CASO DO MÊS
Sociedade Brasileira de Patologia

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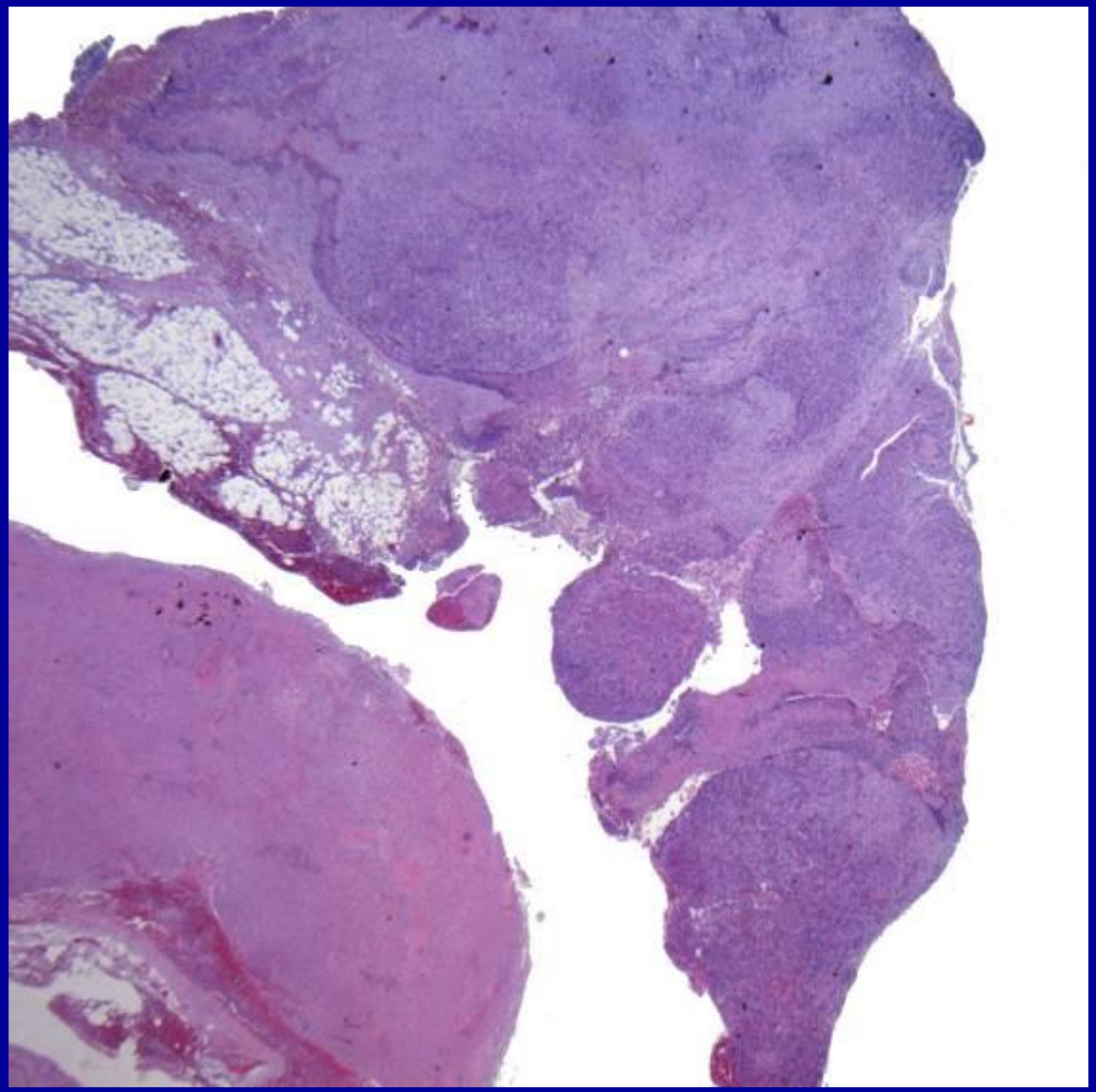
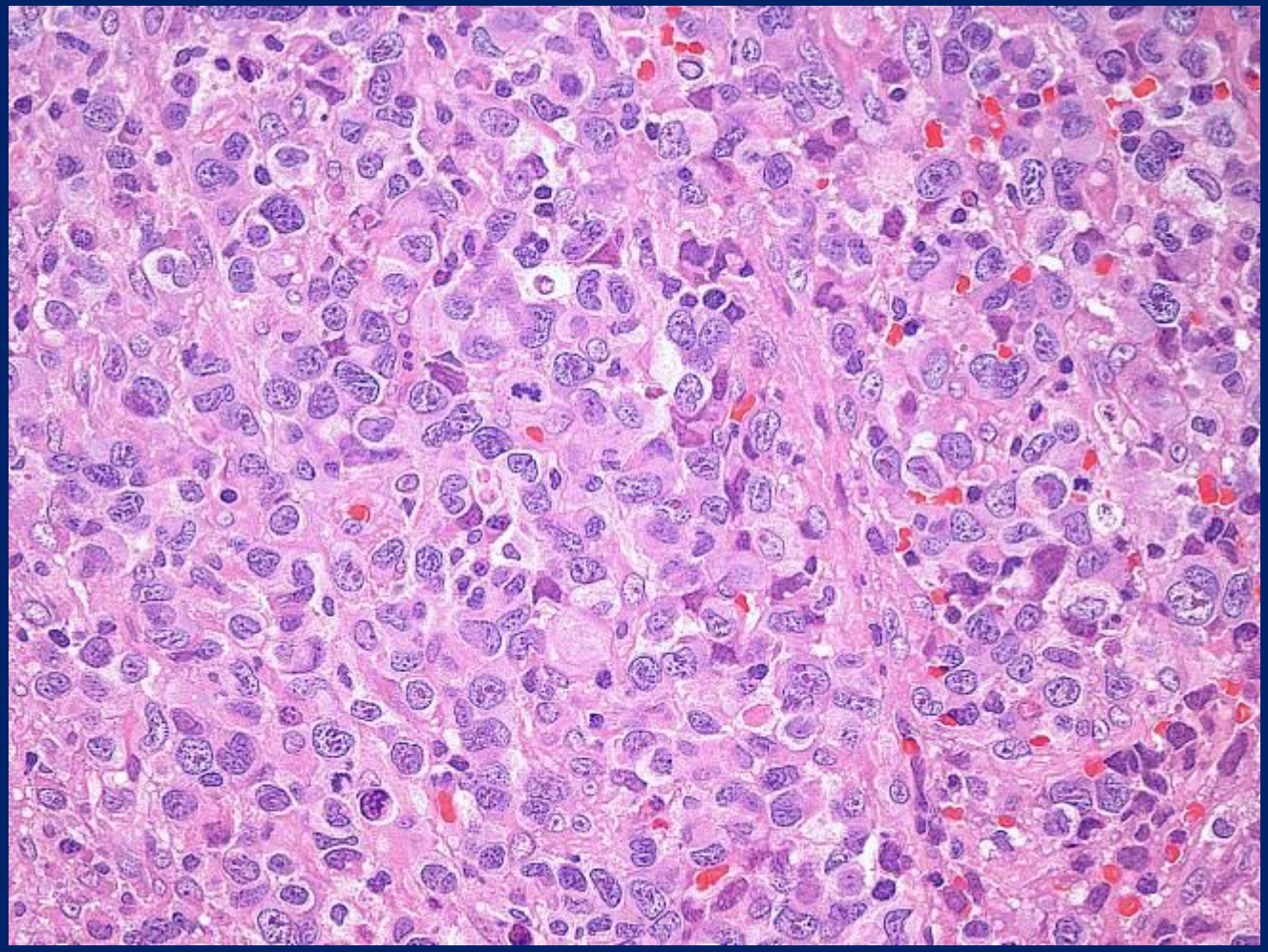
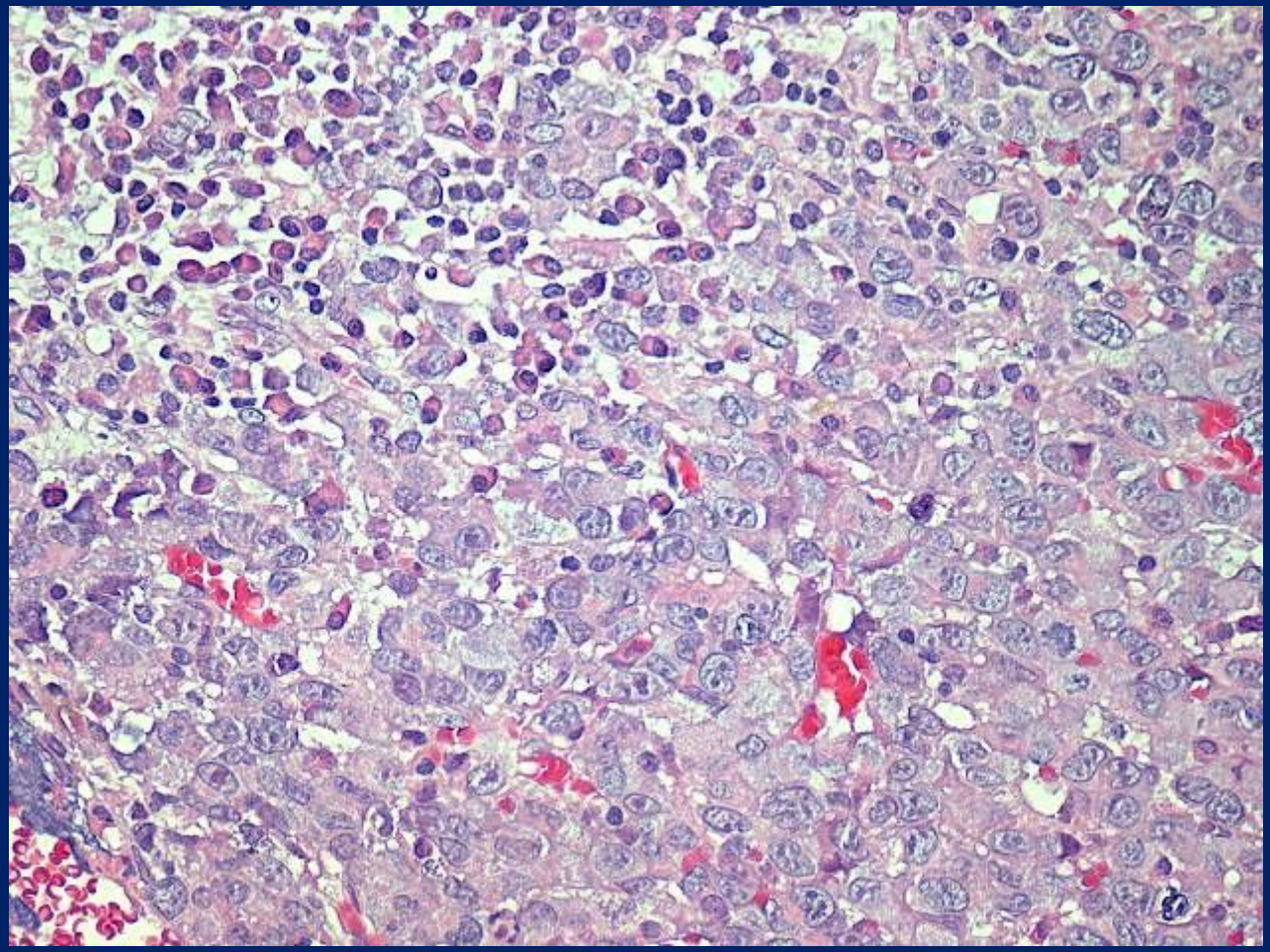
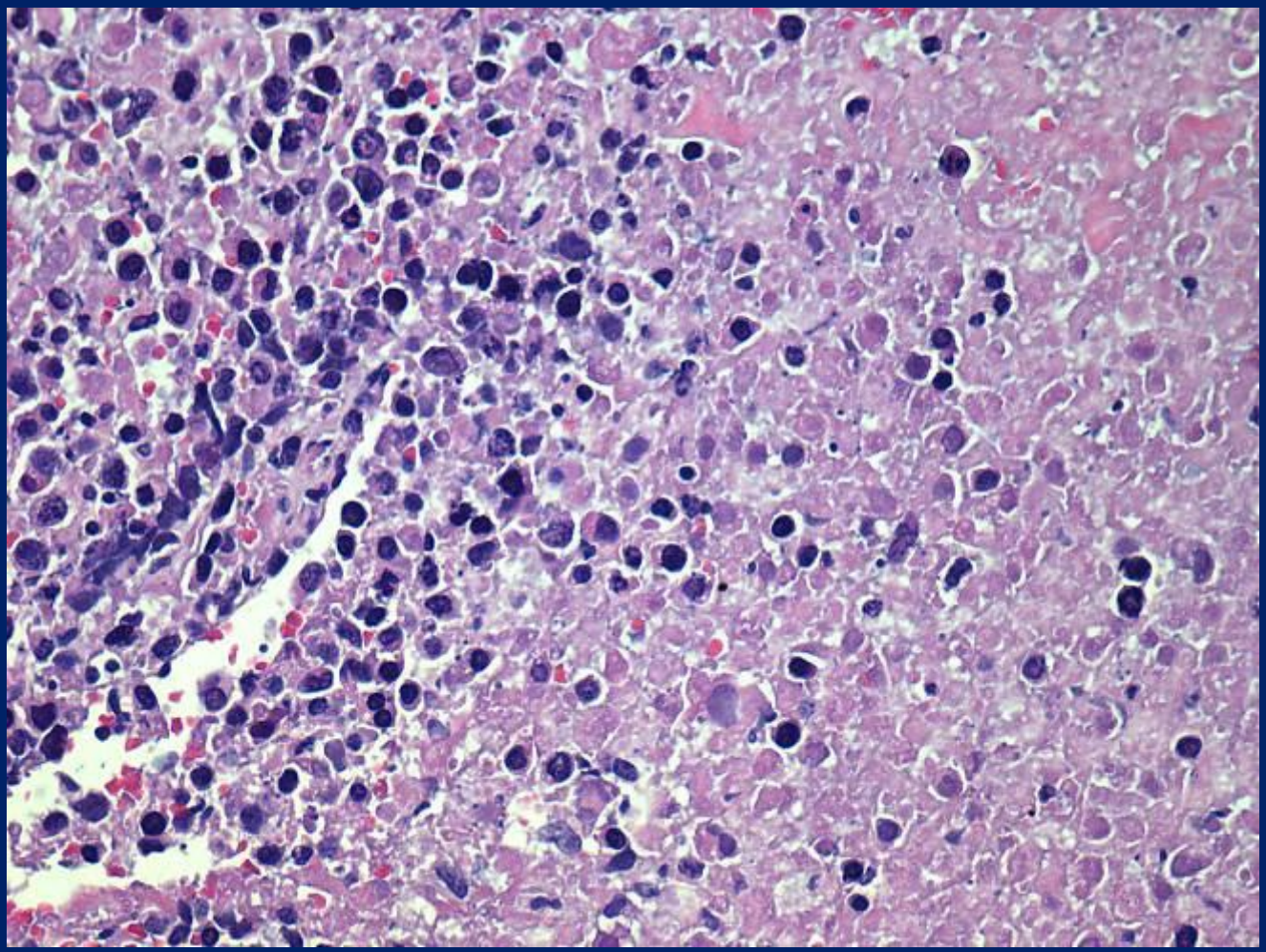
resumo clínico

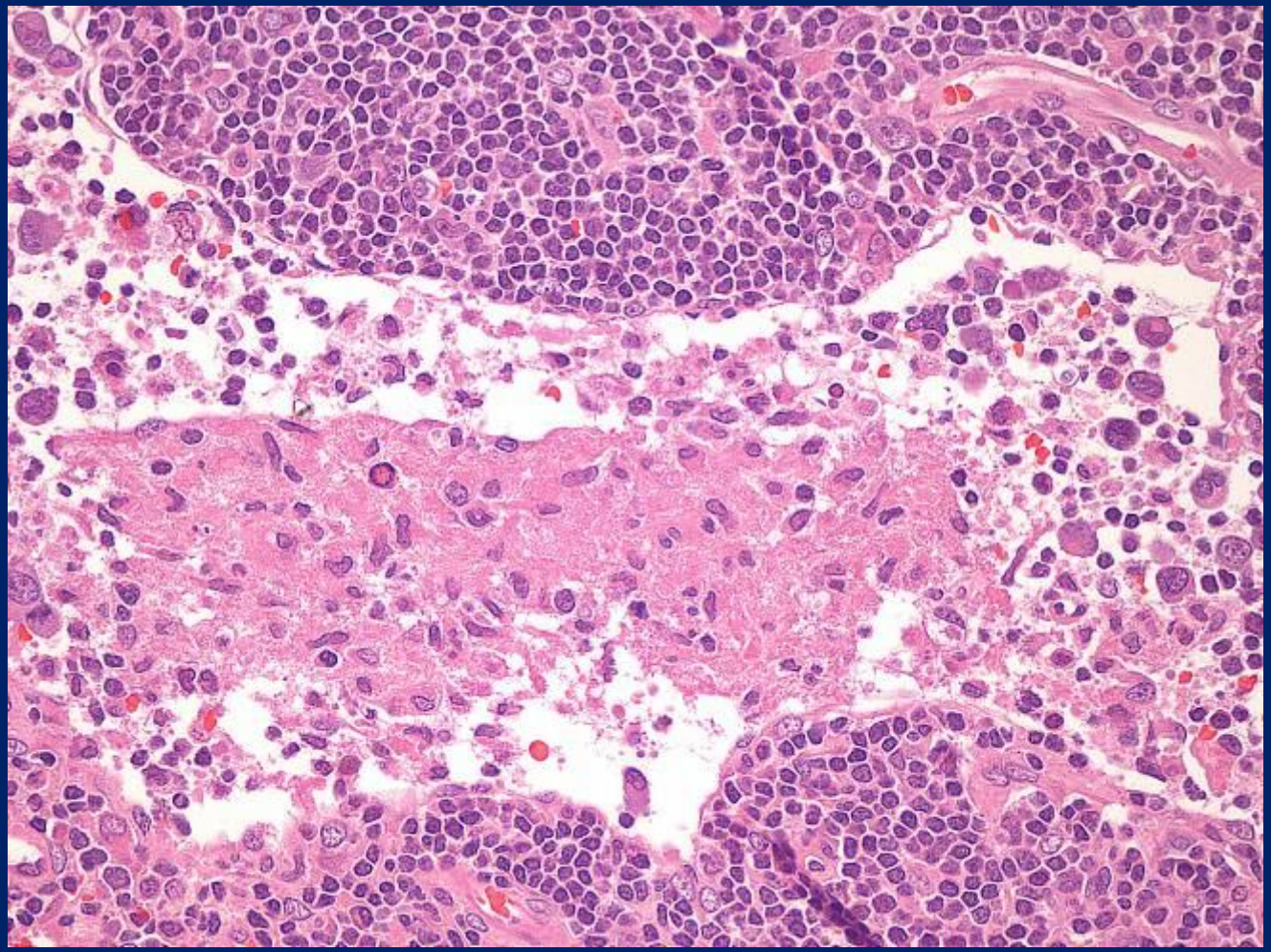
- Paciente F, 34a. HIV+, tendo abandonado a terapia antiretroviral
- Emagrecimento acentuado e linfonodomegalia abdominal, inguinal e pélvica
- Realizada biópsia de LN inguinal











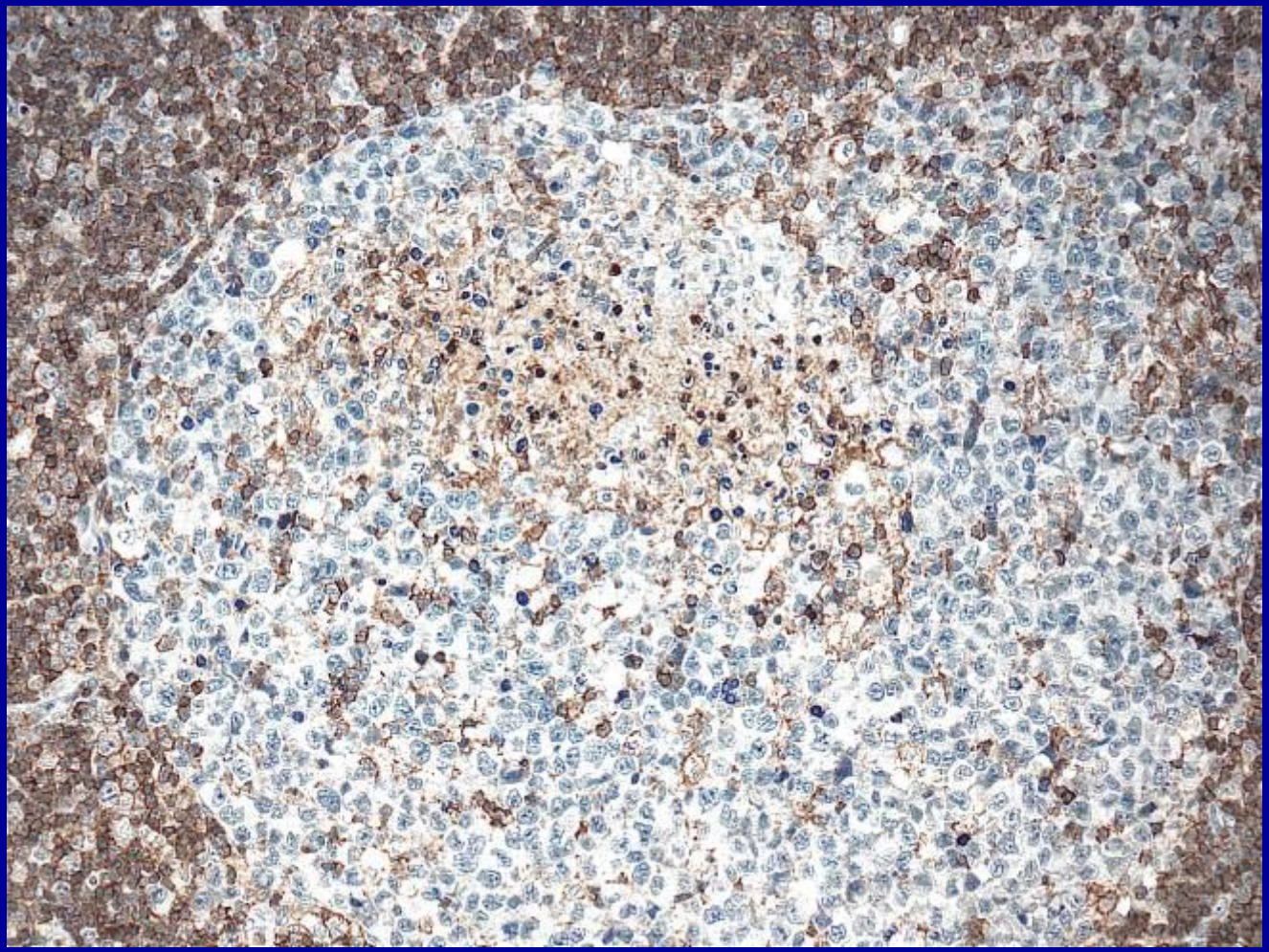
Neoplasia maligna pouco diferenciada com áreas de necrose (ver nota)
Nota: Achados histológicos sugestivos de LNH agressivo. Exame IHQ em andamento

Imunohistoquímica

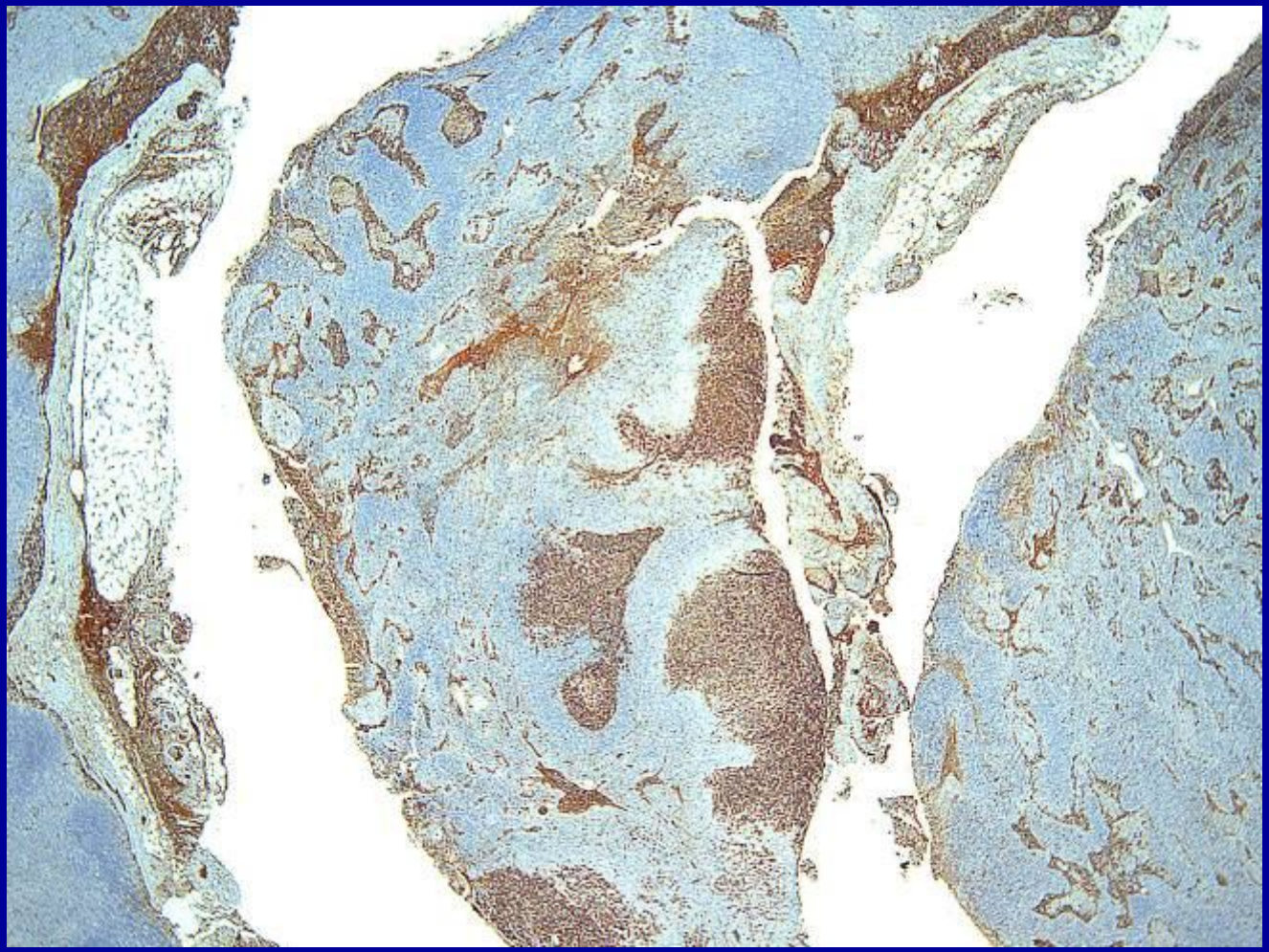
- CD45 – neg
- AE1/AE3 – neg
- CD20 – neg
- CD3 – neg
- CD30 - positivo

- CD15 – neg
- ALK1 – positivo
- CD43 – negativo
- CD5 – positivo
- EMA - negativo
- Granzima B - positiva
- EBV (LMP1) - neg
- Ki67~100%

CD45



CD30



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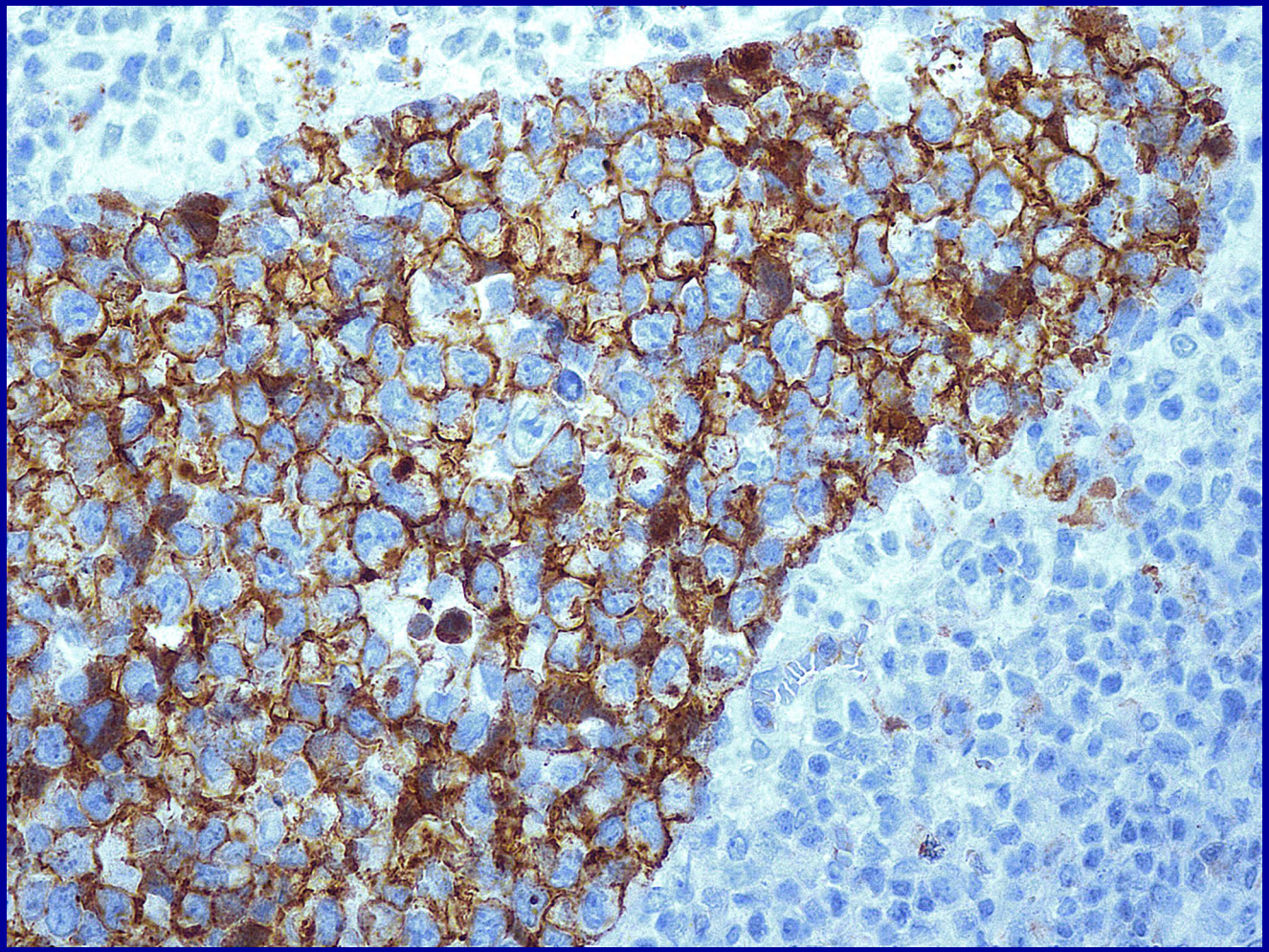
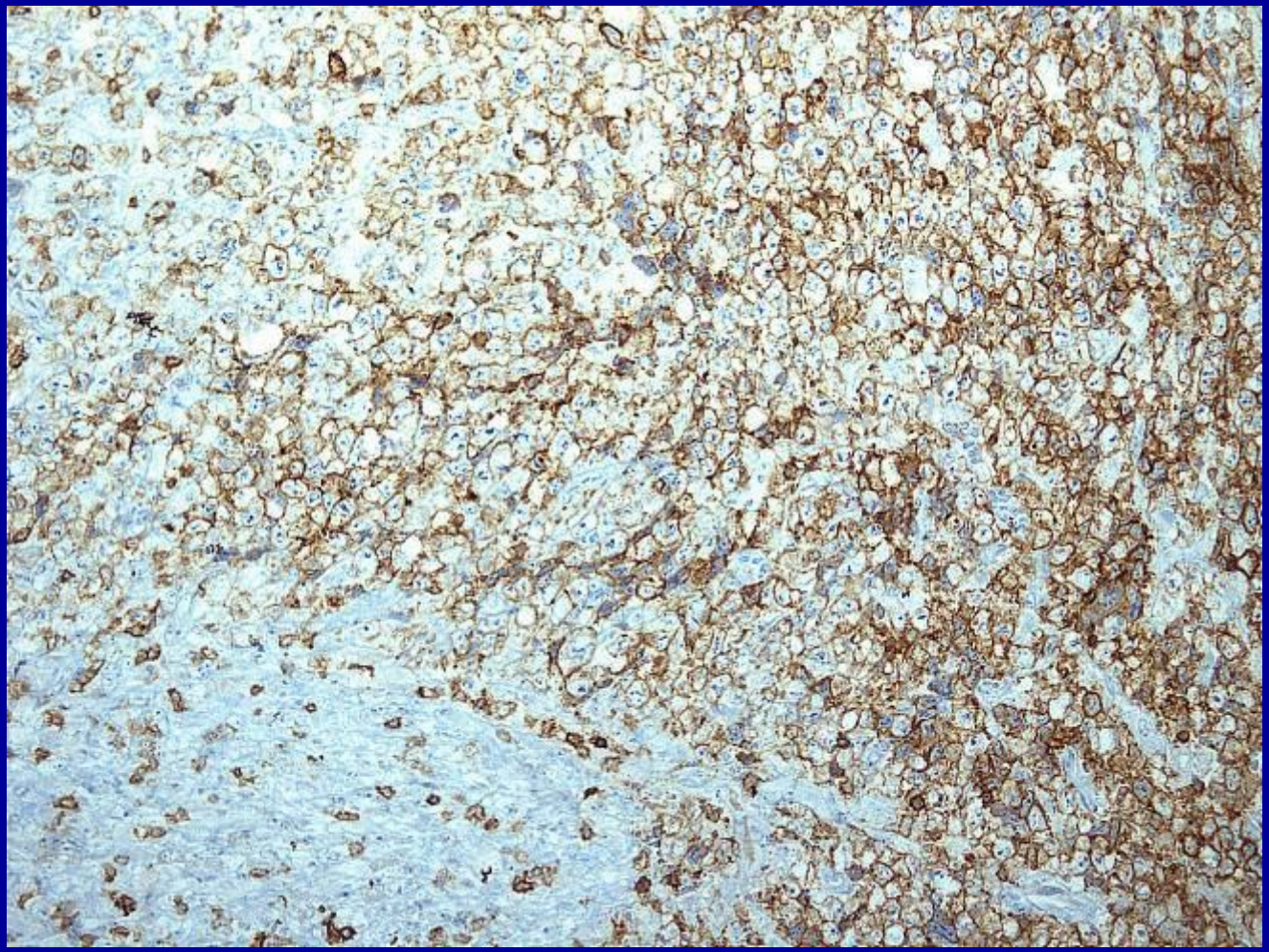
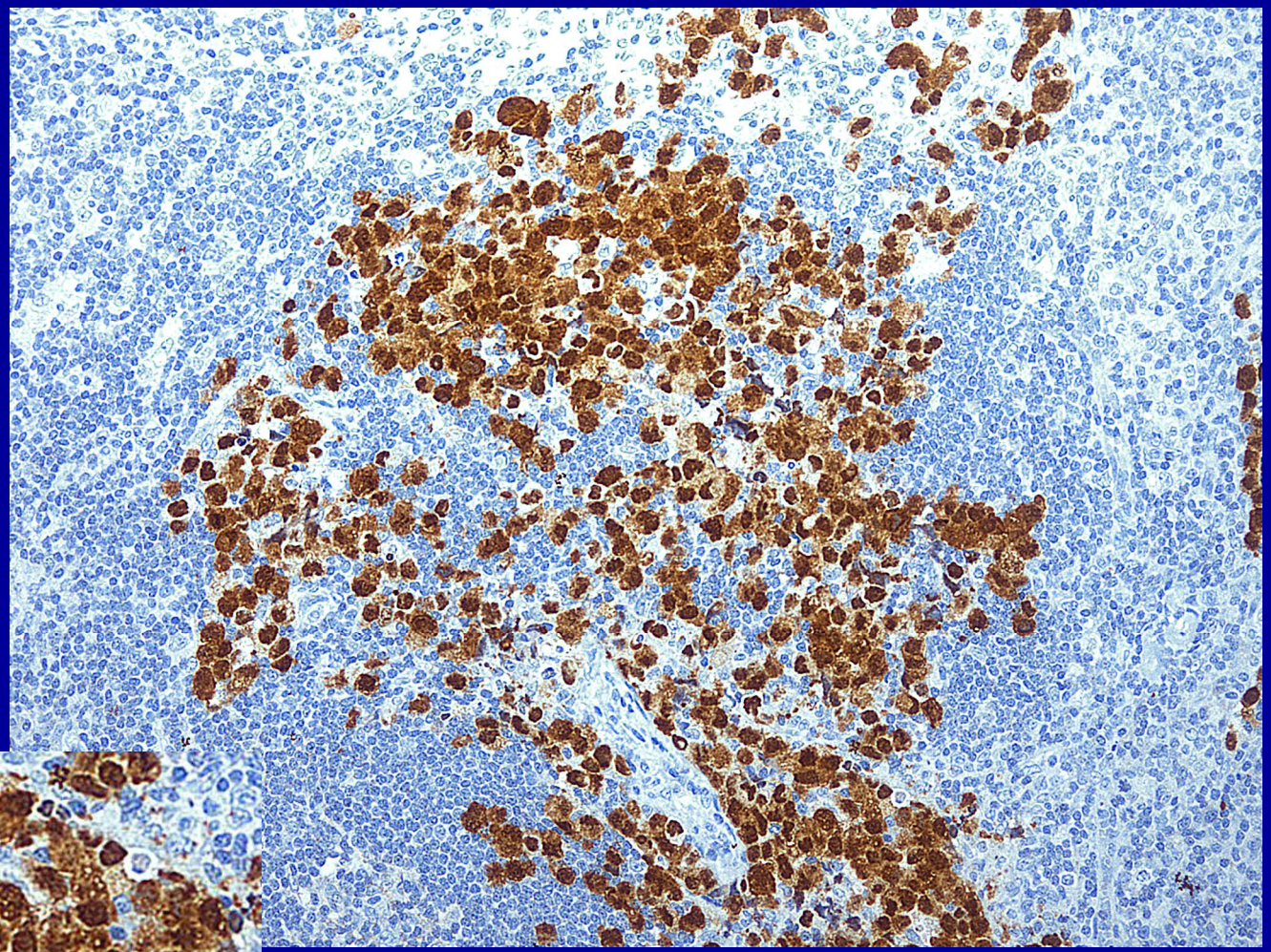
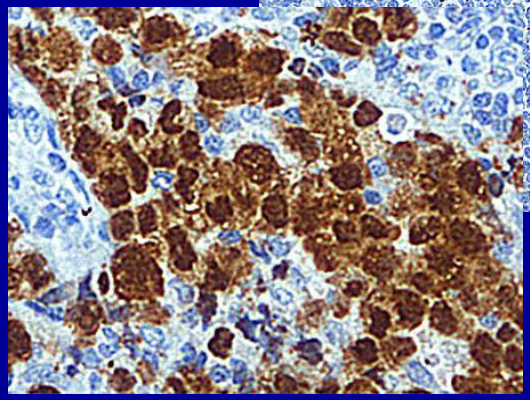


CD5

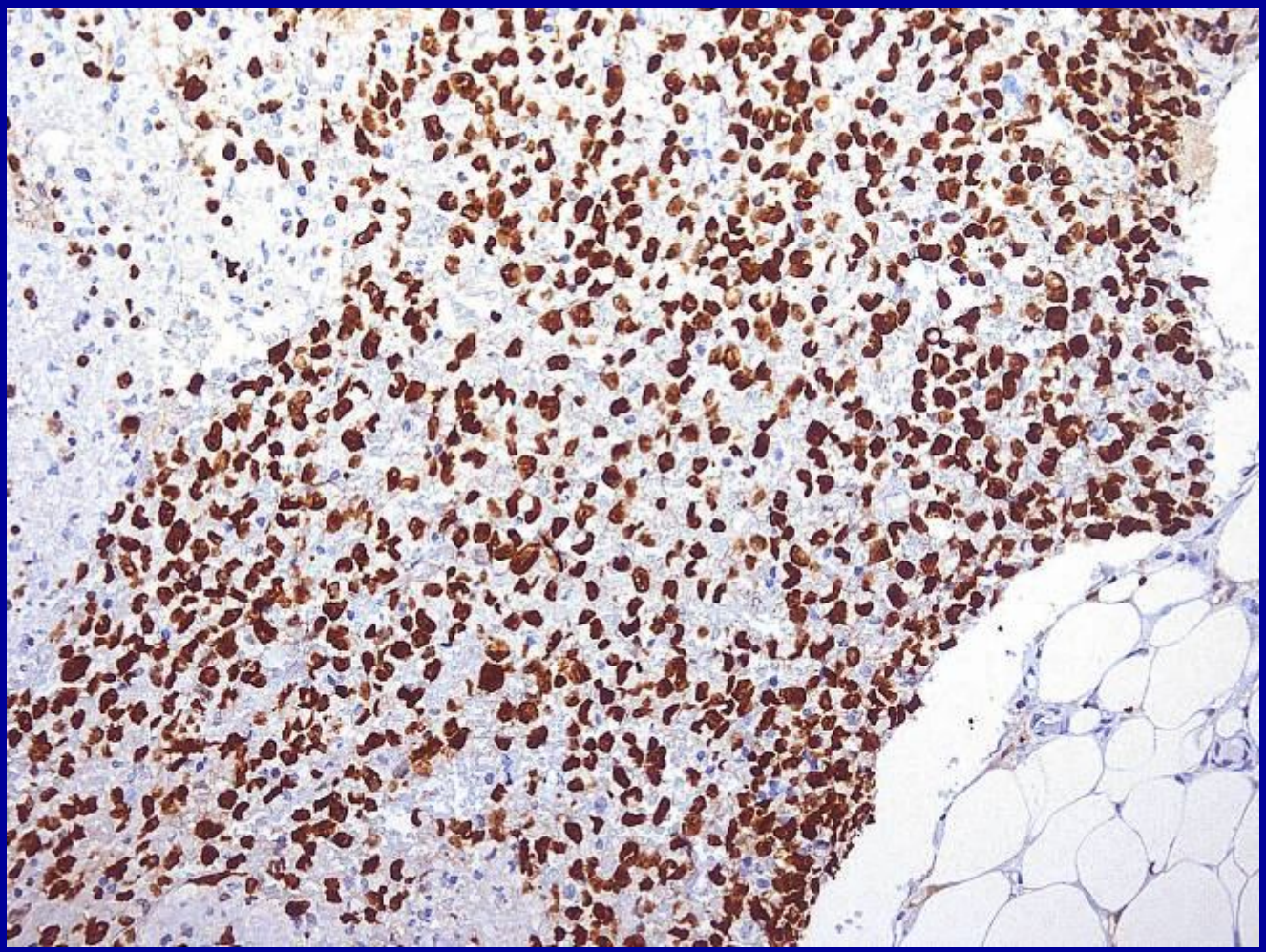


ALK1





Ki67



diagnóstico

Morfologia / CD30 + / ALK+

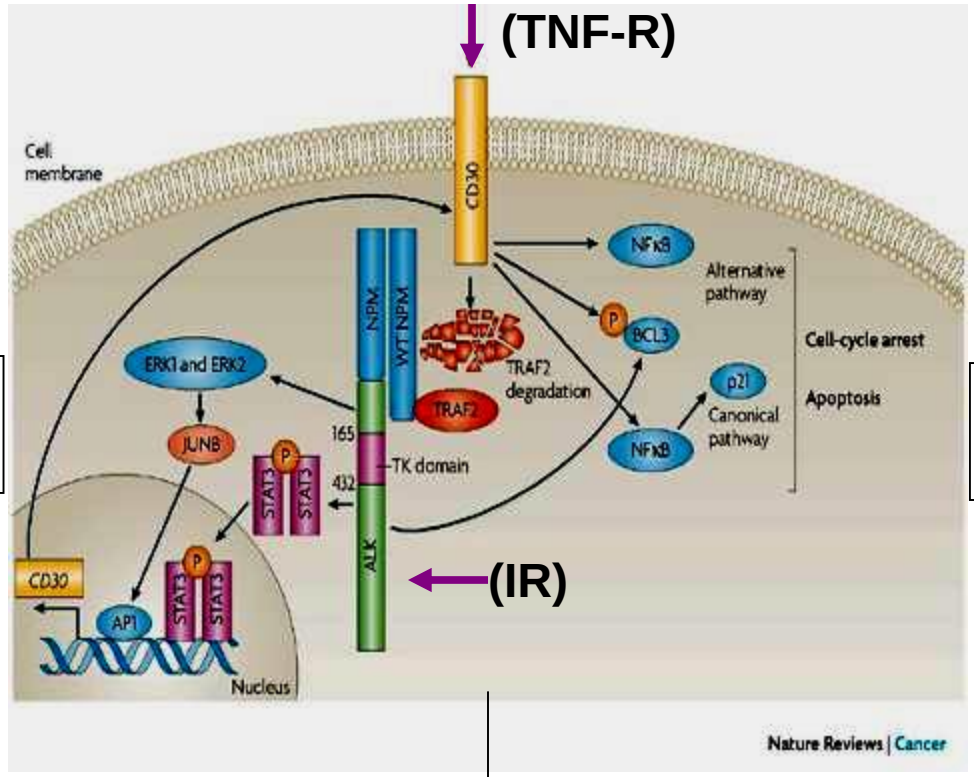
- Linfoma de grandes células anaplásicas, ALK+ (WHO, 08)

- Aspectos a serem discutidos
  - **CD30**
  - **ALK**
  - **LNH-T – WHO, 08**
  - **LGCA na AIDS**

CD30 e ALK no LGCA

ALK
"kinase do LA"
(ALK1-DAKO)

Células normais:
? - SNC e SNP



CD30
(BerH2- DAKO)

Células normais:
Linfócitos ativados

❖**Neoplasias**:

❖LGCA ALK+, TMI, LDGC ALK+

❖ **todas as translocações envolvendo ALK (cr2) produzem proteínas de fusão com atividade tirosinoquinase constitutiva, levando a ↑ proliferação e da sobrevida da célula**

❖**ALK+(IHQ) <u>preditiva</u> de uma alteração molecular envolvendo o gene ALK**

❖**Neoplasias:**

❖LGCA* **(100%)**; LH **(95%)**

❖Carcinoma embrionário **(>80%)**

❖**Raramente + outros TCG**

❖**Útil DD Ca embrionário x CA somático metástases**

❖Melanomas - ?

Neoplasias com translocações recorrentes envolvendo ALK

LGCA ALK+, TMI, LDGC ALK+

Table 1 | **Recurrent chromosomal translocations involving ALK in cancers**

Chromosomal translocation	Partner protein	Frequency (%)	Fusion protein (KDa)	Cellular localization	Type of tumour	Refs
t(2;5)(p23;q35)	Nucleophosmin (NPM)	75–80	NPM–ALK (80)	Nucleus, nucleolus and cytoplasm	ALK$^+$ ALCL and ALK$^+$ DLBCL	11,144–146
t(1;2)(q25;p23)	Tropomyosin 3 (TPM3)	12–18	TPM3–ALK (104)	Cytoplasm	ALK$^+$ ALCL and IMT	44,147,148
t(2;3)(p23;q21)	TRK-fused gene (TFG)	2	TFG–ALK (113, 97, 85)	Cytoplasm	ALK$^+$ ALCL	19,149
inv(2)(p23;q35)	ATIC	2	ATIC–ALK (96)	Cytoplasm	ALK$^+$ ALCL and IMT	20,21,150
t(2;17)(p23;q23)	Clathrin heavy chain-like 1 (CLTC1)	2	CLTC1–ALK (250)	Granular cytoplasmic	ALK$^+$ ALCL, IMT and ALK$^+$ DLBCL	22,151,152
t(2;X)(p23;q11–12)	Moesin (MSN)	<1	MSN–ALK (125)	Cell-membrane associated	ALK$^+$ ALCL	23,153
t(2;19)(p23;p13)	Tropomyosin 4 (TPM4)	<1	TPM4–ALK (95–105)	Cytoplasm	ALK$^+$ ALCL and IMT	44,154
t(2;17)(p23;q25)	ALO17	<1	ALO17–ALK (ND)	Cytoplasm	ALK$^+$ ALCL	155
t(2;2)(p23;q13) or inv(2)(p23;q11–13)	RAN binding protein 2 (RANBP2)	<1	RANBP2–ALK (160)	Periphery of the nucleus	IMT	46
t(2;22)(p23;q11.2)	Non-muscle myosin heavy chain (MYH9)	<1	MYH9–ALK (220)	Cytoplasm	ALK$^+$ ALCL	156
t(2;11;2)(p23;p15;q31)	Cysteinyl-tRNA synthetase (CARS)	<1	CARS–ALK (130)	Unknown	IMT	47,155
ins(3′ALK)(4q22–24)	Unknown	<1	Unknown	Granular cytoplasmic	ALK$^+$ DLBCL	157
t(2;4)(p23;q21)	SEC31 homologue A (*S. cerevisiae*) (SEC31L1)	<1	SEC31L1–ALK (ND)	Cytoplasm	IMT	158
inv(2)(p21;p23)	Echinoderm microtubule-associated protein-like4 (EML4)	6	EML4–ALK (ND)	Unknown	NSCLC	41

Nb, Rabdomiossarcoma alveolar, Ca de mama, Ca de esôfago, Histiocitose ALK+

Broad Clinical Pipeline – Medarex and Partners

Phase I		Phase I/II – Phase II	Phase III
MDX-1307 Cancer	**MEDI-545 – MedImmune** Lupus	**MDX-010 – MEDX/BMS** Other Cancers	**MDX-010 – MEDX/BMS** Melanoma
MDX-1100 Ulcerative Colitis	**MDX-1106 – Ono** Cancer	**MDX-066/MDX-1388 – MBL** C. Difficile Disease	**CNTO 148 – Centocor** Inflammation
MDX-1303 –PharmAthene Anthrax	**MDX-1401** CD30 Lymphomas	**MDX-060** Hodgkin's Disease, ALCL	**CNTO 1275 – Centocor** Inflammation
NVS Ab #1 – Novartis Auotimmune Disease	**Roche Ab – Genmab** Undisclosed	**MDX-018 – Genmab** Undisclosed	**HuMax-CD20 – Genmab** Lymphoma
NVS Ab #2 – Novartis Autoimmune Disease	**Undisclosed – Undisclosed** Undisclosed	**AMGN Ab #1 – Amgen** Undisclosed	**HuMax-EGFR – Genmab** Head and Neck Cancer
AMGN Ab #2 – Amgen Undisclosed	**NI-0401 – NovImmune** Autoimmune Disease	**CNTO 95 – Centocor** Cancer	**HuMax-CD4 – Genmab** Lymphoma
AMGN Ab #3 – Amgen Undisclosed	**IMCL Ab – ImClone Systems** Cancer		**CP 675,206 – Pfizer** Cancer
FG-3019 – Fibrogen Idiopathic Pulmonary Fibrosis	**Undisclosed – Undisclosed** Undisclosed		
HGS-TR2J – Kirin Cancer	**AMGN Ab #4 – Amgen** Undisclosed		
LLY Ab – Eli Lilly Undisclosed	**AMG 714 – Genmab** Rheumatoid Arthritis		
BMS-66513 – BMS Cancer	**IMC-3G3 – ImClone Systems** Cancer		

IND Prep			
MDX-1333 – MedImmune Lupus	**MDX-1411 (αCD70)** Cancer	**MDX-1342 (αCD19)** Cancer	**αSDF-1– Ono** Multiple indications
αB7H4 Cancer	**αPtk7** Cancer	**PacMab Ab** Cancer	**UPT Toxin Programs**

Proprietary products (dark blue) / Technology Licensing Products or Equity Interest (light blue) / Products with Potential for Double-Digit Royalties (yellow)

ALK – forte candidata para drogas inibidoras de sua atividade tirosinoquinase ou em sua utilização como oncoantígeno para a produção de vacinas antitumorais

Poucas células normais

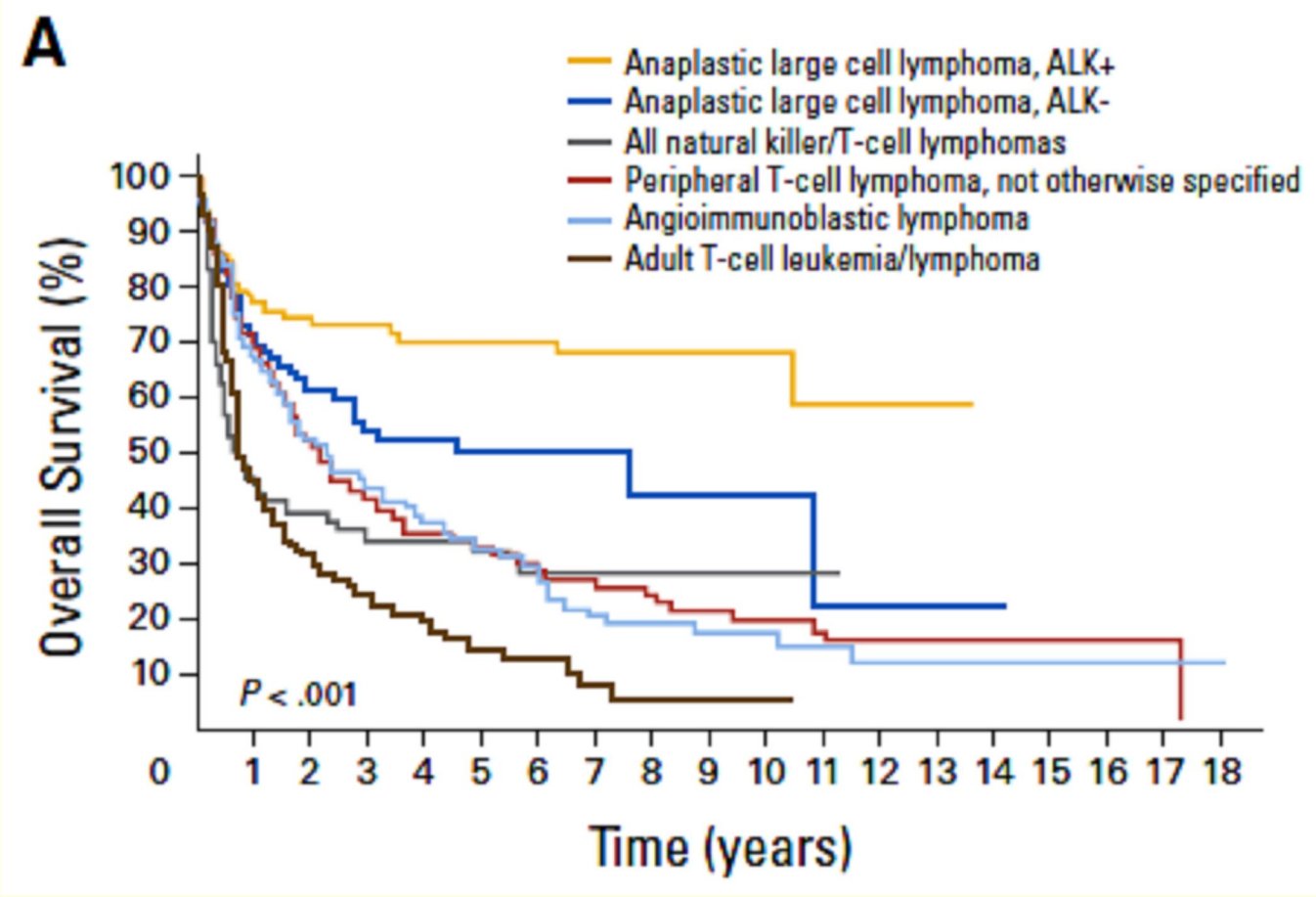
Respostas imunológicas anti-ALK não devem induzir doenças autoimunes

Relevante nas crianças com LGCA/ALK+

WHO 08 -Neoplasias de células T / NK maduras

- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukaemia
- Aggressive NK cell leukemia
- Adult T-cell leukemia/lymphoma
- ➔ *Chronic NK-cell lymphoproliferative disorder****
- ➔ Systemic EBV+ T-cell lymphoproliferative disease of childhood (associated with chronic active EBV infection)
- ➔ Hydroa vacciniforme-like T-cell lymphoma
- Extranodal NK/T cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis Fungoides
- Sezary Syndrome
- Primary cutaneous CD30+ T-cell lymphoproliferative disorders
- ➔ Primary cutaneous gamma-delta T-cell lymphoma
- ➔ *Primary cutaneous aggressive epidermotropic CD8 positive*
- *cytotoxic T-cell lymphoma****
- ➔ *Primary cutaneous small/medium CD4 positive T-cell lymphoma****
- Peripheral T-cell lymphoma, not otherwise specified
- Angioimmunoblastic T-cell lymphoma
- ➔ Anaplastic large cell lymphoma (ALCL), ALK positive
- ➔ *Anaplastic large cell lymphoma (ALCL), ALK negative****

“International T-cell Lymphoma Study”
Linfomas T/NK - Subtipos mais comuns e sobrevida



Perfil imunofenotípico dos Linfomas de células T periféricas

Doença	Imunofenótipo
Peripheral T-cell lymphoma, NOS	CD4>CD8; perda freqüente de Ags(CD7, CD5, CD4/CD8, CD2)
Angioimunoblastic lymphoma	CD4+ ou misto CD4/CD8, CD10+/-, BCL6+/-, CXCL13+, PD1+, hiperplasia de FDC, EBV+ em blastos CD20+
Adult T-cell leukemia/lymphoma	CD4+, CD25+, CD7-, CD30-/+, CD15-/+,FOXP3+/-
Anaplastic large cell lymphoma	CD30+. ALK+/-, EMA+, CD25+, granulos citotóxicos+, CD4+/-, CD3-/+, CD43+

CD3, CD4, CD5, CD7, CD8, CD30, CD43, ALK, CXCL13, FOPXP3

LGCA e AIDS

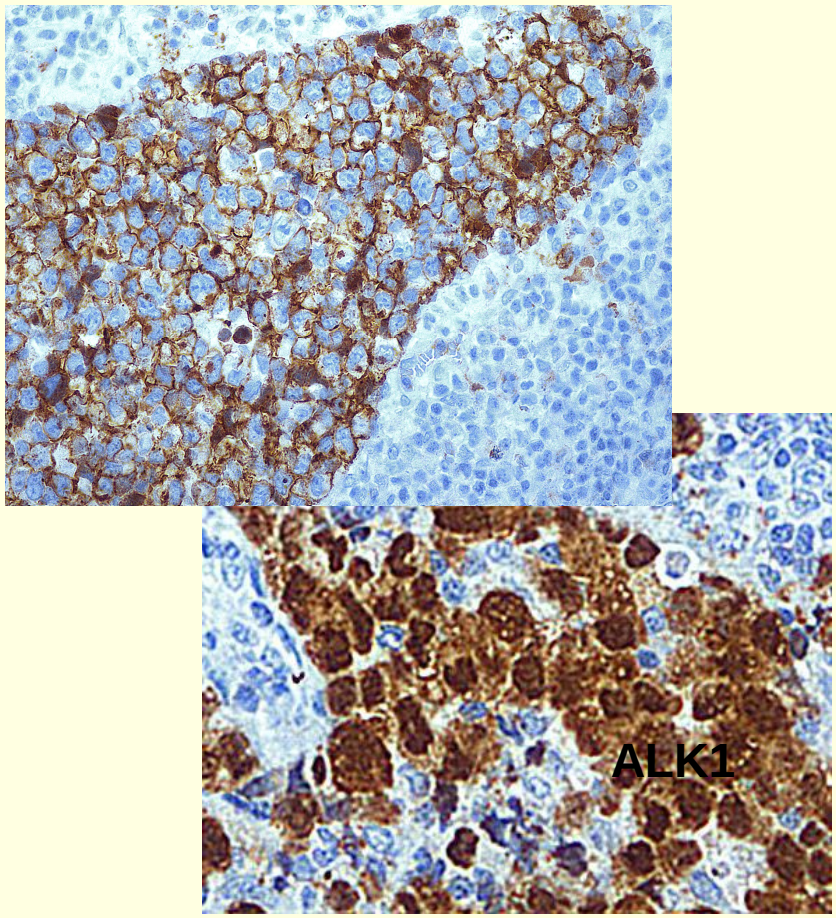
- Linfomas T – 3% dos LNH – AIDS
- LGCA – 18 casos relatados
  - ALK+ raro (1/11); EBV-negativo
  - 2/12 vivos (9 e 18m)

Table 1. Summary of the clinical features and immunophenotypic and molecular analysis in the current and published anaplastic large-cell lymphoma cases with proven T-cell derivation.

Case	Sites	Age/sex	Race	Stage	CD30	T-Ag	EMA	ALK	LMP	EBER	B-Ag	CD15	TCR	Treatment	Follow-up	Status	Reference
1	Skeletal muscle (Quadriceps)	37/W	Af-A	IV	+	+	+	–	–	–	–	–	+	None	1.5 months	Dead	Current report
2	Liver, bones	32/M	Af-A	IV	+	+	–/+	–	–	–	–	–	+	Radiation	1 month	Dead	Current report
3	LN BM	41/M	Af-A	IV	+	+	–	–	–	–	–	–	ND	CHOP	1 year	Dead	Current report
4	LN BM	21/M	C	IV	+	+	+	NR	NR	NR	–	NR	NR	CHOP	18 months	Alive	[4]
5	Skin Muscle	48/M	NR	IV	+	+	–	NR	NR	–	–	–	+	MBACOB	2 months	Dead	[5]
6	Pleura	34/M	C	IV	+	+	+	–	NR	NR	–	–	+	None	?	Lost	[6]
7	Pericardium	42/M	NR	IE	+	+	–	+	–	NR	–	NR	+	None	?	Sudden death	[7]
8	Scalp	41/M	NR	I	+	+	+	–	NR	–	–	–	NR	CHOP	6 months	Dead	[8]
9	Scalp	44/M	NR	I	+	+	+	–	NR	–	–	–	NR	CHOP	6 months	Dead	[8]
10	NR	NR	NR	NR	+	+	–	–	–	NR	–	NR	NR	CHOP	54.6 months	Alive	[2]
11	NR	NR	NR	NR	+	+	+	–	–	NR	–	NR	NR	CHOP	3.6 days	Dead	[2]
12	NR	NR	NR	NR	+	+	+	–	–	NR	–	NR	+	COPE	9.9 months	Alive	[2]
13	Skin	29/M	NR	IE-B	+	+	+	NR	NR	NR	–	–	NR	PBV and RAD	6 months	Lost	[3]
14	Skin	30/M	NR	IE-B	+	+	NR	NR	NR	NR	–	NR	NR	None	18 months	Lost	[3]
15	Lung	40/M	NR	IE-A	+	+	+	NR	NR	NR	–	–	NR	CDVP	3 months	Dead	[3]
16	Skin LN	14/M	NR	II	+	+	+	NR	NR	–	–	NR	NR	Prednisone	5 months	Dead	[14]
17	Liver	33	H	II	+	+	+	NR	–	–	–	–	NR	Supportive	10 days	Dead	[13]
18	Brain	46	NR	II	+	+	+	–	NR	NR	–	NR	+	Surgery, radiation	2 months	Dead	[15]

AIDS 2008, 22:1885–1896

mensagens



- As moléculas detectadas por IHQ para diagnóstico:
  - Podem ter papel patogenético nas doenças
  - Passam a ter um papel nas estratégias terapêuticas
  - Definem um novo papel do patologista na medicina moderna