



## MTB SELNET NOVEMBER 21, 2024

### Coordinate team

- Dr. Dorian García Ortega Surgical Oncologist
- Dr. Haydee Caro Sánchez Oncology Pathologist
- Dr. Gabriela Alamilla García Medical Oncologist



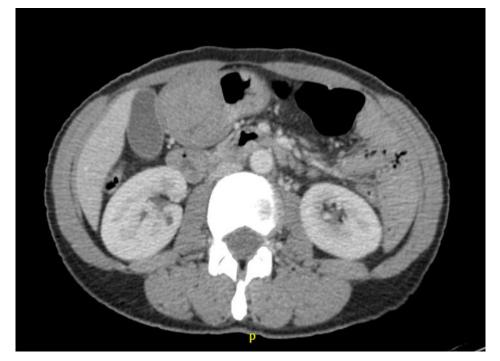
FUNDACIÓN INSTITUTO VALENCIAN' DE ONCOLOGÍA

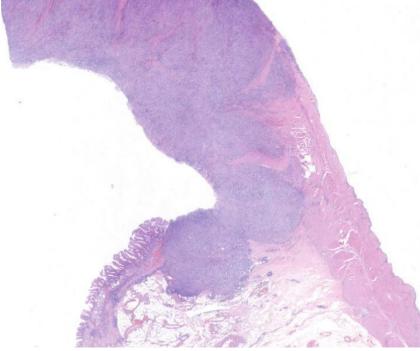
## CASE 1

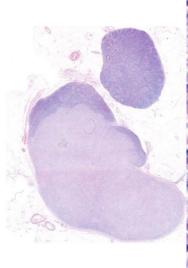
Dr. Isidro Machado

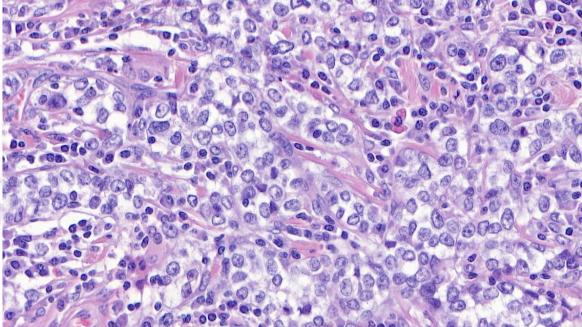
SELNET Session November
IVO. Isidro Machado, Reyes Claramunt, Hector
Aguilar

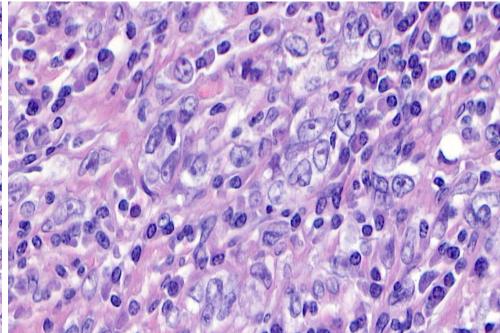
76 y/o/w abdominal pain and gastric mass. Endoscopic biopsy: Undifferentiated round cell tumor/sarcoma vs carcinoma vs GIST

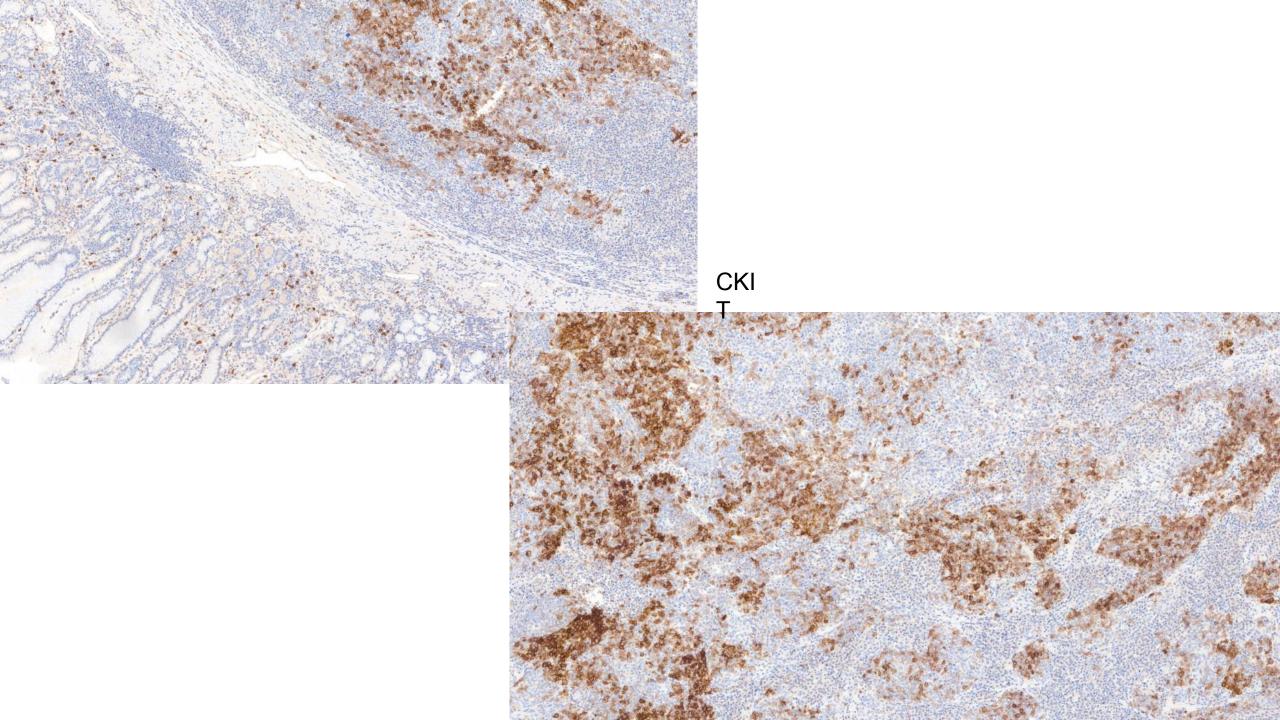


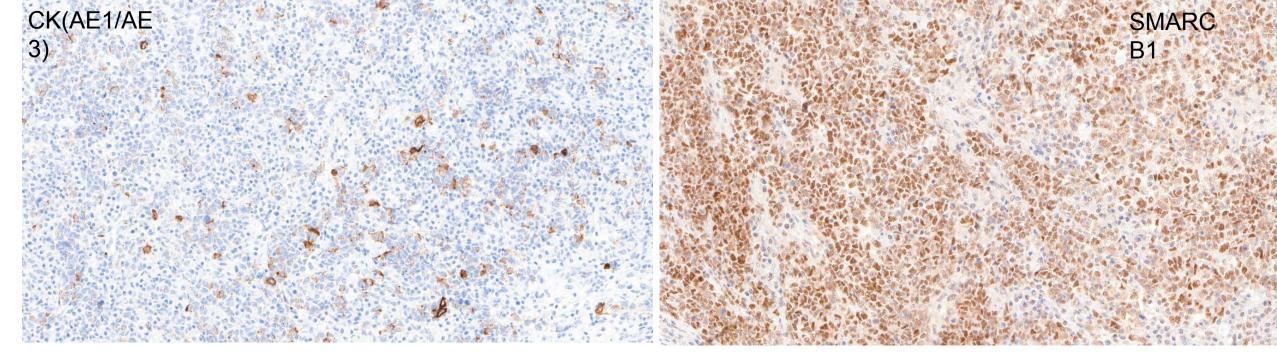












IHC positive: panCK (focal), CKIT, INI1,SALL4,SDHB
IHC negative: DOG1,CD99, CD45, S100,MPO, SMA, CD34 PAX5,NKX2.2,ERG,TTF1,PAX8, CD1a,Desmin,Myog, MyoD1, ALK, EMA, p16,MDM2, BCOR, SYT, Synapto, CD56,Chrom, CD21,CD35, p40,GATA3, CK7, CK5/6, HMB45, Melan-A

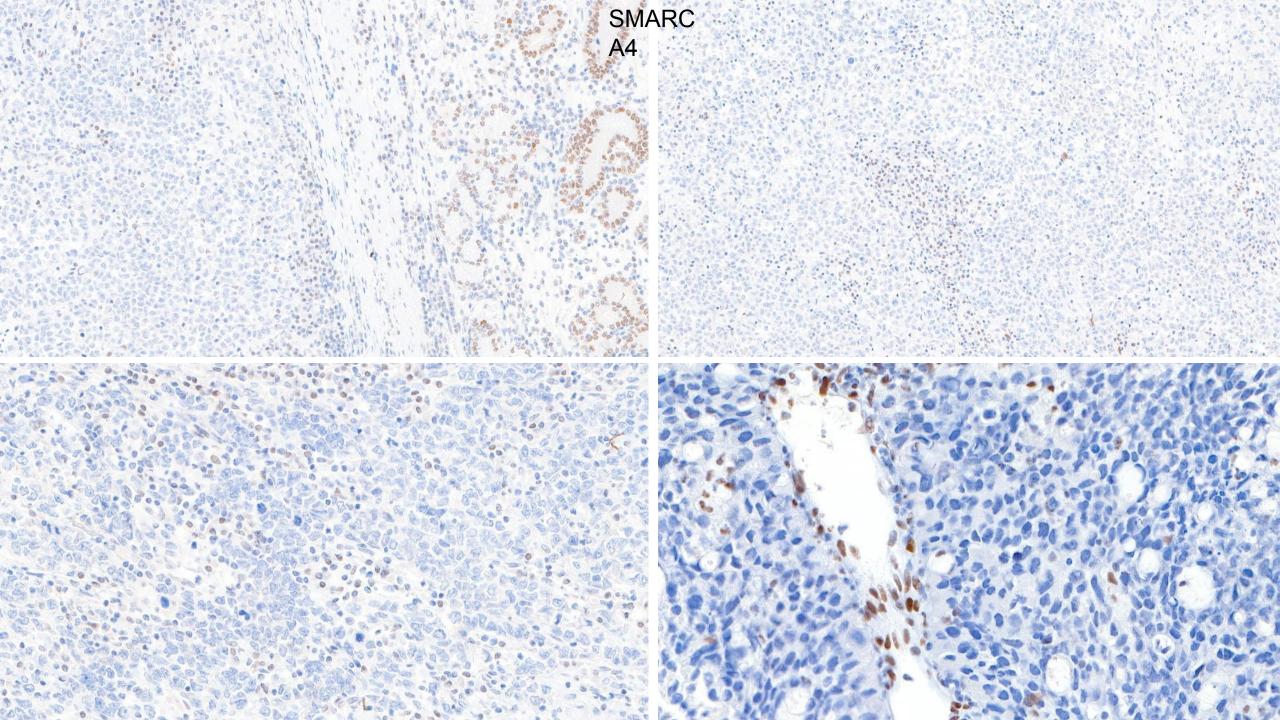
Archer fusion panel: no fusion

Oncomine panel: negative

Hotspot genes				Full-length genes			Copy number genes		Gene fusions (inter- and intragenic)		
AKT1 AKT2 AKT3 ALK AR ARAF AXL BRAF BTK CBL COND1 CDK4 CDK6 CTHEK2 CSF1R CTNNB1 DDR2 EGFR ERBB3 ERBB4 ERCC2	ESR1 EZH2 FGFR1 FGFR2 FGFR3 FGFR4 FLT3 FOXL2 GATA2 GNA11 GNAQ GNAS HISTIHIBB HNF1A HRAS IDH1 IDH2 JAK1 JAK2 JAK3 KDR	KIT KNSTRN KRAS MAGOH MAP2K1 MAP2K2 MAP2K4 MAPK1 MAX MDM4 MED12 MET MTOR MYC MYCN MYDN MYD88 NFE2L2 NFAS NTRK1 NTRK2 NTRK3 PDGFRA	PDGFRB PIK3CB PIK3CB PIPSTIA PPPRITA PTPN11 RAC1 RAF1 RET RHEB RHOA ROS1 SF3B1 SMAD4 SMO SPOP SRC STAT3 TERT TOP1 U2AF1 XPO1	ARID1A ATM ATR ATRX BAP1 BRCA1 BRCA2 CDK12 CDKN1B CDKN2A CDKN2B CHEK1 CREBBP FANCA FANCD2 FANCI	FBXW7 MLH1 MRE11 MSH6 MSH6 MSH2 NBN NF1 NF2 NOTCH1 NOTCH2 NOTCH3 PALB2 PIK3R1 PMS2 POLE PTCH1	PTEN RAD50 RAD51 RAD51B RAD51C RAD51D RNF43 RB1 SETD2 SLX4 SMARCA4 SMARCB1 STK11 TP53 TSC1 TSC2	AKT1 AKT2 AKT3 ALK AXL AR BRAF CCND1 CCND2 CCND3 CCNE1 CDK2 CDK4 CDK6 EGFR ERBB2 ESR1 FGF19 FGF3 FGFR1 FGFR2 FGFR3	FGFR4 FLT3 IGF1R KIT KRAS MDM2 MDM4 MET MYC MYCN NTRK1 NTRK2 NTRK2 PDGFRA PDGFRA PIK3CA PPARG RICTOR TERT	AKT2 ALK AR AXL BRCA1 BRCA2 BRAF CDKN2A EGFR ERBB2 ERBB4 ERG ESR1 ETV1 ETV4 ETV5 FGFR1	FGFR2 FGFR3 FGR FLT3 JAK2 KRAS MDM4 MET MYB MYBL1 NF1 NOTCH1 NOTCH4 NRG1 NTRK1 NTRK2 NTRK3	NUTM1 PDGFRE PDGFRE PIKSOCA PRKACC PRKACC PTEN PPARG RAD51B RAF1 RB1 RELA RET ROS1 RSPO2 RSPO3 TERT

ALK BCOR BRAF CAMTAL CCNB3 CIC CSF1 CTNNB1 CTNNB1 CFTV BEFV6 BCOR BRAF CAMTAL CCNB3 CIC CSF1 CTNNB1 CTNNB1 CFTV BEFV6 CFT

List of gene targets in the Oncomine Comprehensive Assay v3.



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#### Clinicopathological and molecular characterization of SMARCA4-deficient thoracic sarcomas with comparison to potentially related entities

Akihiko Yoshida<sup>1,2</sup>, Eisuke Kobayashi<sup>2,3</sup>, Takashi Kubo<sup>4</sup>, Makoto Kodaira<sup>2,5,12</sup>, Toru Motoi<sup>6</sup>, Noriko Motoi<sup>1</sup>, Kan Yonemori<sup>2,5</sup>, Yuichiro Ohe<sup>7</sup>, Shun-ichi Watanabe<sup>8</sup>, Akira Kawai<sup>2,3</sup>, Takashi Kohno<sup>9</sup>, Hiroshi Kishimoto<sup>10</sup>, Hitoshi Ichikawa<sup>4,11</sup> and Nobuyoshi Hiraoka<sup>1</sup>

Table 2 Immunohistochemical and molecular results of SMARCA4-deficient thoracic sarcomas

Cases	SMARCA4 IHC	SMARCA2 IHC	AE1/AE3 IHC	CD34 IHC	SOX2 IHC	SALL4 IHC	р53 ІНС	Claudin-4 IHC	SMARCA4 mutation	Other genetic alterations <sup>a</sup>
1	Lost	Lost	3+ (m)	2+ (s)	3+ (s)	3+ (s)	Pos	0	1658del19 (L553fs)	MAP3K1, RET, NTRK3, TP53, NF1
2	Lost	Lost	$0_{\rm p}$	3 + (s)	3 + (s)	1+ (w)	Neg	0	NA	NA
3	Reduced	Lost	$0_{\rm p}$	2 + (s)	2+(s)	2+ (w)	Neg	0	NA	NA
4	Lost	Lost	1+ (m)	1+ (m)	3+(m)	0	Pos	NA	NA	NAc
5	Reduced	Lost	0	2 + (s)	3 + (s)	3 + (s)	NA	NA	NA	NA
6	Lost	Retained	3+(s)	0	0	0	Pos	0	C3034T (Q1012X)	CDKN2A, CREBBP, TP53, NF1, EP300
7	Reduced	Lost	$0_{\rm p}$	3 + (s)	3 + (s)	2 + (s)	Neg	NA	NA	NA <sup>c</sup>
8	Lost	Lost	1 + (s)	3 + (s)	3 + (s)	3 + (s)	NA	NA	NA	NAc
9	Lost	Lost	1+ (s)	0	3+(s)	3 + (s)	Pos	0	NA	NA
10	Reduced	Lost	$0_{\rm p}$	3 + (s)	3 + (s)	3 + (s)	Pos	0	2396delA (H799fs)	TP53, KEAP1
11	Lost	Lost	0	1 + (s)	$0_{\rm p}$	2+(s)	Pos	0	G2098T (E700X)	ARID1A, PTCH1, TP53
12	Lost	Lost	3+(s)	1 + (s)	3 + (s)	1 + (s)	Pos	0	1629delC (D543fs)	CDKN2A, KRAS, TP53, MYC (amp)

Abbreviations: amp, amplification; IHC, immunohistochemistry; m, moderate; NA, data not available; neg, negative; pos, positive; s, strong; w, weak. aOnly known, registered, or truncated mutations are listed; refer to Supplementary Table 5 for the full list of the detected mutation variants.

Review > Histopathology. 2024 Jan;84(1):86-101. doi: 10.1111/his.15063. Epub 2023 Oct 24.

#### NUT carcinoma and thoracic SMARCA4-deficient undifferentiated tumour: facts and controversies

Akihiko Yoshida 1 2





#### Treatment of Thoracic SMARCA4-Deficient Undifferentiated Tumors: Where We Are and Where We Will Go

Vito Longo 1,\*, Annamaria Catino 1, Michele Montrone 10, Elisabetta Sara Montagna 1, Francesco Pesola 1, Ilaria Marech 1, Pamela Pizzutilo 1, Annalisa Nardone 20, Antonella Perrone 1, Monica Gesualdo 1 and Domenico Galetta 100

#### Treatment:

Surgery

High rate of recurrence; useful only for stage I.

Chemotherapy Radiotherapy

Weak response. Resistance.

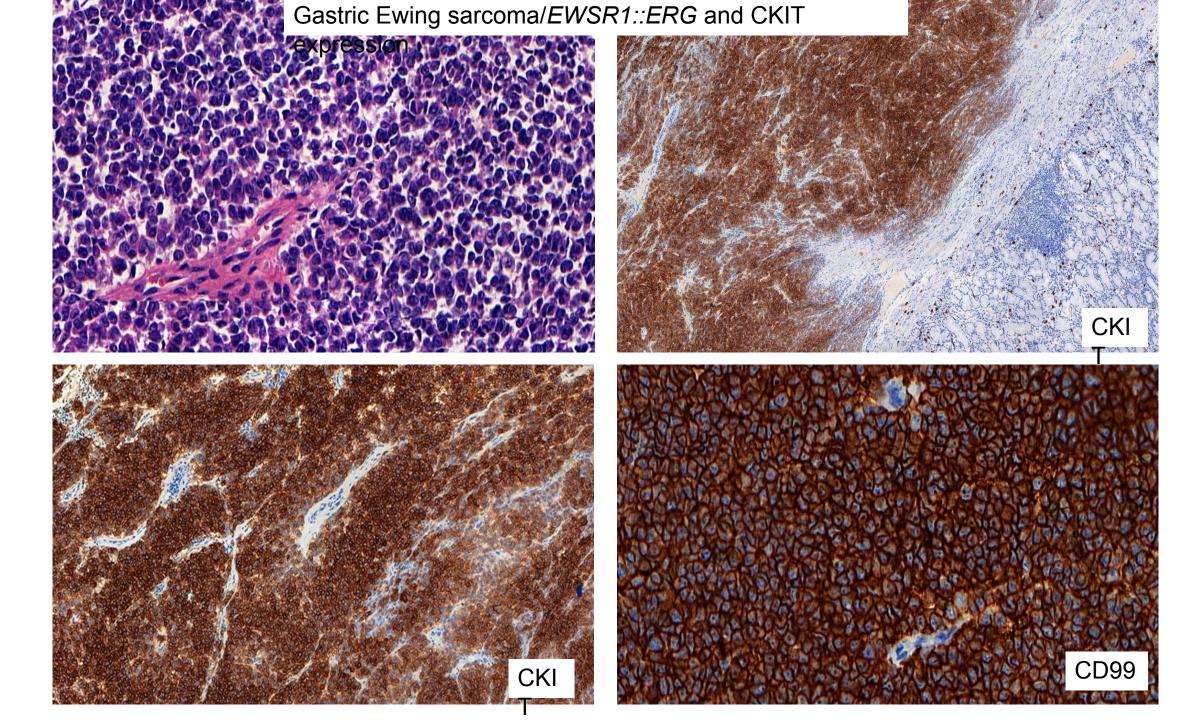
Promising efficacy

[4-9,56,60,62,63]

Immunotherapy

bStaining in < 1% of cells.

<sup>&</sup>lt;sup>c</sup>Complex karyotypes by conventional cytogenetics.







## CASE 2

Dr. Mary Ann Stevens



## Clinical Case

Dr. Mary Ann Stevens P.

Medical Oncologist.

SELNET meeting 21 / 11 / 2024.

## Clinical history

• Female, born 1999 (25 years old).

- No smoking history, no alcohol overuse, no comorbidities.
- No relevant concomitant medication.
- No relevant family history

## Initial presentation and history

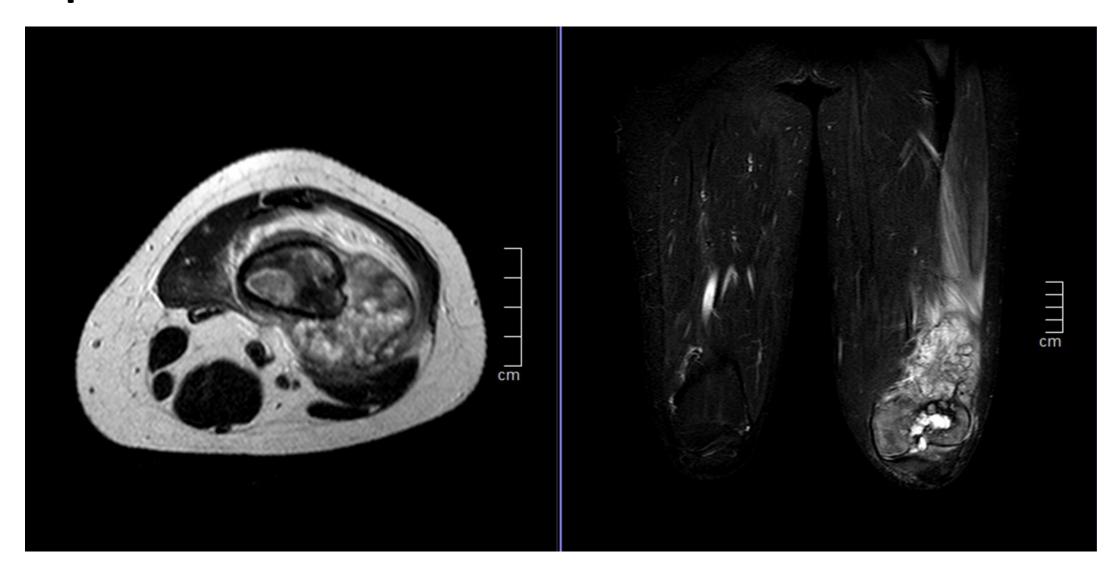
#### **April 2019 (19 years old):**

• Noted Increased volume in the left distal femur.

#### September 2019:

- MRI Findings: Tumor in the distal femur, maximum diameter 11 cm.
- **Histology:** High-Grade (3/3) Osteosarcoma (osteoblastic subtype with pleomorphic component).
- **Staging Workup:** TC-TAP and PET scan negative for distant metastases.

## September 2019



#### **Initial Treatment**

#### Neoadjuvant Chemotherapy:

Oct 2019 – Jan 2020: MAP protocol: 3 cycles Cisplatin + Adriamycin, 2 cycles Methotrexate.

#### Surgical Intervention:

29 Jan 2020: Block excision with left knee prosthesis reconstruction.

Pathology Report: Good response with 92% tumor necrosis.

#### Complications Post-Surgery:

Prosthesis infection, treated with antibiotics and replacement.



## Adjuvant Treatment and Follow-up

#### **Adjuvant Treatment**

- July 2020 Feb 2021: 6 months after surgery
  - 3 cycles Adriamycin, 3 cycles Cisplatin, 7 cycles Methotrexate (total 6AP/9MTX)

#### Follow up

• Dec 2021:MRI femur: Negative.

CT Thorax: Suspicious 6 mm pulmonary nodule (LSI).

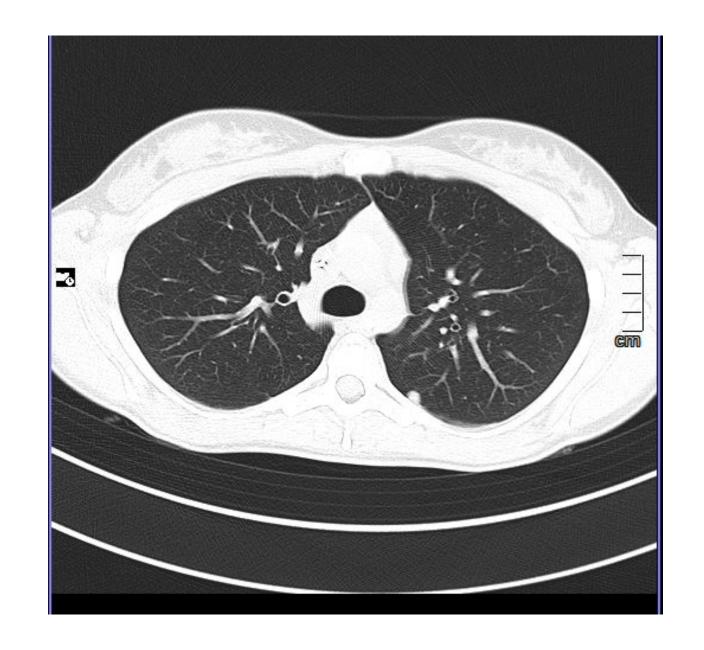
• Feb 2022:CT Thorax: Nodule increased to 8 mm.

#### Feb 2022:

• Pulmonary nodule 8 mm.

#### **April 2022:**

- VATS right upper lobe resection.
- Pathology: Metastatic osteosarcoma, necrosis absent, mitotic index 25/10 HPF.

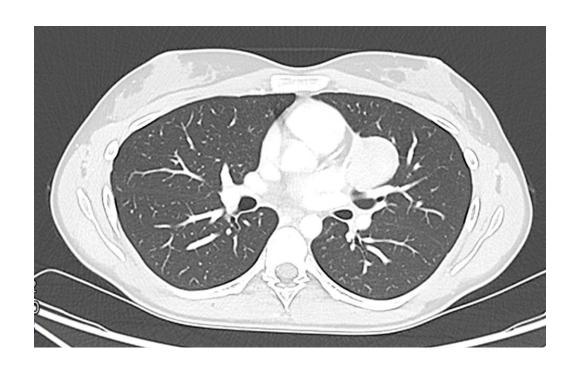


#### Treatment and evolution - Osteosarcoma femur

#### March 2023:

• New 39 mm nodule (LSI).





• Ifosfamide High Dose (HD): Prolonged infusion over 14 days, every 28 days.

May 2023: Progression after 2 cycles

#### Treatment and evolution - Osteosarcoma femur

#### May 2023:

- **Gemcitabine + Docetaxel:** Completed 5 cycles by Oct 2023.
- Outcome: Partial Response.

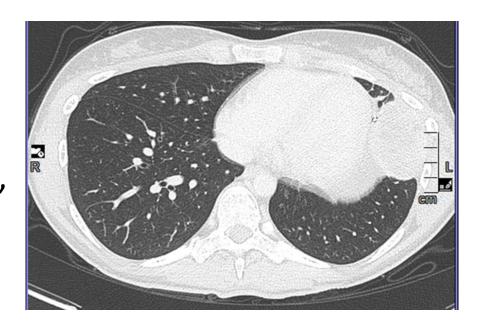
#### Nov 2023:

- VATS left upper lobe resection.
- Post-op: Complicated by massive hemothorax requiring surgery.



May 2024: (6 months after the last lobectomy)

• New 6 cm expansive lesion in the left cardiogenic angle, adherent to the diaphragm, lateral chest wall, and pericardium.

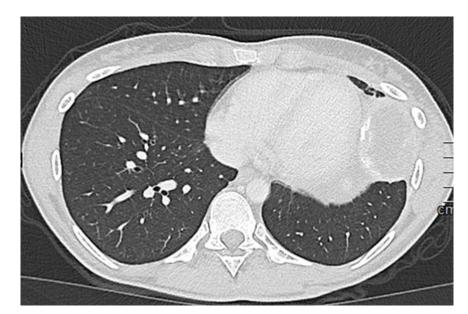




 Gemcitabine + Docetaxel (first 2 cycles only GEM due to toxicity)

TC after 3c: SD

Oct 2024: Stable Disease after 6 cycles.

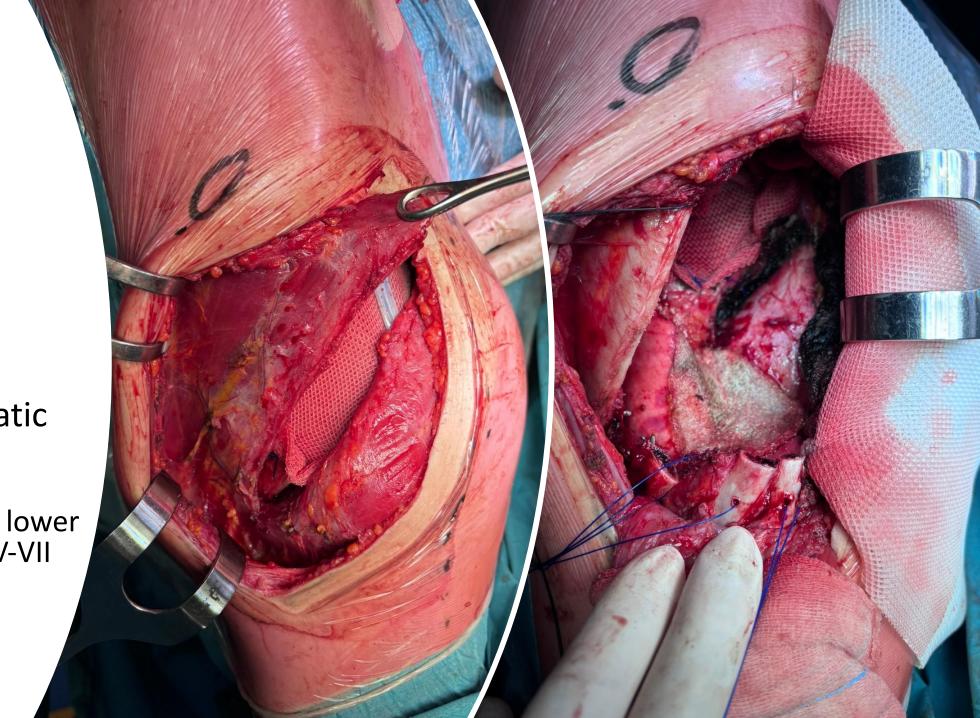


October 2024:

**Surgery:** Lateral thoracotomy

 Block excision of supradiaphragmatic neoplasm

> Resection of diaphragm, left lower lung lobe, ribs V-VII



## **Pathology Report**

- **Specimen:** 7 cm supradiaphragmatic mass
- Histology: Pleomorphic and spindle cell morphology with prominent osteoid matrix production
- Vital Tumor: 85% viable tumor cells
- Mitotic Activity: High mitotic index (20 mitoses per 10 HPF)

The tumor exhibited extensive necrosis and hemorrhage. It infiltrated surrounding soft tissues, pleura, diaphragm, and the periosteum of ribs V and VI, confirming a high-grade metastatic osteosarcoma with significant local invasion.

## Discussion points

#### **Surgical Intervention:**

- Option for left pleuropneumonectomy?
- In the event of another thoracic relapse, what factors should guide the decision of a further surgery?

#### **Role of Radiotherapy:**

 Could radiotherapy be an effective modality for controlling recurrent pulmonary metastatic nodules in osteosarcoma?

#### **Systemic Therapy Options:**

- Any role for pseudo-adjuvant ChT treatment?
- Further options?

## CASE 3

• Dr. Tomás Soulé



INSTITUTO ALEXANDER FLEMING

Female PS 0

Medical history

2011 Graves síndrome (Radiotherapy)

2013 Cardiac ablation

2018 Uterine Prolapse



#### 07/2024

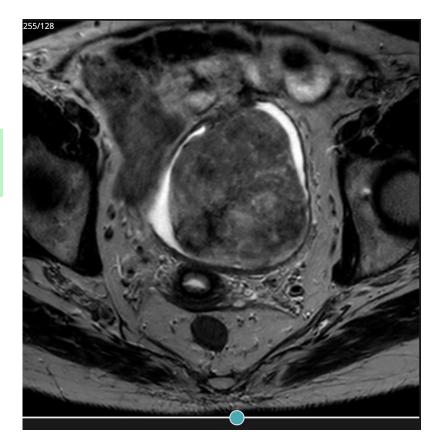
#### Lower abdominal pain

US: bladder

polyp

MRI: the lesion occupying the entire of the

intravesical space



Medical history

Female

PS 0

2011 Graves síndrome (Radiotherapy)

2013 Cardiac ablation

2018 Uterine Prolapse



#### 09/2024

In another institution tried to Access to do the biopsy by cystoscopy, but they can't do so due to the stoppage of the lesion at the bladder entrance

They decided to do it by Pfirenstein incisión: with partial cistectomy

Medical history

Female PS 0

2011 Graves síndrome (Radiotherapy)

2013 Cardiac ablation

2018 Uterine Prolapse

09/2024

Pathology report: leiomyosarcoma IHQ:

- Vimentine +
- AML +
- Desmine +
- AE1AE3, S100 negative



#### PATOLOGÍA ALTA COMPLEJIDAD

Dr. Ricardo Sánchez Marull MN 73.118 Dr. Esteban Maronna MN 101.241 Dra. María Carla Adami MN 102.836

Médicos consultores: Dr. Claudio Lewin MN 65.046

Médicos colaboradores: Dra. Gloria Inurrigarro MN 108.208 - Dra. María Fernanda Agost Carreño MN 101.079

Dra. Victoria Gramigna MN 105.601 - Dra. Maria Dolores Sciaccaluga MN 140.617
Dra. Agustina Dupont MN 148.476 - Dra. Patricia Vega MN 129.918
Dra. Maria Clara Corrales Morey MN 133.259 - Dra. Agustina Bruno MN 162.496

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Dra. M. Victoria Cavoti Sadonio MN 111.677 - Dra. Maria Belén Centurión MN 161.306

Dr. Julio César Barrozo MN 170.635

ertenece a LOPREIATO MARIA CRISTINA

Protocolo

24A-034243

Chernobilsky Victor

Fecha

13 de septiembre de 2

Indicado por

SANATORIO ANCHORENA

Registro

Afiliado

39728623

Obra social
Material:

AVALIAN Vejiga

#### MACROSCOPIA:

1) Se recibe vejiga en dos fragmentos irregulares que en conjunto miden  $10 \times 7 \times 6$  cm. Superficie externa irregul sectores despulida y retraída. Al corte se observa lesión tumoral blanquecina, friable y focos de hemorragia que n  $6.5 \times 6 \times 5$  cm. Infiltra toda la pared. (1A-1F: VF/R)

2) Se reciben dos fragmentos parduscos que miden 1,5 x 1,3 cm. (2F/R)

#### MICROSCOPIA:

1) Los cortes histológicos muestran una proliferación de células neoplásicas ahusadas, con núcleos elongados de moderada anisonucleosis y presencia de figuras mitóticas (hasta 8 por milímetro cuadrado), dispuestas formando fascículos entrecruzados, con focos de necrosis que comprometen menos del 50% del tumor.

Se realizaron técnicas de inmunohistoquimica con los siguientes resultados:

Vimentina: Positivo

Actina de musculo liso: Positivo

Desmina: Positivo

Citoqueratina AE1AE3: Negativo

Proteina S100: negativo

Ki-67: 25%

 Los cortes histológicos muestran fragmentos de tejido conectivo y muscular con fibrosis. No se observan célu atípicas.

#### DIAGNOSTICO:

1) VEJIGA, RESECCION:

-LEIOMIOSARCOMA (GRADO 2)

2) VEJIGA (TOMA PROFUNDA), BIOPSIA:

-FIBROSIS

Octubre 03, 2024

En

ml



Female PS 0

Medical history

2011 Graves síndrome (Radiotherapy)

2013 Cardiac ablation

2018 Uterine Prolapse



#### 09/2024

#### Review in our institution: Dr. Gonzalez Lucia

- Spindle cells with plump nuclei and moderate to abundant, pale to eosinophilic citoplasma
- Cells are set in long intersecting fascicles perpendicular to the plane of section
- Moderate nuclear pleomorphism is usually noted
- Mitotic figures and foci of necrosis

#### IHQ:

AML +

Desmine +

S100 -

Sox 10 -

Tle1 -

CD34 -

Ck8/18 -

Medical history

Female

PS<sub>0</sub>

2011 Graves síndrome (Radiotherapy)

2013 Cardiac ablation

2018 Uterine Prolapse



#### 09/2024

#### Review in our institution

- Spindle cells with plump nuclei and moderate to abundant, pale to eosinophilic citoplasma
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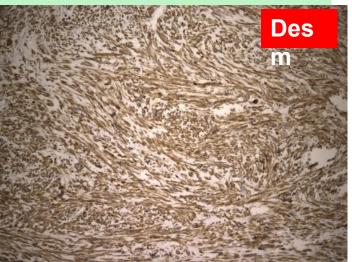
• Mitotic figures and facine fractions

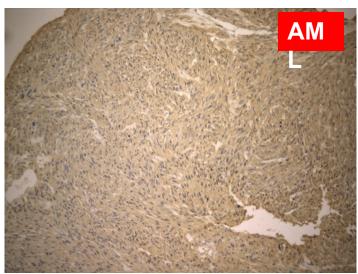
IHQ

AML +

Desmine +

\$100 
Sox 10 
Tle1 
CD34 
Ck8/18 -





Medical history

Female

PS<sub>0</sub>

2011 Graves síndrome (Radiotherapy)

2013 Cardiac ablation

2018 Uterine Prolapse



#### 10/2024

#### PET-FDG:

- Hypermetabolic focus projected onto the anterior and superior wall of the bladder, without clear morphological translation in the CT scan. Maximum SUV 29.8.
- Slight metabolic increase projected onto the post-surgical anatomical traces on the anterior abdomino-pelvic wall.
   Maximum SUV 3.6.

Medical history

Female

PS 0

2011 Graves síndrome (Radiotherapy)

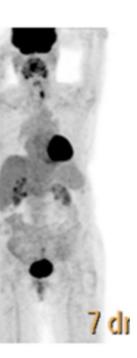
2013 Cardiac ablation

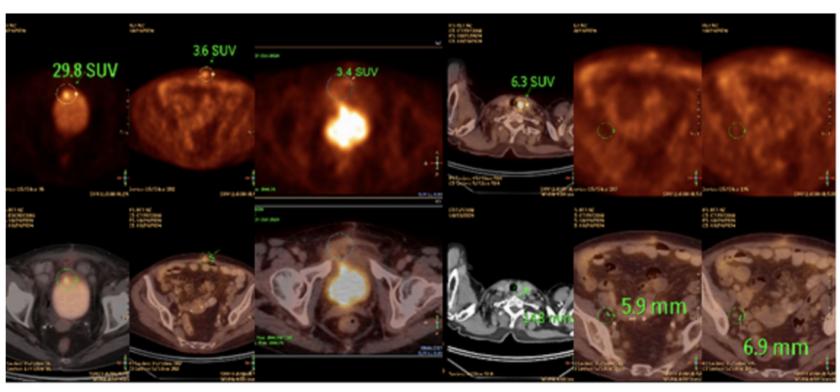
2018 Uterine Prolapse



#### 10/2024

PET-FE
• Hype wall the C
• Sligh anat Maximum





Female PS 0

Medical history

2011 Graves síndrome (Radiotherapy)

2013 Cardiac ablation

2018 Uterine Prolapse



#### 10/2024

#### MRI:

 Post-surgical changes in the right anterolateral wall of the bladder, identifying subtle segmental parietal thickening with post-contrast enhancement.



#### **Questions to the MDT:**

- Adjuvant chemotherapy
- Need for cystectomy (pending transurethral resection)



# Instituto Nacional de Cancerología

CASE 4

- Dr. Karen Archaga Fiallos R2 OM
- Dr. Kevin Reyna Perez R2OM
- Dr. Haydee Caro Oncology Patologist



## Medical Record

- 22-year-old woman.
- Family history: Grandmother with Diabetes mellitus, non specified arrythmia.
- Non Pathological
  - Tobacco, 1 cigar per week for 7 years.
  - Alcohol, twice a week for 7 years, stopped 3 months ago.
  - Drugs: Ecstasy, cocaine, hallucinogenic mushrooms, regular marijuana use.

- Pathological
  - Arrythmia, Heart Failure Reduced LVEF, Empaglifozin 10 mg QD, Propranolol 10 mg BID, Ivabradine 2.5 mg QD
  - PCOS 17 yr old
  - Abril 2024 radical left nefrectomy
  - No allergies, blood transfusions.





#### February 2024

Increase in abdominal circumference, accompanied with pain.

Image studies: left kidney tumor and apparent tumor thrombus in the vena cava.



#### Abril 2024

Open radical left nefrectomy + tumoral thrombus in vena cava



#### May 2024

Histopathological report: primary monophasic synovial sarcoma of the kidney with necrosis and hemorrhage, tumor size 12 cm, lymphovascular infiltration (+), 1/6 lymph nodes with metastasis; IHC vimentin (+), CD99 (+), Bcl-2 (+)

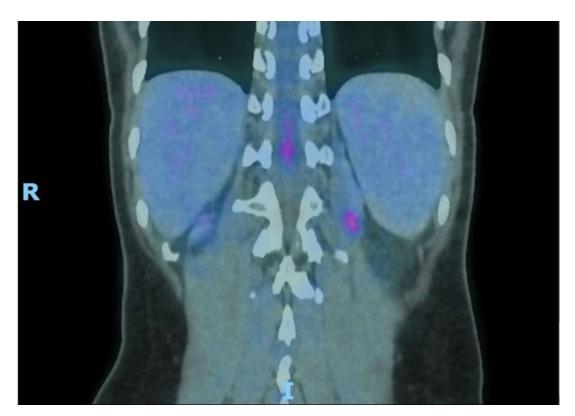


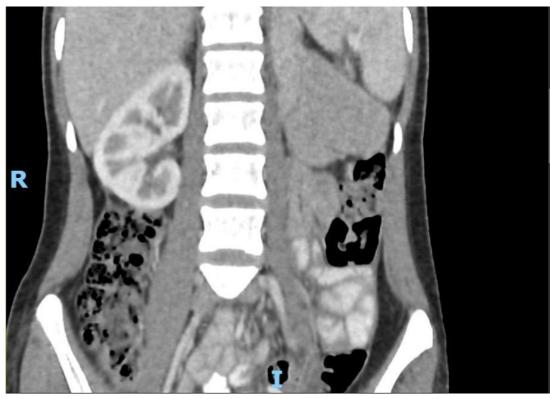
#### June 2024

PET CT 18 FDG: marker overexpression, paraaortic SUVmax 3.11, left psoas SUVmax 2.4

## Oncological Medical History

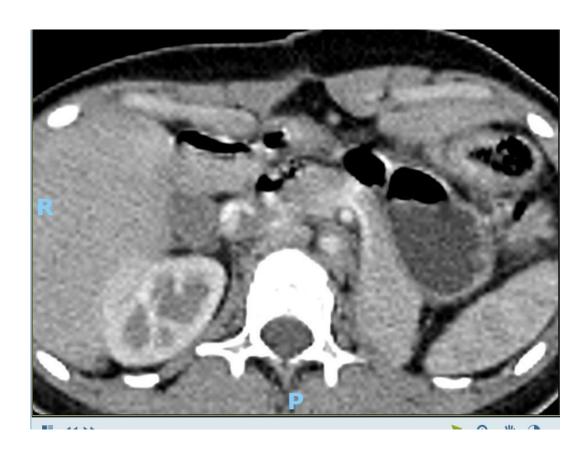
PET 06/11/2024





## Oncological Medical History

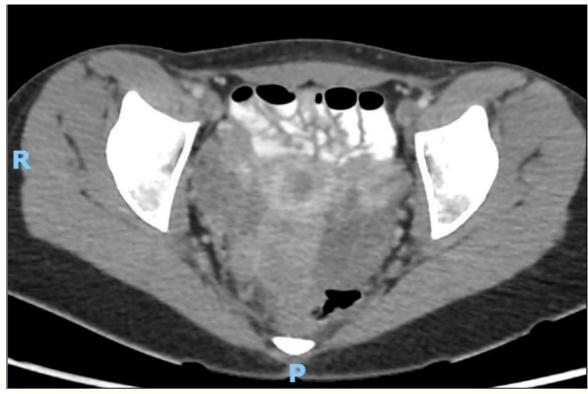
PET 06/11/2024



## Oncological Medical History

PET 06/11/2024









### Physical examination

Laboratory

Midline wound with keratotic scar.

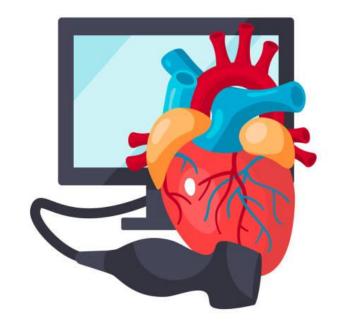
No lymphadenopathy was identified. • Hematological, liver and kidney function within reference levels.



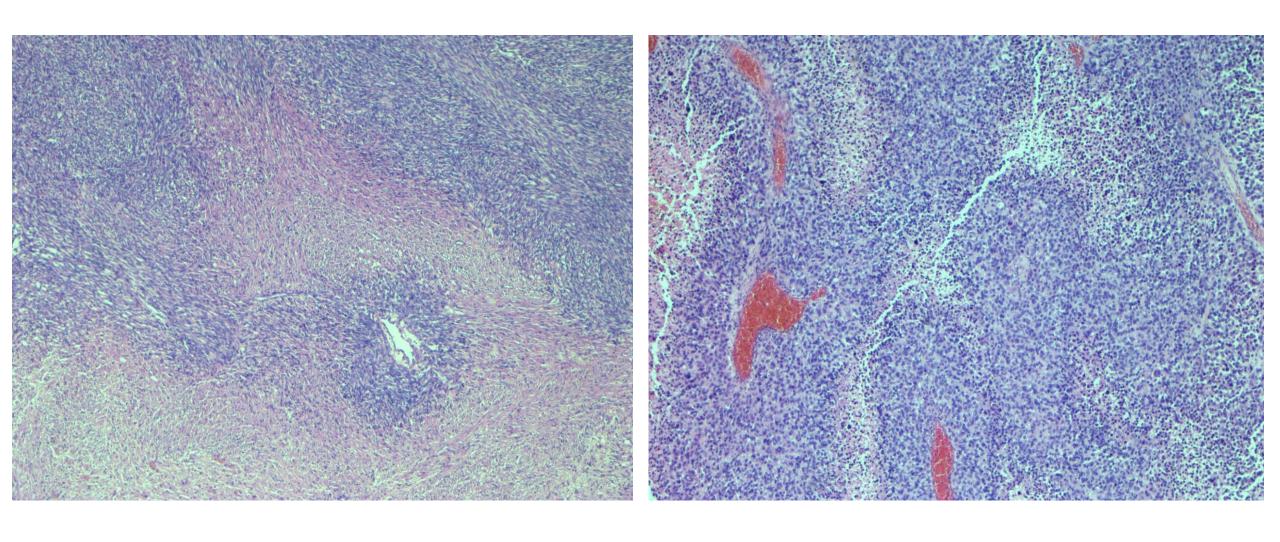


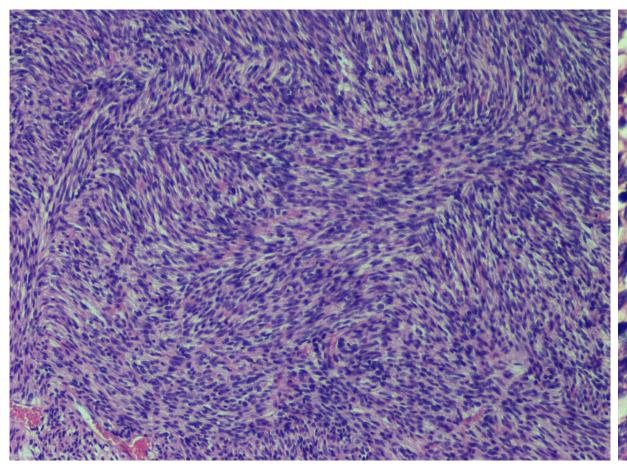
### Echocardiogram 10/18/2024

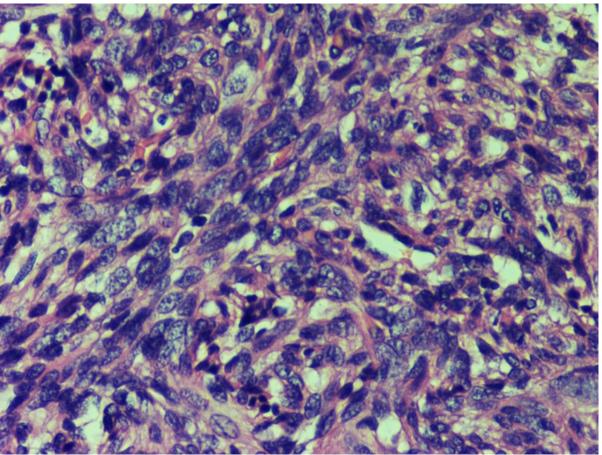
• Echocardiogram: Left ventricle not dilated, normal with generalized hypokinesia, left ventricular systolic dysfunction, LVEF 40%, ejection fraction 39%, mild functional tricuspid insufficiency.

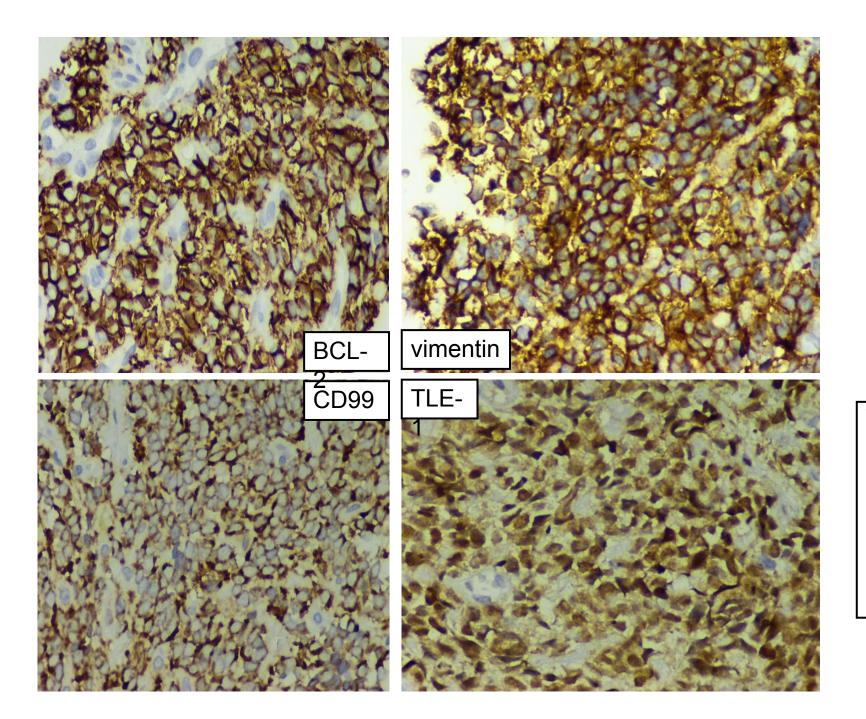


## LEFT NEPHRECTOMY FOR SECOND OPINION









# FIRST IHQ RESULTS:

- S100, WT1, CKAE1/E3, CD34, DESMIN, EMA NEGATIVE
- CD99 and VIMENTIN POSITIVE

#### We add:

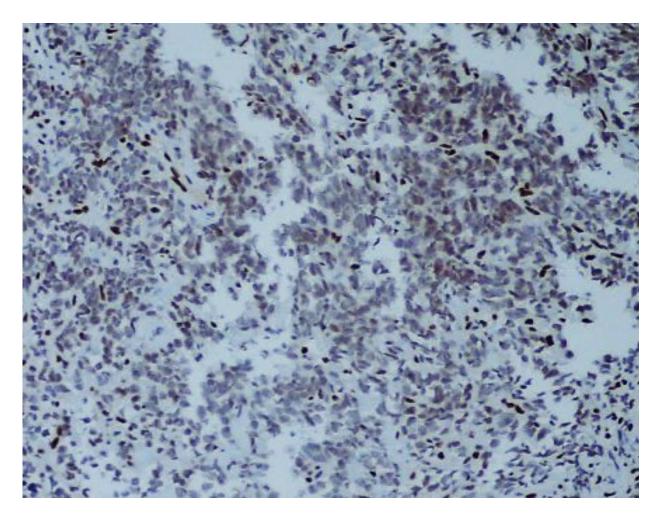
- Bcl-2 Positive
- CD10 Negative
- Sinaptofisin Negative
- TLE-1 Positive

#### PARAFFIN BLOCKS AND SLIDES FOR SECOND OPINION

#### LEFT NEPHRECTOMY:

- MONOPHASIC SYNOVIAL SARCOMA (G3) WITH 15% NECROSIS
- WITHOUT INFILTRATION OF THE CAPSULE
- TUMORAL SIZE: 12 CM (ORIGINAL REPORT)
- SECTION EDGES: NOT EVALUABLE.

\*WITH A TUMORAL THROMBUS IN THE RENAL VEIN



SS18 focal



### INFORME DE ESTUDIO DE HIBRIDACIÓN IN SITU FLUORESCENTE (FISH) SS18 (18q11.2) Break Apart Probe

#### Métodología

El FISH se realizó en las zonas marcadas por el patólogo, una laminilla se hibridó con la sonda Vysis LSI SS18 (18q11.2) Dual Color Break Apart Rearrangement Probe (Abbott Molecular). Se contaron 50núcleos en un microscopio de fluorescencia Zeiss para establecer la cantidad, patrón y distribución de señales. Se considera presente cuando se identifica la alteración > o igual al 12%

#### Los resultados fueron los siguientes:

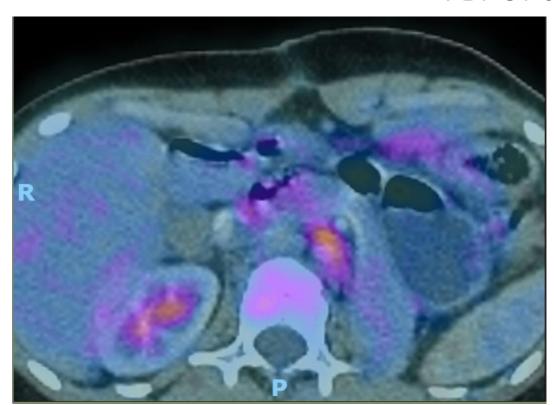
Sonda	% de nucleos con rearreglo								% de nucleos con patrón . citogenético no mal							Interpretación									
SS18 (18q11.	0%							58%							RUPTURA AUSENTE										
Probe																									

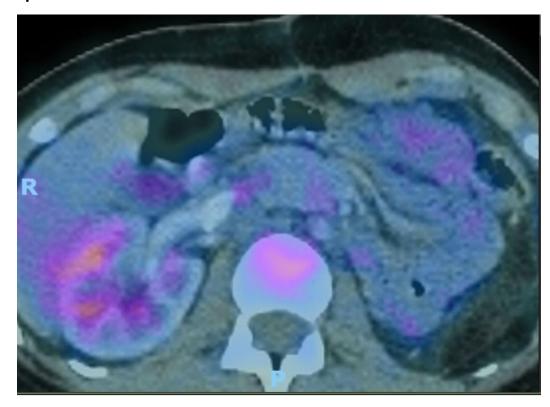
Observaciones:





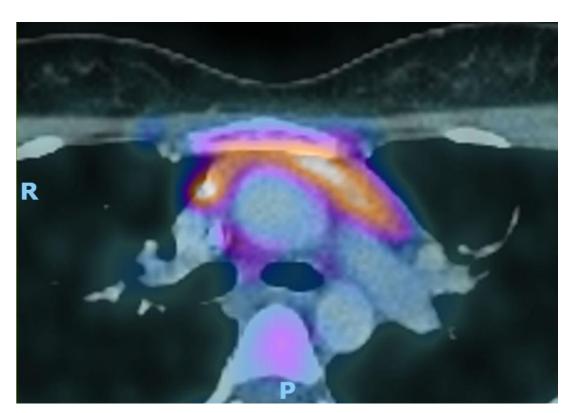
PET CT 09/25/24

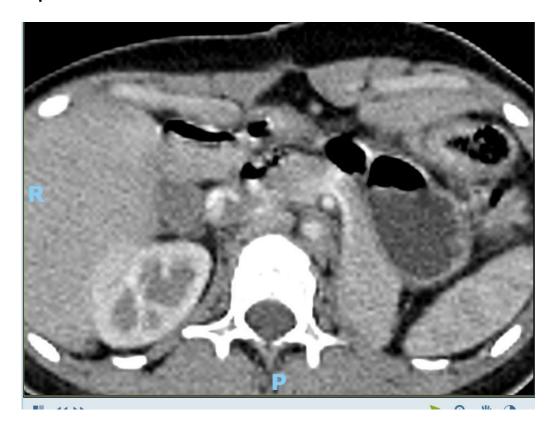






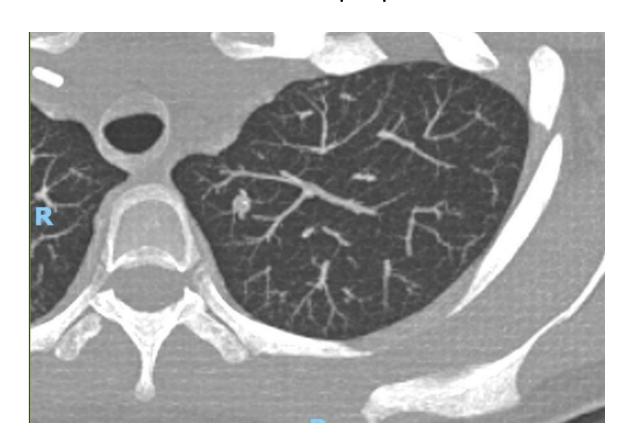
### PET CT 09/25/24



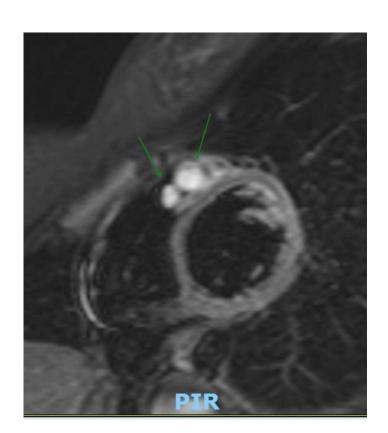




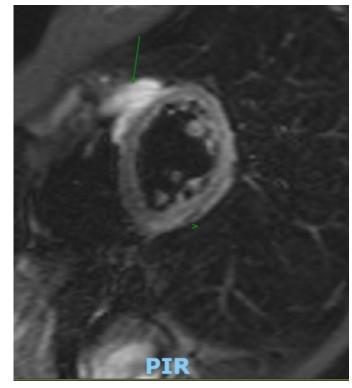
### PET CT 09/25/24







### **Cardiac MRI 11/12/24**

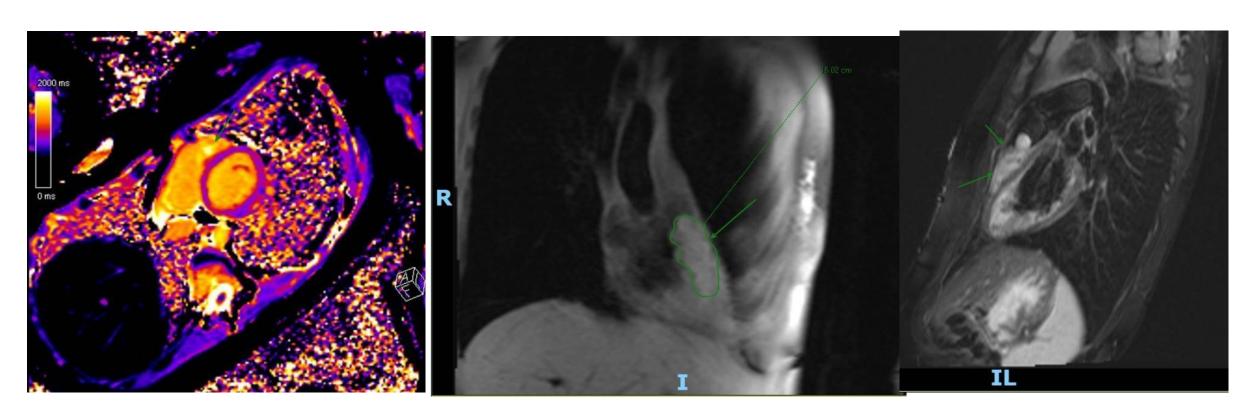


Heterogeneous lesion in the right ventricle and right ventricular outflow tract, similar lesion in the right atrium, suggestive of secondary deposits.

Left ventricle with mild systolic dysfunction (LVEF 51%)



### Cardiac MRI 11/12/24





### Discussion

• What is your opinion about systemic treatment, ¿which scheme?



