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# Interhospital conference

## Case 3

24<sup>th</sup> December 2021

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# Introduction

- An increased rate of AIDS and non-AIDs defining cancers

## AIDS defining cancers

- Kaposi sarcoma : HHV8
- B-cell non-Hodgkin lymphoma : **EBV**
- Uterine cervical neoplasia : HSV
- Primary effusion lymphoma : **EBV**, HHV8
- Primary CNS lymphoma : HSV

## Non-AIDS defining cancers

- Hodgkin lymphoma : **EBV**
- Head and neck cancer : HPV, **EBV**
- Anal cancer : HPV
- Lung cancer

- Smooth muscle tumors :

### Leiomyomas

- Smooth muscle hamartoma
- Angioleiomyoma
- Cutaneous leiomyomas
- Estrogen receptor positive
- GI Mural leiomyoma
- GI Muscularis mucosae leiomyomas
- Bronchial leiomyoma
- Urinary bladder
- Visceral organ
- **EBV-associated**

### Leiomyosarcomas

Nuclear atypia and mitotic activity  
(potential for metastasis)

- Peripheral soft tissue
- Retroperitoneal leiomyosarcomas
- GI leiomyosarcoma
- Urinary bladder
- Visceral organ
- **EBV-associated**

# EBV-Associated Smooth Muscle Tumors

- EBV entry via receptor CD21 on smooth muscle cells
- Found in immunocompromised host
  - HIV infection
  - Post-transplantation
  - Others: autoimmune disease, common variable immunodeficiency syndrome

TABLE 1: Countries reporting SMT in patients with HIV/AIDS.

Region	Country	# of Publications	# of SMT cases	
North America	USA	19	38	54%
	Canada	1	1	
Asia	Thailand	3	11	17%
	Hong Kong	2	3	20%
	Taiwan	1	1	
	Singapore	1	1	
Europe	France	4	5	17%
	Spain	2	2	
South America	Argentina	1	1	
	Peru	1	1	

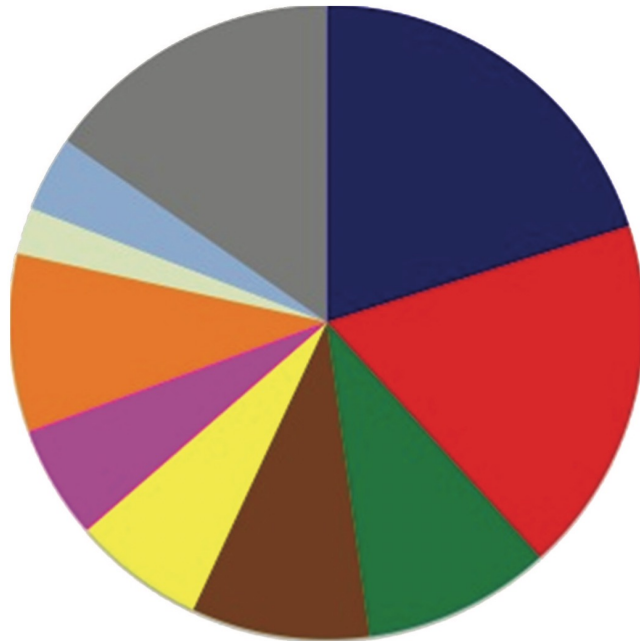
## Epidemiology Findings

- Male : female ratio = 1.3 : 1
- Average 25 years of age (2.7 – 49 yrs old)
  - 30% age <10 years old
  - 5% age 10-20 years old
  - 66% age >20 years old
- Modest immunosuppression :
  - Mean CD4 count = 60cells/ $\mu$ L  
(0 - 330cells/ $\mu$ L)
  - Mean HIV viral load = 203,302copies/mL
- The time from HIV diagnosis to SMT presentation : <1 month to 18 years

TABLE 2: Age and gender distribution of SMTs in patients with HIV/AIDS.

Patient age (years)	Male	Female
<10	7	12
10–20	1	2
>20	28	14
<b>Total Cases</b>	<b>36</b>	<b>28</b>

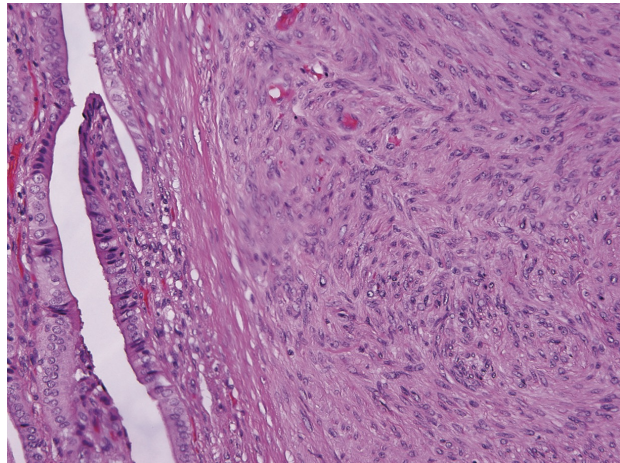
## Clinical Features



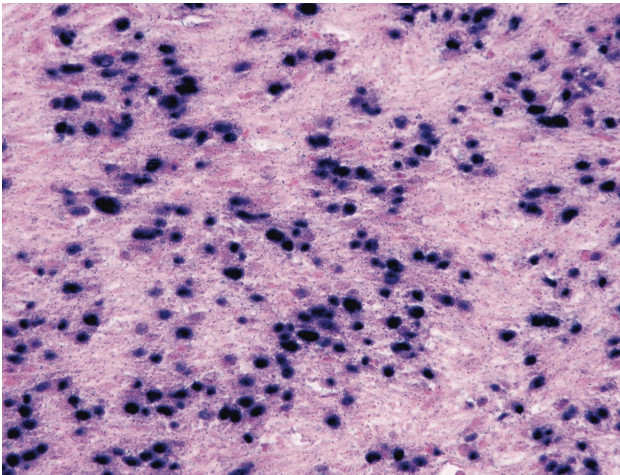
- CNS (brain and spinal cord) *N* = 24
- Soft tissue *N* = 22
- Lung *N* = 12
- Liver *N* = 11
- Adrenal *N* = 8
- Hematopoetic (spleen (4), lymph nodes (3)) *N* = 7
- Head and neck (oropharynx (4), nose/sinus (1), larynx (3), eye/orbit (3)) *N* = 11
- Bone *N* = 3
- Other less frequent sites (gallbladder (1), genital tract (1), kidney (1), serosal membranes (2)) *N* = 5 total
- GI tract (large intestine (9), small intestine (4), stomach (3))

- EBV-SMT involved almost every body location :
  - 1<sup>st</sup> CNS : dural, epidural, or extradural
  - 2<sup>nd</sup> soft tissue : thigh, gluteal, abdominal wall and paraspinal
  - 3<sup>rd</sup> GI tract : tongue, palatine tonsil, stomach, small intestine, gallbladder and colon
  - 4<sup>th</sup> Lung
  - 5<sup>th</sup> Liver
  - 5<sup>th</sup> Head and neck : oropharynx, larynx(vocal cord), eye/orbit and nose/sinus
  - 6<sup>th</sup> Adrenal gland
  - 7<sup>th</sup> Hematopoetic
  - 8<sup>th</sup> Bone : vertebrae
  - Others : Genitourinary tract(renal, vulva), serosal membranes(pleura,pericardium)

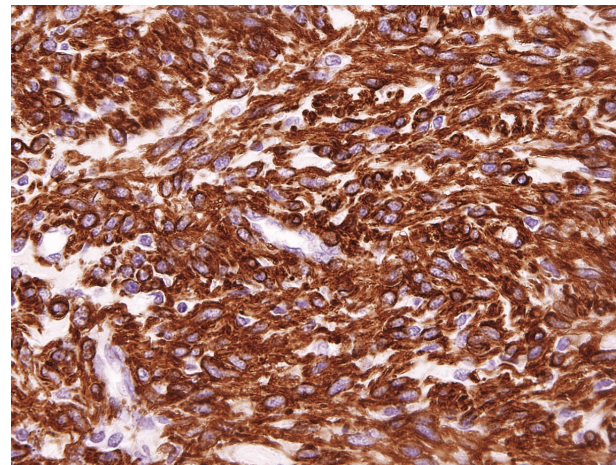
# Histological Findings



**H&E stain :**  
Atypical spindle cells with blunt-ended nuclei and eosinophilic cytoplasm



**In situ hybridization :**  
Epstein-Barr virus encoded RNA (EBER) positive in the tumor cell nuclei (blue)



**Immunohistochemical stain :**  
strongly positive for alpha smooth muscle actin

TABLE 4: Immunohistochemical stains with positive immunoreactivity in EBV-SMT.

Immunostain	Positive cases	Negative cases
Smooth muscleactin (SMA)	39	0
alpha-smooth muscle actin (AMA)	17	0
Muscle-specific actin (MSA)	9	0
Desmin	42	6
Vimentin	5	2
CD21 (C3d Receptor; EBV receptor)	9	2
Caldesmon	1	0
Myosin Smooth muscle heavy chain (SMHC)	1	0
Calponin	1	0



## Case report of EBV-Associated tumors at adrenal gland

Source	Presentation	Age/Sex	CT finding	Histology	Immunodeficiency state	Associated clinical disease	Treatment	Outcome
Heffernan et al, 1995	Autopsy	2/ Male	-	Leiomyoma	AIDs	non-Hodgkin lymphoma of the brain	-	-
Zetler et al, 1995	-	30/ Male	-	Leiomyosarcoma	AIDs	-	Surgery	No recurrence at 20 mo resection
Shaw et al, 2012	2-month abdominal and back pain	12/ Female	Rt - 21x12x11 cm Lt - 6x5x4.5 cm	-	Natural killer cell deficiency	-	Surgery	No recurrence at 26 mo resection
Petrilli et al, 2014	failure to thrive	7/ Female	Bilat - inhomogeneous mass with central necrosis and a solid rim		Common variable immunodeficiency	Nasal cavity and brain DLBCL	Surgery with BM transplatation	No immune recovery and died 5 yrs later from DLBCL

**Table. Characteristics of 17 AIDS Patients with EBV-associated Smooth-muscle Tumors (SMTs)** **Case report of EBV-Associated tumors in Thailand**

Year	Age (years), sex	Tumor site(s)	SMTs				HIV			EBV			Treatment		Outcome, FU duration (months)
			Duration, month(s)	Age at HIV diagnosis	EBER-1 ISH	Mitoses No/HPF	CD4 count cells/ $\mu$ L (%)	HIV VL	VL (copies/mL)	VCA (titer)		EBNA IgG (titer)	SMTs	HIV (before or at SMT diagnosis)	
										IgM	IgG				
2001	4, F	Iris and abdominal wall <sup>a</sup>	1	Newborn	Positive	>10	5 (1)	NA	NA	NA	NA	NA	Incomplete removal	AZT, ddI (at)	DOD, 12
2001	34, F	Spinal epidura and adrenal glands <sup>a</sup> and abdominal wall	1	26	Positive	1-3	160 (5)	BDL	NA	NA	NA	NA	Incomplete removal, RT	d4T, 3TC, NVP (before) switched to TDF, 3TC, EFV	AWD, 24
2002	49, F	Cranial and spinal epidura, adrenal glands <sup>a</sup> , vocal cord <sup>a</sup> and orbit	12 (spinal) and 1 (orbit, and vocal cord)	46	Positive	1-3	26 (5)	79,530	22.5	Negative	Positive (>140)	Positive (>100)	Incomplete removal, RT	AZT, ddI (before); switched to d4T, 3TC, NVP	DOD, 48
2002	38, M	Liver and lung <sup>a</sup>	4	28	Positive	1-3	150 (15)	470,870	45,108	Negative	Positive (>140)	Positive (>100)	Biopsy	AZT, ddI (before)	DOD, 6
2002	43, F	Cranial and spinal epidura	24 (spinal) and 3 (brain)	39	Positive	>10	26 (4)	NA	BDL	Negative	Positive (>140)	Positive (>100)	Incomplete removal, RT	AZT, ddI (before); switched to d4T, 3TC, NVP	DOD, 4
2003	34, F	Cranial epidura	3	28	Positive	1-3	7 (1)	NA	BDL	Negative	Positive (>140)	Positive (>100)	Incomplete removal	d4T, 3TC, NVP (before)	DOD, 8
2003	31, F	Cranial and spinal epidura	3	31	Positive	1-3	3 (1)	NA	BDL	Negative	Positive (>140)	Positive (>100)	Incomplete removal, RT	NA	DOD, 5
2004	36, M	Cranial epidura and thigh	1	36	Positive	1-3	20 (1)	44,900	BDL	Negative	Positive (>140)	Positive (>100)	Complete removal	AZT, 3TC, EFV (at); switched to TDF/FTC, EFV	ANED, 96
2004	39, M	Cranial epidura	12	37	Positive	1-3	209 (9)	6,780	BDL	Negative	Positive (>140)	Positive (>100)	Complete removal	d4T, 3TC, NVP (at)	ANED, 36
2004	32, F	Cranial epidura	2	22	Positive	NA	319 (18)	BDL	BDL	Negative	Positive (>140)	Positive (>100)	Complete removal, RT	d4T, 3TC, NVP (before)	ANED, 84
2004	32, M	Vocal cord	6	28	Positive	>10	131 (5)	BDL	BDL	Negative	Positive (>140)	Positive (>100)	Complete removal	d4T, 3TC, NVP (before) switched to TDF, 3TC, EFV	ANED, 84
2007	33, F	Cranial and spinal epidura and pleura <sup>a</sup>	7	28	Positive	1-3	98 (10)	BDL	BDL	Negative	Positive (>140)	Positive (>100)	Incomplete removal, RT	AZT, 3TC, NVP (before) switched to TDF, 3TC, NVP	ANED, 48
2010	31, F	Spinal epidura	10	30	Positive	1-3	25 (2)	NA	BDL	Negative	Positive (>140)	Positive (>100)	Complete removal	d4T, 3TC (at) switched to TDF, 3TC, EFV	ANED, 12
2010	35, M	Liver	2	30	Positive	NA	8 (3)	NA	BDL	Negative	Positive (>140)	Positive (>100)	Biopsy	d4T, 3TC, NVP (before)	AWD, 12
2010	36, F	Spinal epidura	NA	30	Positive	NA	N/A	NA	BDL	Negative	Positive (>140)	Positive (>100)	Biopsy	NA	DOD, 9
2011	29, F	Cranial epidura	3	27	Positive	0	156 (10)	NA	BDL	Negative	Positive (>140)	Positive (>100)	Complete removal, RT	d4T, 3TC, NVP (before)	AWD, 6
2011	36, F	Cranial epidura, lung <sup>a</sup> and kidney <sup>a</sup>	3	29	Positive	NA	15 (1)	29,00	BDL	Negative	Positive (>140)	Positive (>100)	Incomplete removal	TDF 3TC EFV (at)	AWD, 2

## Treatment

- **Mainstay treatment :**

1. **Surgical resection**

2. **HAART**

- Improve immune status → improves outcome
- Report showed stable or shrinkage after ARV

- **Therapeutic options (limit published data) :**

- Complete surgical removal sometimes not possible due to the multifocal nature

- 1.) **Radiation**

- 2.) **Chemotherapy** - Gemcitabine

- EBV-SMT : resistant to cytotoxic chemotherapy + poorly tolerated by immunocompromised patients

- 3.) **Immunotherapy** : mTOR inhibitors - Sirolimus

- Inhibit cell growth and proliferation

TABLE 5: Outcome of SMT in HIV-infected patients.

Clinical outcome	Number of patients (N = 64)	Months recorded average (range)
Alive with no evidence of SMT	8 (13%)	9 (5–20)
Alive with SMT	19 (30%)	17 (0.5–60)
Died of SMT	4 (6%)	7 (4–12)
Died of other cause(s)	14 (22%)	3 (0–11)
Lost to follow up	2 (3%)	Not applicable
No published data available	17 (27%)	Not applicable

LMS: leiomyosarcoma.

Thank you

