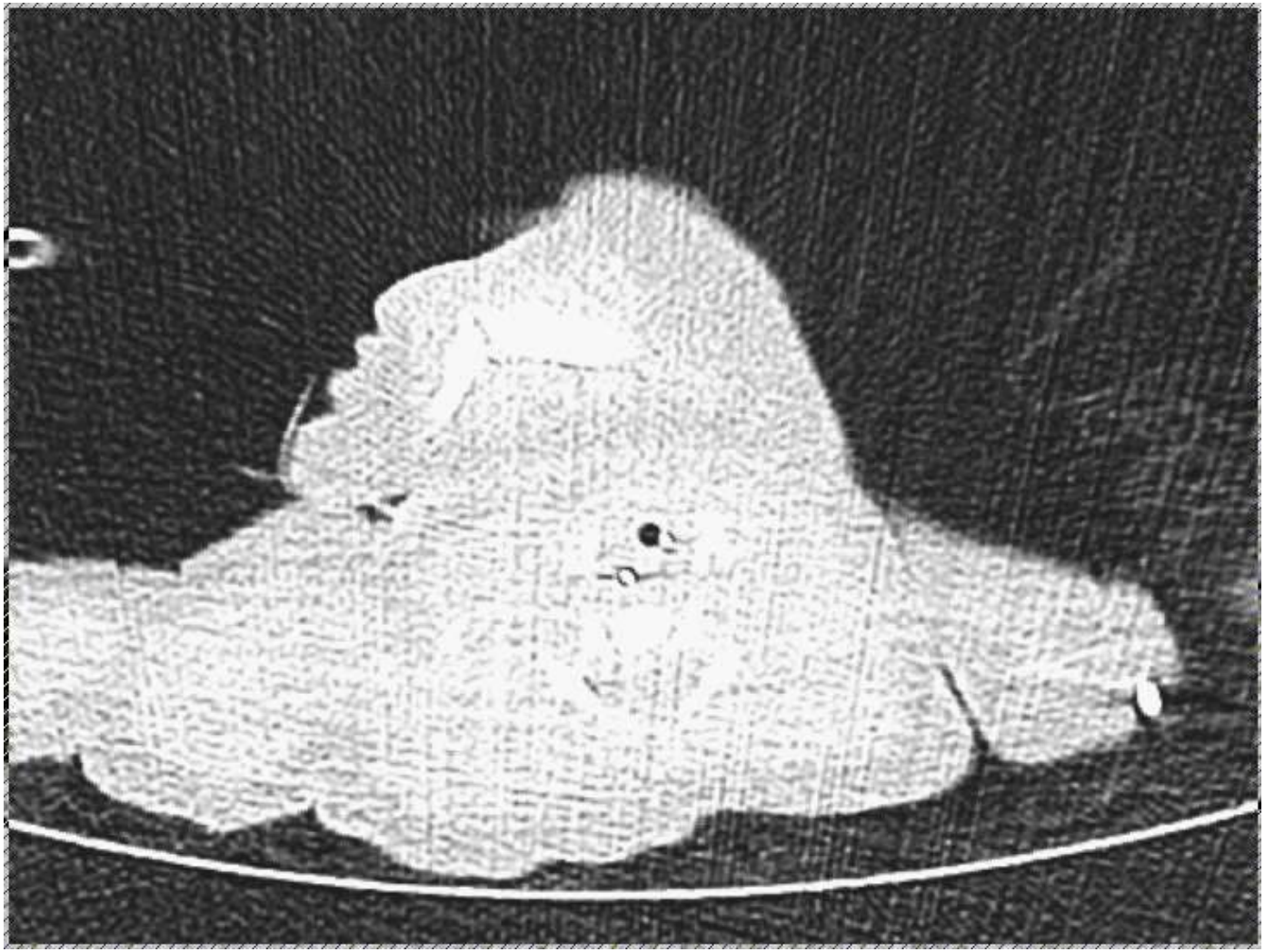
- Tachypnea, cyanosis, no fever
- ER – Dyspnea, O_2 Sat - 88%
- Diminished breathing sound – Right thorax



At the age of 6 days

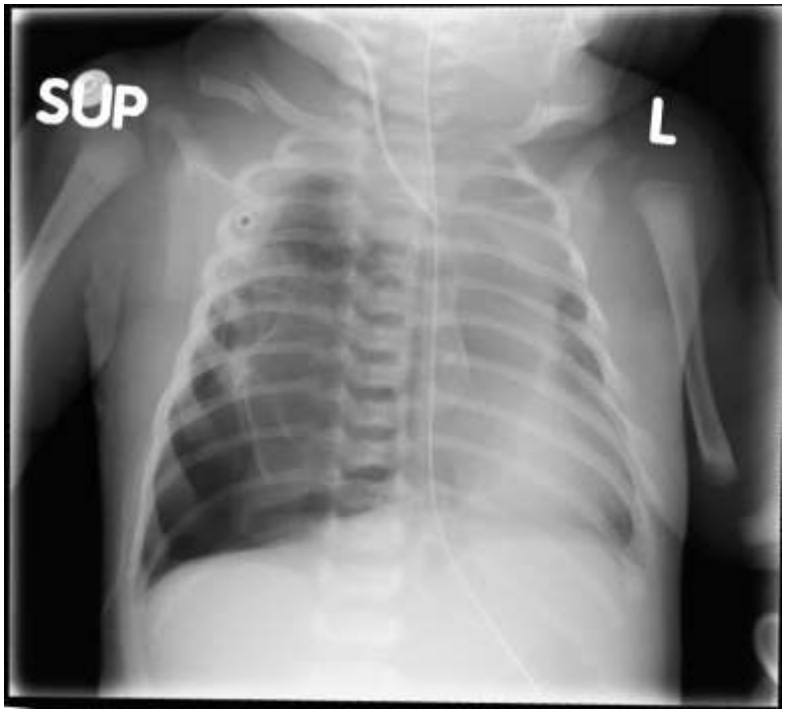


CT scan



Transferred to our PICU

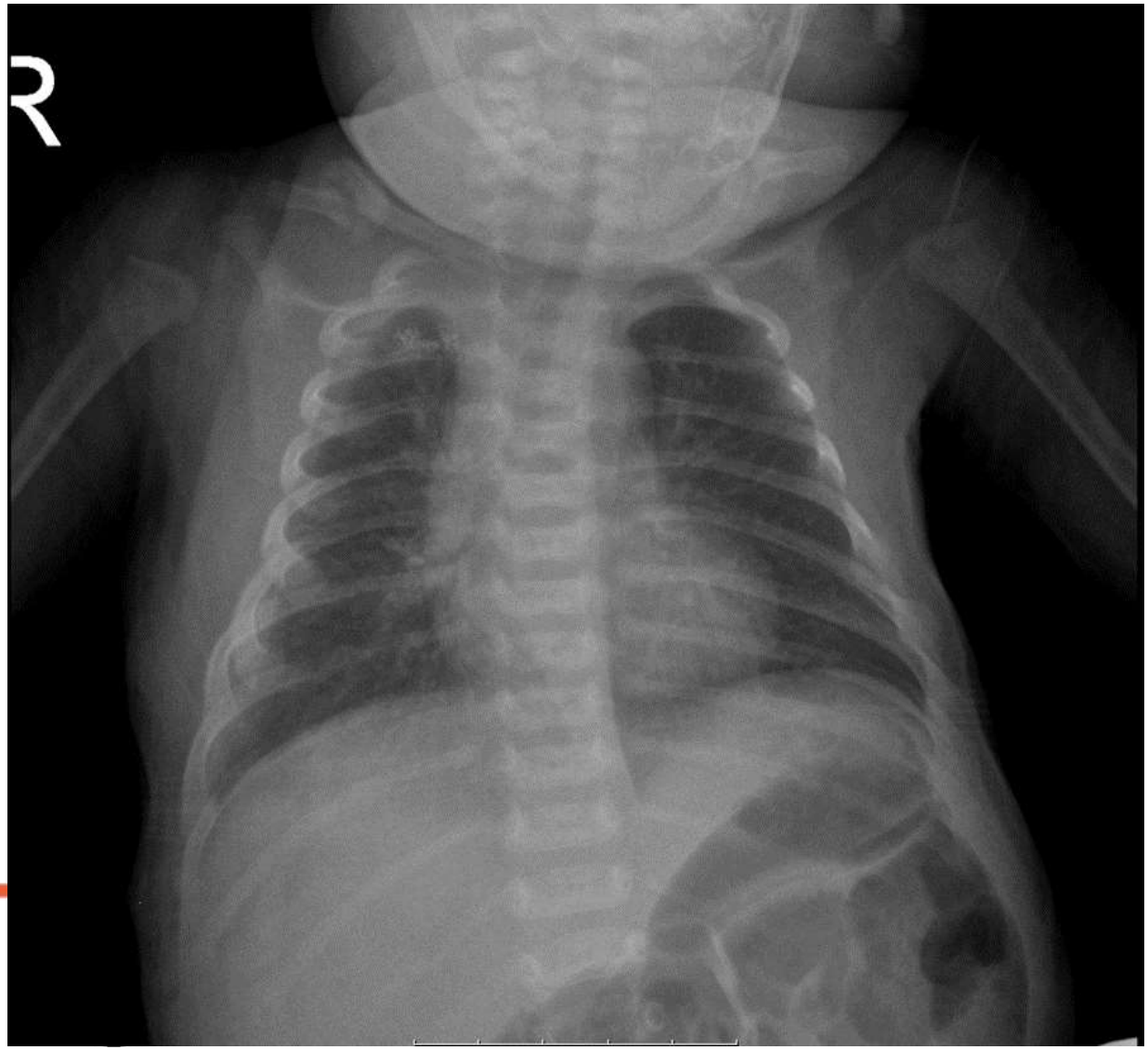
- Recurrent pneumothoraces (3)
- Recurrent drainage
- Mechanical ventilation



Decision – lobectomy

- Large Bulla from the anterior segment of RUL
- **Anterior Segmental resection of RUL**
- Discharged at age of 23 days

Decision – lobectomy



Follow up

- Monthly follow up
  - Excellent well being
  - Good weight gain
  - No respiratory symptoms
- Pathology:
  - Neonatal CPAM Type IV (Rambam & Hadassah)
- How should we proceed?
  - Lobectomy?
  - Follow up?

Concerns

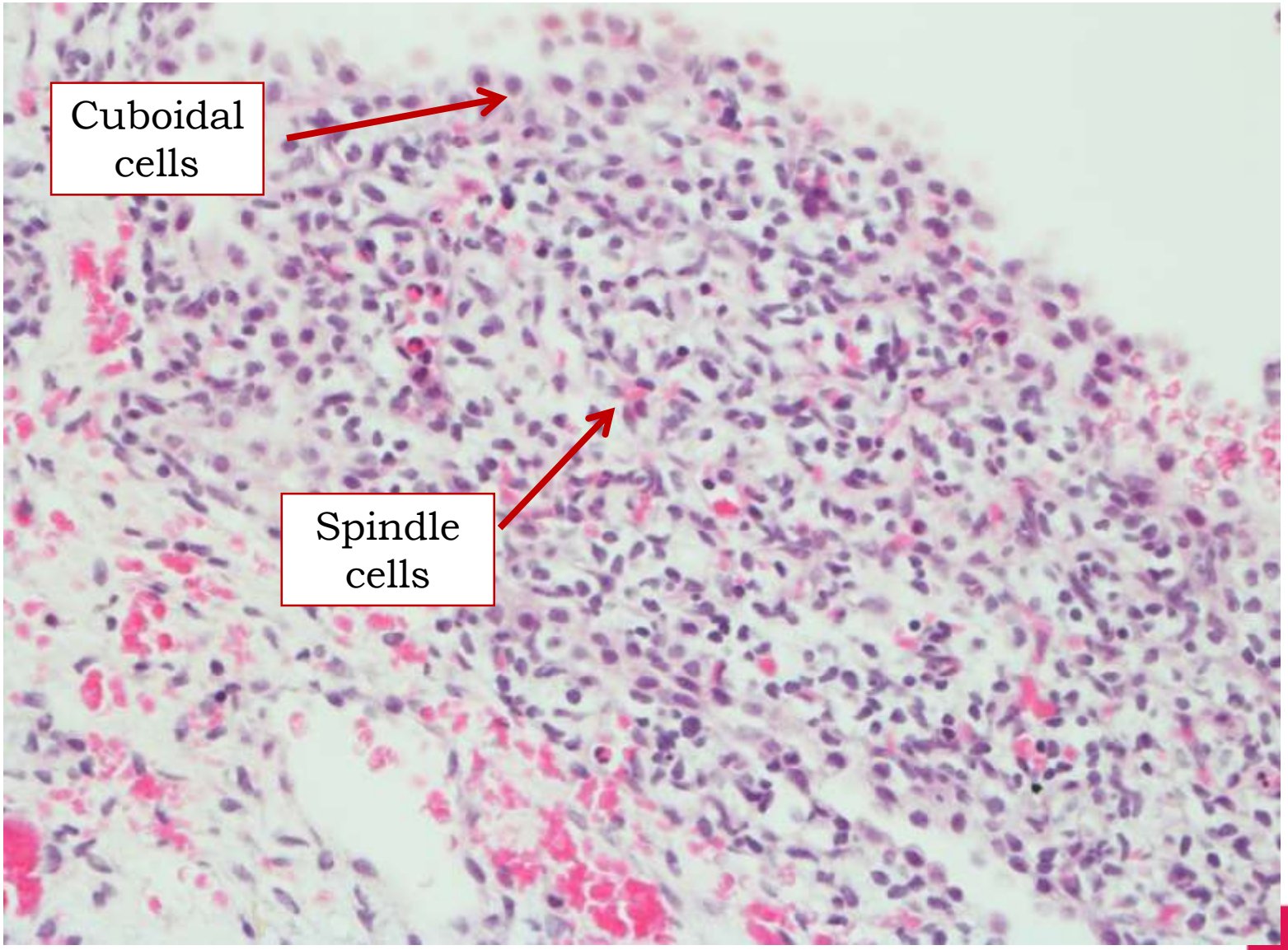
- No prenatal diagnosis
- Early pneumothorax
- CPAM Type IV

- Consultation:
- The International Pleuropulmonary Blastoma registry (Dr. Kris Ann P. Schultz)

→ **Pleuropulmonary Blastoma Type 1**

The International Pleuropulmonary Blastoma Registry

Pathology



CPAM - Congenital Pulmonary Airway Malformation

- Developmental malformation
- Most common congenital lung lesion
- Incidence –1 per 8300 to 35,000 live births
- Increase in the prenatal diagnosis of CPAM d/t widespread use of antenatal US

- Classified according to the location of the developmental site of malformation
- Type 0 – Acinar Dysplasia
- Type 1 – most common – Bronchial/Bronchiolar
- Type 2 – Bronchiolar
- Type 3 – Alveolar
- Type 4 – Peripheral
  - Very rare
  - Peripheral, thin walled cysts, multiloculated

CPAM Type 4

- Etiology obscure
- Likely a spectrum of disease between CPAM 4 and Type 1 Pleuropulmonary Blastoma
- Difficult to differentiate pathologically between CPAM type 4 and Type 1 Pleuropulmonary Blastoma

Pleuropulmonary Blastoma

- Rare malignant tumor of intrathoracic mesenchyme of childhood (pulmonary, pleural, combined)
- Most common primary malignancy of lung in pediatric population
- Mostly in children < 6 years of age
- Probably pulmonary analog of common developmental neoplasms of childhood
  - Wilms tumor, Hepatoblastoma, Neuroblastoma

PPB

- Type I - cystic lesion
- Type II - cystic/solid mass
- Type III - solid high-grade sarcoma

Type	I	Ir	Total Cystic	II	II/II	III	Total II & III
n (%)	89 (25%)	26 (7%)	115 (33%)	124 (35%)	21 (6%)	90 (26%)	235 (67%)
Median Age (months)	8	47	12	35	36	41	37
5-year OS	89%	100%	91%	71%		53%	62%

- 350 cases (Messinger et al. Cancer, 2014)
- Currently 490 cases in the IPPB Registry

Malignancy	Associated cyst type	Number of cases in patients <20 years of age	Gross morphology	Age at diagnosis		Common presentations[1]
				Median	Range	
Type I PPB	Type I PPB (CPAM type 4)	~450	Cystic	9 mo	0–114 mo	Dyspnea, pneumothorax in 40%, or incidental discovery
Type II PPB			Cystic and solid	36 mo	6–236 mo[3]	Dyspnea, pneumothorax in 28%, "pneumonia," or incidental discovery
Type III PPB			Solid	43 mo	18–147 mo	Dyspnea, "pneumonia"

- Possibly stages of one malignant process on a biological continuum from cystic Type I PPB (early stage in tumorigenesis) to cystic/ solid Type II PPB, and then to solid Type III PPB

- Priest JR, Williams GM, Hill DA, et al. Pulmonary cysts in early childhood and the risk of malignancy. Pediatr Pulmonol 2009; 44:14.

Genetics of PPB

- 40% of children with PPB or their relatives may have other cysts or tumor growths:
  - benign cystic kidney tumors
  - Intestinal polyps
  - benign eye and nasal tumors
  - rhabdomyosarcoma
  - benign thyroid nodules or thyroid cancer
  - leukemia
  - gonadal tumors
    - ovarian Sertoli-Leydig cell tumors and dysgerminoma
    - testicular seminoma

- Priest JR, Williams GM, Hill DA, et al. Pulmonary cysts in early childhood and the risk of malignancy. Pediatr Pulmonol 2009; 44:14.

Role of *DICER1*

- Important gene in the biogenesis of microRNA
- Germline mutations in *DICER1* - associated with increased risk for a wide variety of neoplastic conditions
- Seen in nearly 70% of all children with PPB
- Diagnosing PPB should prompt germline *DICER1* mutations, a finding which has importance for individual and family screening

CPAM vs PPB

- Factors predictive of PPB:
  - Symptoms (pneumothorax)
  - Bilateral or multisegment involvement
  - Type 4 CPAM
  - *DICER1* germline mutation

Feinberg A, Hall NJ, Williams GM, et al. Can congenital pulmonary airway malformation be distinguished from Type I pleuropulmonary blastoma based on clinical and radiological features? J Pediatr Surg 2016; 51:33.

Priest JR, Williams GM, Hill DA, et al. Pulmonary cysts in early childhood and the risk of malignancy. Pediatr Pulmonol 2009; 44:14.

CPAM vs PPB

- Factors favoring a diagnosis of CPAM:
  - Prenatal detection
  - Presence of a systemic feeding vessel
  - Asymptomatic
  - Hyperinflated lung

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Back to our patient

- Respiratory distress , Pneumothorax 6 days old
- Surgery - Segmentectomy
- CPAM type IV → Pleuropulmonary Blastoma Type I

- Possible options:

    1. Observation only

    2. Surgery - Lobectomy

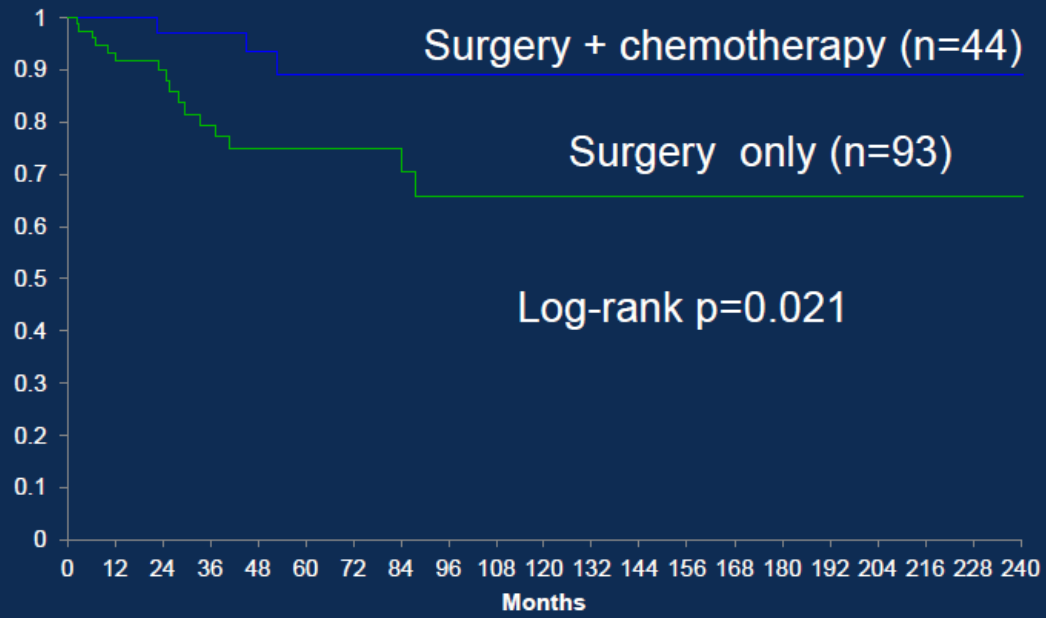
    3. Chemotherapy

1. Observation:
   - very good chance, but not guarantee that tumor would not progress
   - consequences may be significant
   - very careful follow- up q3 month CTs through highest time of risk

2. Surgery- Lobectomy
    - No clear margins
    - malignant cells spilled?
    - false sense of security?

3. Chemotherapy
    - Progression not inevitable
    - Good well being
    - Toxicity

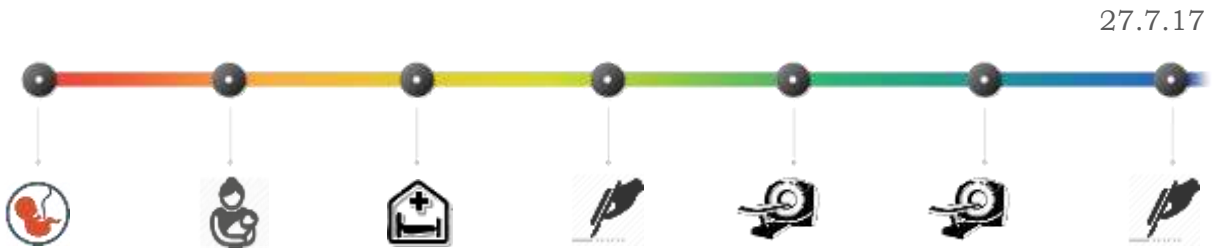
- Overall survival Type I - 95%, Ir - 100%

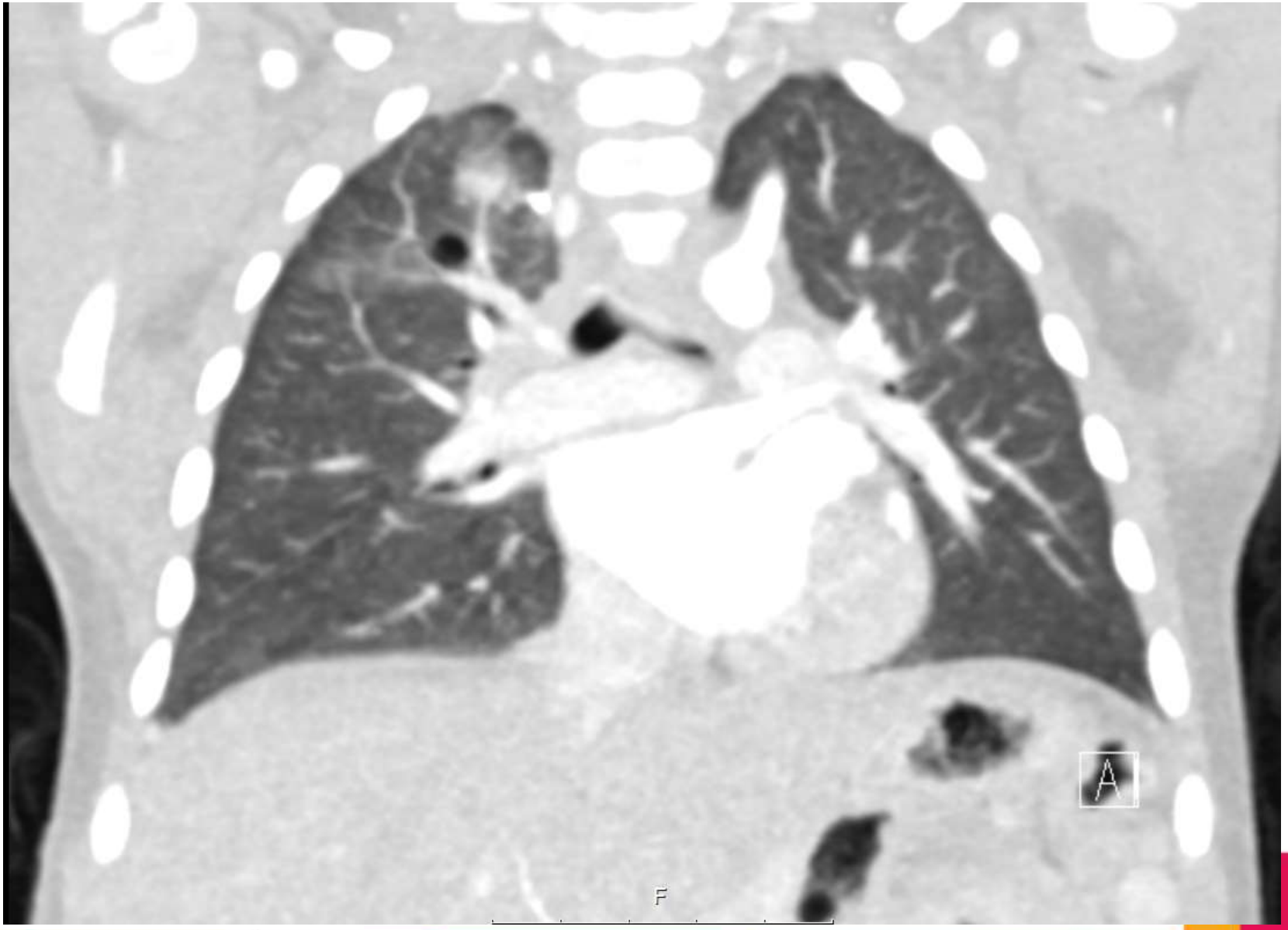


Williams et al. ASCO 2016

- Thorax CT scans:
  - 6 months - No residual disease
  - 9 months - New bullous lesion (6 mm) in RUL

→ Proceed with RUL Lobectomy

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- Pathology results from IPPB Registry
- Non resected previous cyst? recurrence ?
- *DICER 1* mutation gene counseling
- Should we consider chemotherapy?

Take Home Message

- CPAM Type IV and PPB Type I are rare
- Difficult to differentiate clinically/pathologically
- High index of suspicion
- How far should we proceed ?

Thank you for listening!!