Alveolar Soft Part Sarcoma

A Very Rare Case of Pediatric Orbital Alveolar Soft Part Sarcoma with Secondary Squamous Cell Carcinoma and Pulmonary Metastasis After a Decade

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- Fellowship of pediatric hematology and oncology
- Mofid Children Hospital

- 18th IPHOS congress
- Mashhad, 19-20 Shahrivar 1404

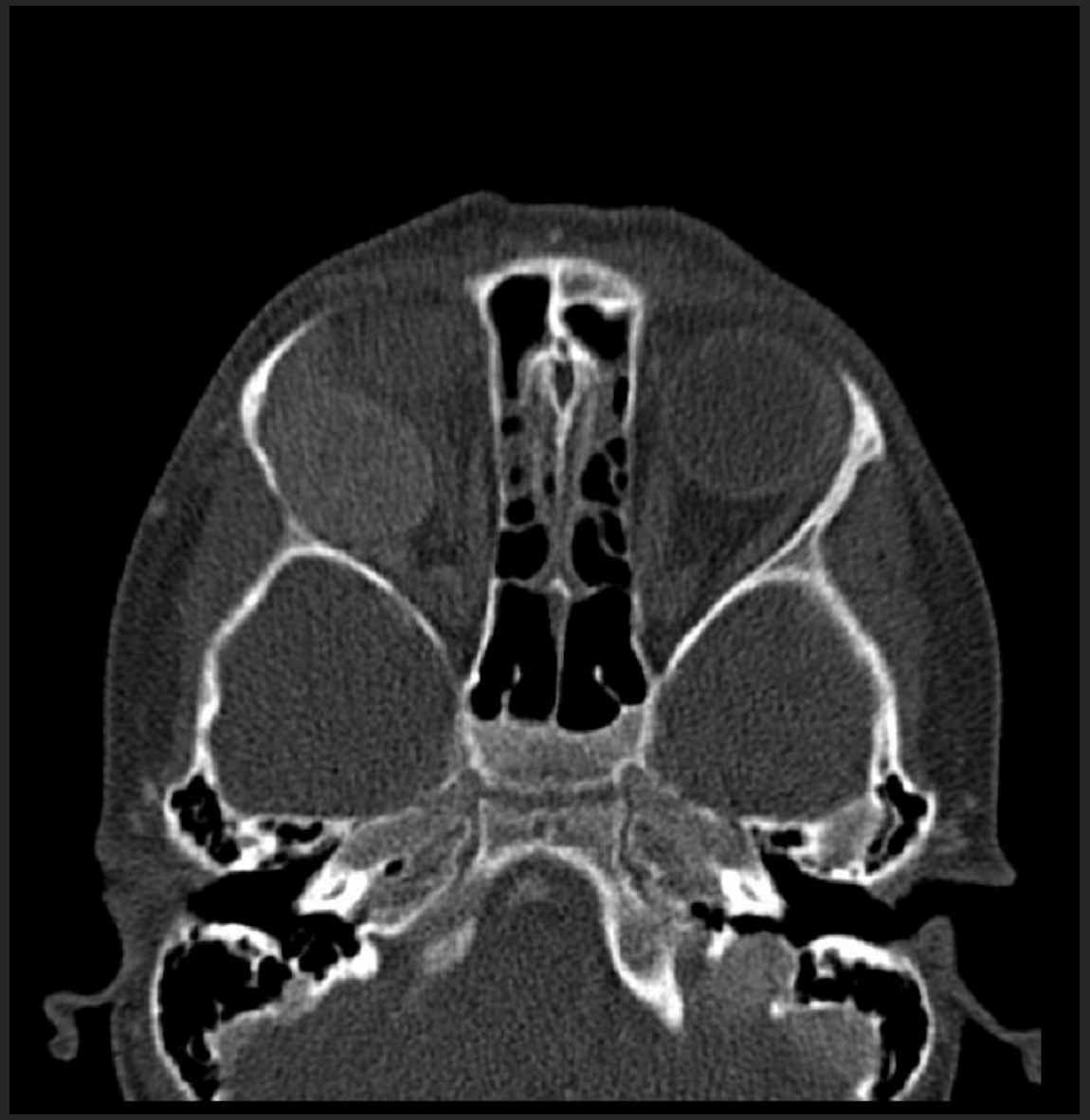
Case Presentation

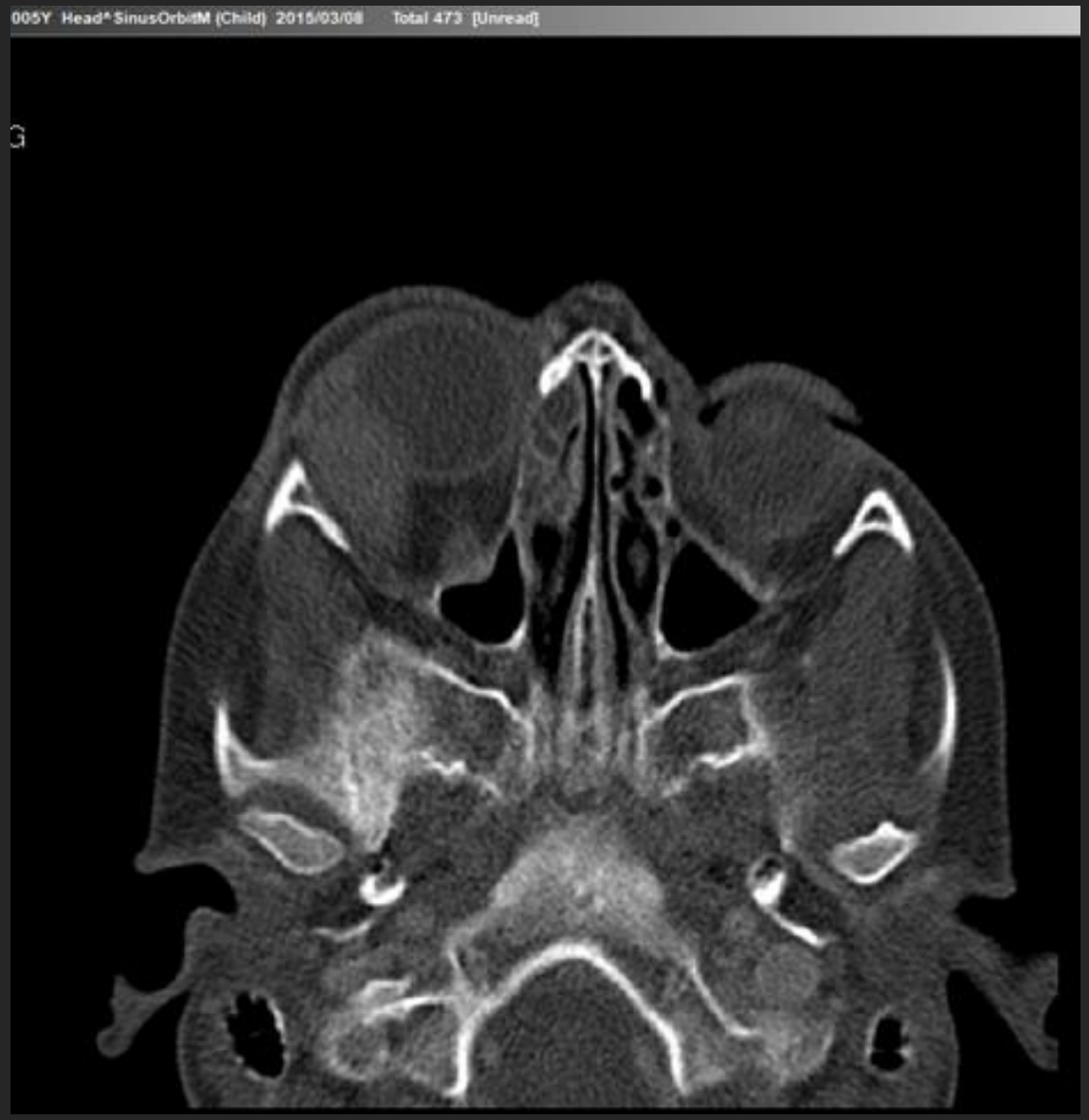
A 5-year-old girl presented with progressive proptosis and restricted eye movement in the right eye.

Orbital MRI revealed a poorly defined, lobulated, isointense mass with mild to moderate enhancement.

Chest CT scan detected a single subcentimeter pulmonary nodule, which could not be biopsied at the time.

Core needle biopsy of the orbital mass confirmed **ASPS**, supported by positive IHC including **PAS, NSE, vimentin, and most notably, TFE3**

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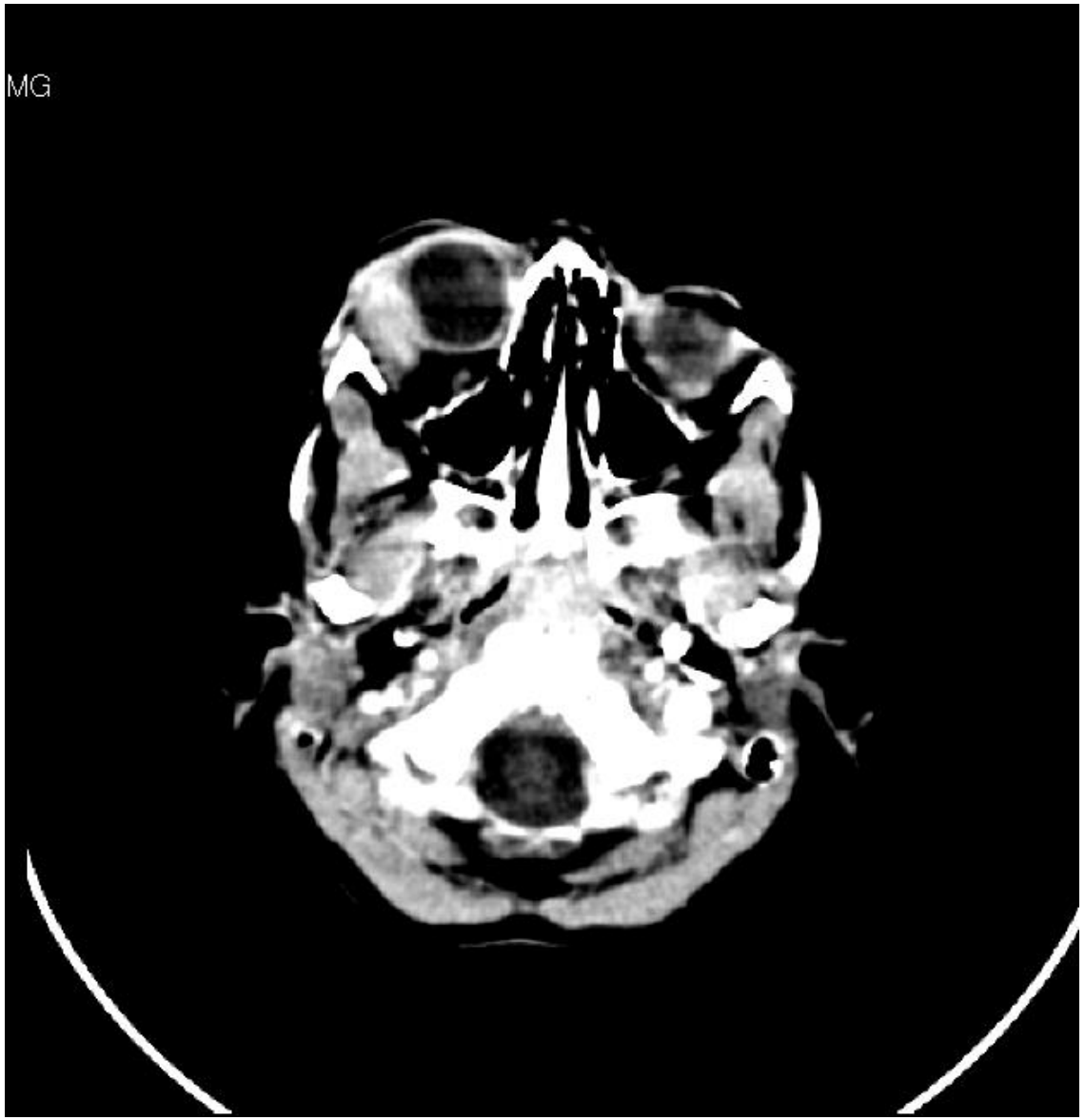
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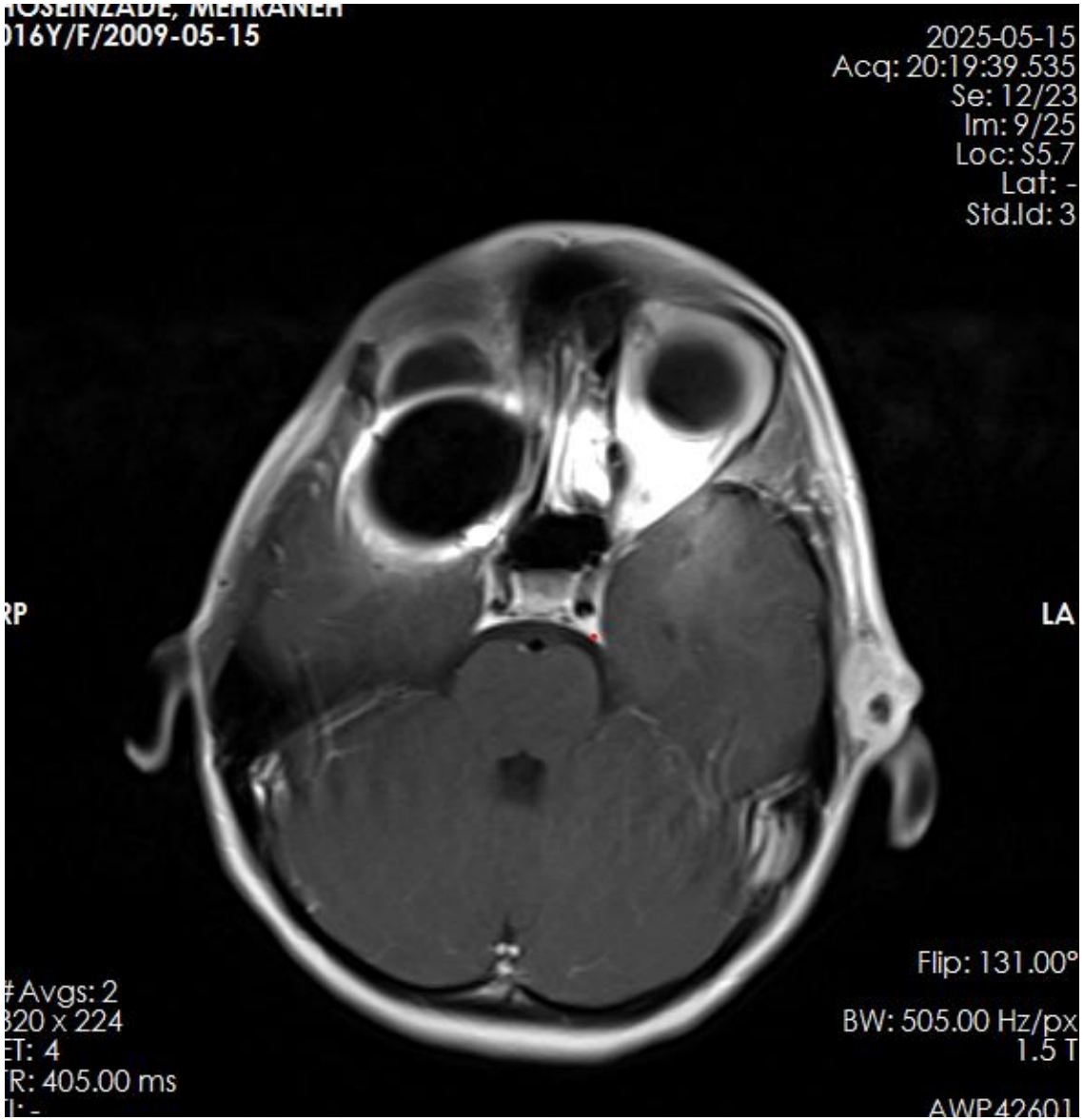
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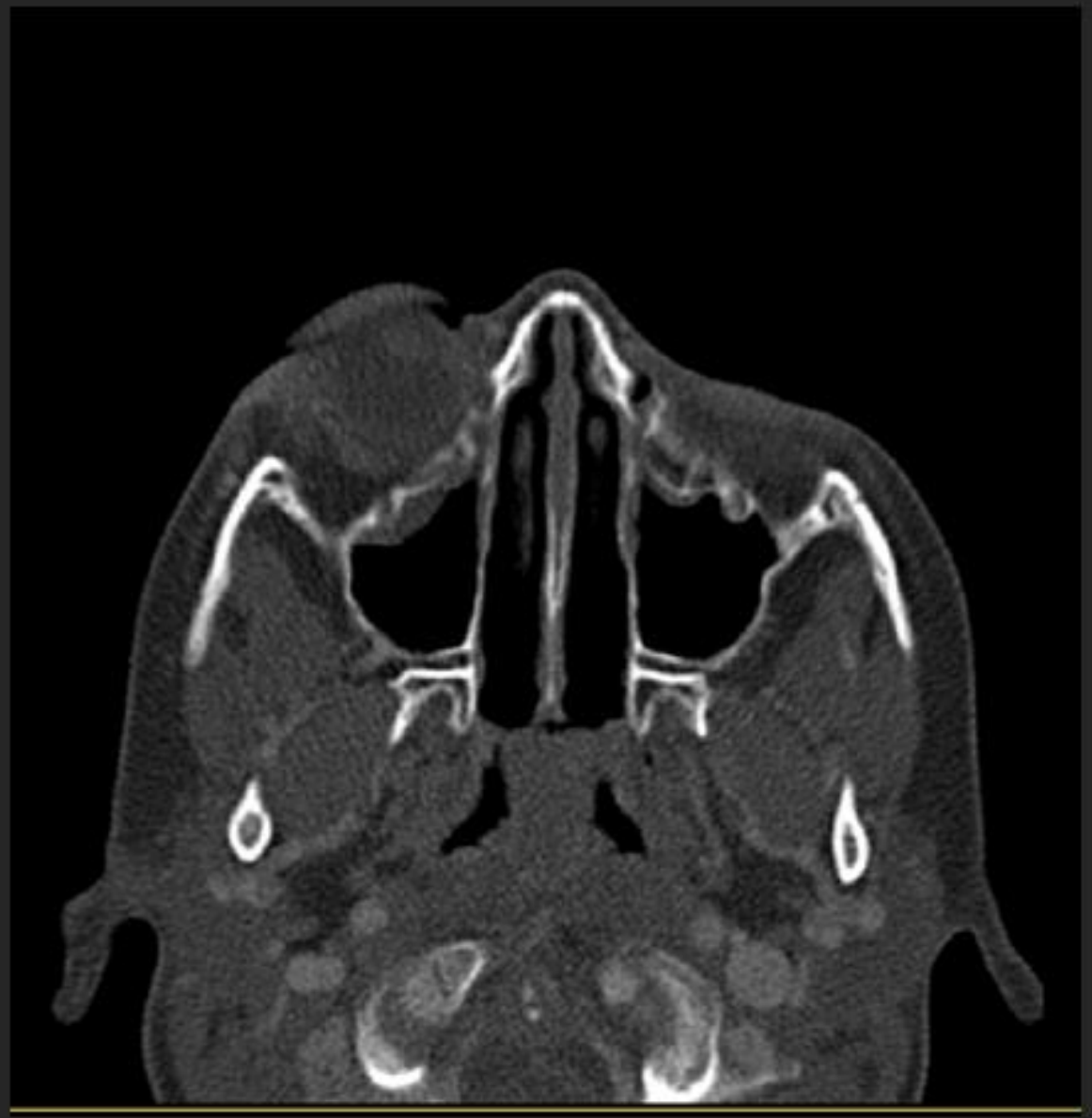


Biopsy.

GROSS DESCRIPTION:

Specimen is received in formalin in one container, consists of a piece of gray
1 x 0.9 x 0.9 cm in dimensions.

Summary of specimen : M /1 Embedded : RSS

MICROSCOPIC DESCRIPTION:

Sections show a neoplastic tissue composed of cells with eosinophilic cytoplas
nuclei, arranged in sinosuidal structures intervining by thin capillaries with bla
dilated capillaries are seen. Mitotic figures are rare.
PAS staining reveales sparse crystaloid materials inside neoplastic cells.

DIAGNOSIS:

- ORBITAL MASS, RIGHT SIDE , BIOPSY:
- CONSISTENT WITH **"ALVEOLAR SOFT PART SARCOMA (ASPS)"**;
- PLEASE SEE MICRO AND NOTE.

NOTE:

For further interpretation and confirmation, immunohistochemical study of avail
required, which could be performed upon request.

The patient received 6 cycles of the **EVAIA protocol** (alternating cycles of Vincristine, Doxorubicin, Cyclophosphamide/Ifosfamide and Etoposide) along with **external beam radiotherapy.**

Due to the tumor's orbital location, surgical resection was not feasible.

The tumor achieved complete remission post-treatment.

She lost her follow-up until 10 years later came back with …….

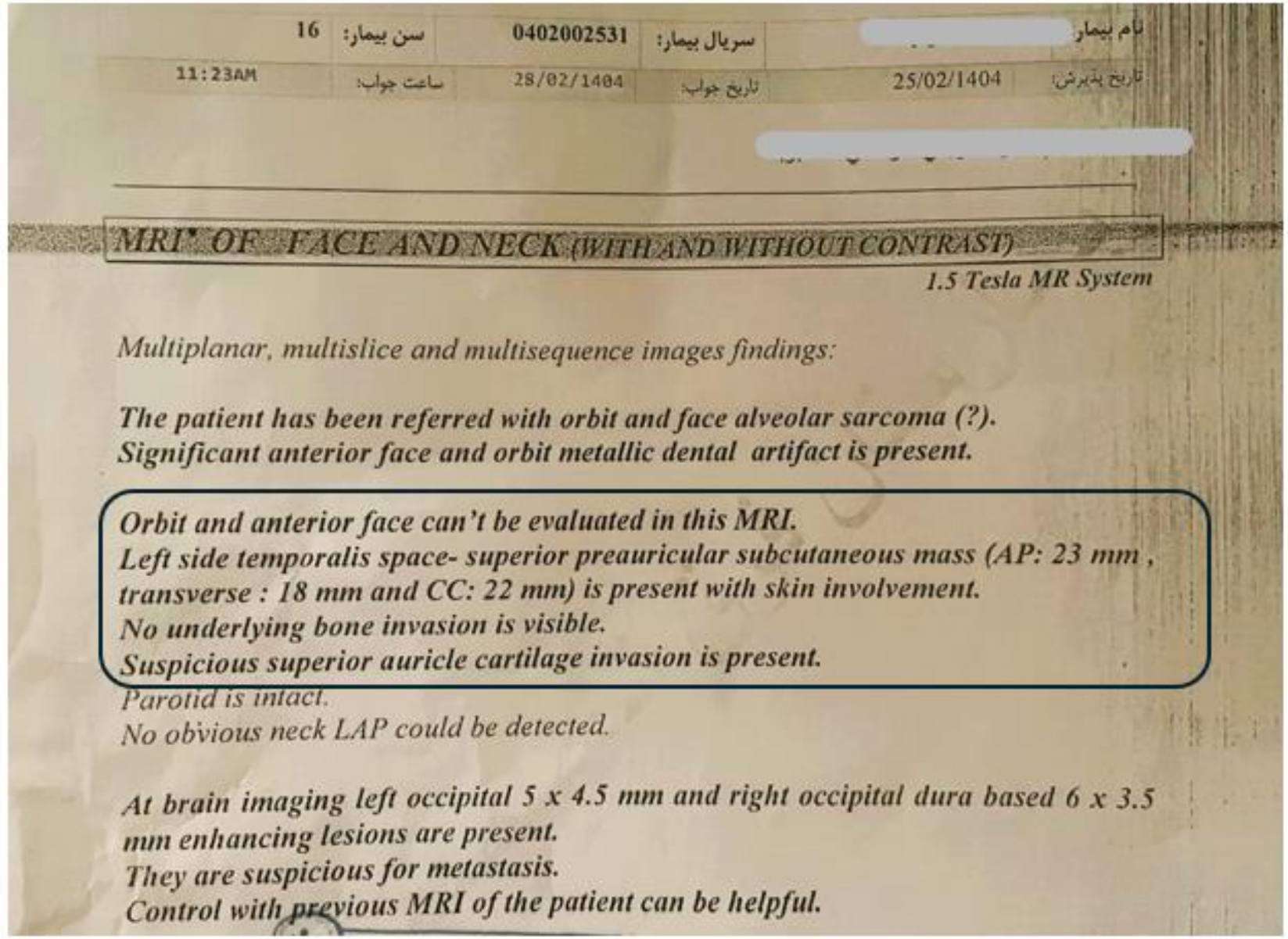
After a 10-year lapse in follow-up, the patient returned with a firm 2×2 cm supra-auricular mass.

PET/CT imaging revealed multiple bilateral pulmonary nodules.

Biopsies of the supra-auricular mass was defined as SCC

Peripheral lung nodule was biopsied percutaneously which was compatible with metastatic ASPS.

MRI of the left supraauricular area



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MRI OF FACE AND NECK (WITH AND WITHOUT CONTRAST)

1.5 Tesla MR System

Multiplanar, multislice and multisequence images findings:

The patient has been referred with orbit and face alveolar sarcoma (?).
Significant anterior face and orbit metallic dental artifact is present.

Orbit and anterior face can't be evaluated in this MRI.
Left side temporalis space- superior preauricular subcutaneous mass (AP: 23 mm , transverse : 18 mm and CC: 22 mm) is present with skin involvement.
No underlying bone invasion is visible.
Suspicious superior auricle cartilage invasion is present.

Parotid is intact.
No obvious neck LAP could be detected.

At brain imaging left occipital 5 x 4.5 mm and right occipital dura based 6 x 3.5 mm enhancing lesions are present.
They are suspicious for metastasis.
Control with previous MRI of the patient can be helpful.

^{18}F-FDG PET/CT Report

[redacted]

Date: 1403.10.11 (Jan 01, 2025)
Weight: 48 Kg
Referring physician: Dr. Azghandi

Age: 15 Y/O
ID: 01187285

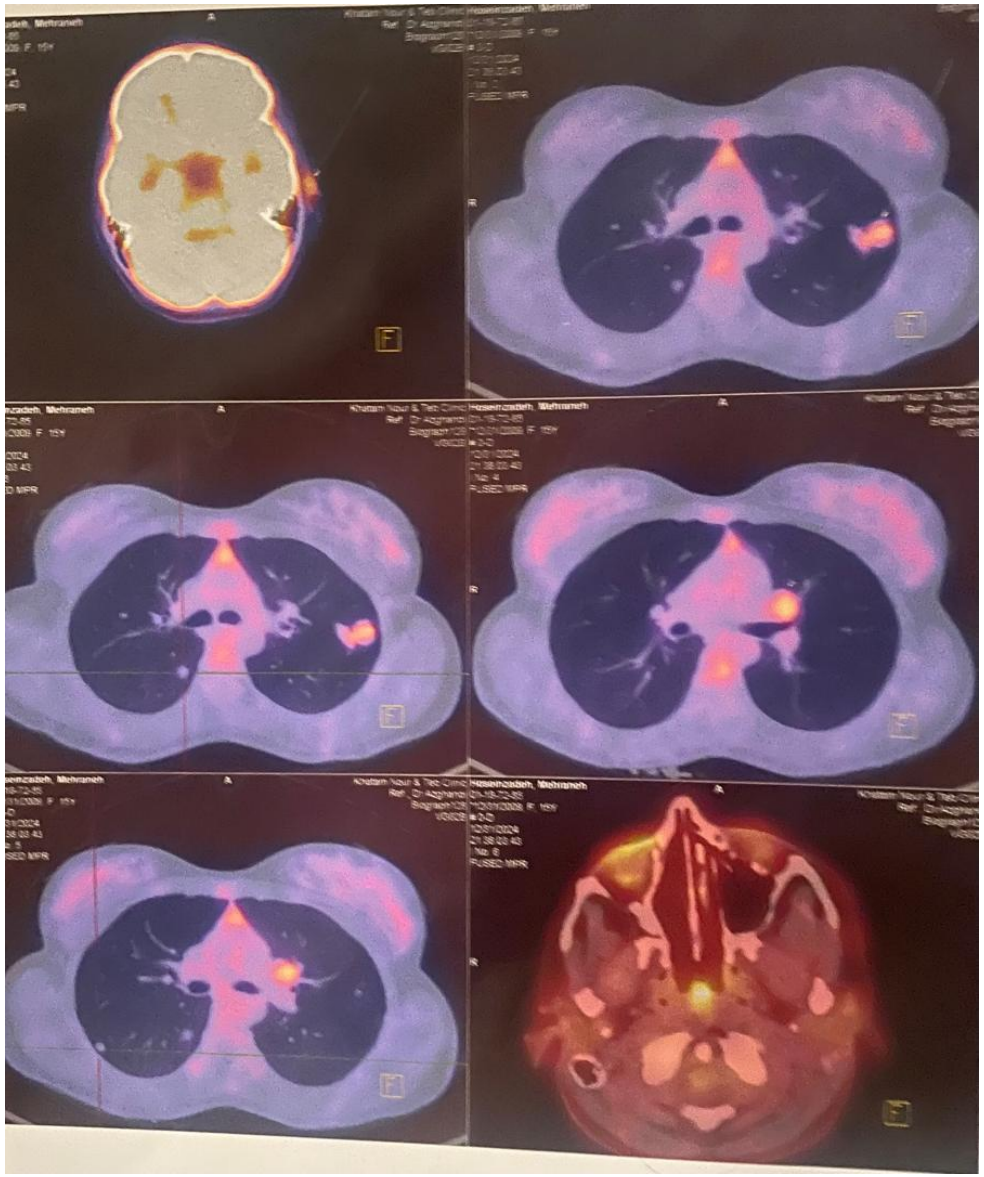
IMPRESSION & COMMENTS:

- *The current study is compatible with FDG avid metastatic disease in:*
  - *Multiple bilateral pulmonary nodules*
  - *A left preauricular lymph node*
- *No metabolic evidence of malignancy in the remainder imaged portion of the body.*

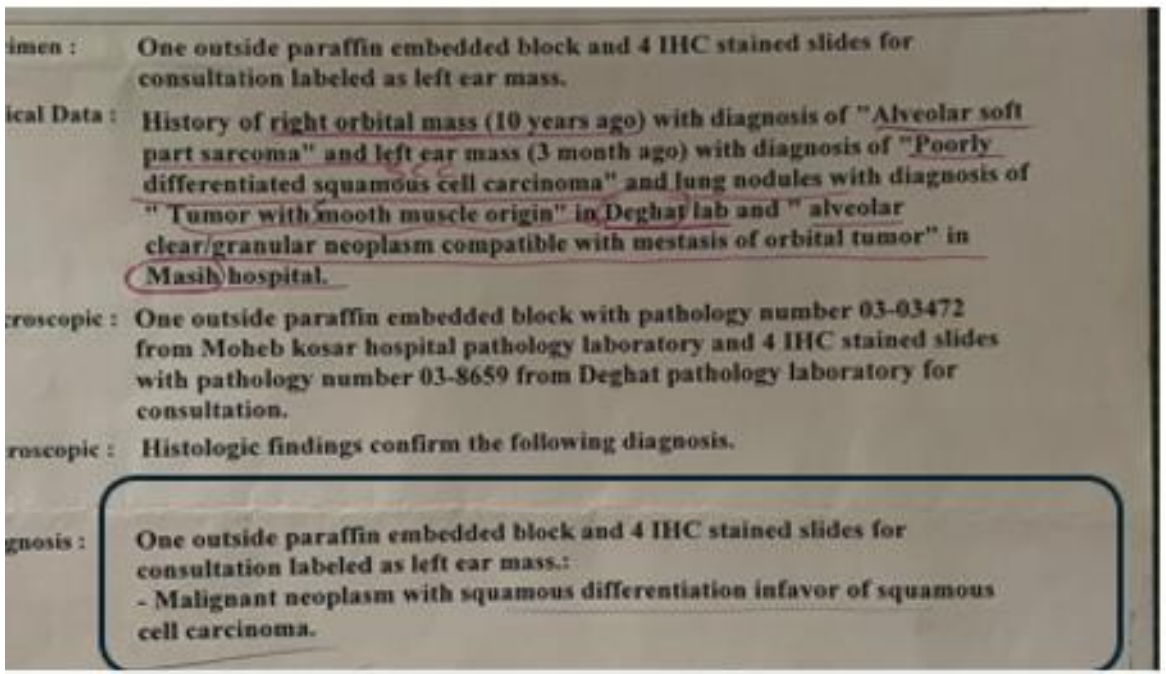
An FDG uptake within nasopharyngeal region most likely physiologic in nature and corresponding to adenoid; however, ENT consultation is recommended.

Sincerely Yours;

[redacted]



Pathology of the supra-auricular mass



imen : One outside paraffin embedded block and 4 IHC stained slides for consultation labeled as left ear mass.

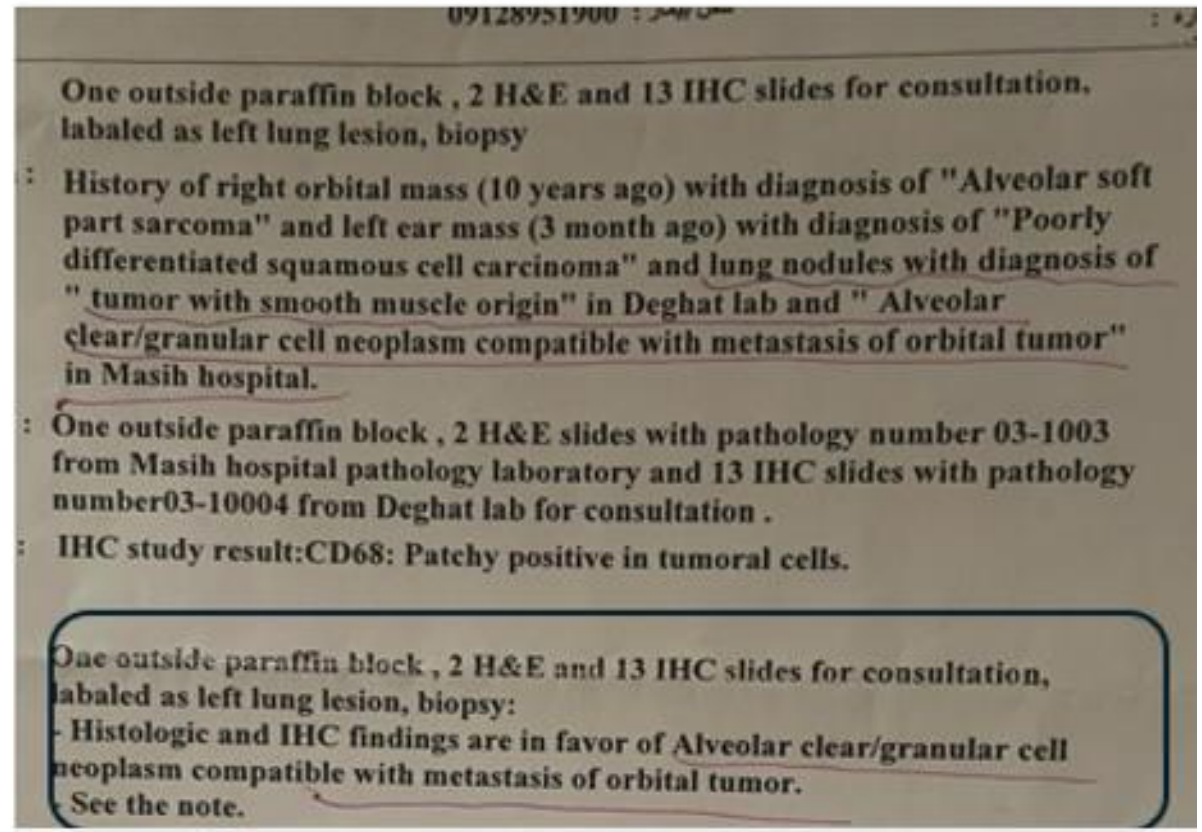
ical Data : History of right orbital mass (10 years ago) with diagnosis of "Alveolar soft part sarcoma" and left ear mass (3 month ago) with diagnosis of "Poorly differentiated squamous cell carcinoma" and lung nodules with diagnosis of " Tumor with mooth muscle origin" in Deghat lab and " alveolar clear/granular neoplasm compatible with mestasis of orbital tumor" in Masih hospital.

roscopic : One outside paraffin embedded block with pathology number 03-03472 from Moheb kosar hospital pathology laboratory and 4 IHC stained slides with pathology number 03-8659 from Deghat pathology laboratory for consultation.

roscopic : Histologic findings confirm the following diagnosis.

gnosis : One outside paraffin embedded block and 4 IHC stained slides for consultation labeled as left ear mass.:
- Malignant neoplasm with squamous differentiation infavor of squamous cell carcinoma.

Pathology of pulmonary Nodule



09128951900 :

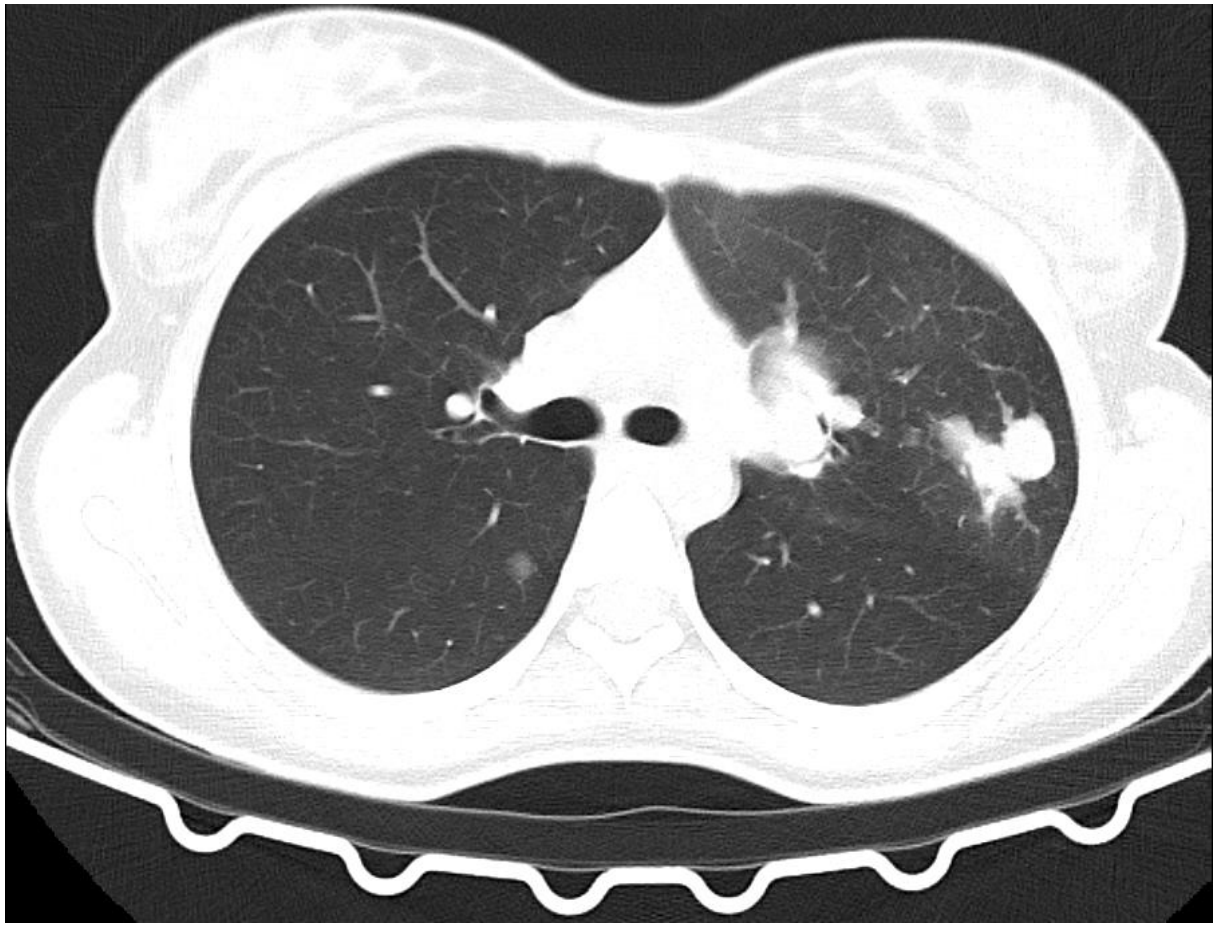
One outside paraffin block , 2 H&E and 13 IHC slides for consultation, labaled as left lung lesion, biopsy

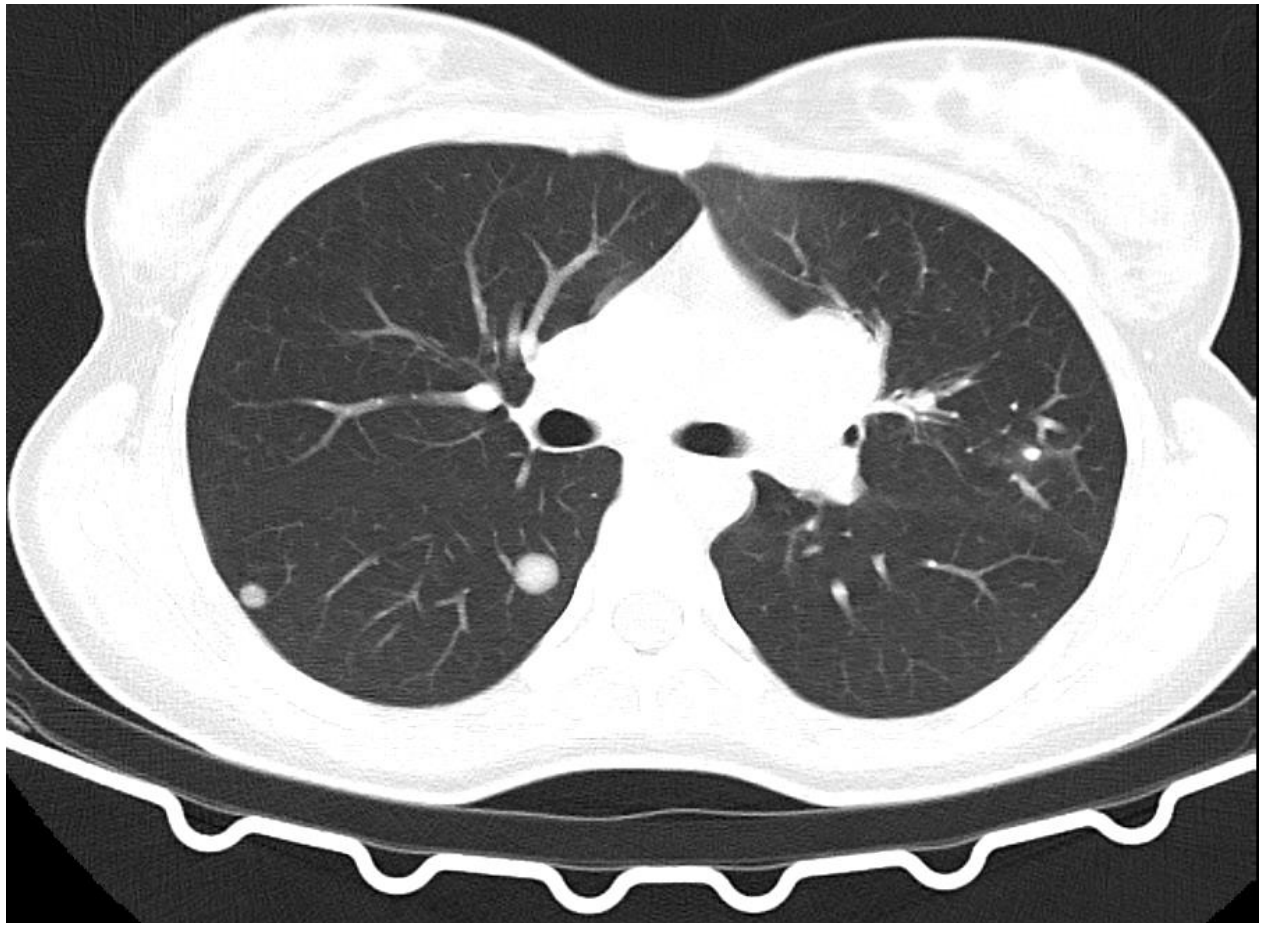
: History of right orbital mass (10 years ago) with diagnosis of "Alveolar soft part sarcoma" and left ear mass (3 month ago) with diagnosis of "Poorly differentiated squamous cell carcinoma" and lung nodules with diagnosis of " tumor with smooth muscle origin" in Deghat lab and " Alveolar clear/granular cell neoplasm compatible with metastasis of orbital tumor" in Masih hospital.

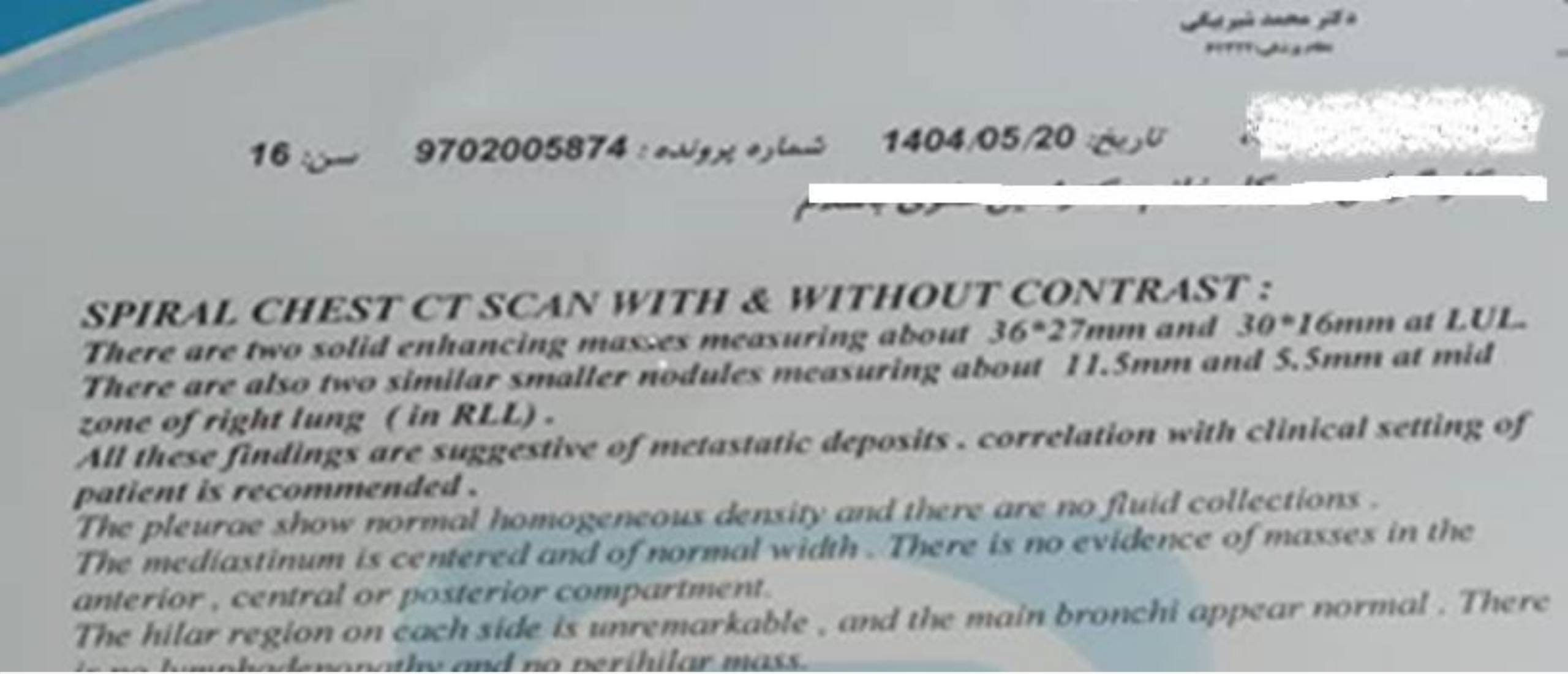
: One outside paraffin block , 2 H&E slides with pathology number 03-1003 from Masih hospital pathology laboratory and 13 IHC slides with pathology number03-10004 from Deghat lab for consultation .

: IHC study result:CD68: Patchy positive in tumoral cells.

One outside paraffin block , 2 H&E and 13 IHC slides for consultation, labaled as left lung lesion, biopsy:
- Histologic and IHC findings are in favor of Alveolar clear/granular cell neoplasm compatible with metastasis of orbital tumor.
- See the note.

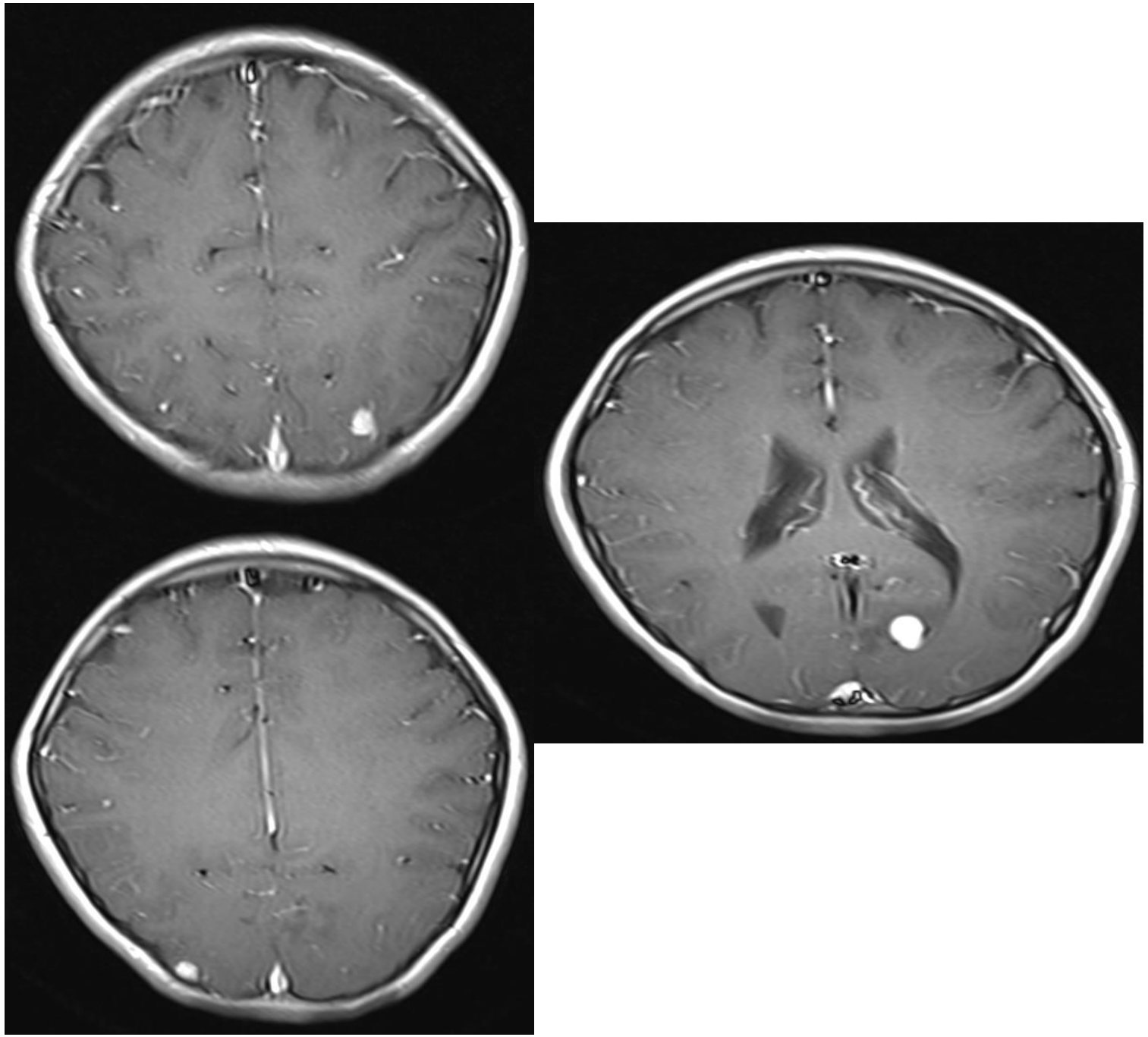






Pulmonary metastases of ASPS at relapse after 10 years

Brain MRI



Alveolar soft-part sarcomas. *Structurally characteristic tumors of uncertain histogenesis*

William M. Christopherson M.D., Frank W. Foote Jr. M.D., Fred W. Stewart M.D.

First published: January 1952 | https://doi.org/10.1002/1097-0142(195201)5:1<100::AID-CNCR2820050112>3.0.CO;2-K | Citations: 399

- **12 cases were reported in 1952. 10 patients were female.**
- **Age range from 3 to 38 years; the majority were in their 20-30.**
- **The primary site was in the extremities in 10 cases. Deep lingual musculature in 1 and anterior abdominal-wall muscle in 1.**
- **Conservative treatment by local excision was performed.**
- **The unique histological pattern and the natural history of the ASPS left no doubt that these tumors were different from previous recognized tumors**

Alveolar soft part sarcoma (ASPS)

- **ASPS is a very rare STS in children under 5 years of age. It accounts for 1% of STS and 5% of pediatric non-rhabdomyosarcoma STS.**

- **It is caused by the ASPSCR1-TFE3 fusion gene, resulting from a balanced translocation: t(X;17)(p11;q25). This fusion acts as tumorigenesis.**

- **Some IHC studies have recently indicated that ASPS may originate from striated muscles, there is still uncertainty to the exact nature of this tumor.**

- **Head and neck region in infants and children are the most common sites of origin, especially the orbit and tongue.**

Alveolar Soft Part Sarcoma: Molecular studies

ASPS is associated with t(X,17) leading to ASPSCR1-TFE3 fusion gene on der (17) and ASPSCR1-TFE3 chimeric transcript, seen in almost all cases.

In pathologically challenging cases, RT-PCR for the fusion transcript or FISH for TFE3 rearrangement will be helpful in making a definitive diagnosis.

Age group	Commonest sites	Other possible sites
Children	Tongue, orbit	Trunk, extremities
Adults	Thigh, buttock, trunk	Rarely head/neck

Natural history of ASPS

- ASPS is unique among STS, to have a small primary with an indolent behavior with late metastasis in the lungs. It is one of the few STS, with a high risk of brain metastasis, becoming symptomatic months to years after diagnosis.

- Despite being a chemoresistant tumor, it is known as a slow-growing mass with prolonged survival even in a few metastatic patients with spontaneous disease stabilization and indolent disease behavior.

- The most common sites of metastasis are lungs, bone, and brain.

How do we Treat Patients with ASPS?

- **Localized Disease:**

- Localized disease is treated with wide local excision followed by adjuvant radiotherapy if there is evidence of microscopic or macroscopic residual disease or if the margin status is questionable

- **Metastatic Disease, Limited Disease Burden:**

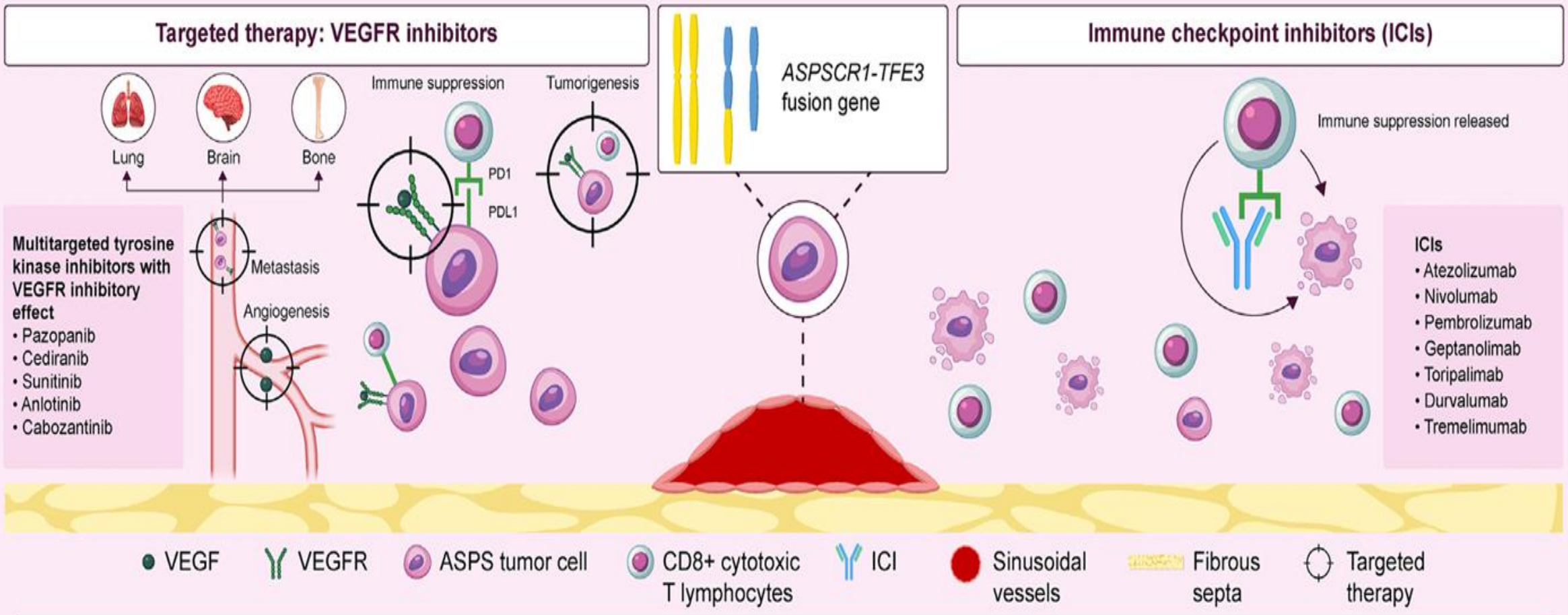
- Patients with limited disease who are asymptomatic may be observed with close follow-up, considering the indolent behavior. Brain metastasis [symptomatic/asymptomatic] should be treated with CNS-directed therapy.

- **Metastatic Disease with Heavy disease burden/Symptomatic/Rapidly progressive Disease:**

- ASPS is a relatively chemoresistant disease. Hence, in both adjuvant and metastatic settings, chemotherapy is not offered.

- First-line therapy includes targeted therapy with antiangiogenic [VEGF] agents pazopanib and sunitinib and immunotherapy with immune checkpoint inhibitors and combinations of both.

Combined Treatment with VEGFR Inhibitors and Immune Checkpoint Inhibitors for Alveolar Soft Part Sarcoma (ASPS)



Combined therapy with VEGFR and ICIs shows improved outcomes in ASPS

Treatment Modality	Key Agents / Examples	Notable Outcomes
Conventional Chemotherapy	Doxorubicin, Ifosfamide, Cisplatin, Gemcitabine-Docetaxel	Low response (~<10%), mostly stable/progressive disease
Trabectedin	—	Minimal activity in ASPS
Targeted Therapy (TKIs)	Cediranib, Sunitinib, Pazopanib, Anlotinib	Response rates 16–46%, PFS up to ~21 months
Other TKIs	Dasatinib, Tivantinib, Crizotinib, Cabozantinib	Low activity; cabozantinib ~25% response in small studies
Immunotherapy (ICIs)	Pembrolizumab, Atezolizumab, Durvalumab+Tremelimumab, ipilimumab+Nivolumab	Objective responses in subset; some durable benefit/control

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Original article

Alveolar soft part sarcoma in children and adolescents: A report from the Soft-Tissue Sarcoma Italian Cooperative Group

M. Casanova,[1] A. Ferrari,[1] G. Bisogno,[2] G. Cecchetto,[2] E. Basso,[3] B. De Bernardi,[4] P. Indolfi,[5] F. Fossati Bellani[1] & M. Carli[2]

Multidisciplinary Approach to STS

- **Conservative surgery:** radical surgery or a primary re-excision
- **Biopsy alone** due to tumor site and extent, **and preoperative chemotherapy, and then conservative radical surgery.**
- **Radiation therapy following conservative surgery or radical re-excision.**
- As in other soft tissue sarcomas, the role of radiotherapy and chemotherapy in the treatment of ASPS remains to be established.

Annals of Oncology 11: 1445-1449, 2000

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Clinical features and therapeutic outcomes of alveolar soft part sarcoma in children: A single-center, retrospective study

Zhichao Tan†, Jiayong Liu*†, Ruifeng Xue†, Zhengfu Fan, Chujie Bai, Shu Li, Tian Gao, Lu Zhang and Xinyu Wang

Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Bone and Soft Tissue Tumor, Peking University Cancer Hospital and Institute, Beijing, China

Records of 56 patients with ASPS were reviewed in a center from China since Jan 2015 to 2022.

All patients were under 12 years at the time of initial diagnosis.

Head and neck (32.1%) , limbs (41.1%), trunk (21.4%).

26 (46.4%) patients developed metastasis at the time of diagnosis or during follow-up.

Observation was recommended for 15 patients with stage IV patients with only pulmonary metastases.

7 (46.7%) patients remained stable until last follow up.

15 patients with progressive disease received mono or combined therapy. 11 patients received PD-1 monotherapy.

4 patients received a combination therapy of PD-1 inhibitors plus TKIs.

All of them remained stable. No disease-related death occurred during follow-up. The 1-year PFS rate was 83.3% and median PFS was 29.4 months.

ASPS exhibits a higher occurrence in head and neck in children. ASPS originating from glossopharyngeal region tends to have a lower metastasis rate.

ASPS displays a more indolent growth pattern in children, which makes observation a preferable choice for children with sole pulmonary metastasis.

Pediatric ASPS appears to be less effective to targeted therapy and immunotherapy than adults.

The treatment of progressive ASPS in children remains challenging.

Table 2. Prospective study of ICIs in patients with ASPS

Drug	Study name/study ID number	Phase	No. of patients with ASPS	ORR, %	mPFS (months)	mOS (months)	Reference
Atezolizumab	NCT03141684	II	52	36.5	20.8	NE	18
Atezolizumab	ALBERT trial/jRCT2031200041	II	20	10.0	10.0	NR	54
Nivolumab	OSCAR trial/UMIN000023665	II	14	7.1	6.0	NR	55
Pembrolizumab	AcSé trial/NCT03012620	II	14	57.1	6.6	NR	56
Geptanolimab	NCT03623581	II	37	37.8	6.9	NR	57
Toripalimab	NCT02836834	I	12	25.0	11.1	34.7	58
Durvalumab + tremelimumab	NCT02815995	II	10	40 (irRECIST)	34.23	NR	59

ASPS, alveolar soft part sarcoma; ICIs, immune checkpoint inhibitors; irRECIST, immune-related RECIST; mOS, median overall survival; mPFS, median progression-free survival; NE, not evaluated; NR, not reached; ORR, overall response rate.

Atezolizumab

In December 2022, FDA approved Atezolizumab for adults and children 2 years and older with advanced alveolar soft part sarcoma.

This is the first drug ever approved for this rare disease.

Take Home Messages

- ASPS is a rare orphan disease, with an indolent yet relentless clinical course.
- A detailed clinico–radio-pathological evaluation is the key to diagnosis.
- It usually presents as a painless slow-growing vascular soft tissue mass in the lower limb of adolescents and young adults, predominantly females.
- It has characteristic histopathology with Pseudo-alveolar patterns and intracytoplasmic crystals. IHC with TFE3 and Molecular studies for ASPSCR1-TFE3 help in challenging situations.
- Metastatic disease to lung/bone/brain leads to poor prognosis. It is unique among STS to have brain metastasis.
- Localized disease is managed with wide local excision followed by adjuvant radiotherapy if microscopic or macroscopic residual disease.
- It is essentially a chemoresistant disease with an almost negligible role for Adjuvant chemotherapy.
- Metastatic disease is treated with targeted anti-VEGF agents such as pazopanib/sunitinib and immunotherapy such as pembrolizumab or combination.
- With many novel agents in the pipeline and pathway-driven Basket trials with collaborative prospective clinical trials, the future of management of ASPS looks promising. It is truly a therapeutic journey from Nihilism to cautious optimism.

What is your opinion on the treatment of this patient?

Special thanks to Prof. S. Alavi for her assistance in preparing this presentation, and to all of you for your attention.