Lung Metastasis in Pediatric Osteosarcoma
A 5 year-old Boy

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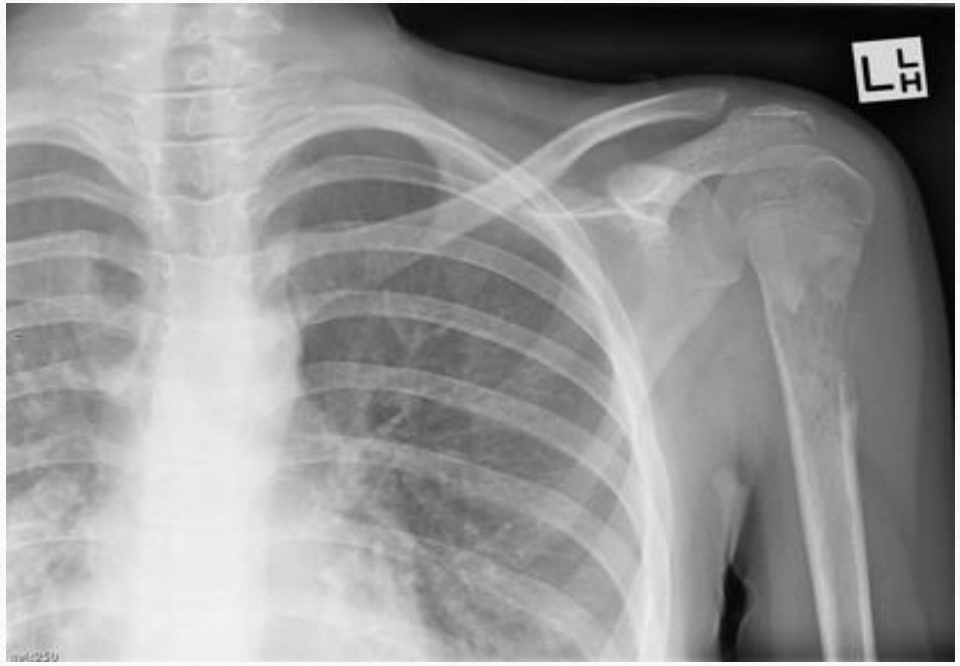
Case Introduction

- 5-year-old boy
- Initial presentation: left arm pain → humerus fracture diagnosed and cast applied
- Progressive swelling noticed by parents → initially attributed to cast/soft tissue changes
- Repeated visits, **delayed further investigation**



Diagnosis

- X-ray: suspicious bony lesion
- CT scan:
  - Osteolytic lesion in left humerus
  - Multiple pulmonary nodules (max 22 × 15 mm)
- Biopsy: **Osteosarcoma**

  -Multiple lung metastases

Initial Management

- Started systemic chemotherapy
- Followed by surgical resection of primary lesion, Total Resection
- Pathology: 90% necrosis
- Size of previous tumor is about 7 cm
- Continued chemotherapy + I, E
  - → **No change in lung nodules**

Disease Progression

- Referral for precision medicine: limited drug availability

CCND3 , PTEN,…

Regorafenib

oral multikinase inhibitor used as an anti-cancer medication. It blocks several protein kinases involved in tumor growth, angiogenesis (formation of new blood vessels), and the tumor microenvironment.

- Developed seizures → brain mass detected
- **Palliative Care**

Pulmonary Metastases in Pediatric Osteosarcoma

- Lungs = most common metastatic site in osteosarcoma
- Present in ~20% of patients at diagnosis
- May be solitary or multiple
- Associated with poor prognosis

Diagnosis

- Chest CT = gold standard
- Typically multiple well-defined nodules
- **Histology:** biopsy rarely required if typical in known primary

Treatment Approaches

- **Systemic chemotherapy** (MAP protocol: Methotrexate, Adriamycin, Cisplatin)
- **Surgical resection (metastasectomy):**
  - Best outcomes if complete resection possible
  - Even for multiple nodules, staged thoracotomies may be attempted
- **Radiotherapy / SBRT**: limited role in children
- **Targeted / precision therapy:** emerging but often limited by access

Prognosis

- Survival depends on:
  - Resectability of lung metastases
  - Response to chemotherapy
  - Timing of metastasis (at diagnosis vs. relapse)
- Long-term survival ~20–30% if complete resection feasible
- Diffuse/unresectable disease → very poor outcome

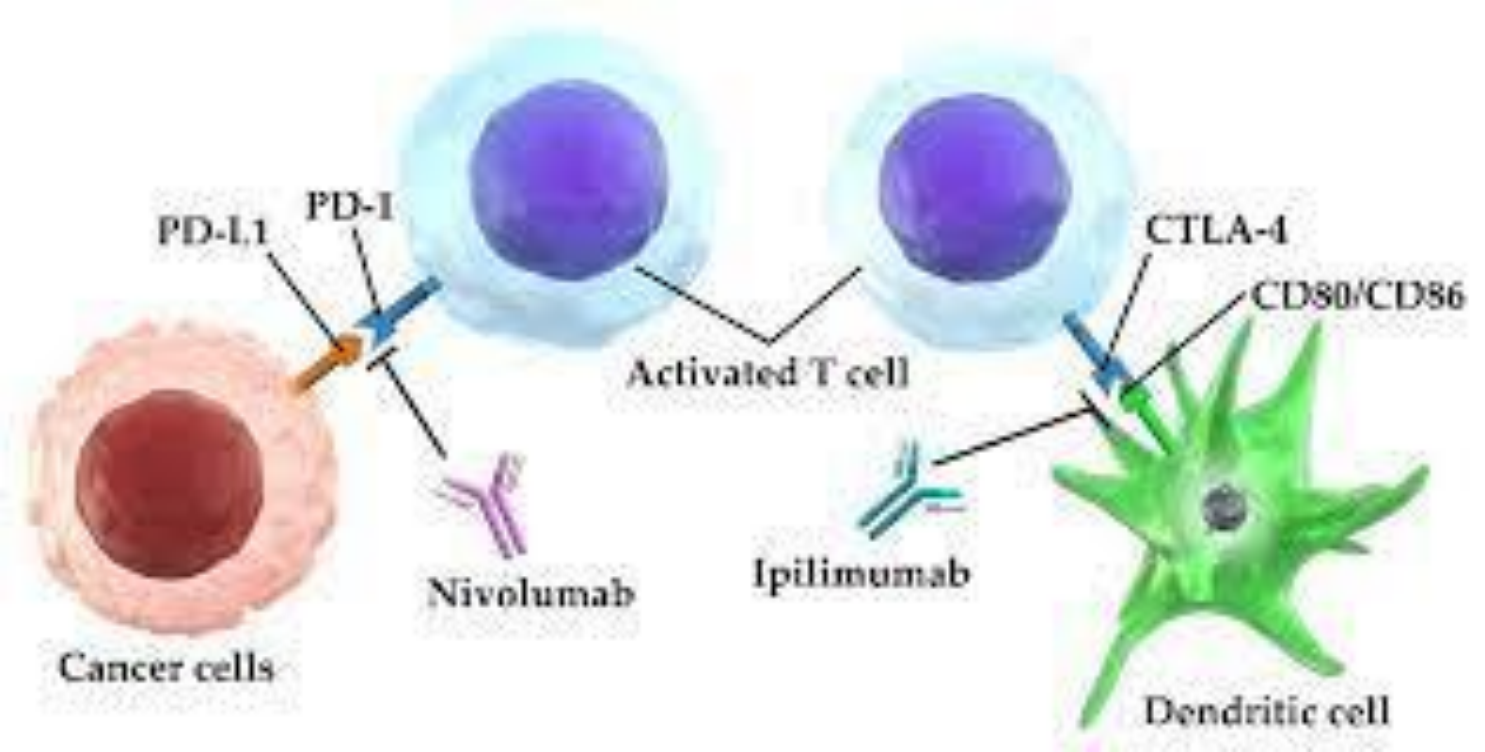
Palliative Care

- Important role in end-stage disease
- Focus on quality of life, symptom control, and family support

PD.1, PDL1

- **PD-1** (programmed cell death protein-1) and
- Tumor **PD-L1** (programmed cell death protein ligand-1) interaction promotes T cell tolerance through suppressing release of immunostimulatory cytokines while directly inhibiting T cell cytotoxicity
- Overexpression of PD-1 and PD-L1 and their interactions are well-characterized immune escape mechanisms of osteosarcoma.
- **PD-1 was increased in circulating T cells in osteosarcoma patients**, and PD-L1 expression in osteosarcoma was related to early metastasis and poorer outcome
- ICIs reverse this process by reinvigorating cytotoxic T lymphocytes (CTLs), reviving immune response directed at neoantigens distinct from those on host tissues

- PD-L1 gene in osteosarcoma cells revealed that PD-L1 regulates osteosarcoma growth and drug resistance
- PD-1 inhibitor could effectively control osteosarcoma pulmonary metastasis


PD-L1
PD-1
CTLA-4
CD80/CD86
Activated T cell
Nivolumab
Ipilimumab
Cancer cells
Dendritic cell

Combination

- Such combinations have had mixed response so far in bone sarcomas. A combination of **nivolumab and ipilimumab** **failed** to show efficacy in patients with osteosarcoma.
- Combination of **durvalumab (anti-PD-1) and tremelimumab (anti-CTLA4)** resulted in **two partial responses** out of five osteosarcoma patients
- Several cases reported that the **combination of anti-CTLA4 and anti-PD-1 antibodies** induced **remission** and tumor stabilization in patients with metastatic osteosarcoma

- **Combination therapy** for OS has shown promising results using anti-CTLA-4 and anti-PD L1 antibodies which showed **improved overall survival** in a murine model with OS, whereas no benefits were noted when treated with anti-CTLA-4 antibody alone
- combination strategy rather than a stand-alone therapy may be the path to the future

CTLA4

- **Cytotoxic T-lymphocyte-associated protein 4 (CTLA4)** (CD152)

- it is apparent that **single PD-1/PD-L1 ICI therapy** may **not be effective enough** for treating OS.
- Lussier et al. combined CTLA-4 with a PD-1 ICI in the K7M2 murine model of metastatic OS and the tumors were completely under control in most of subjects as expected
- To date, although the therapeutic effect of ICI combination in OS **has not been confirmed in clinical trials**, several cases reported that immunotherapy with **ipilimumab plus nivolumab** displayed notable tumor manifestation remission and tumor mass stabilization with metastatic OS patients

Systematic Review (2024): *Do Children With Osteosarcoma Benefit From Pulmonary Metastasectomy?*

- Reported outcomes: some cohorts show better survival with complete resection.
- Lack of randomized controlled trials (RCTs).
- Prognostic factors: fewer nodules, metachronous presentation, good chemo-response.
- Clinical message: PM reasonable **in selected patients** but not universally proven.
- **Decision-making:** should remain multidisciplinary (oncology, thoracic surgery, radiology).

Narrative Review (2023): *Pulmonary Metastasectomy in Pediatric Patients*

- **Discusses surgical approaches**: open thoracotomy vs minimally invasive VATS.
- **VATS advantages:** less pain, shorter hospital stay, quicker recovery.
- **VATS limitation:** risk of missing very small or deep nodules without tactile feedback.
- **Survival** depends mainly on **achieving complete resection**.
- Bilateral disease: staged surgeries or combined approaches may be needed.
- Choice of technique depends on disease burden and institutional expertise.

Retrospective Analyses
Survival and Morbidity After PM

- **Multi-institutional retrospective** data in pediatric/AYA osteosarcoma.
- **No clear survival difference** between open vs VATS approaches.
- Thoracotomy associated with higher morbidity (pain, recovery time).
- Prognostic factors: number of nodules, synchronous vs metachronous, interval to relapse.
- Complete resection remains the strongest predictor of outcome.
- Limitation: heterogeneity in chemo protocols, retrospective design.
- **Clinical message: technique selection less important** than biology and completeness.
- Practical: VATS reasonable for selected patients, balancing efficacy and QoL.

SBRT for Pulmonary Metastases (2023–2025)

- Concept: stereotactic body radiation therapy (SBRT) delivers **high-dose focused radiation.**
- Pediatric series: feasible, safe, good short-to-midterm local control.
- Indications: **non-resectable nodules**, high surgical risk, need for lung function preservation.
- Dosing: typically hypofractionated (e.g., 30 Gy / 3 fx).
- Toxicity: acceptable so far; long-term pulmonary toxicity still under study.
- Limitation: no robust survival data yet.
- Future directions: **combining SBRT with immunotherapy to enhance systemic effect**.
- Clinical use: option for selected patients not suitable for surgery.

Immunotherapy & Novel Systemic Strategies

- Standard systemic therapy remains **MAP-based chemo** (methotrexate, doxorubicin, cisplatin).
- **Checkpoint inhibitors:** limited responses, mostly negative single-agent trials.
- **CAR-T cells, bispecific antibodies**: in early-phase studies; modest activity.
- Major challenge: **low immunogenicity & immunosuppressive tumor microenvironment**.
- Strategies under investigation: tumor vaccines, oncolytic viruses, microenvironment modulation.
- Potential synergy: RT or SBRT + immunotherapy.
- Current role: clinical trial enrollment strongly recommended.
- Clinical message: immunotherapy is experimental; no proven survival benefit yet.

Thank You