WHAT'S NEW IN T AND NK CELL LYMPHOMAS?

John K.C. Chan

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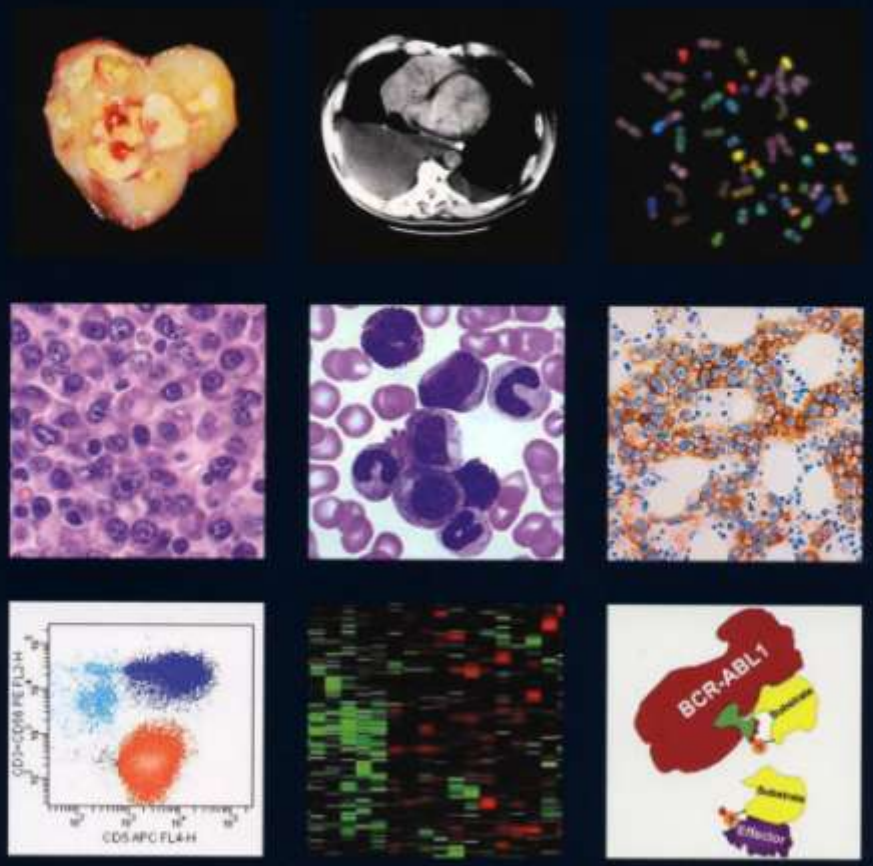
Hong Kong

Mature T-cell & NK-cell neoplasms (WHO 2001)

- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- Aggressive NK cell leukemia
- Extranodal NK/T cell lymphoma, nasal & nasal-type
- Mycosis fungoides, Sezary syndrome
- Angioimmunoblastic T cell lymphoma
- Peripheral T-cell lymphoma unspecified
- Adult T-cell leukemia/lymphoma
- Anaplastic large cell lymphoma (T or null cell), primary systemic type
- Primary cutaneous anaplastic large cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Enteropathy-type intestinal T-cell lymphoma
- Hepatosplenic T-cell lymphoma

WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues

Edited by Steven H. Swerdlow, Elias Campo, Nancy Lee Harris, Elaine S. Jaffe, Stefano A. Pileri, Harald Stein, Jürgen Thiele, James W. Vardiman



4th Edition
2008

Mature T- and NK-cell Neoplasms

T-cell prolymphocytic leukaemia

T-cell large granular lymphocytic leukaemia

Chronic lymphoproliferative disorders of NK cells

Aggressive NK cell leukaemia

EBV-positive T-cell lymphoproliferative disorders of childhood

Adult T-cell leukaemia/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

Sézary syndrome

Primary cutaneous CD30 positive T-cell lymphoproliferative disorders

Primary cutaneous gamma-delta T-cell lymphomas

Peripheral T-cell lymphoma, NOS

Angioimmunoblastic T-cell lymphoma

Anaplastic large cell lymphoma (ALCL), ALK positive

Anaplastic large cell lymphoma (ALCL), ALK negative

13 → 20

New additions to the family of peripheral T-cell and NK-cell neoplasms

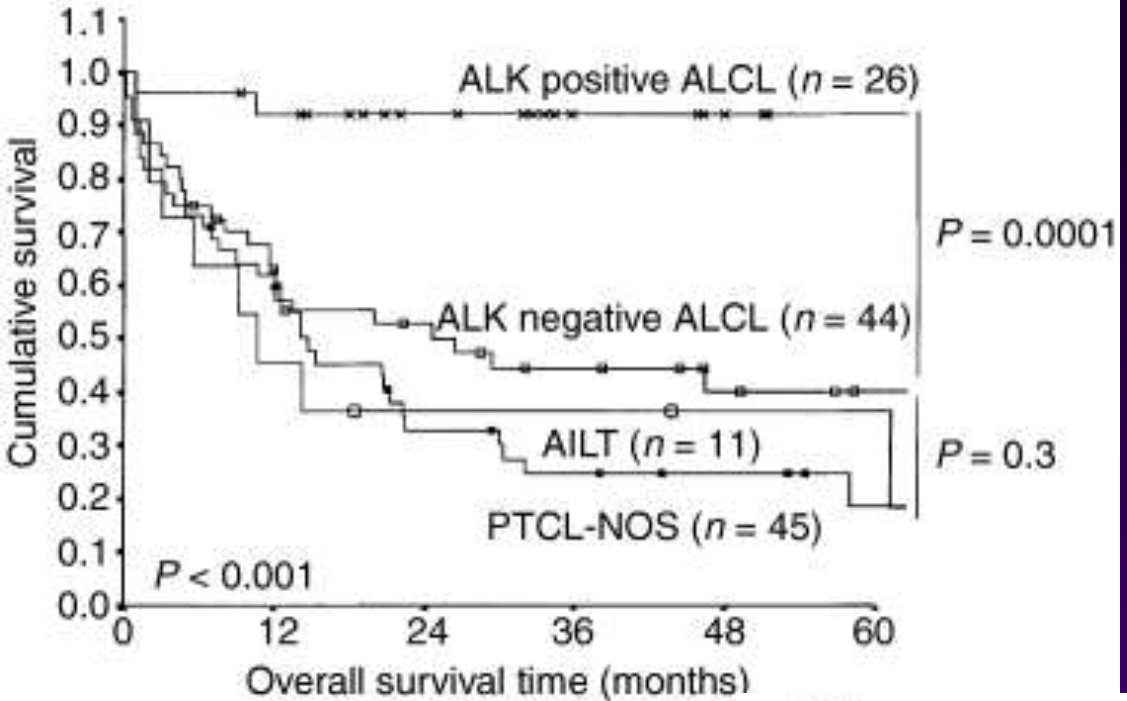
- Systemic EBV+ T-cell lymphoproliferative disease of childhood
- Hydroa vacciniforme-like lymphoma
- Chronic lymphoproliferative disorder of NK cells
- Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma
- Primary cutaneous γδT-cell lymphoma
- Primary cutaneous CD4+ small/medium T-cell lymphoma

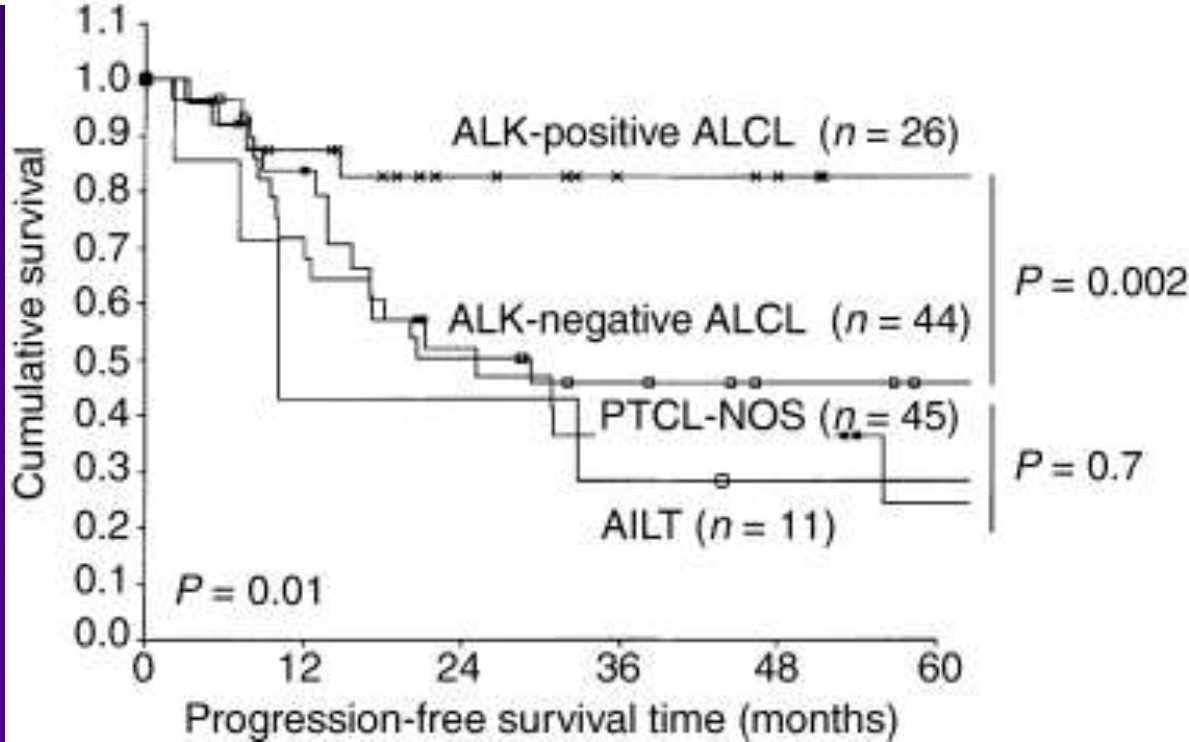
WHAT'S NEW IN ANAPLASTIC LARGE CELL LYMPHOMA?

- Clinical outcome of ALK- anaplastic large cell lymphoma
- Primary cutaneous anaplastic large cell lymphoma – new findings in molecular genetics
- Primary systemic ALK- anaplastic large cell lymphoma – new findings in molecular genetics
- New entity: Seroma-associated ALK- anaplastic large cell lymphoma

PRIMARY SYSTEMIC ALK- ANAPLASTIC LARGE CELL LYMPHOMA

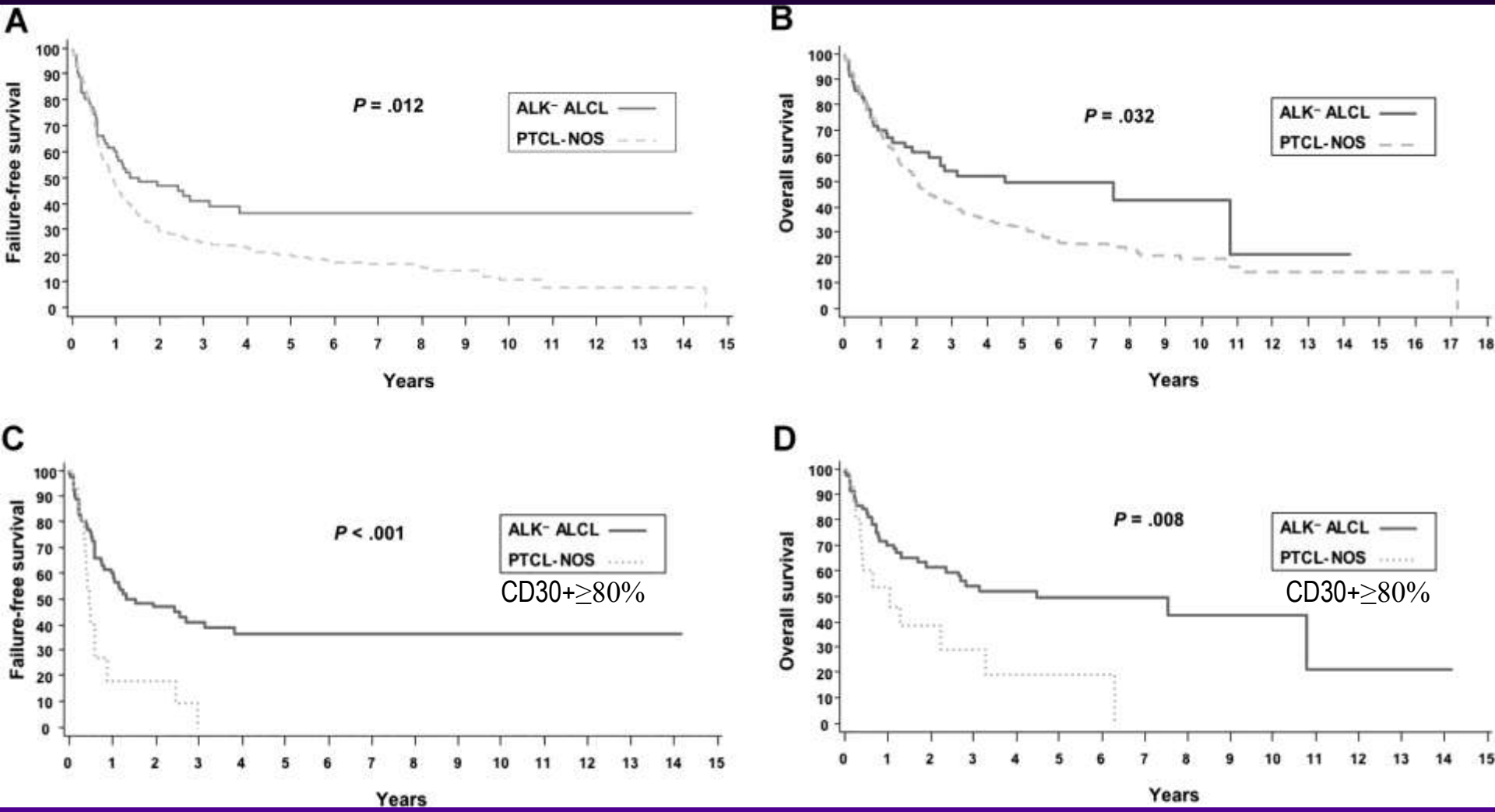
- There are controversies on whether ALK-anaplastic large cell lymphoma is a distinct entity
- Any difference in survival compared with peripheral T-cell lymphoma not otherwise specified?





ten Berge RL.
Histopathology, 2003

Survival of ALK− ALCL and PTCL-NOS.

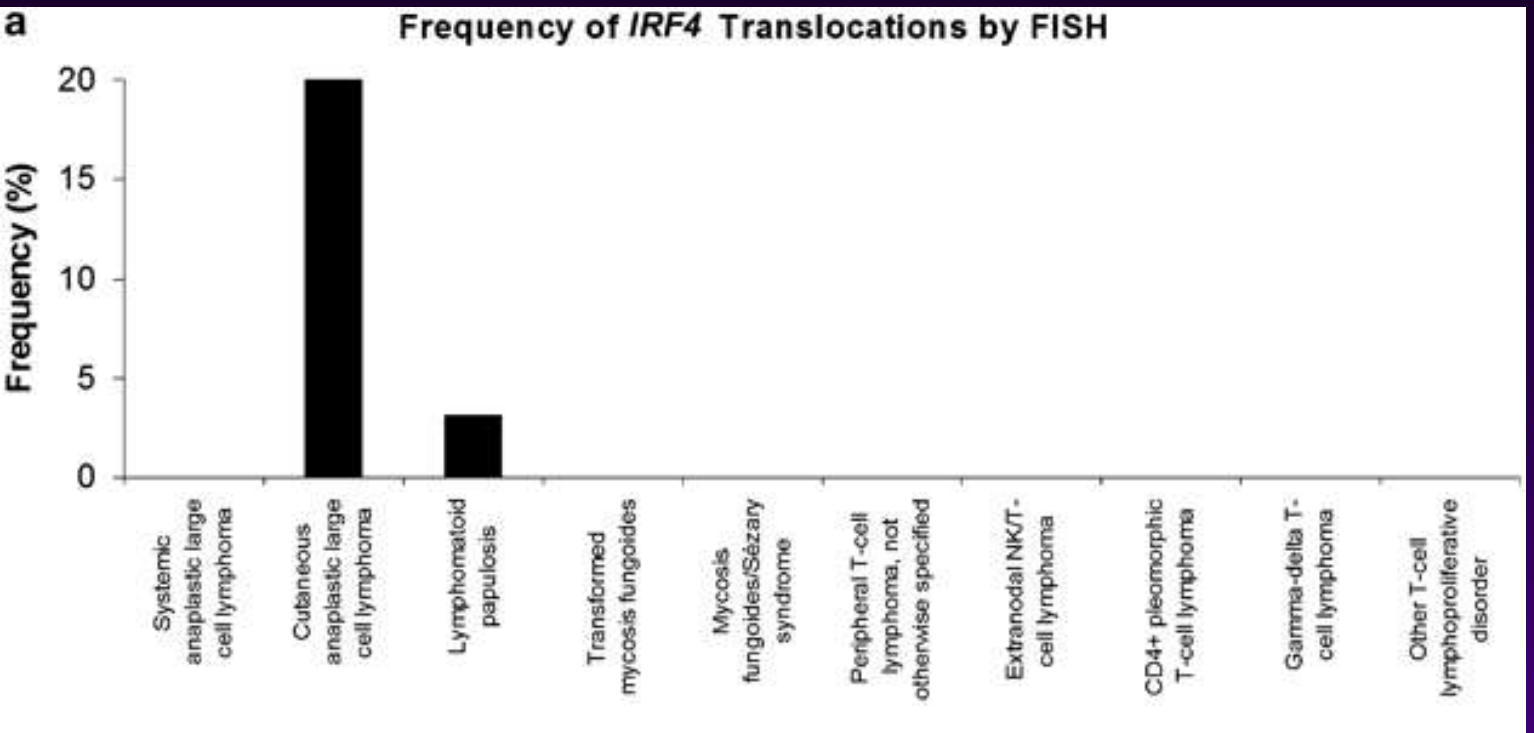


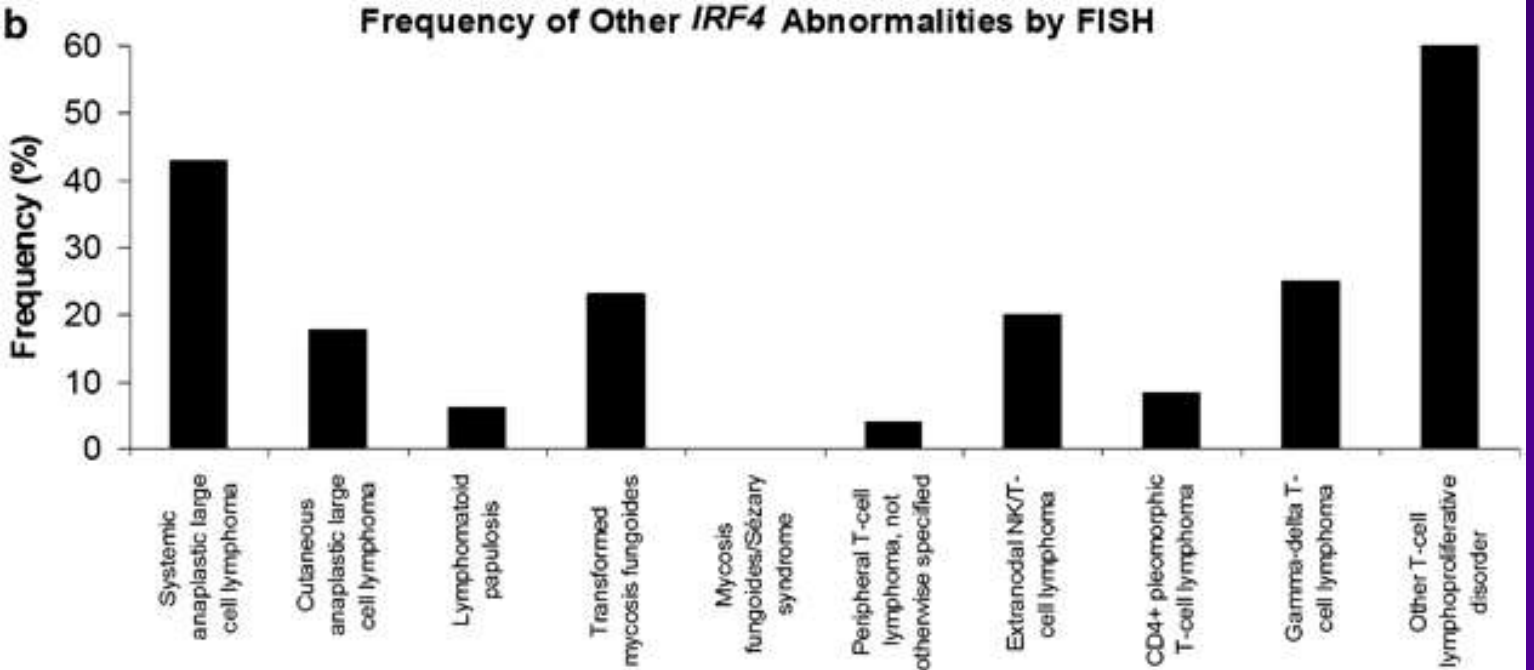
International Peripheral T-cell Lymphoma Project

Savage K J et al. Blood 2008;111:5496-5504

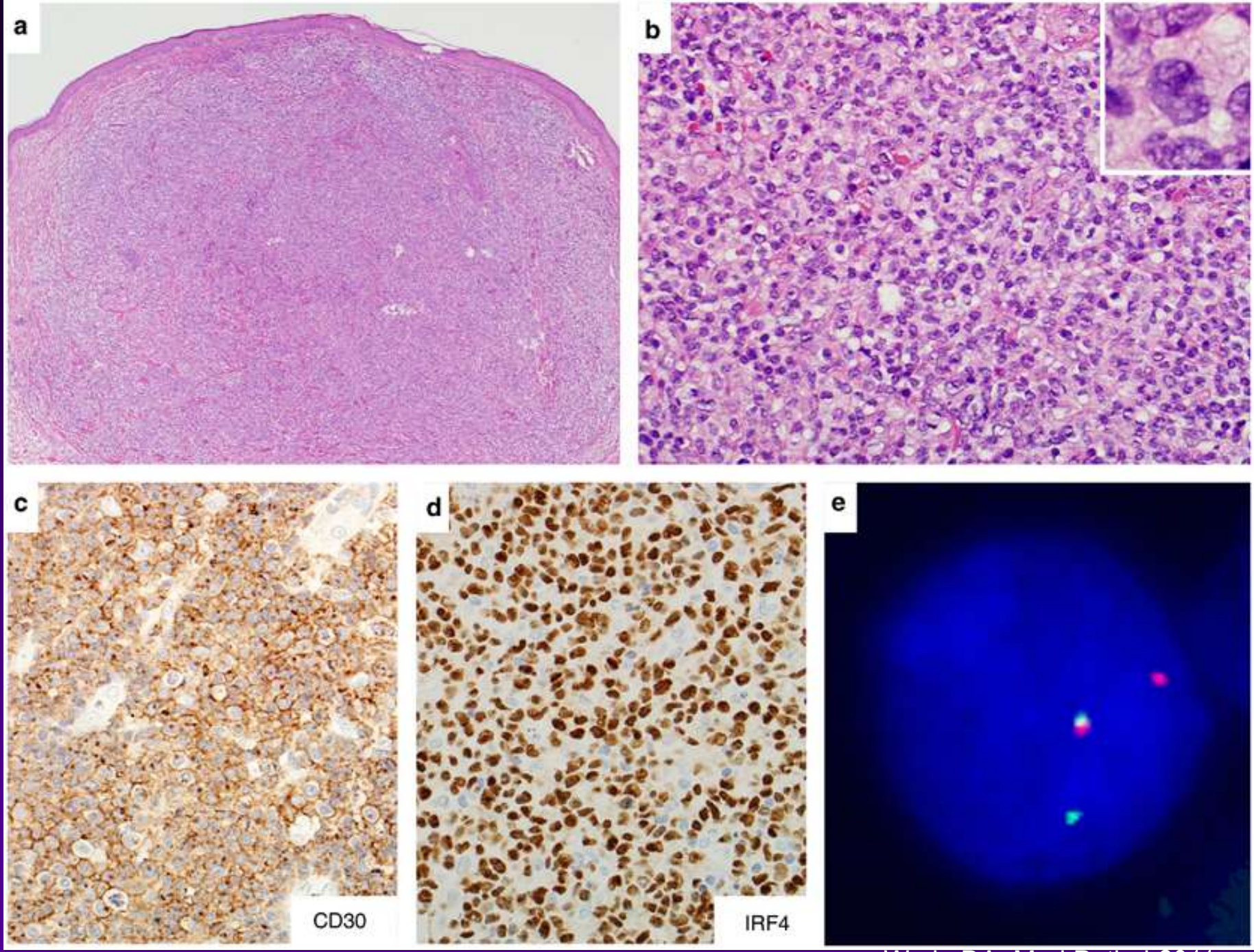
PRIMARY CUTANEOUS ANAPLASTIC LARGE CELL LYMPHOMA & RELATED ENTITIES

- Distinct entity characterized predominantly by local disease
- Little known about the molecular genetics
- New findings on genetic alterations:
  - *IRF4* (interferon regulatory factor-4) translocation in ~20% of cases [*IRF4* also known as MUM1]
  - Absent in other cutaneous T-cell lymphoid lesions
  - May have diagnostic value when present





Wada DA. Mod Pathol 2011



Wada DA. Mod Pathol 2011

ALK- anaplastic large cell lymphoma

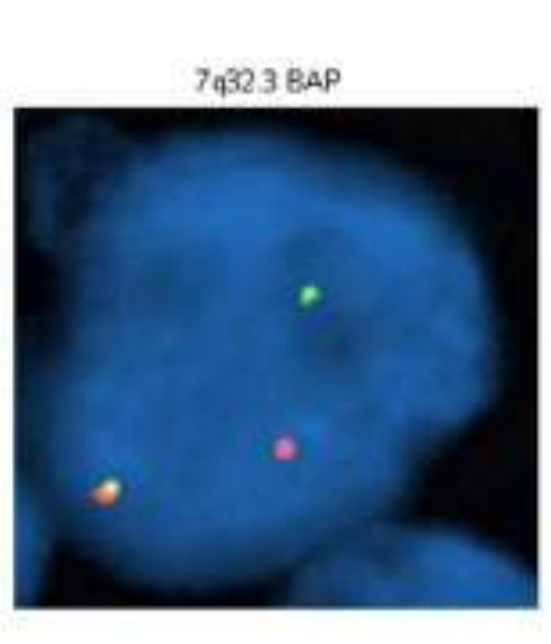
Discovery of recurrent t(6;7)(p25.3;q32.3) translocations in ALK-negative anaplastic large cell lymphomas by massively parallel genomic sequencing

Andrew L. Feldman,[1] Ahmet Dogan,[1] David I. Smith,[1] Mark E. Law,[1] Stephen M. Ansell,[2] Sarah H. Johnson,[3] Julie C. Porcher,[2] Nazan Özsan,[4] Eric D. Wieben,[5] Bruce W. Eckloff,[5] and George Vasmatzis[3]

Blood 2011;117:915-919

ALK- anaplastic large cell lymphoma

- Through massive parallel sequencing, a new translocation t(6;7)(p25.3;q32.3), fusing *DUSP22* with *FRA7H*, is identified in a proportion of cases of ALK- anaplastic large cell lymphoma
- The lymphoma may belong to the primary systemic form or primary cutaneous form
- Translocation results in down-regulation of *DUSP22* gene



FISH: Break-apart probes for 7q32.3

Feldman AL. Blood 2011

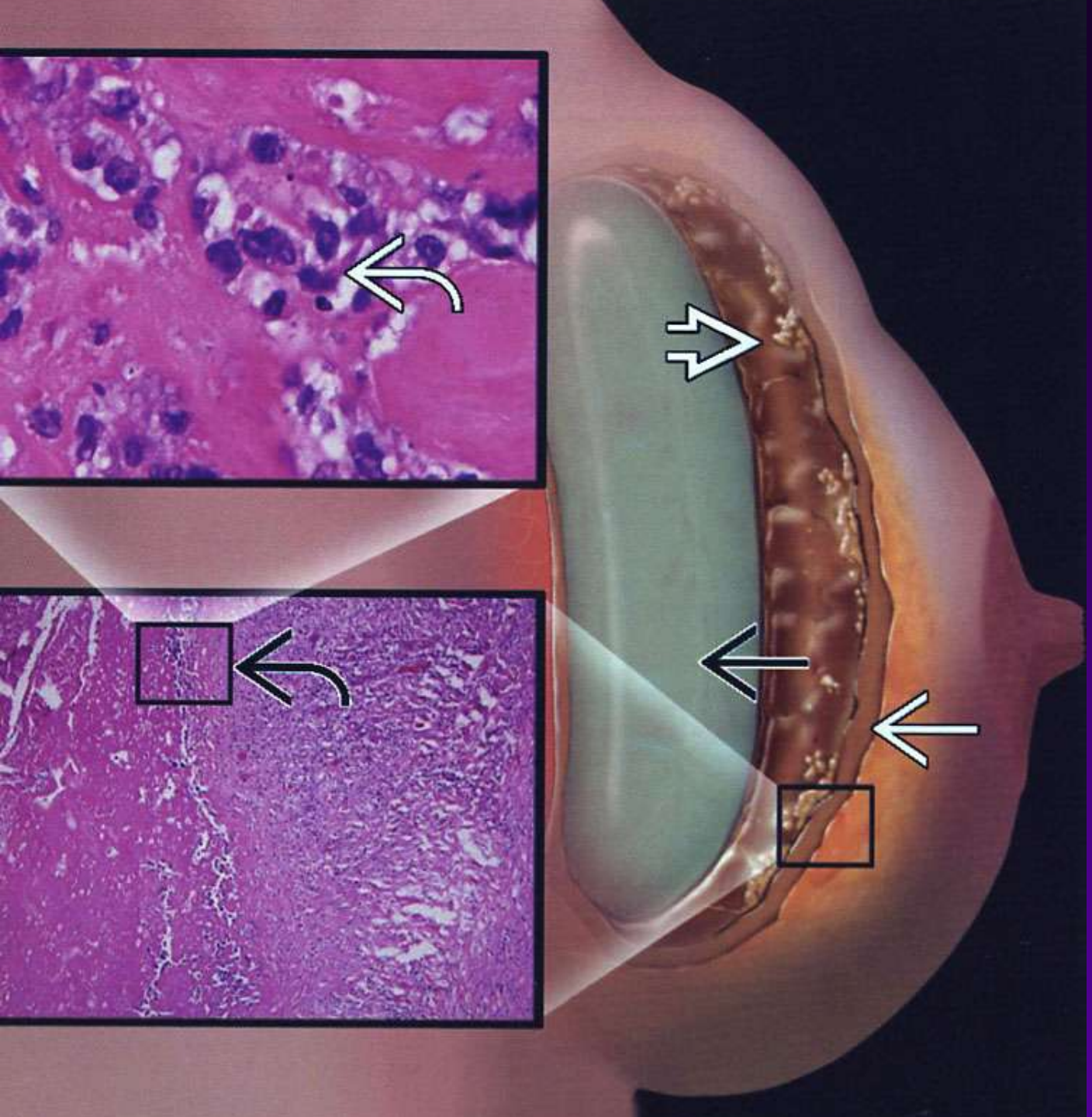
NEW ENTITY NOT INCLUDED IN 2008 WHO CLASSIFICATION

Modern Pathology (2008) 21, 455–463

www.modernpathology.org

Seroma-associated primary anaplastic large-cell lymphoma adjacent to breast implants: an indolent T-cell lymphoproliferative disorder

Anja C Roden[1], William R Macon[1], Gary L Keeney[1], Jeffrey L Myers[2], Andrew L Feldman[1] and Ahmet Dogan[1]



Medeiros LJ. Diagnostic Pathology - Lymph nodes and spleen with extranodal lymphomas 2011

Seroma-associated anaplastic large cell lymphoma adjacent to breast implant

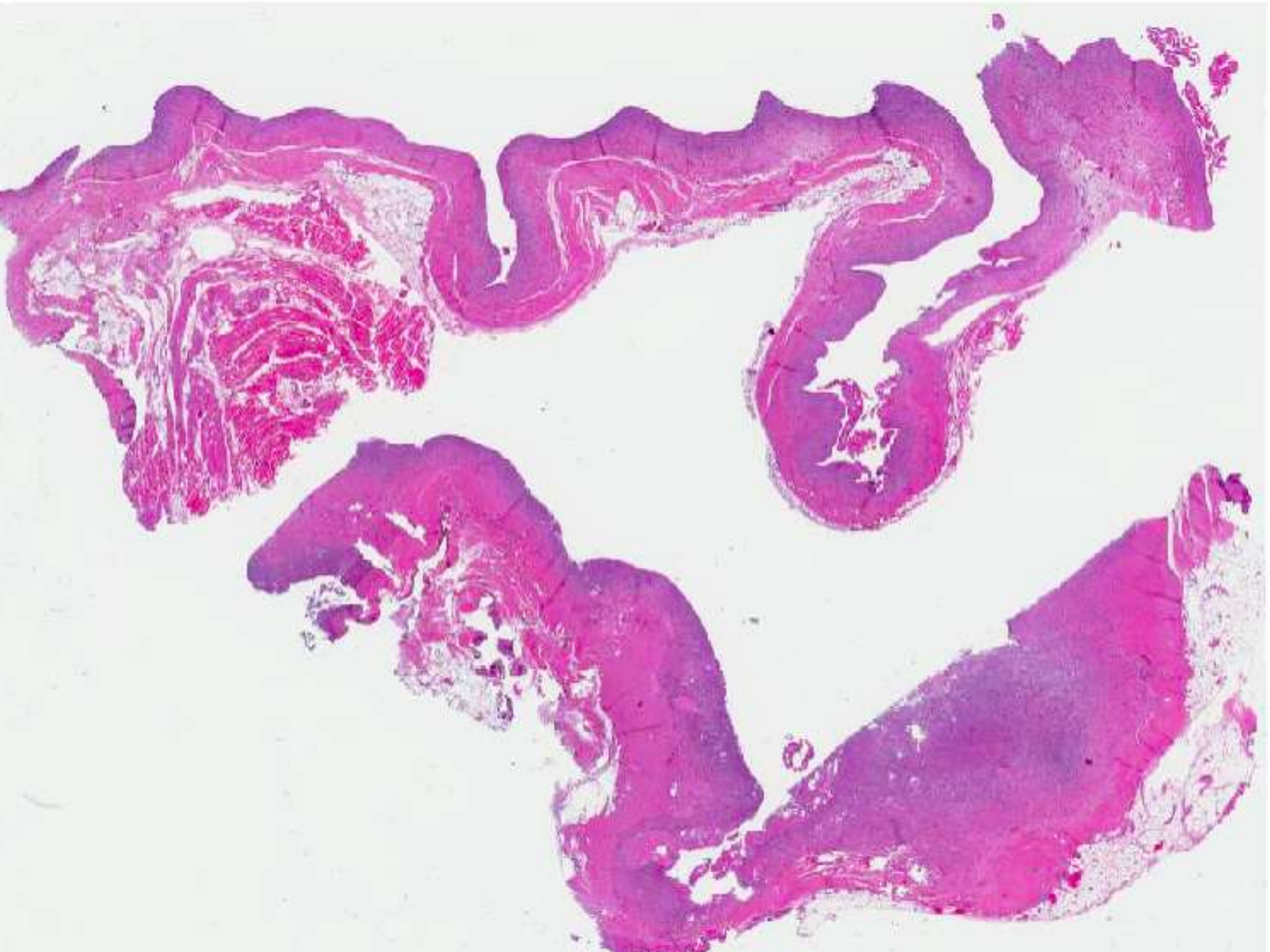
- Lymphoma occurs within the fibrous capsule formed around saline or silicone breast implant
- Morphologically aggressive (ALK- ALCL), but clinically indolent (often localized disease)
- With the limited follow-up data:
  - Excellent prognosis
  - Usually well with no recurrence after surgical removal (capsulectomy)

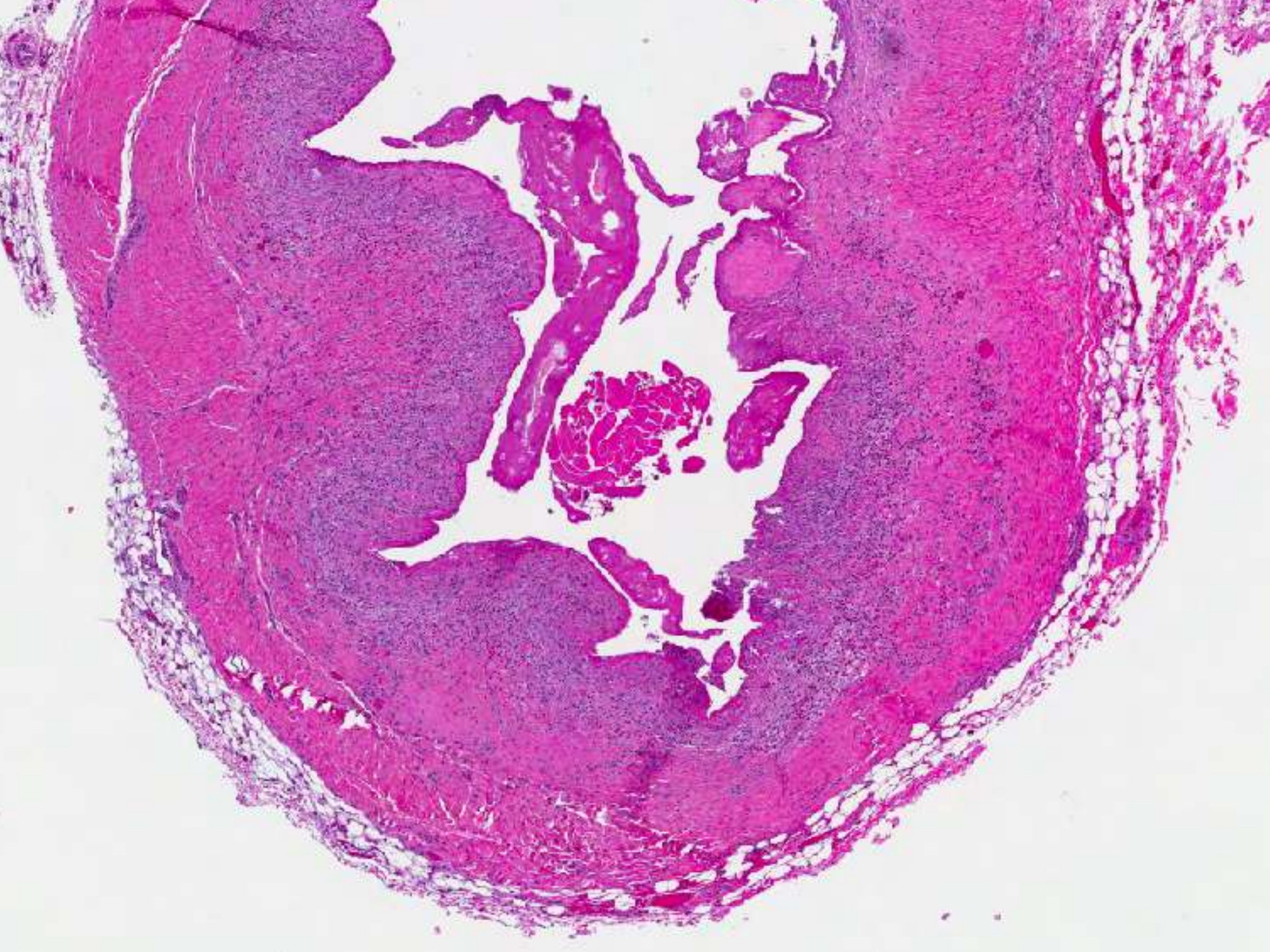
Seroma-associated anaplastic large cell lymphoma adjacent to breast implant

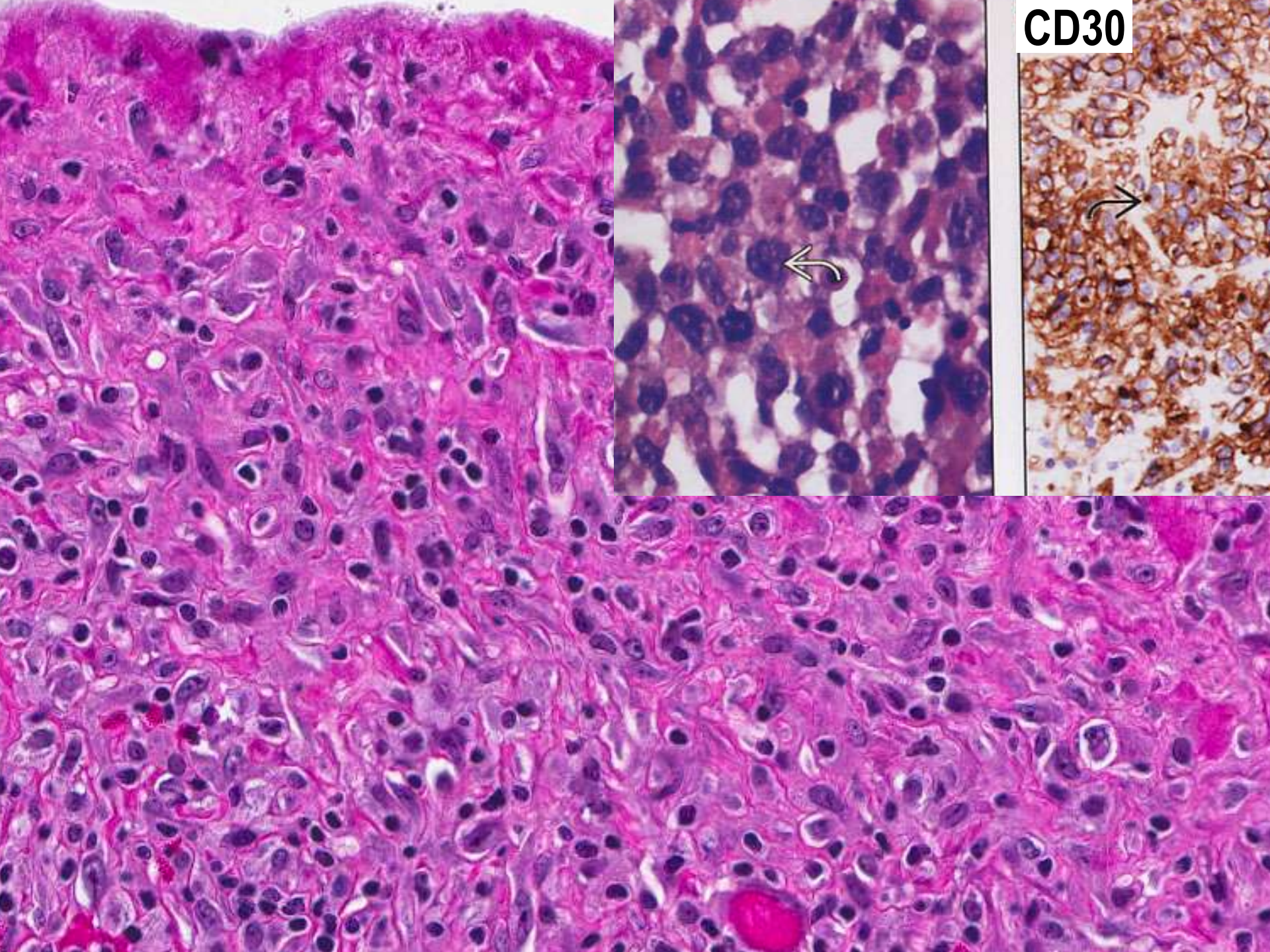
- Incidence is very low (estimated at 1 in 1,000,000 per year of breast implant)
- Age: Median 52 years
- Presentation:
  - Detected 3 to 19 years after implant (median 8 yr)
  - Breast swelling
  - When present, effusion 80-720 ml

Seroma-associated anaplastic large cell lymphoma adjacent to breast implant: Pathology

- Thickened fibrous capsule
- Luminal side extensively covered by fibrin
- Lymphoma cell aggregates often confined to fibrinous material, but occasionally also in fibrous capsule (but not through)
- Large anaplastic cells

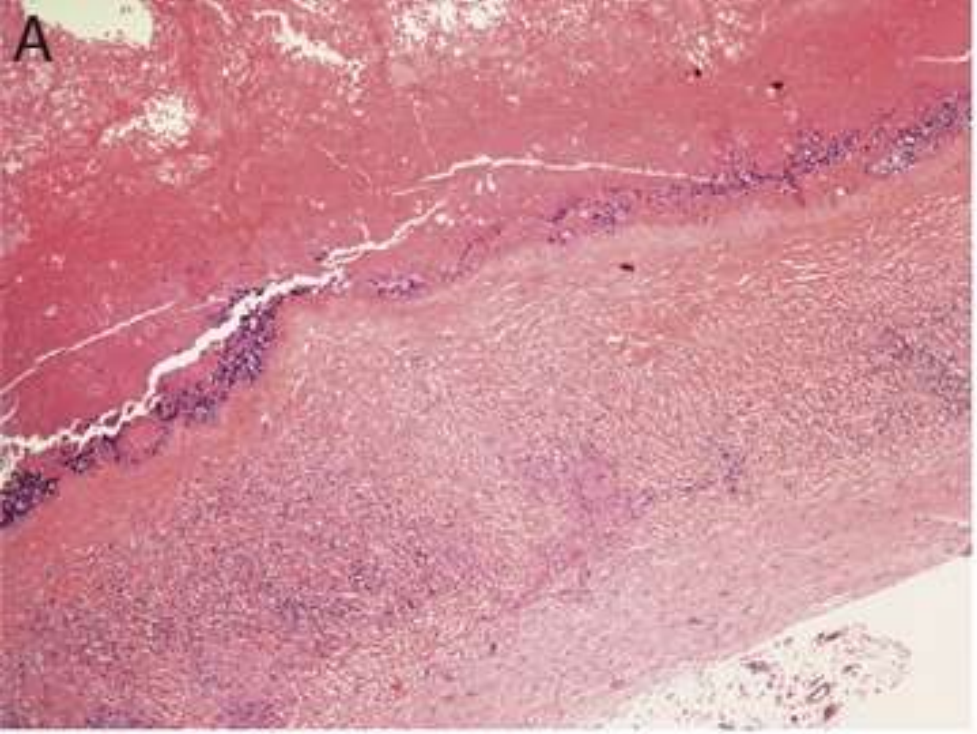





CD30

Seroma-associated anaplastic large cell lymphoma adjacent to breast implant: Immunohistochemistry and genetics

- CD30 +
- ALK -
- T-cell antigens: Variable expression
- EMA +/-
- EBER –
- TCR: clonal rearrangement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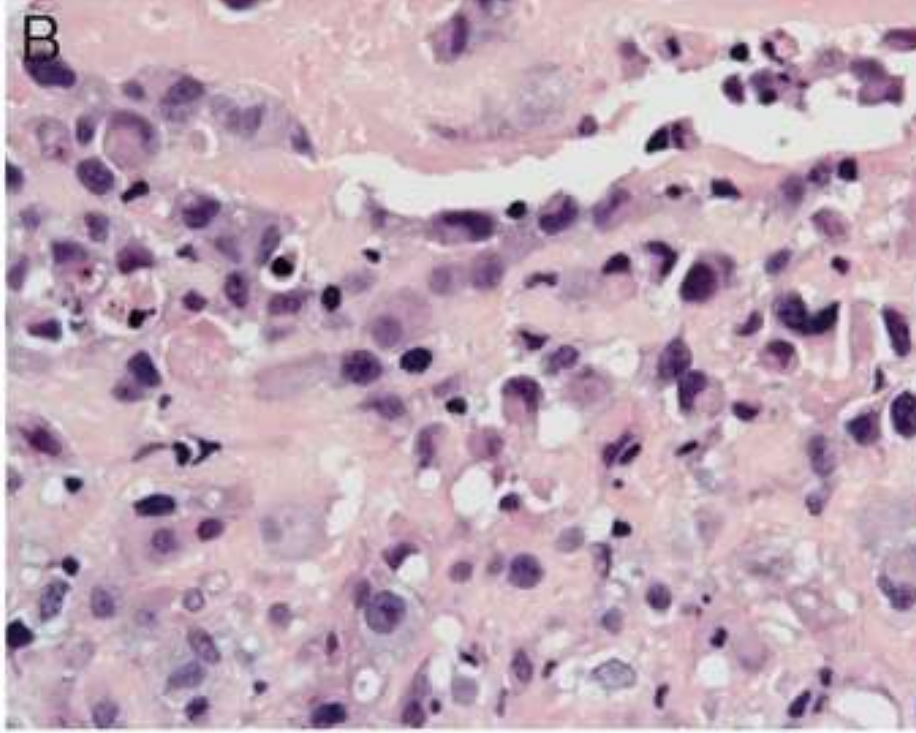
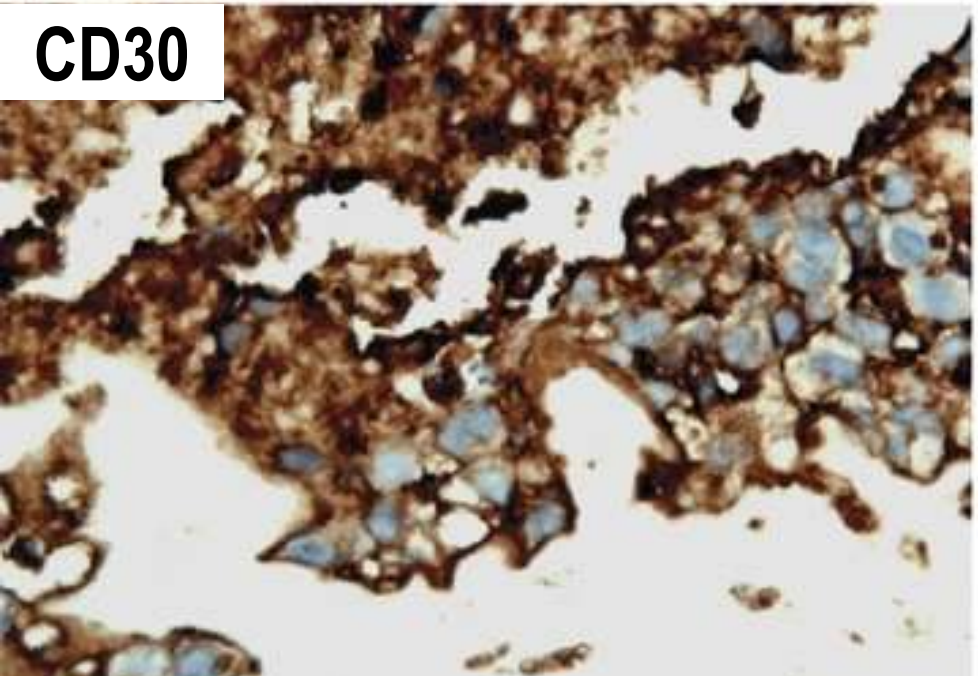
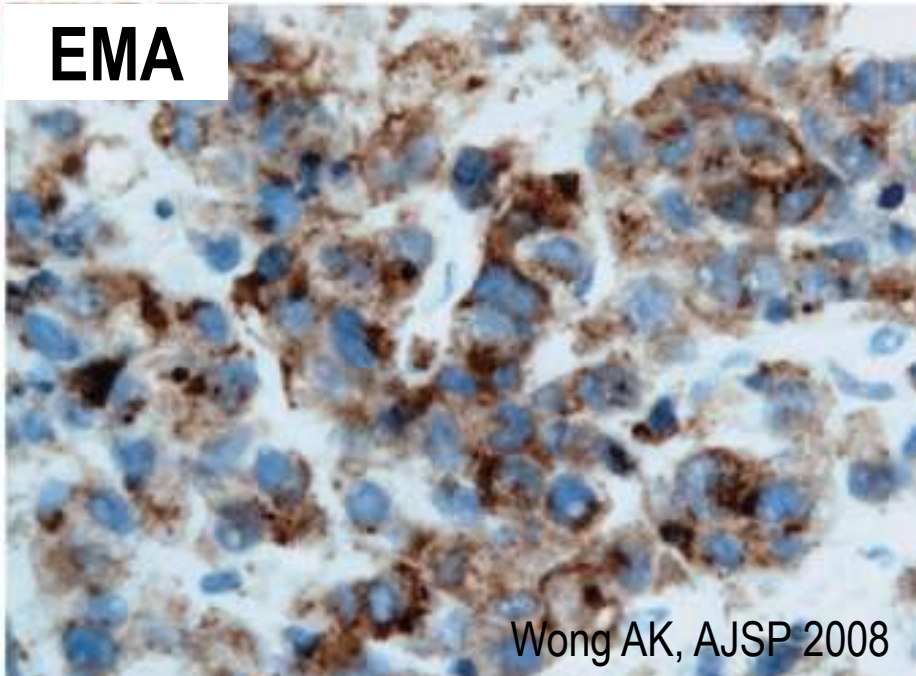
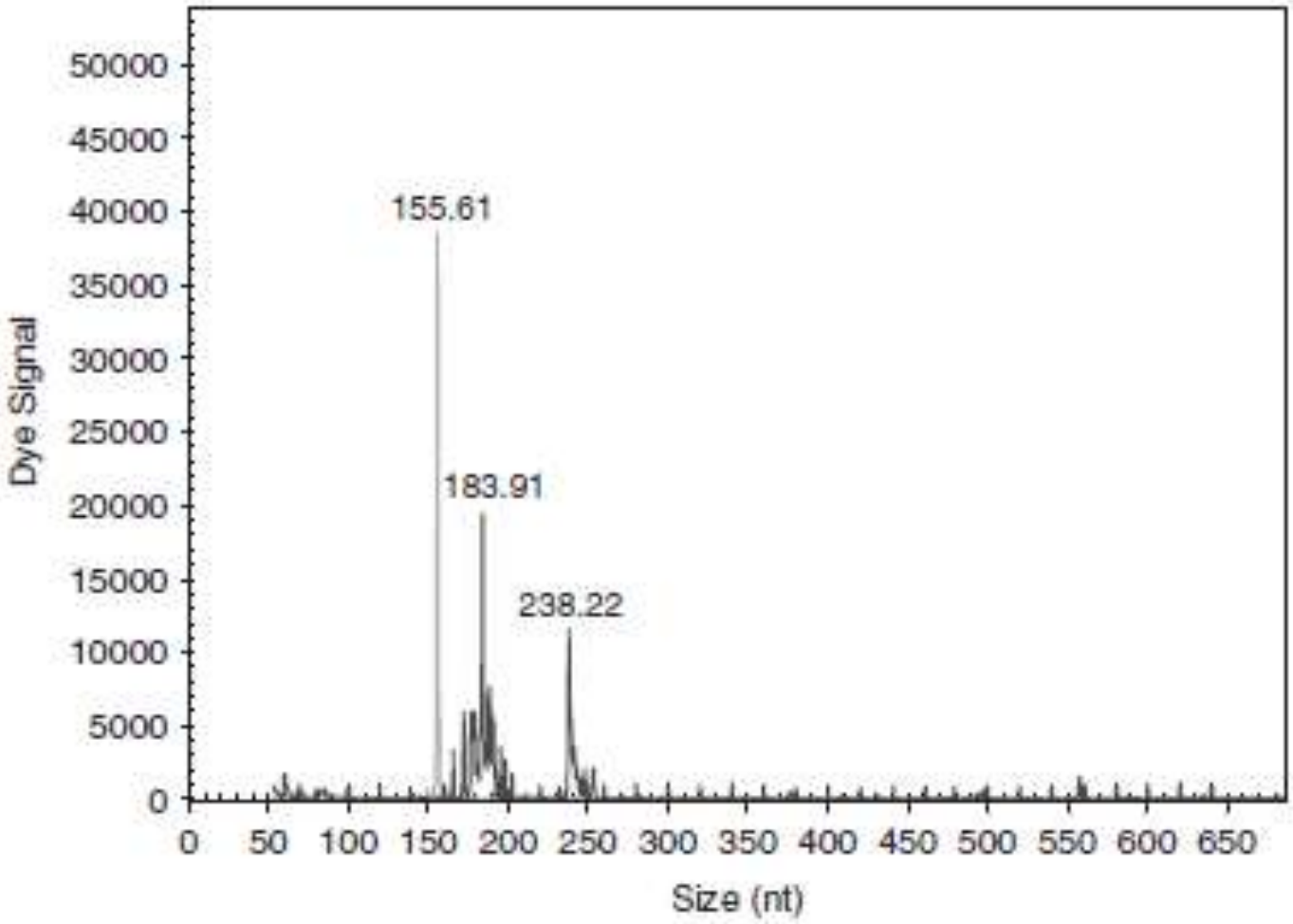

B


CD30


EMA
Wong AK, AJSP 2008



PCR for TCR-γ

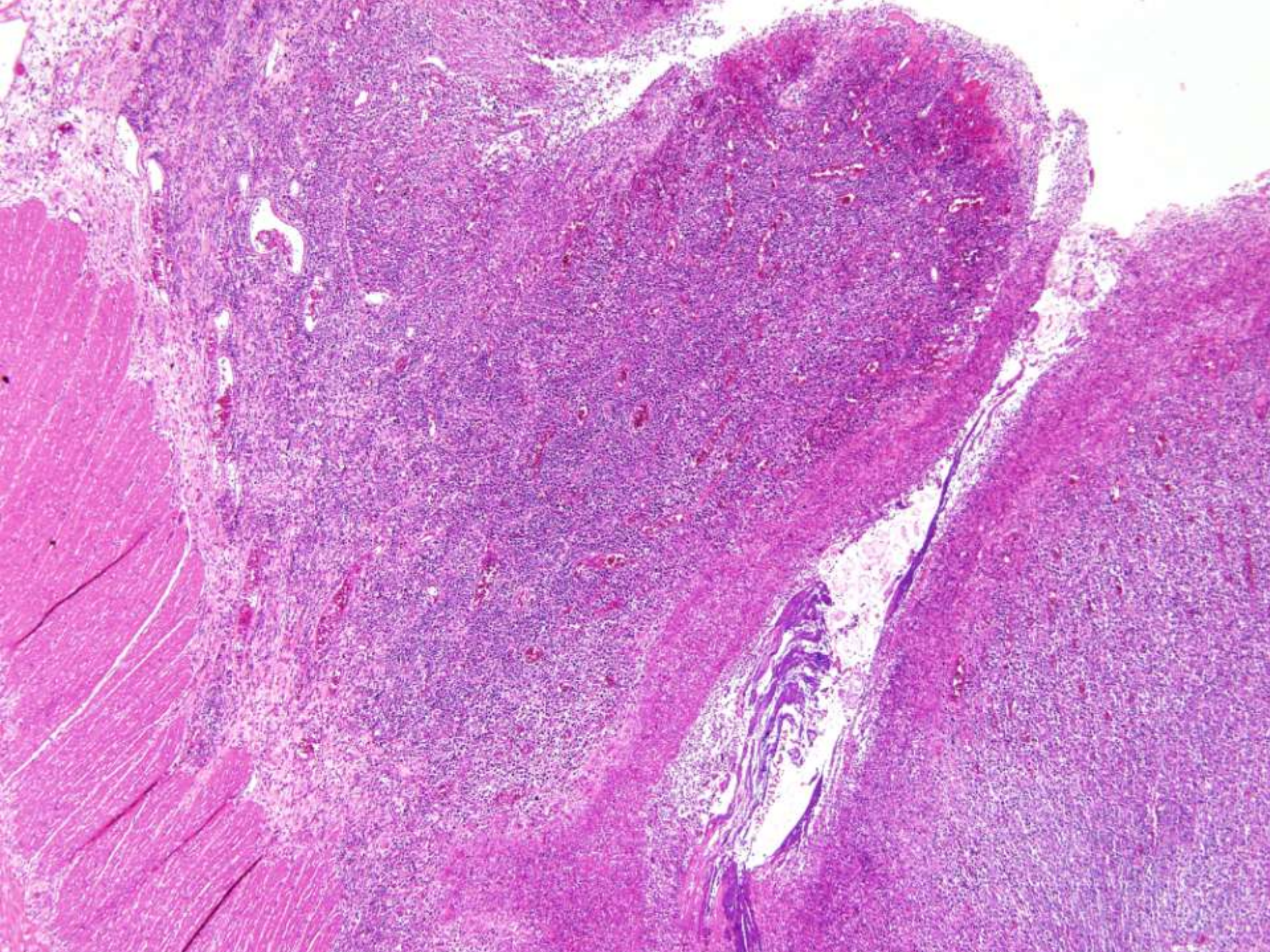
Wong AK, AJSP 2008

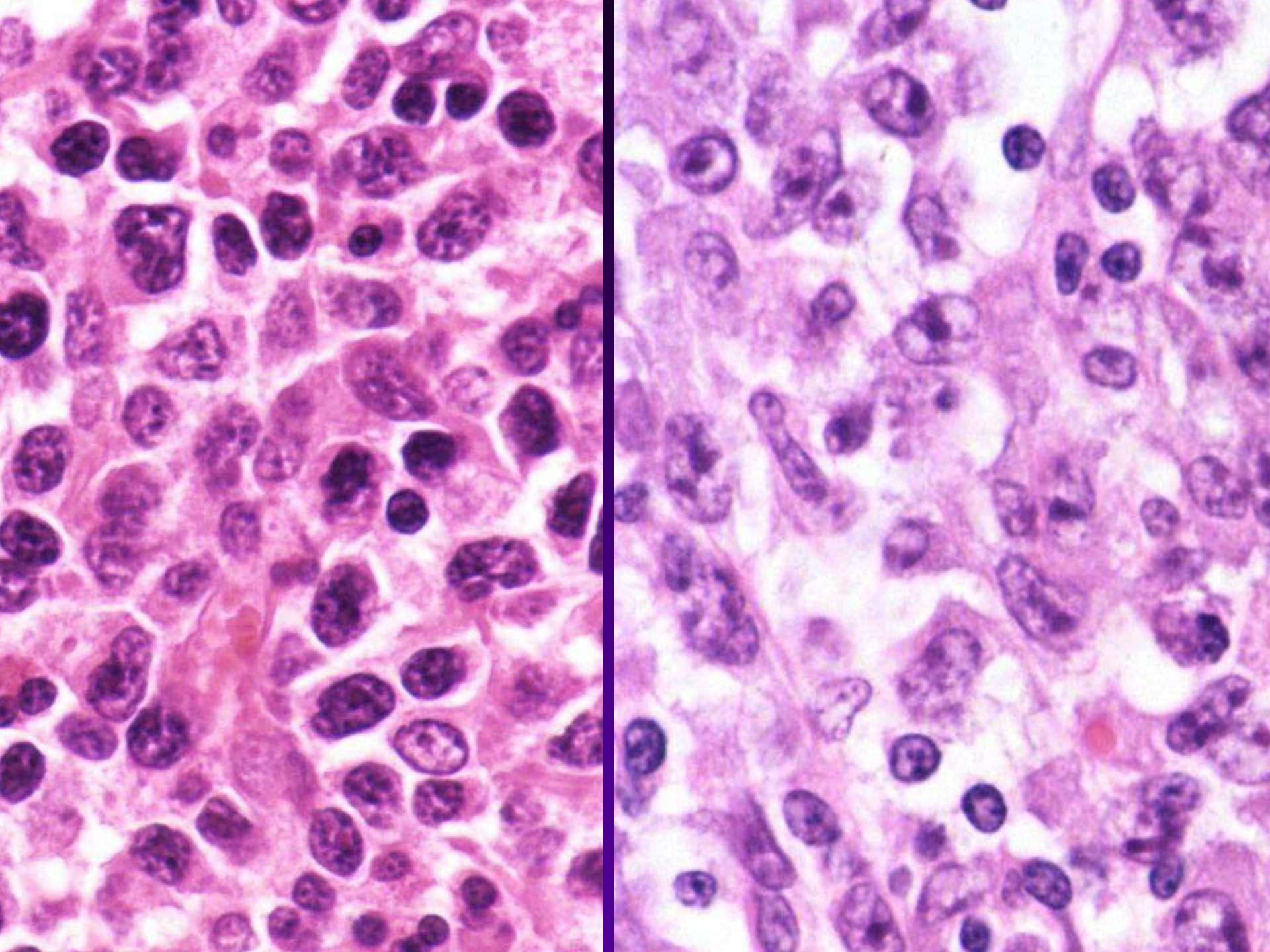
WHAT'S NEW IN ENTEROPATHY-ASSOCIATED T-CELL LYMPHOMA (EATL)?

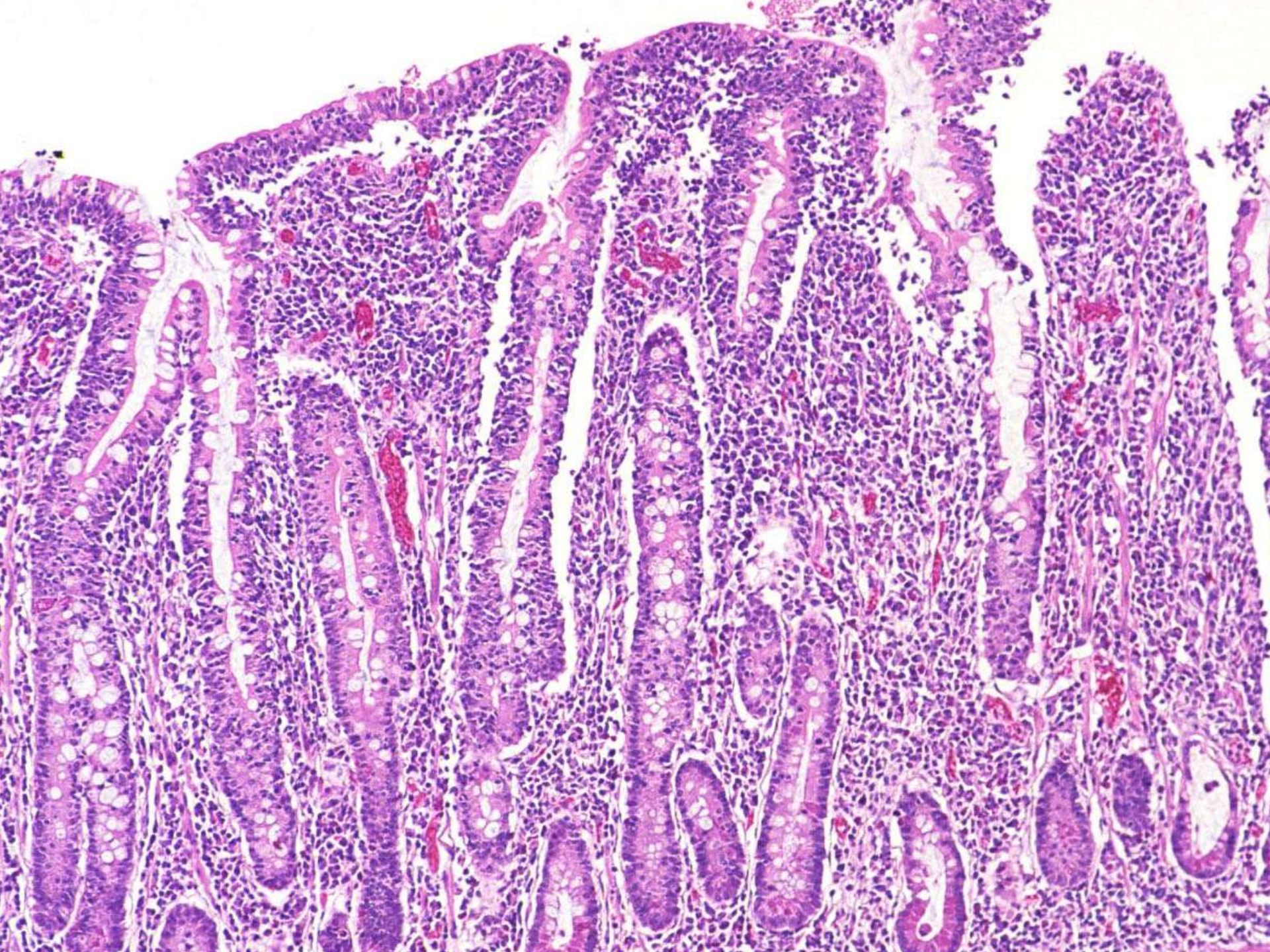
- EATL is a tumor of intestinal intraepithelial T lymphocytes
- Currently two subtypes are recognized:
  - Type I (Classical)
  - Type II
- Type II EATL will likely be considered a separate entity in future classifications, and is usually a γδ T-cell lymphoma

Type I EATL

- Uncommon, but seen with greater frequency in Northern Europe (celiac disease prevalent)
- Association with celiac disease
- Very very rare in Asians
- Histology:
  - Usually large cells, commonly with admixed inflammatory cells (histiocytes, eosinophils)
  - Adjacent mucosa shows features of enteropathy
- Immunophenotype: CD3+, CD5-, CD4-, CD8-/+, CD103+, CD30+/-, CD56-

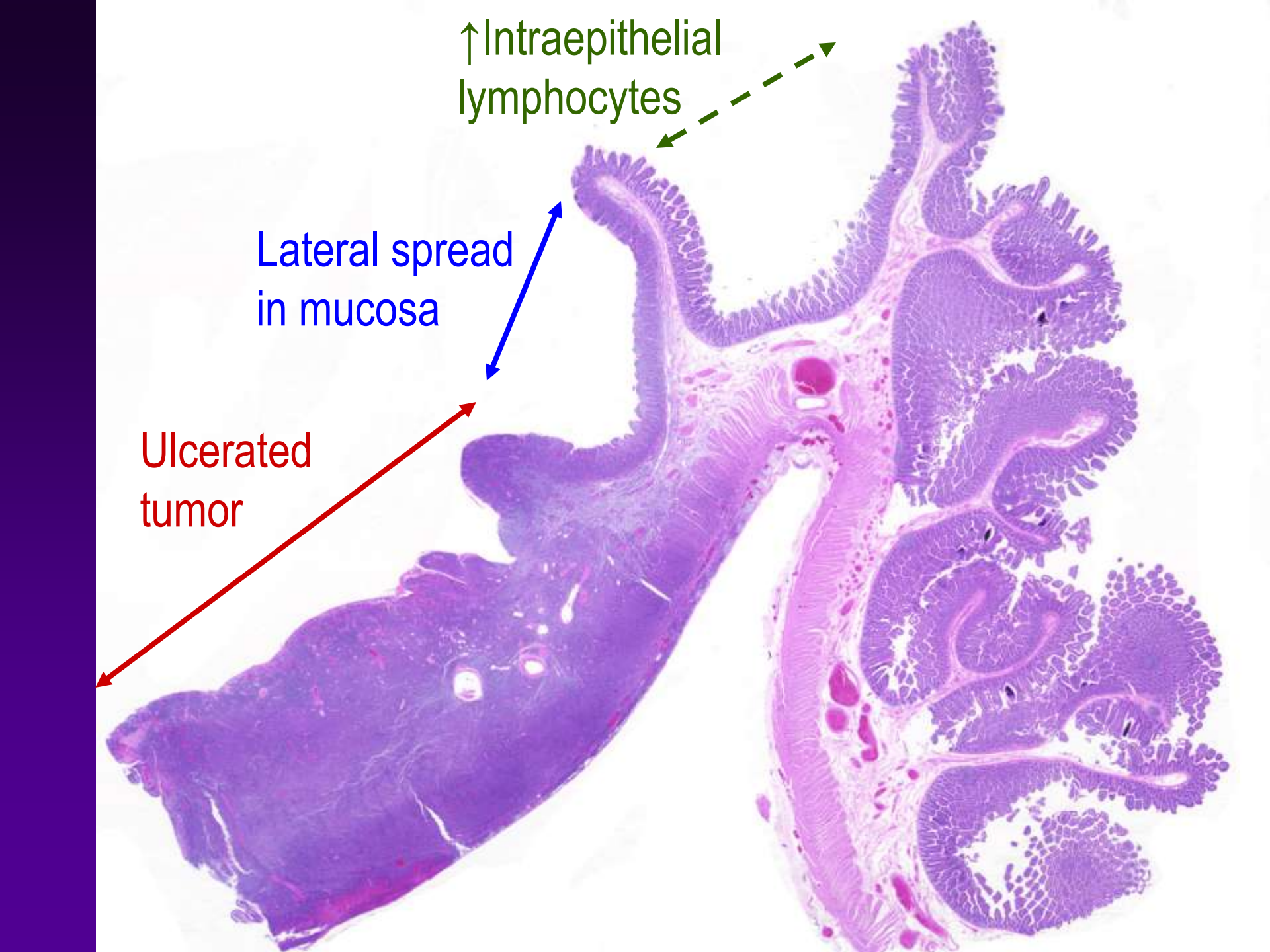


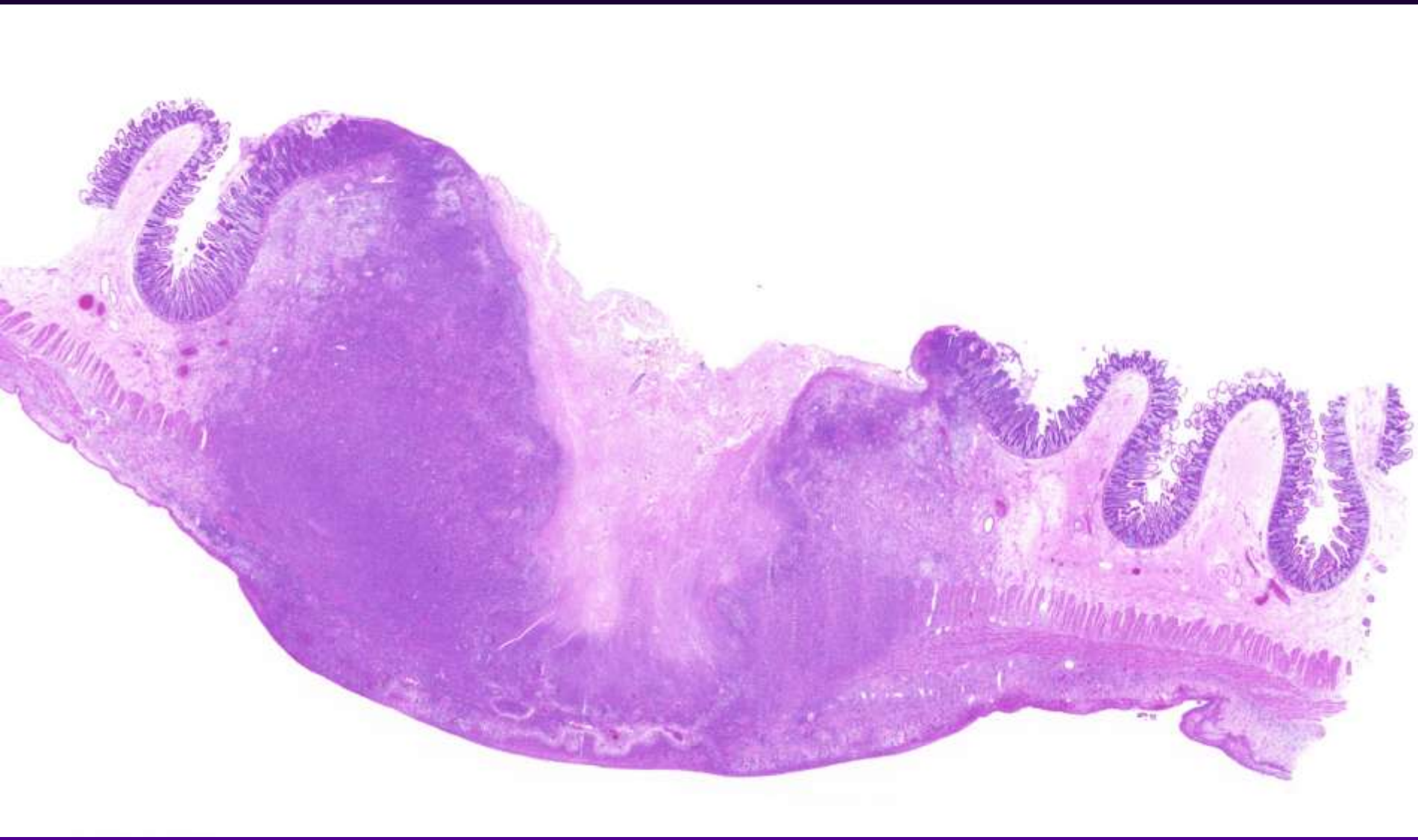


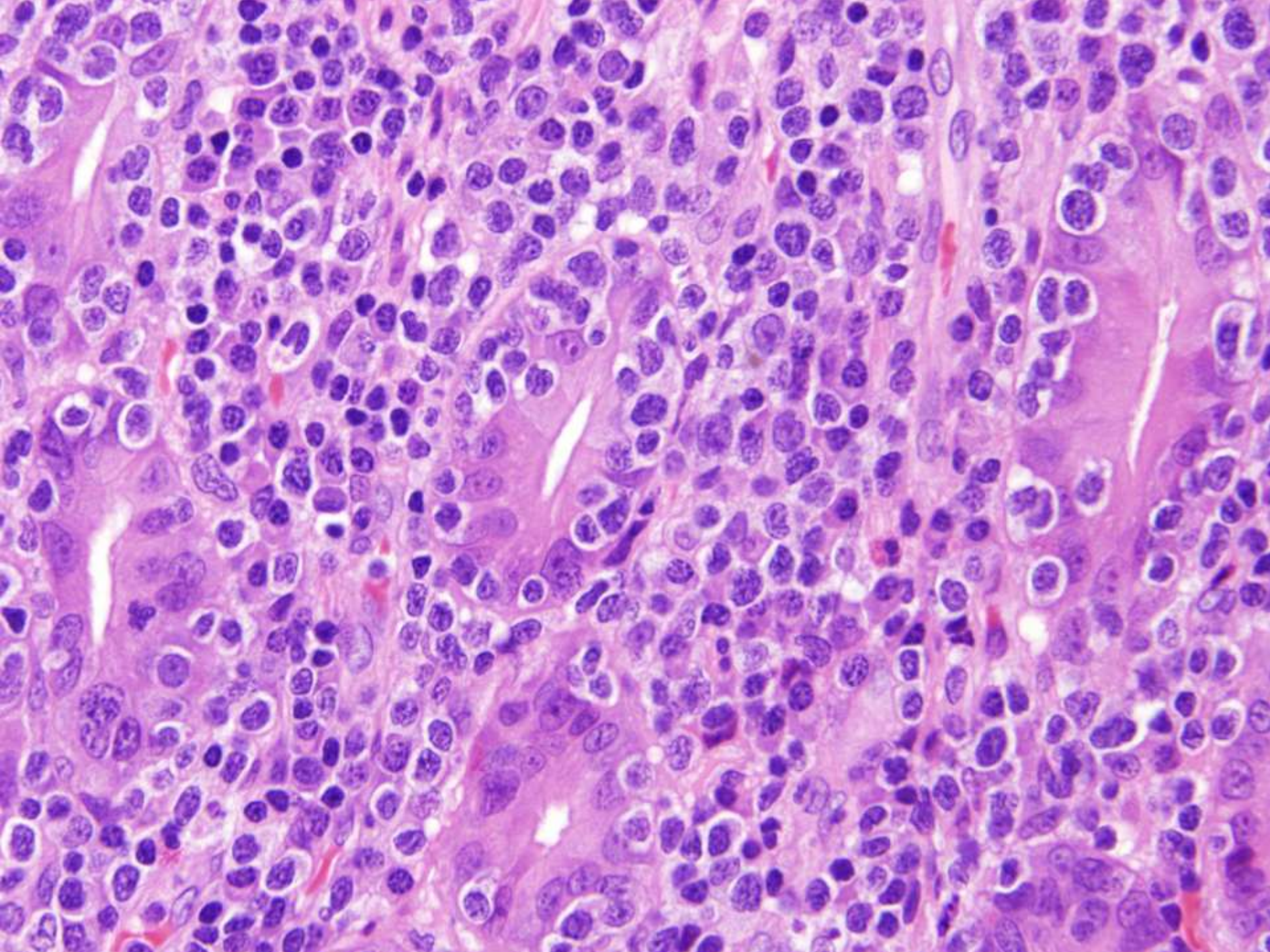


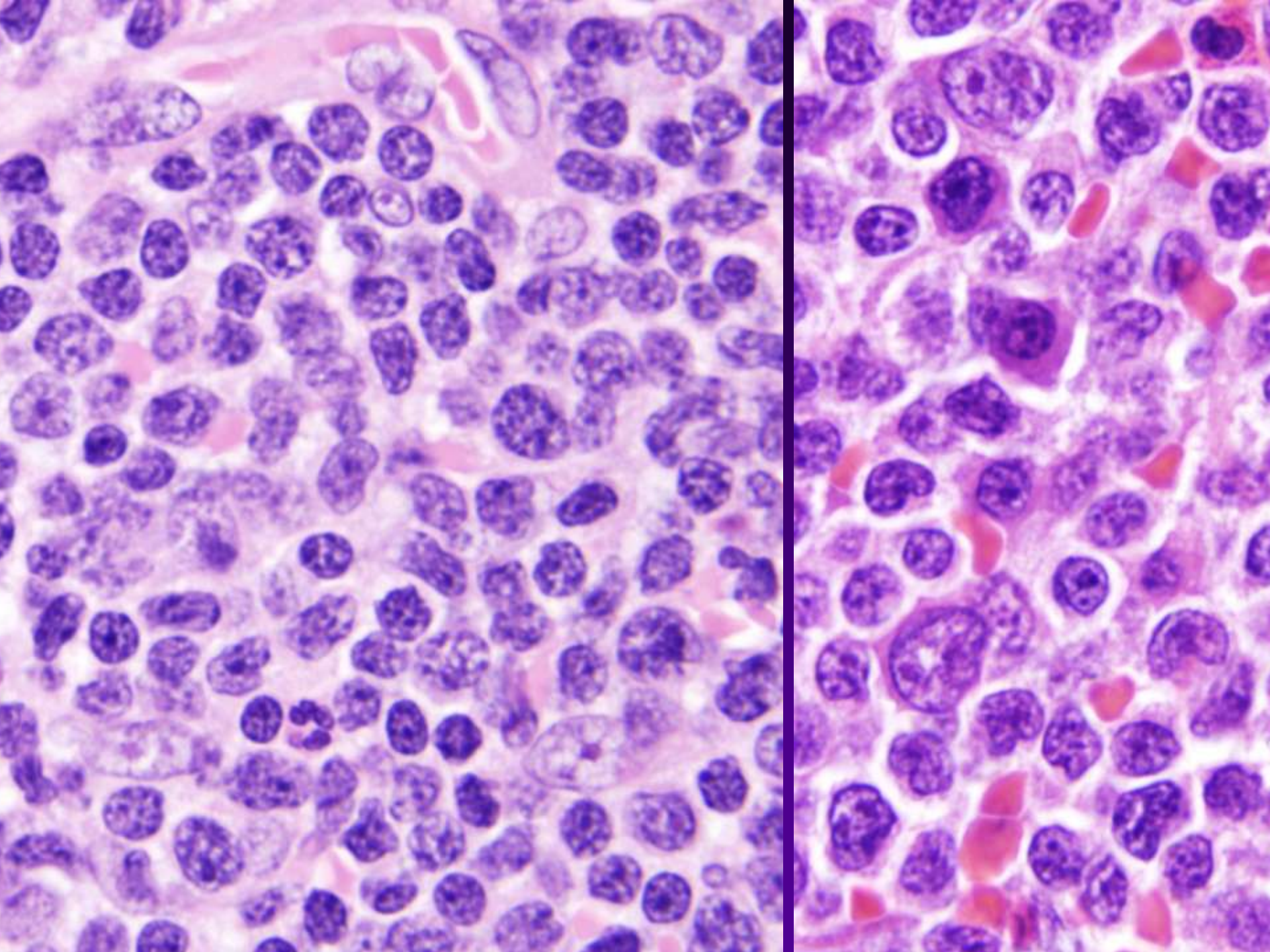
Type II EATL

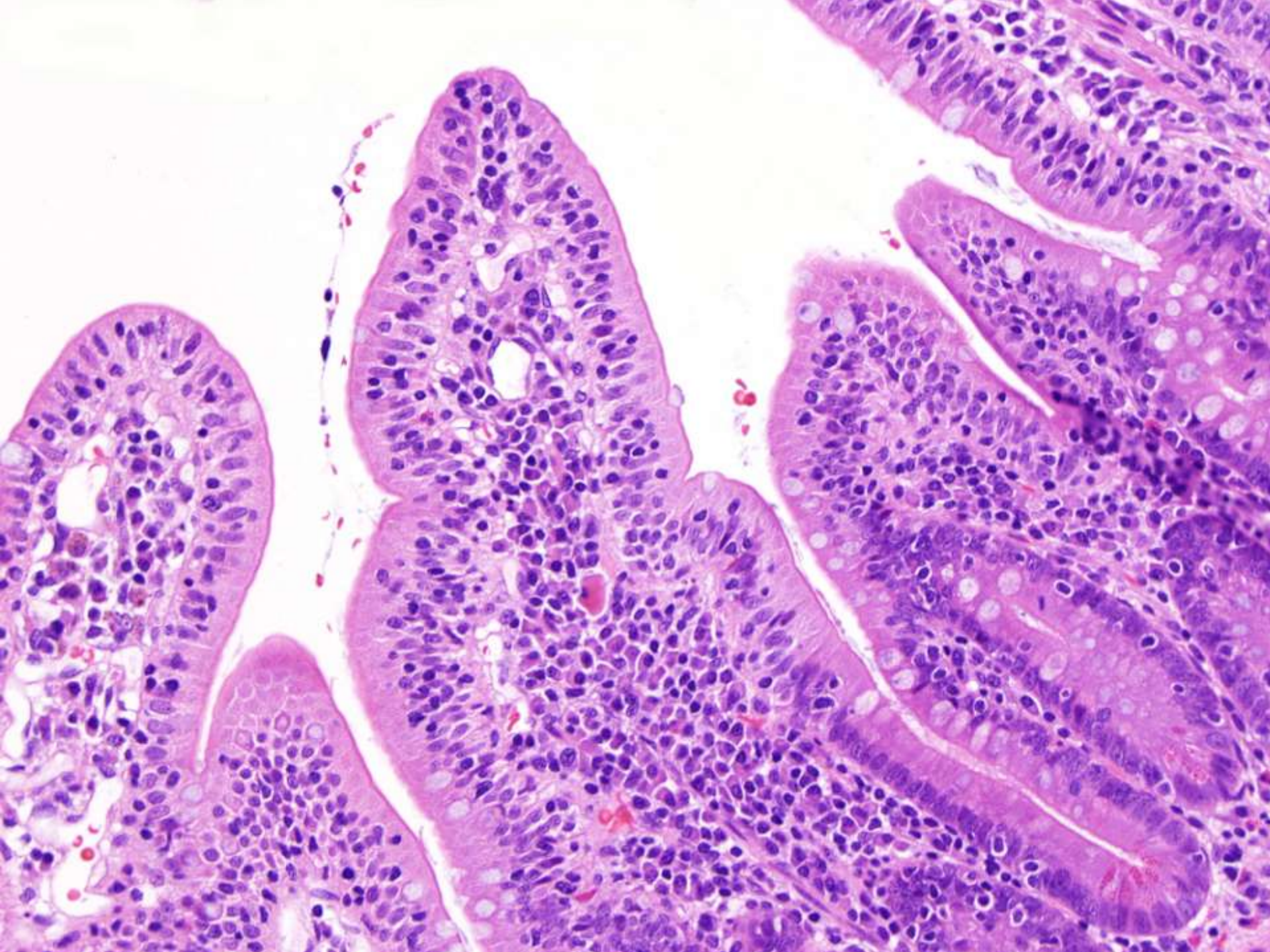
- Uncommon; no obvious racial predilection
- Practically the exclusive type of EATL in Asians
- No association with celiac disease
- Histology:
  - Monomorphic medium-sized cells; no necrosis; few admixed inflammatory cells
  - Adjacent mucosa: Intraepithelial lymphocytosis
- Immunophenotype: CD3+, CD5-, CD4-, CD8+, CD56+, CD30-, TCR γδ > αβ

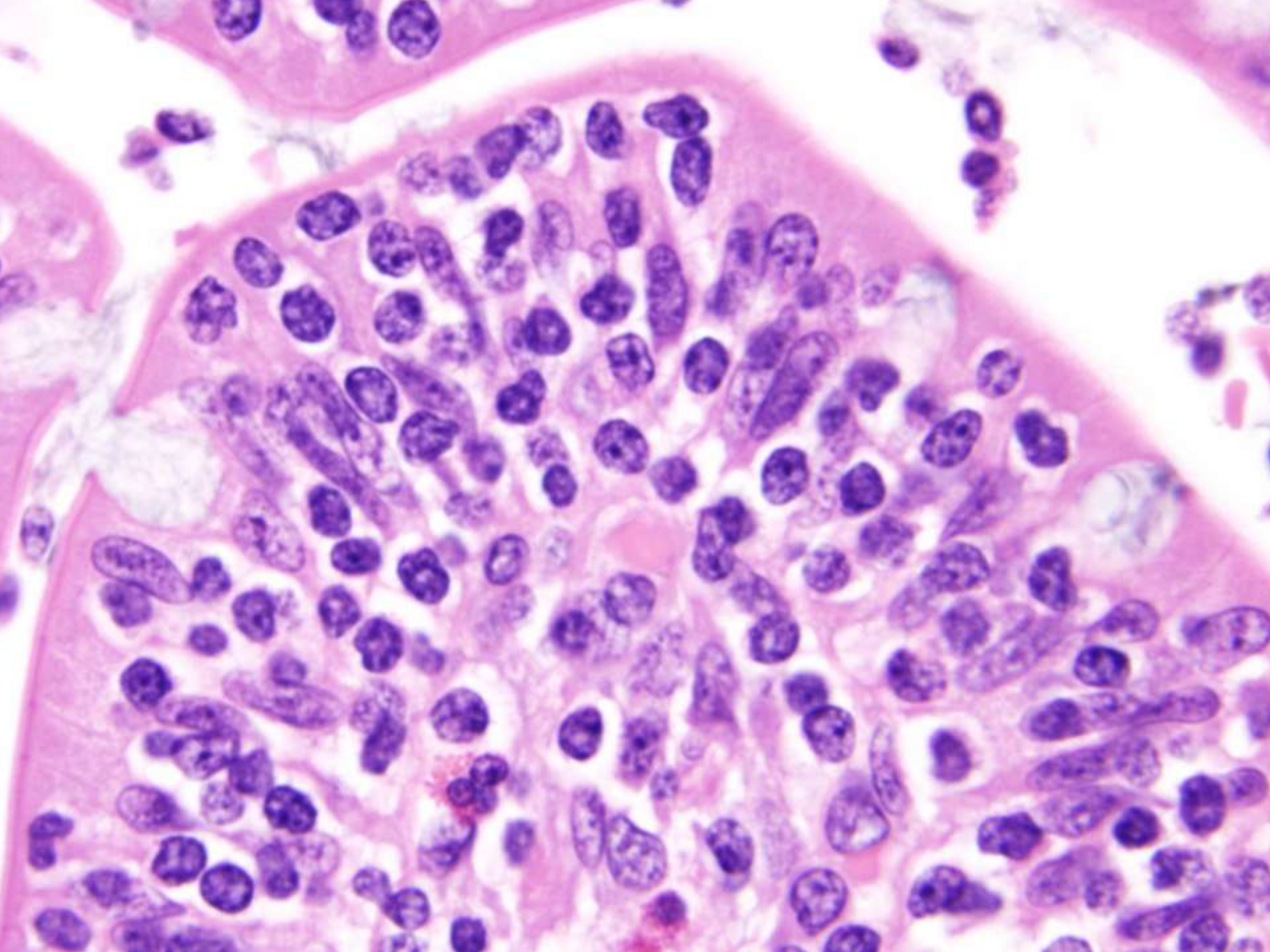

↑Intraepithelial
lymphocytes
Lateral spread
in mucosa
Ulcerated
tumor

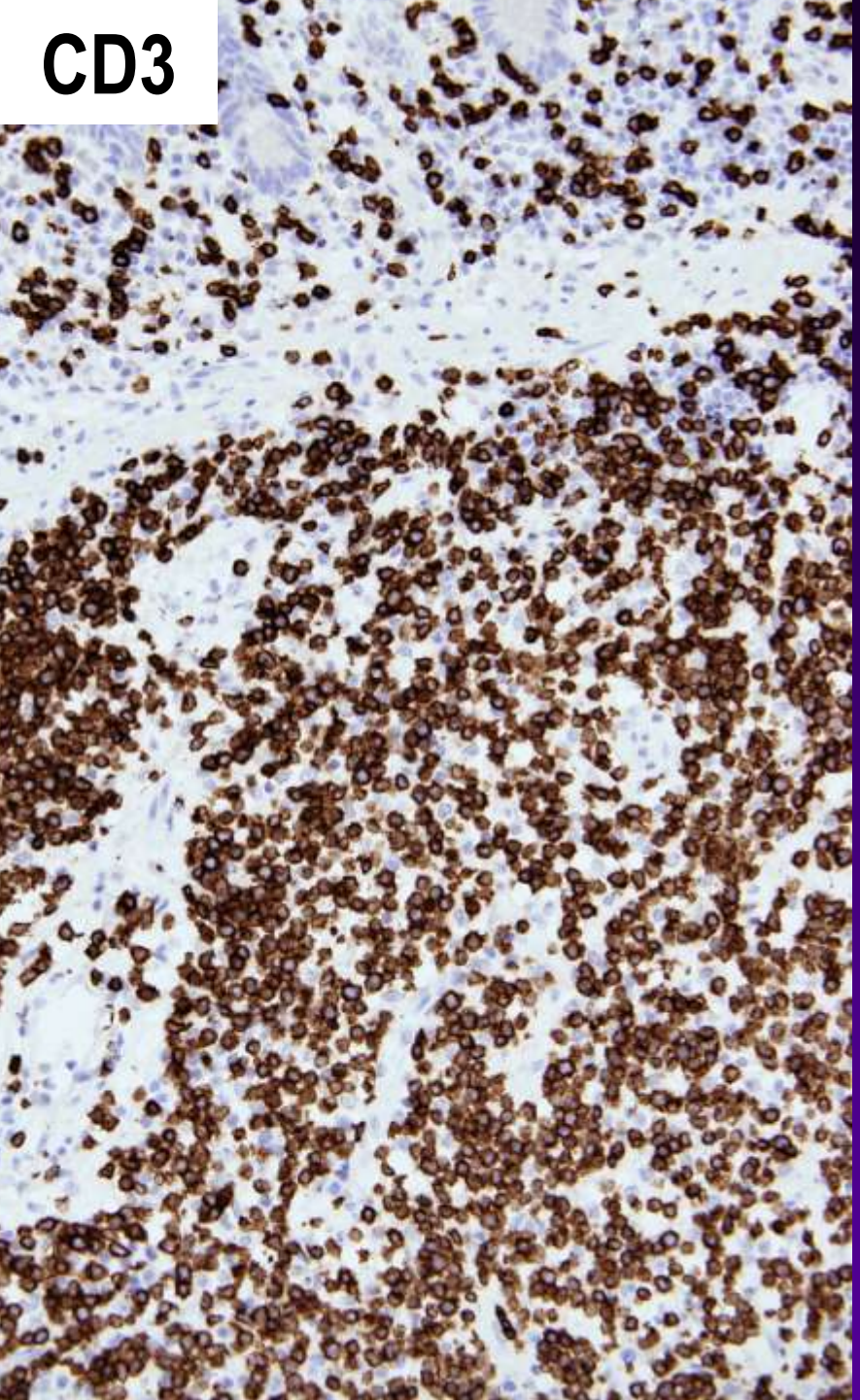


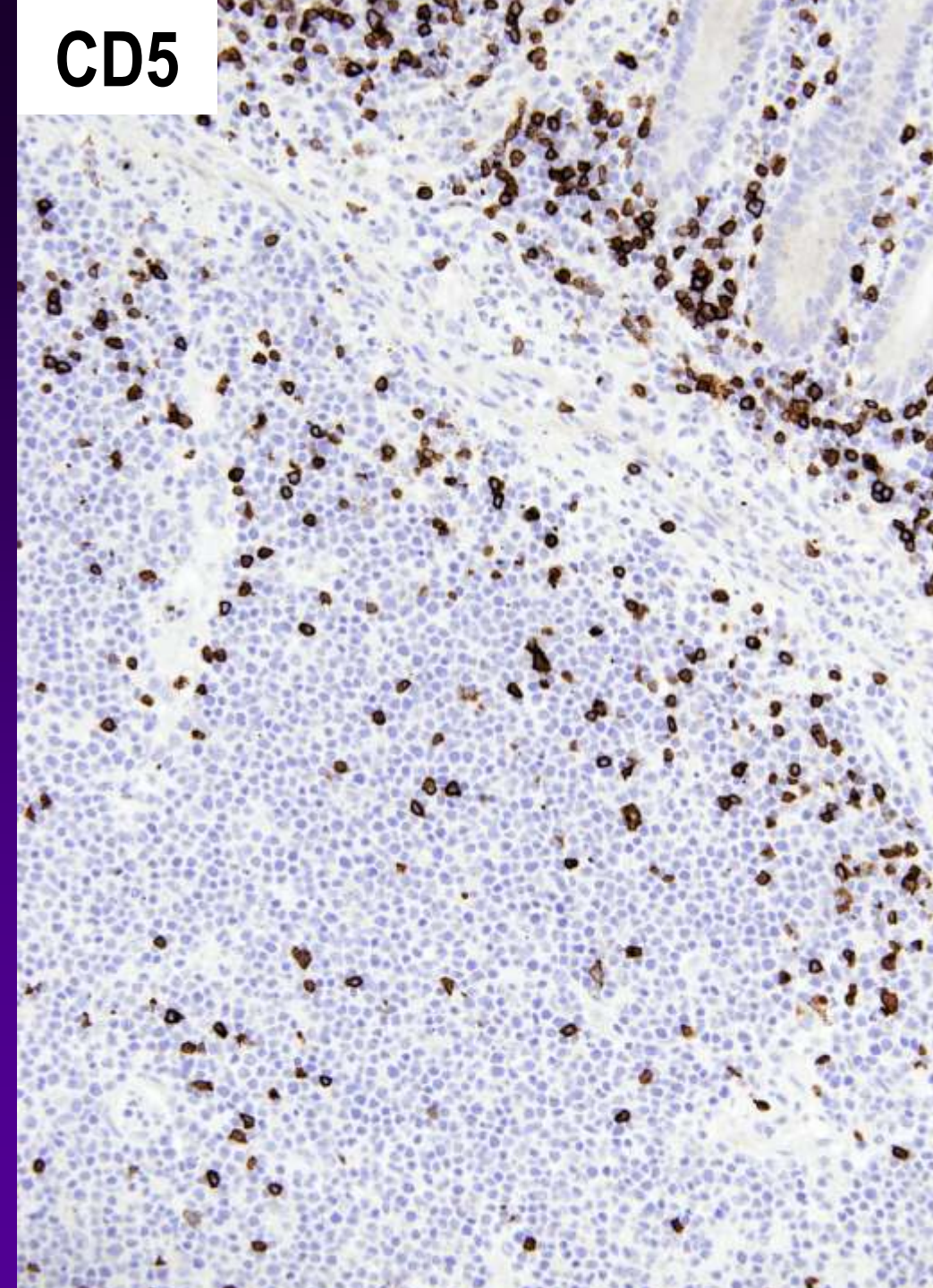


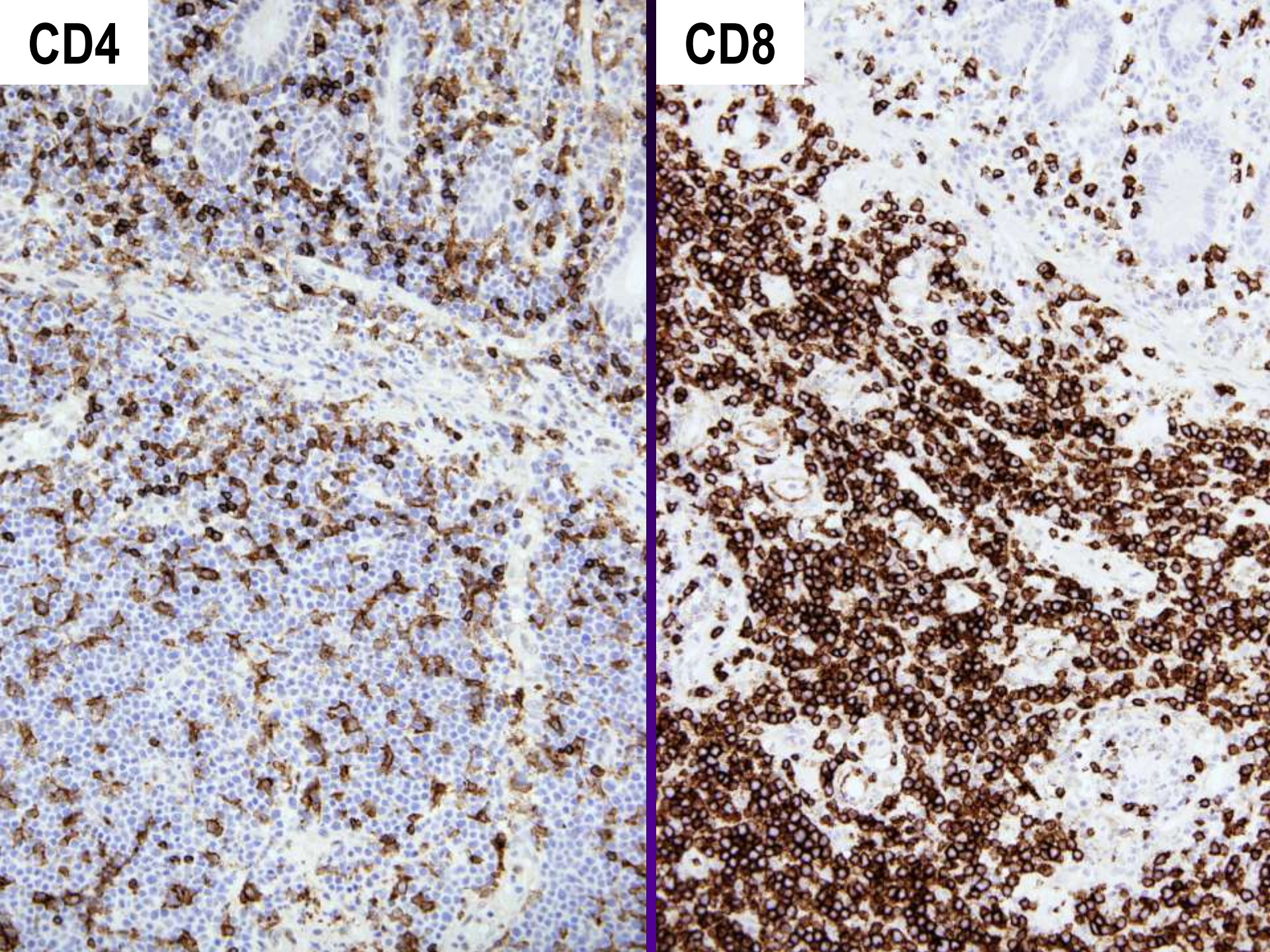




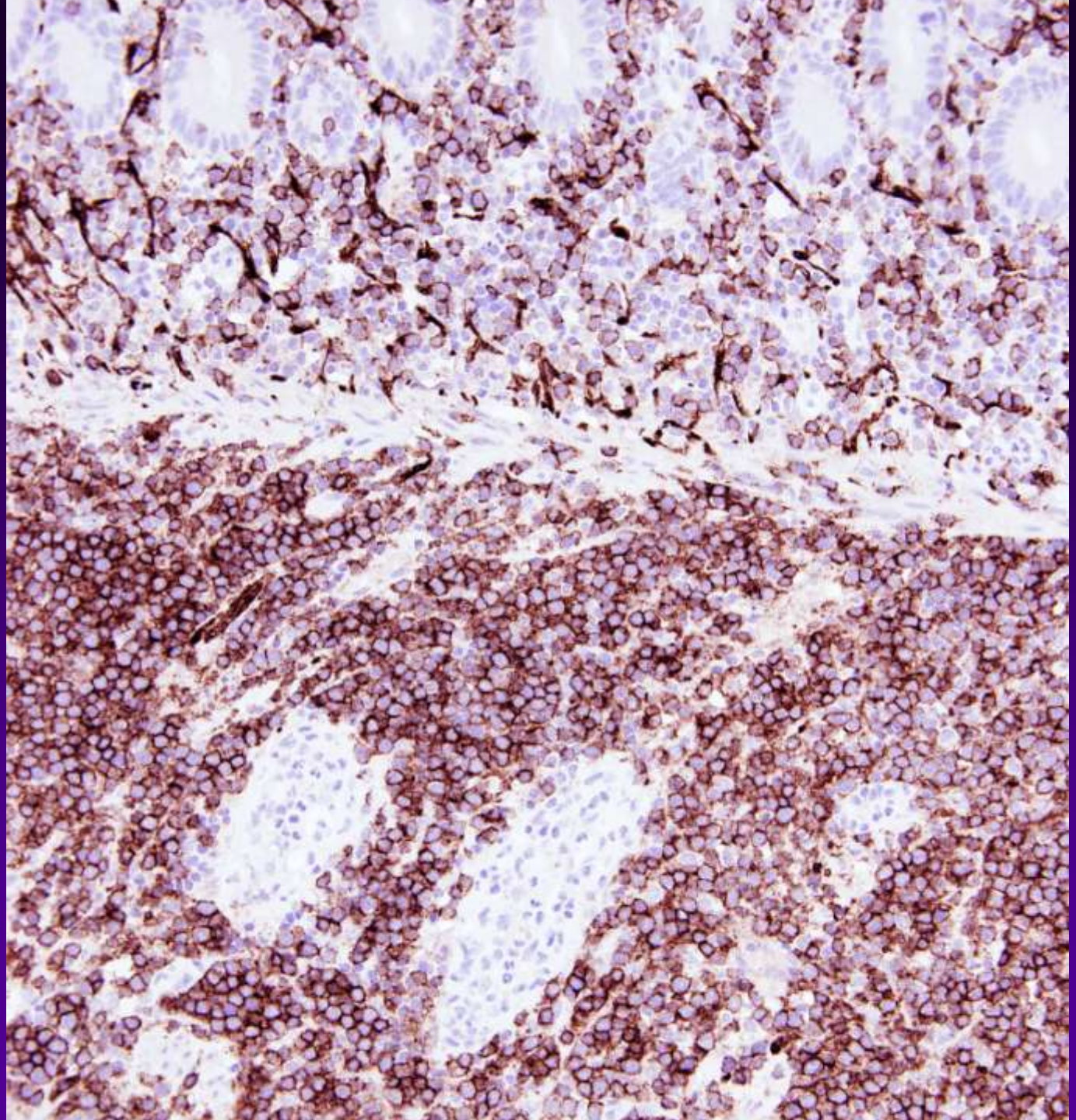



CD3


CD5

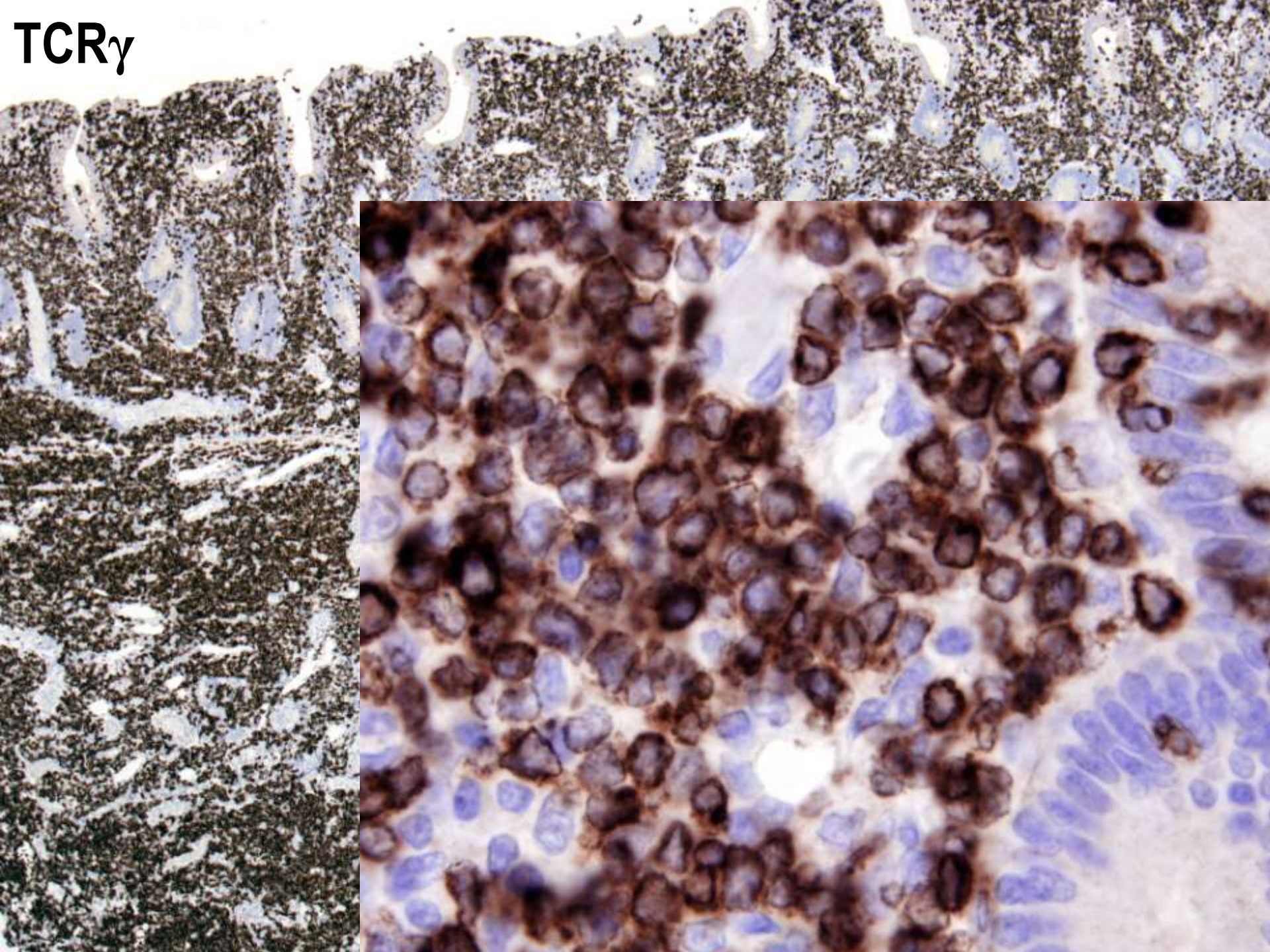

CD4
CD8

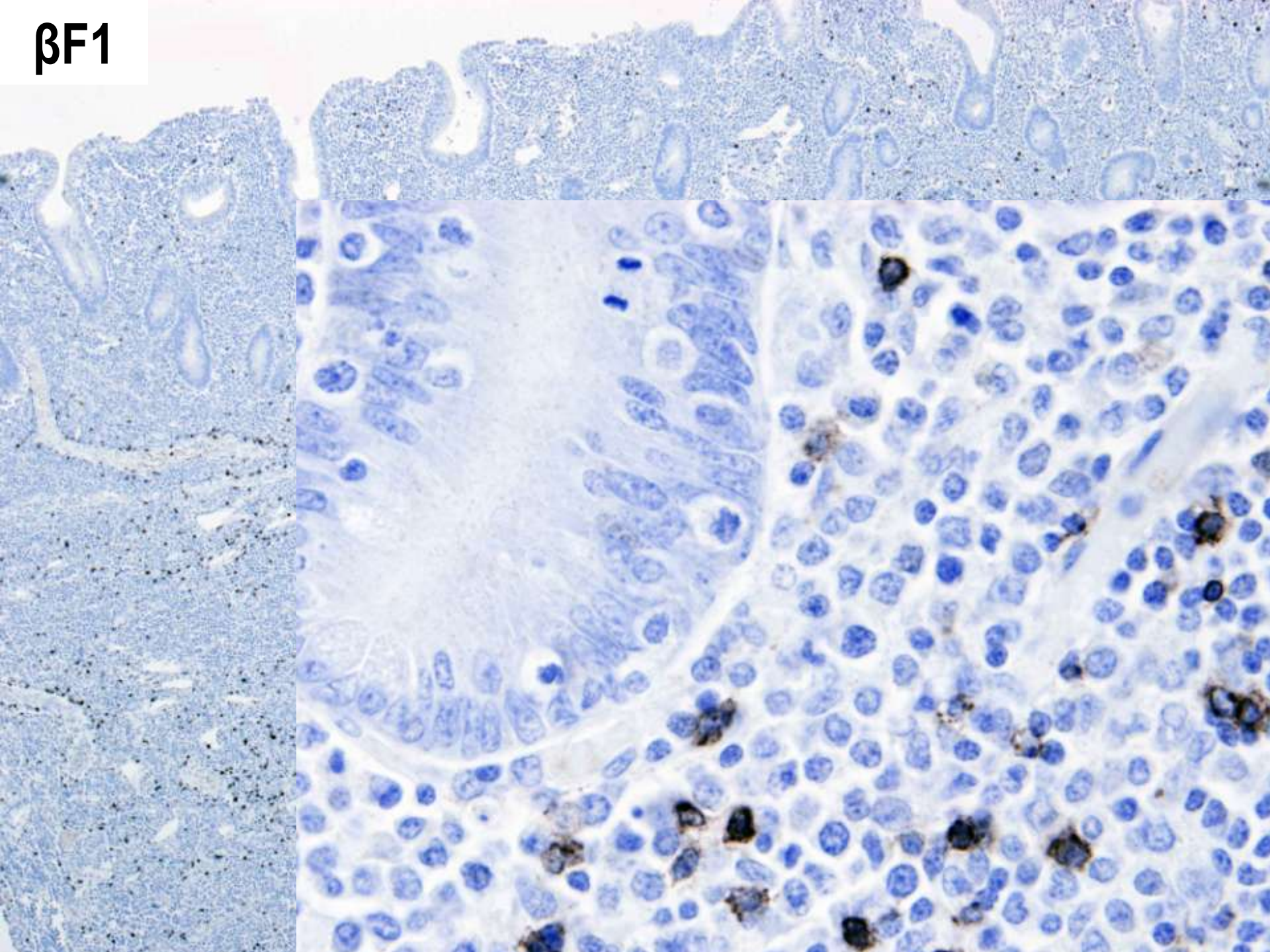
CD56

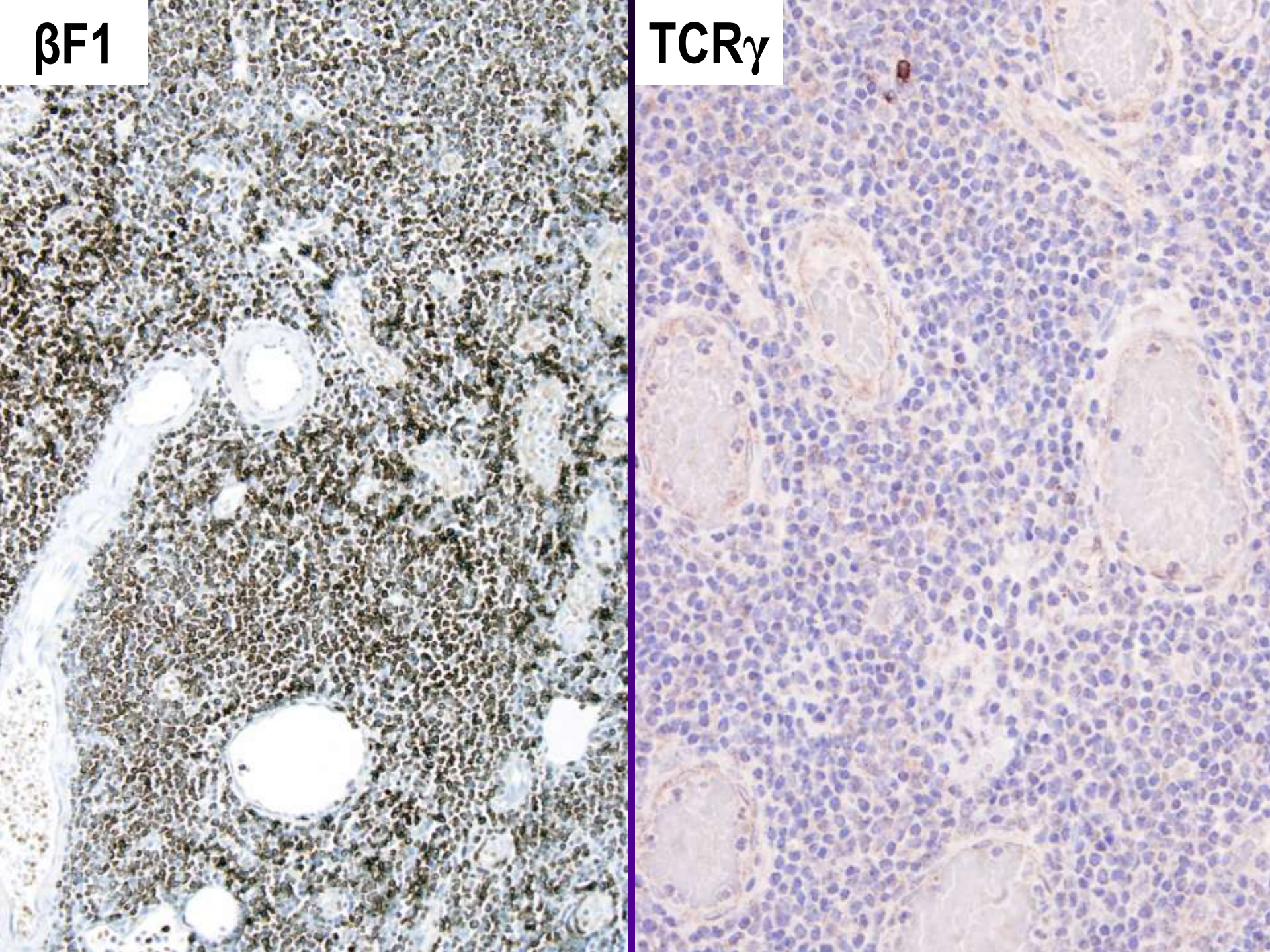


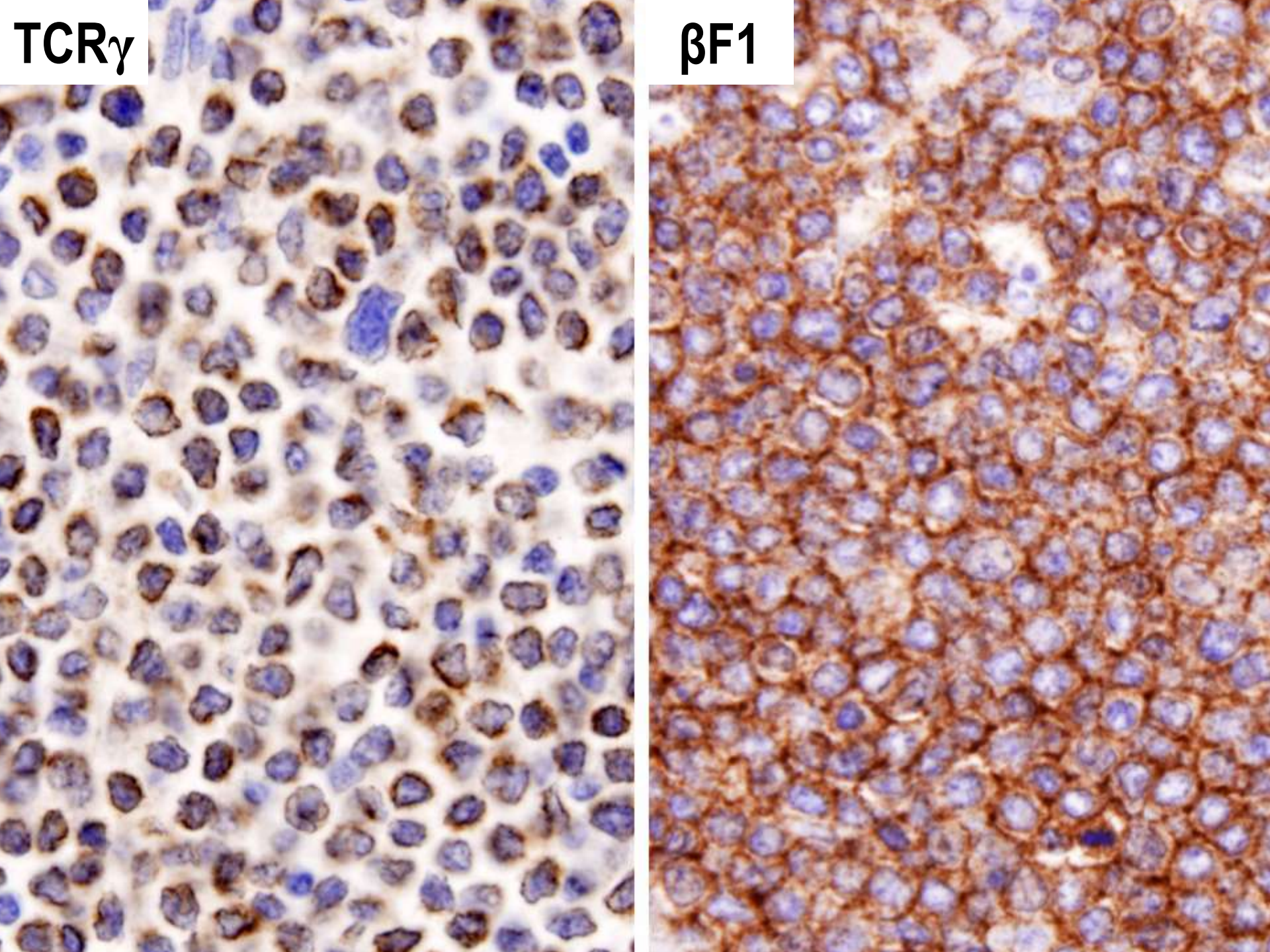
T-cell receptor expression

βF1- TCRγ+	11/18 (61%)
βF1+ TCRγ-	3/18 (17%)
βF1+ TCRγ+	3/18 (17%)
βF1- TCRγ-	1/18 (6%)


TCRγ

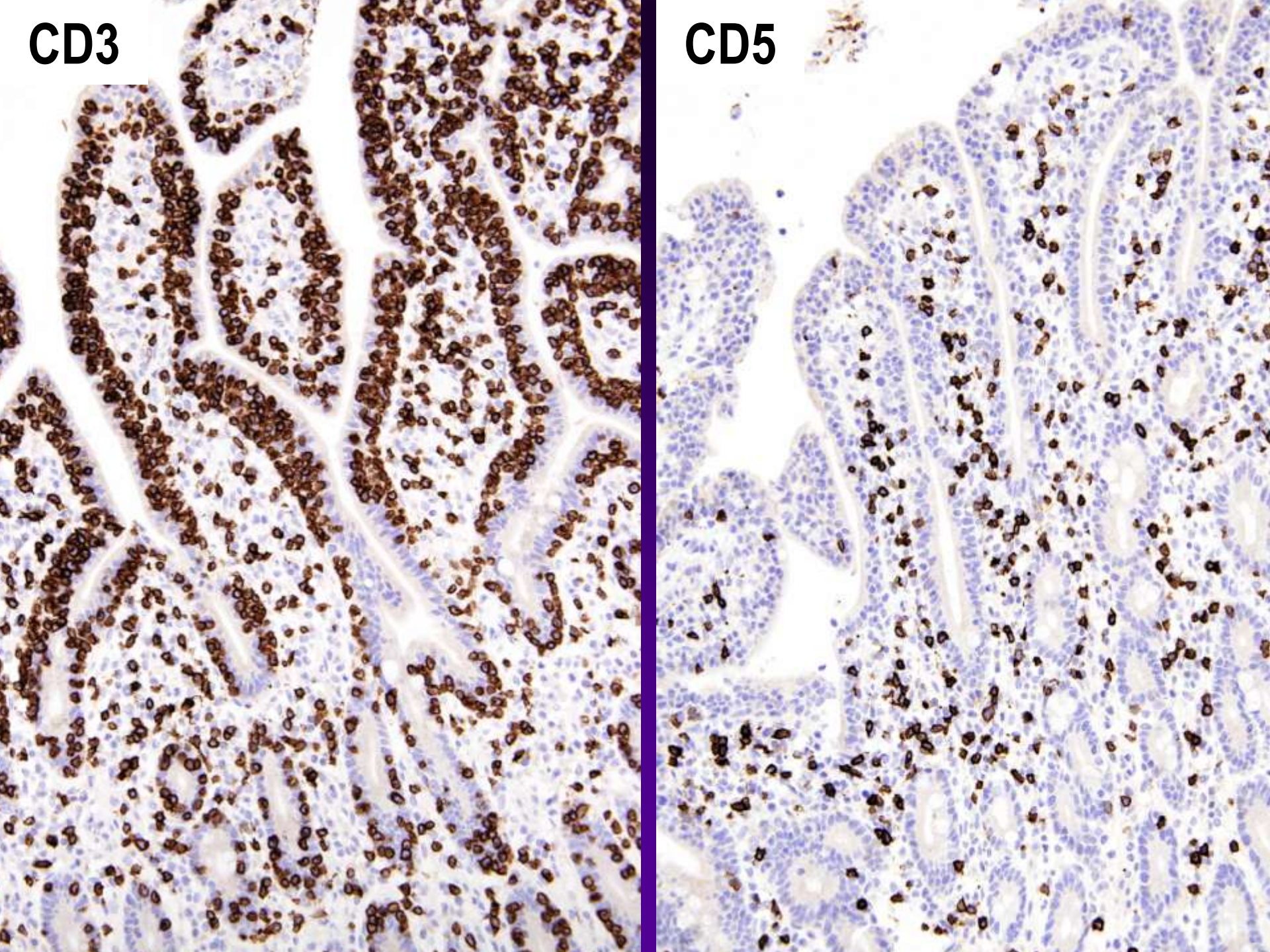

βF1

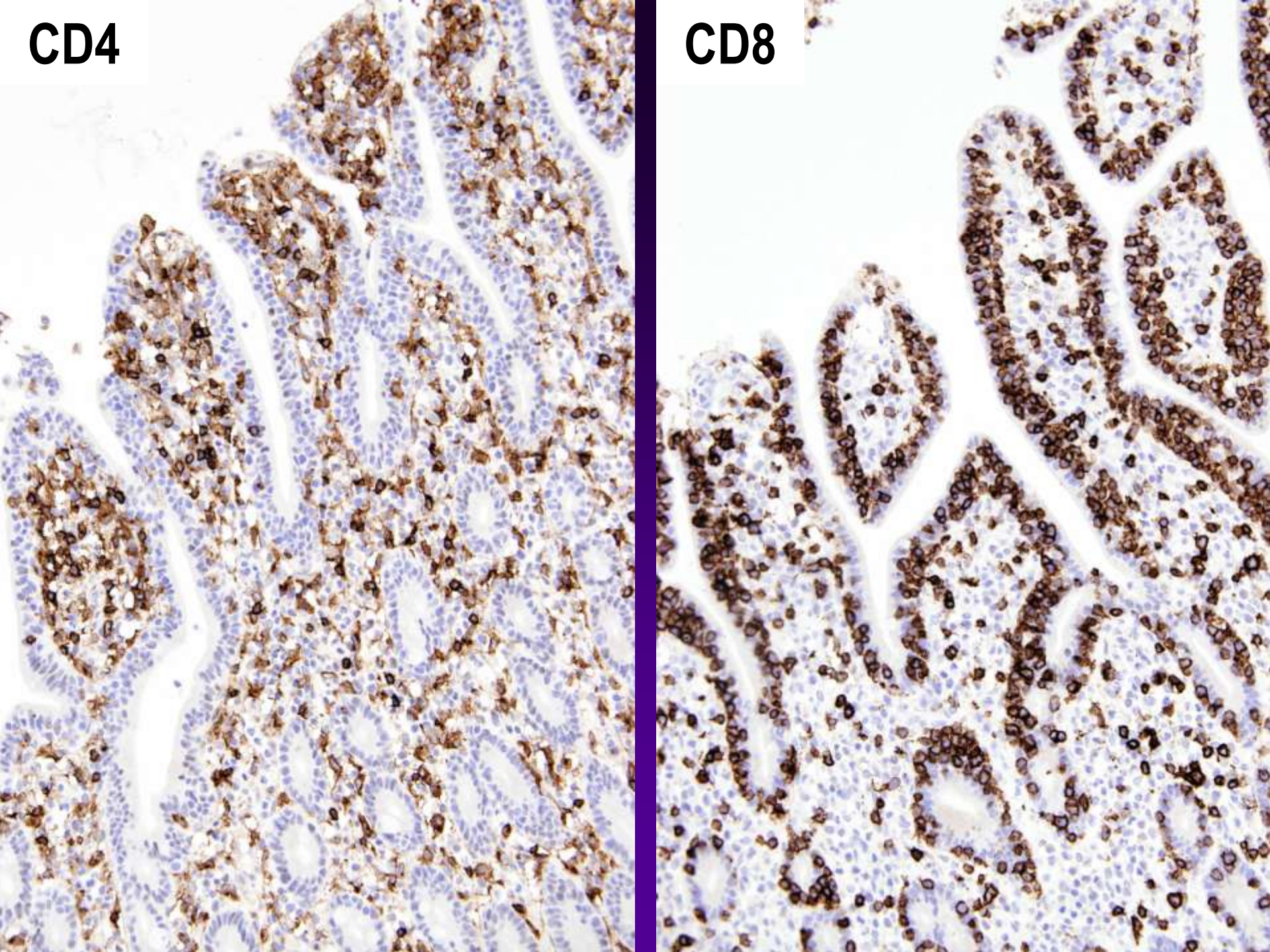

βF1
TCRγ


TCRγ
βF1

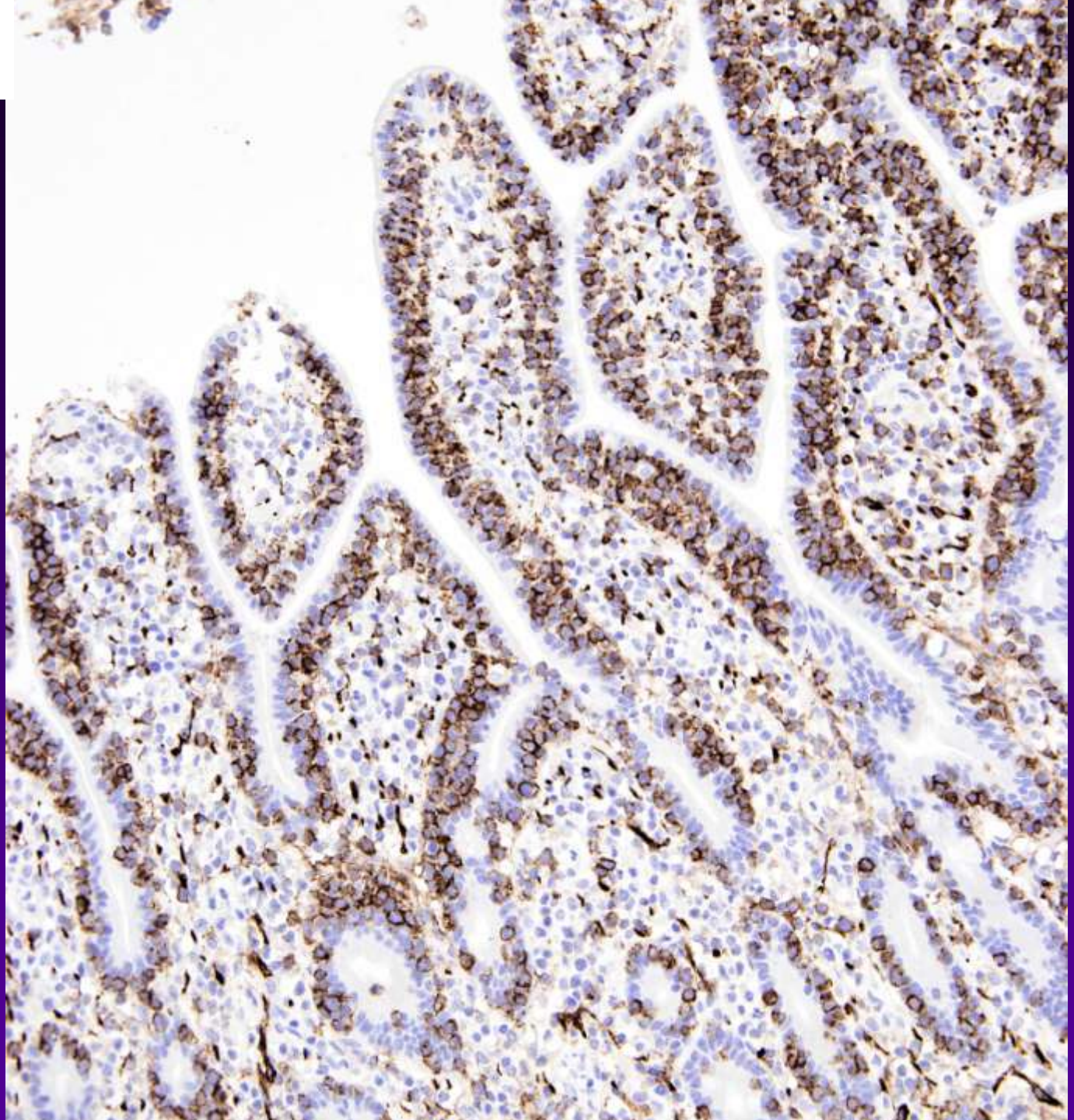
Immunophenotype of adjacent intraepithelial lymphocytosis zone

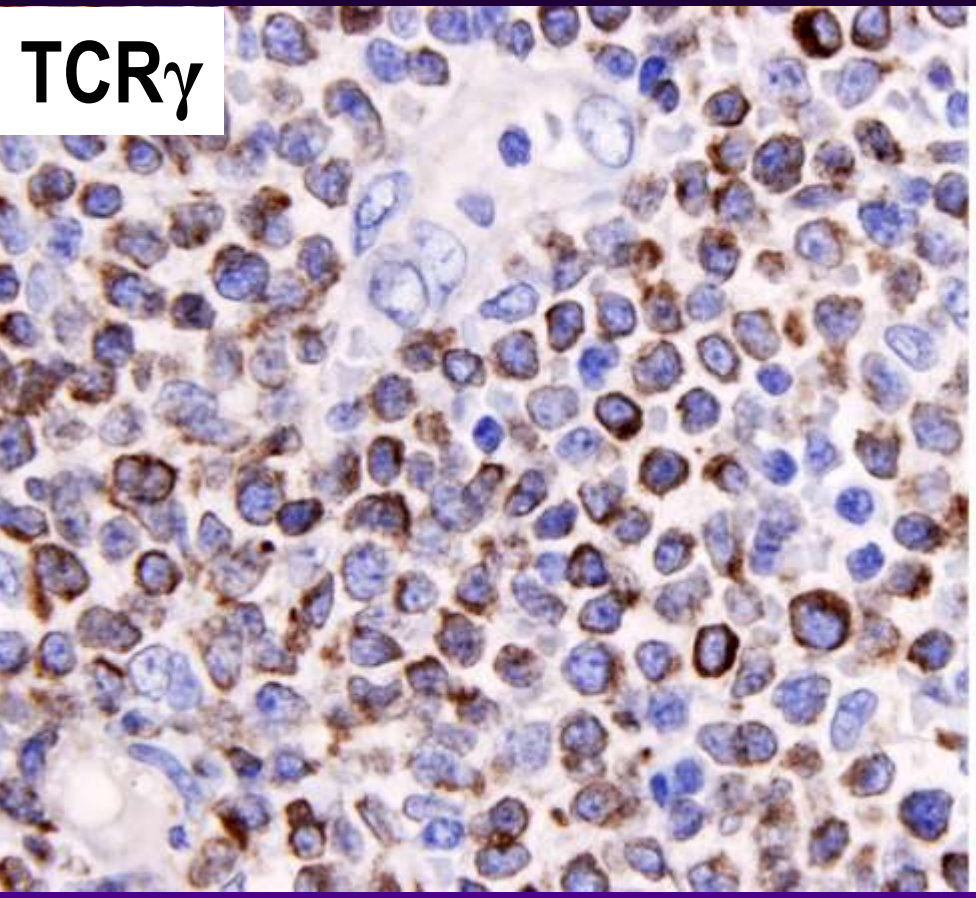
- Discordant with lymphoma (65%)
  - Usually involving CD8 or CD56
- Concordant with lymphoma (35%)


CD3
CD5

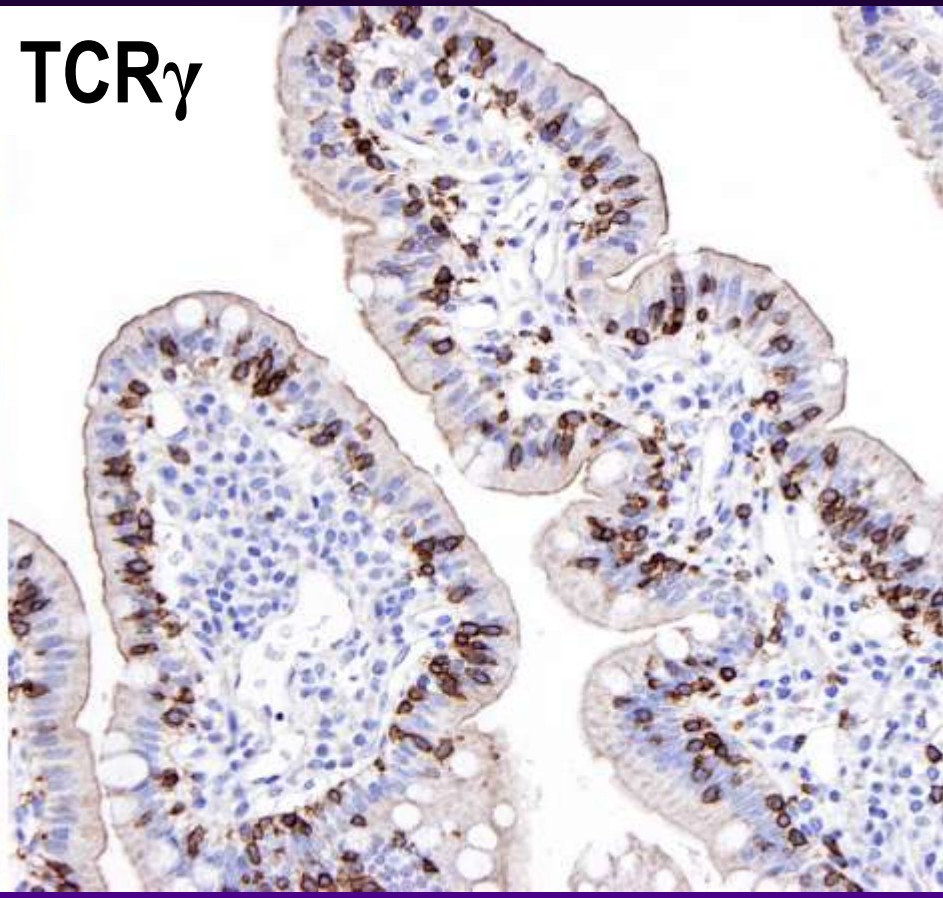

CD4
CD8

CD56

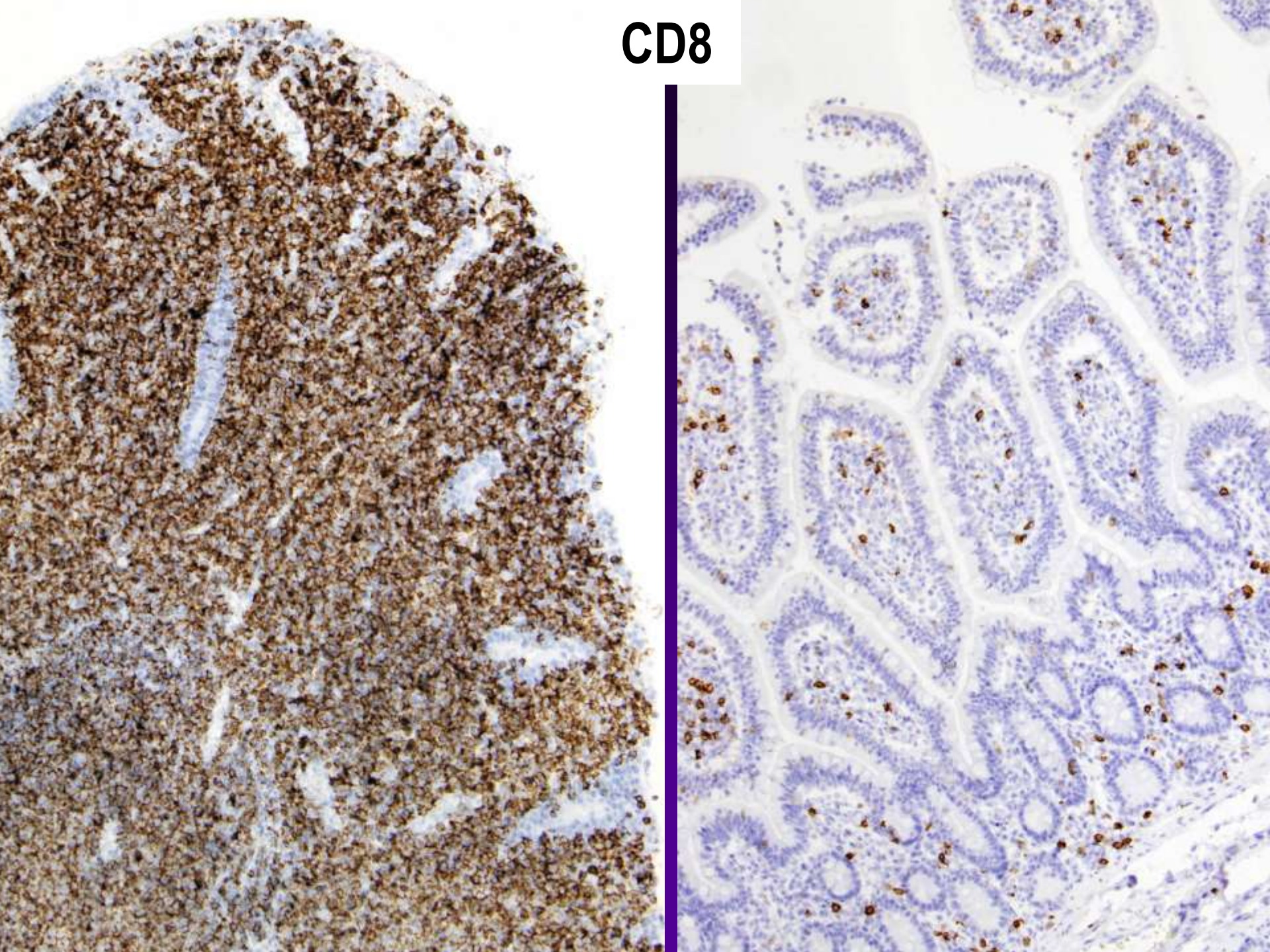


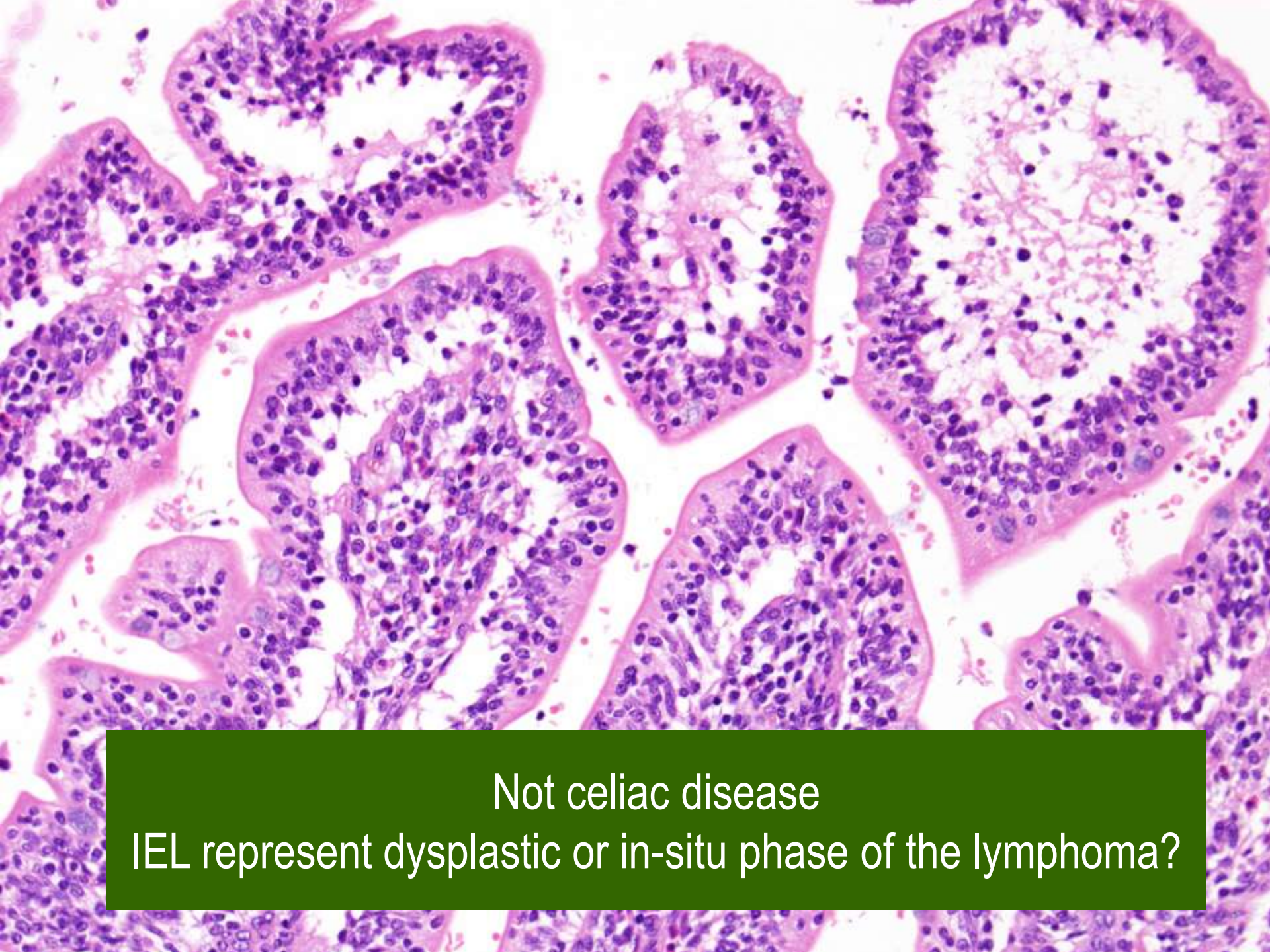


Tumor component



Adjacent intraepithelial lymphocytosis


CD8


Not celiac disease
IEL represent dysplastic or in-situ phase of the lymphoma?

Is it justified to separate type II EATL from type I EATL?

FOR:

- Morphologically and immunophenotypically distinct
- No evidence of celiac disease
- Epidemiologically different (type I practically not seen in Asians)

AGAINST:

- Although there are differences in genetic alterations (+8q24 common in type II; +1q32-q41 and +5q34-q35 common in type I), they share common genetic changes (+8q31, -16q12)

Monomorphic intestinal T-cell lymphoma

NEW ENTITY NOT INCLUDED IN 2008 WHO CLASSIFICATION

Indolent CD8-positive Lymphoid Proliferation of the Ear

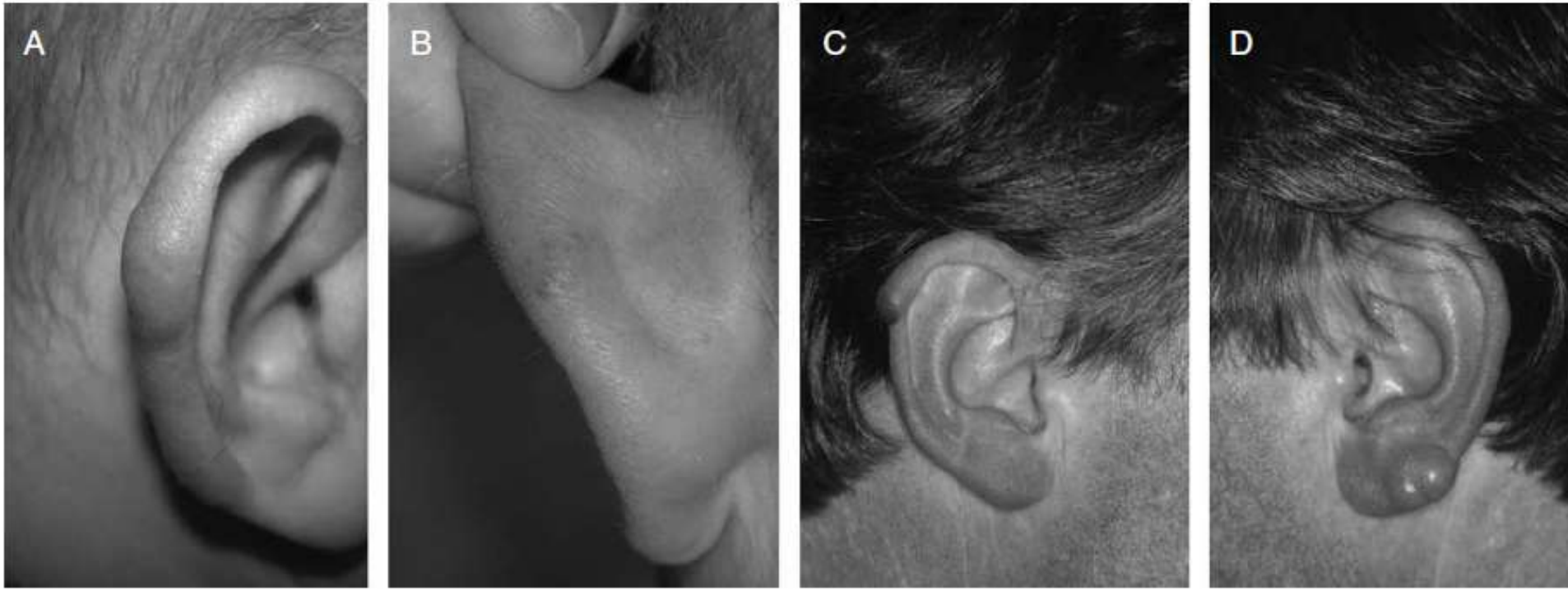
A Distinct Primary Cutaneous T-cell Lymphoma?

Tony Petrella, MD, Eve Maubec, MD,† Pascale Cornillet-Lefebvre, MD,‡ Rein Willemze, MD,§ Michel Pluot, MD,‖ Anne Durlach, MD, PhD,¶ Eduardo Marinho, MD,# Jean-Luc Benhamou, MD,** Patty Jansen, MD, PhD,†† Alistair Robson, MRCPath, DipRCPath,‡‡ and Florent Grange, MD, PhD§§*

(*Am J Surg Pathol* 2007;31:1887–1892)

Indolent CD8+ lymphoid proliferation of the ear

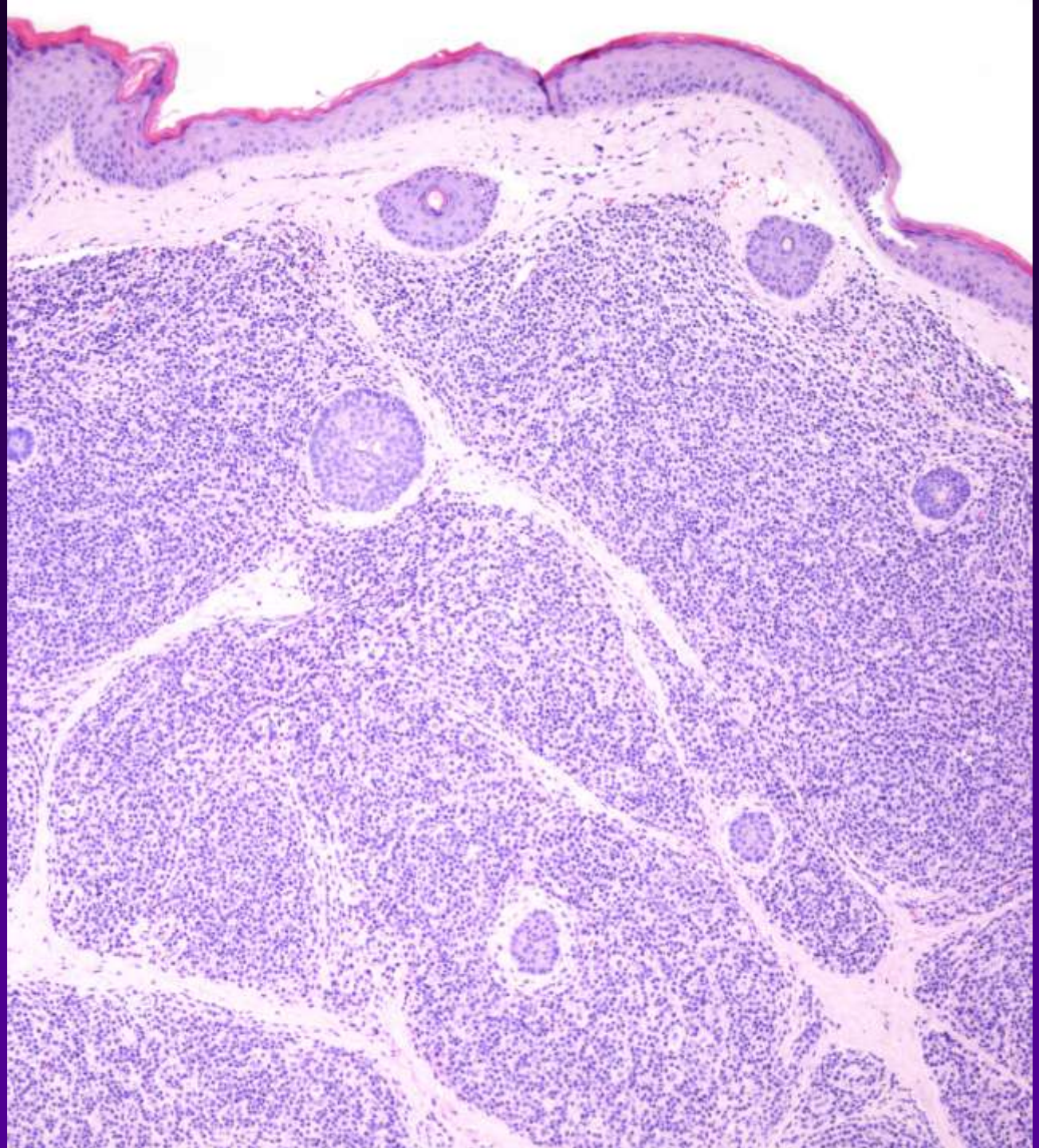
- Age: 29-69 years (young adult to middle-age)
- Tumor: Unilateral or bilateral ear, with ill-defined erythematous papule or nodule
- Clinical course: Indolent – well with local treatment (excision), although recurrence can occur
- Nature:
  - A distinct entity?
  - A phenotypic variant of primary cutaneous CD4+ small/medium T-cell lymphoma?

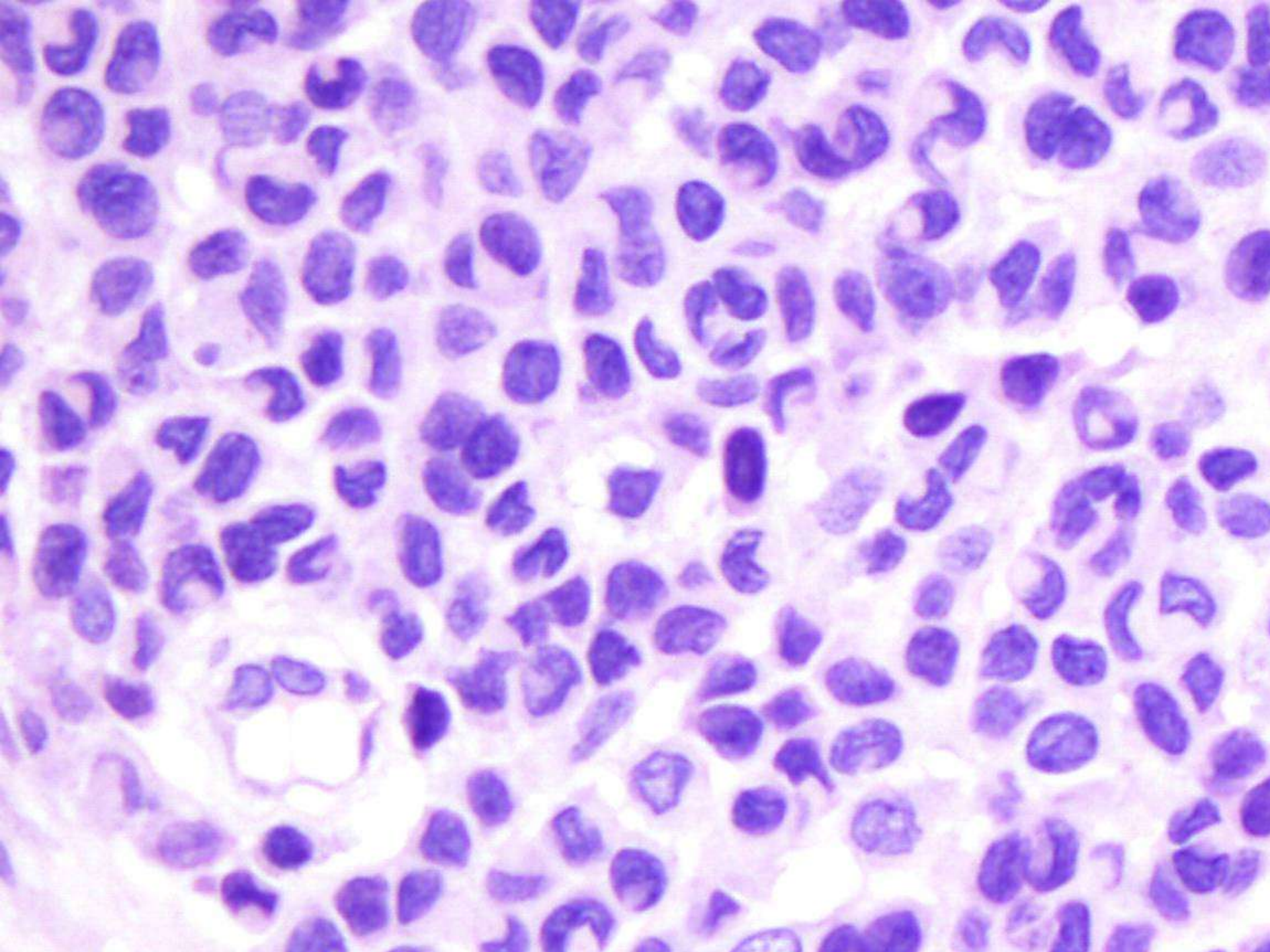


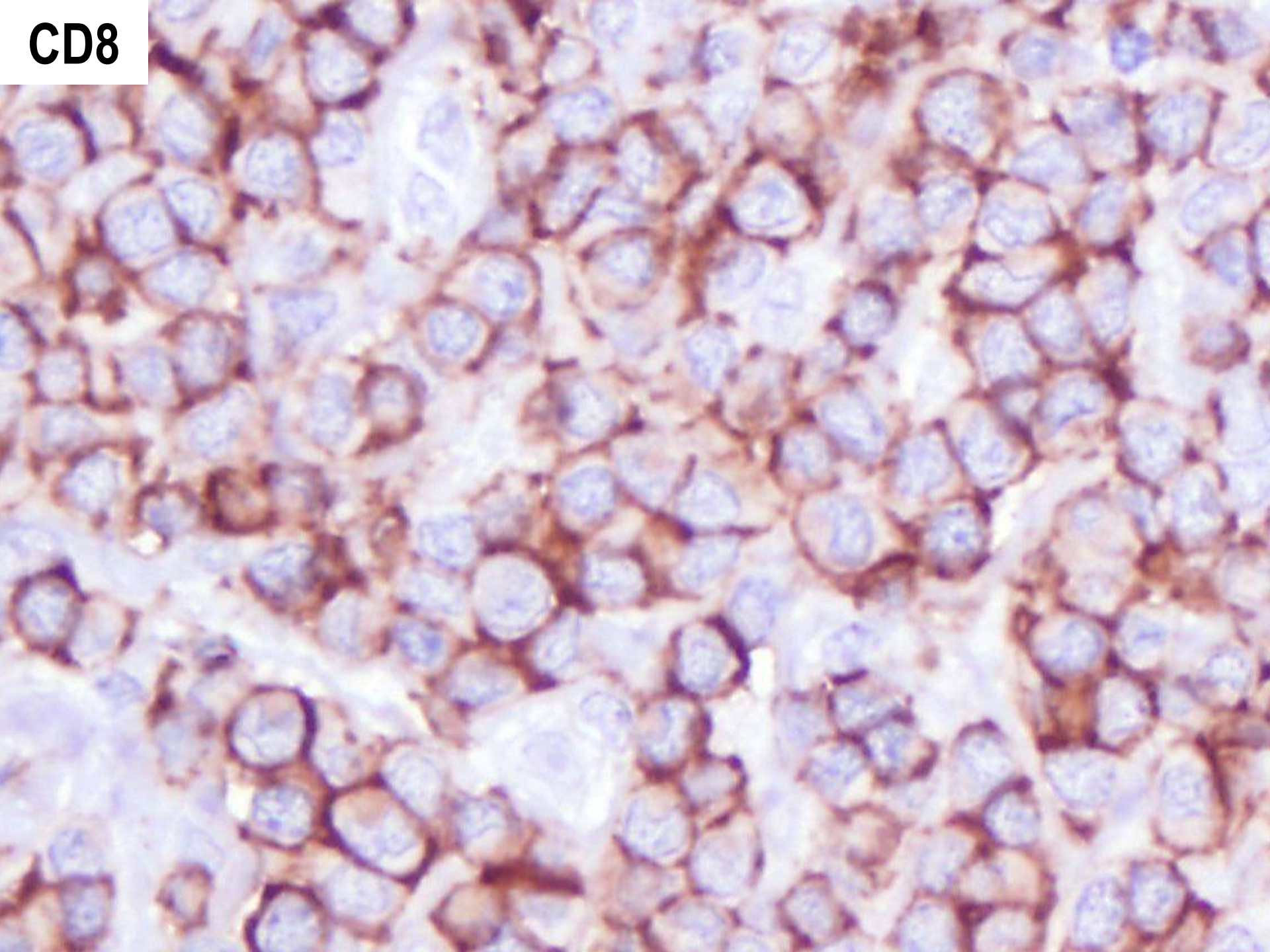
Petrella T, AJSP, 2007

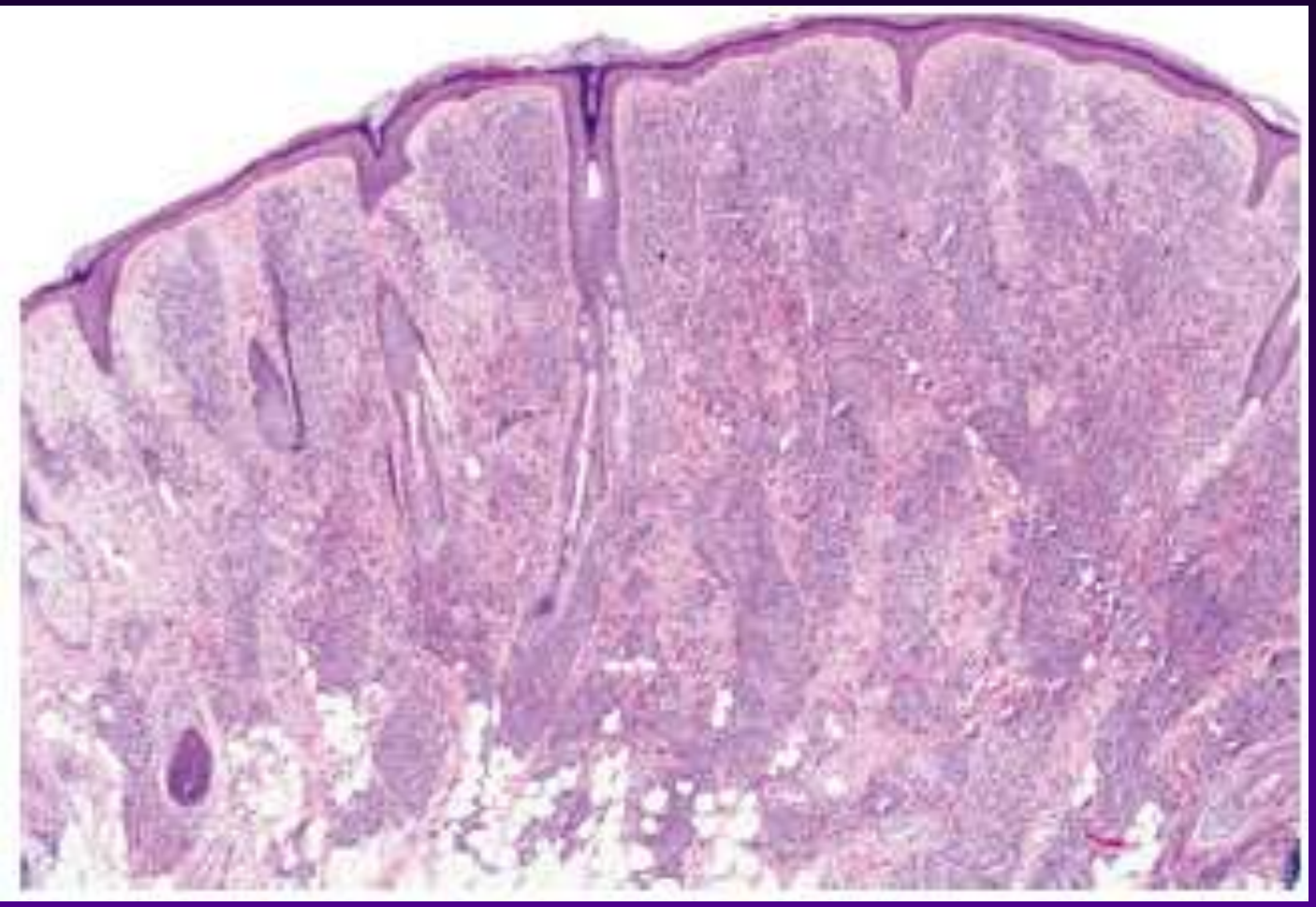
Indolent CD8+ lymphoid proliferation of the ear

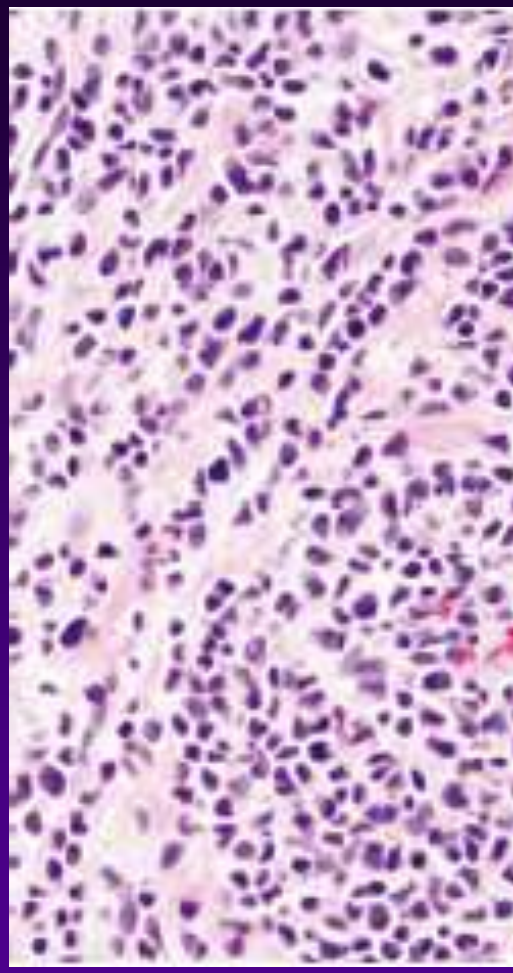
- Histology
  - Diffuse dermal +/- subcutaneous lymphoid infiltrate
  - Grenz zone present
  - Non-epidermotropic
  - Monotonous medium-sized cells with irregular nuclei; sometimes signet ring morphology
  - No necrosis; no angioinvasion
- Immunophenotype: CD3+, CD4-, CD8+, CD56-, EBV-





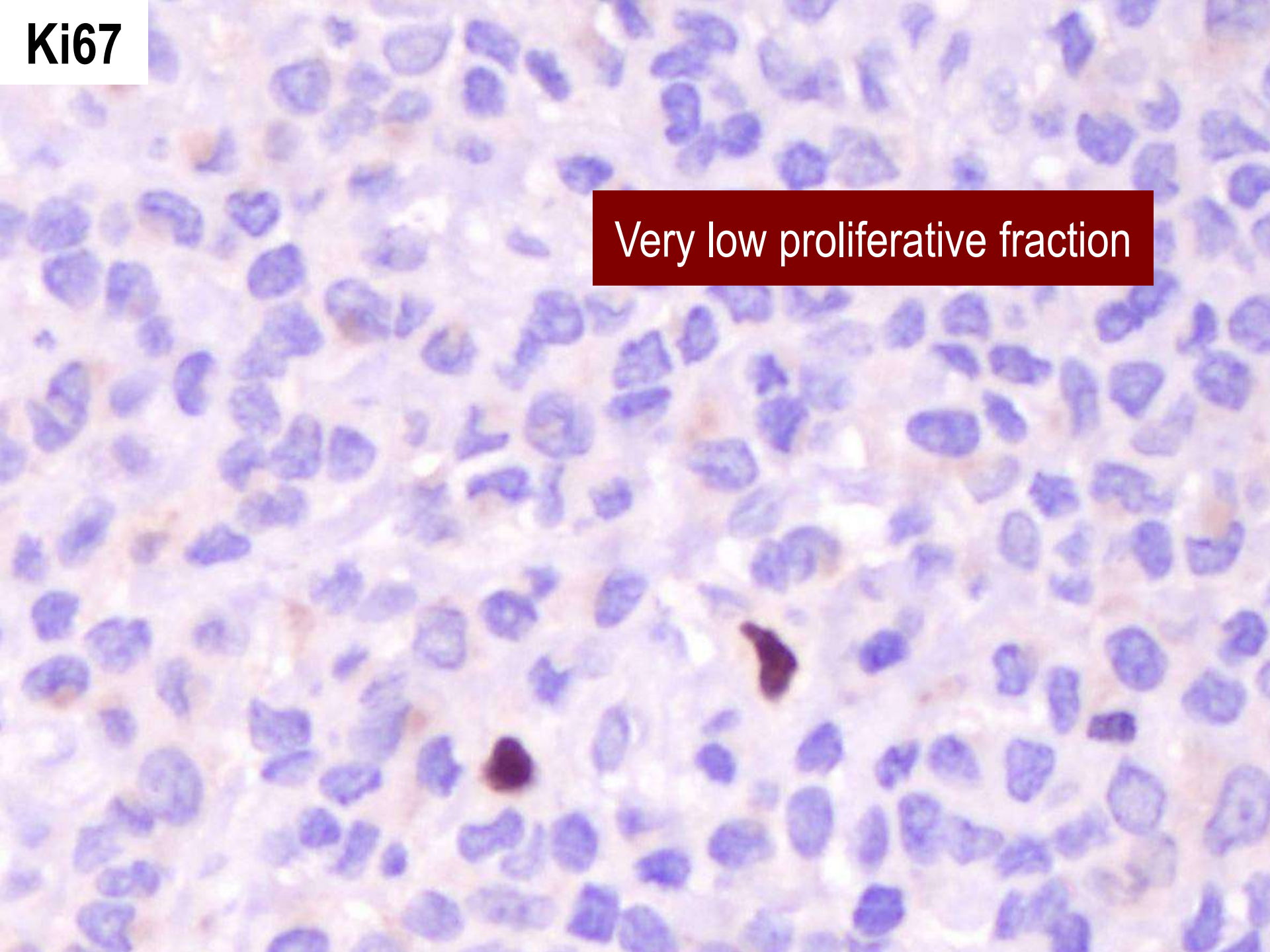

CD8





Swick BL. J Cutan Pathol 2011

Any clue to avoid mistaking it for more aggressive types of lymphoma?


Ki67
Very low proliferative fraction

NEW ENTITY NOT INCLUDED IN 2008 WHO CLASSIFICATION

Lymphomatoid gastropathy: a distinct clinicopathologic entity of self-limited pseudomalignant NK-cell proliferation

Kengo Takeuchi,[1,2] Masahiro Yokoyama,[3] Shin Ishizawa,[4] Yasuhito Terui,[3] Kimie Nomura,[2] Kousuke Marutsuka,[5] Maki Nunomura,[6] Noriyasu Fukushima,[7] Takahiro Yagyuu,[8] Hirokazu Nakamine,[9] Futoshi Akiyama,[2] Kazuei Hoshi,[10] Kosei Matsue,[11] Kiyohiko Hatake,[3] and Kazuo Oshimi[12]

Blood 2010;116:581-587

NK-cell enteropathy: a benign NK-cell lymphoproliferative disease mimicking intestinal lymphoma: clinicopathologic features and follow-up in a unique case series

Adnan Mansoor,[1] Stefania Pittaluga,[2] Paul L. Beck,[3] Wyndham H. Wilson,[4] Judith A. Ferry,[5] and Elaine S. Jaffe[2]

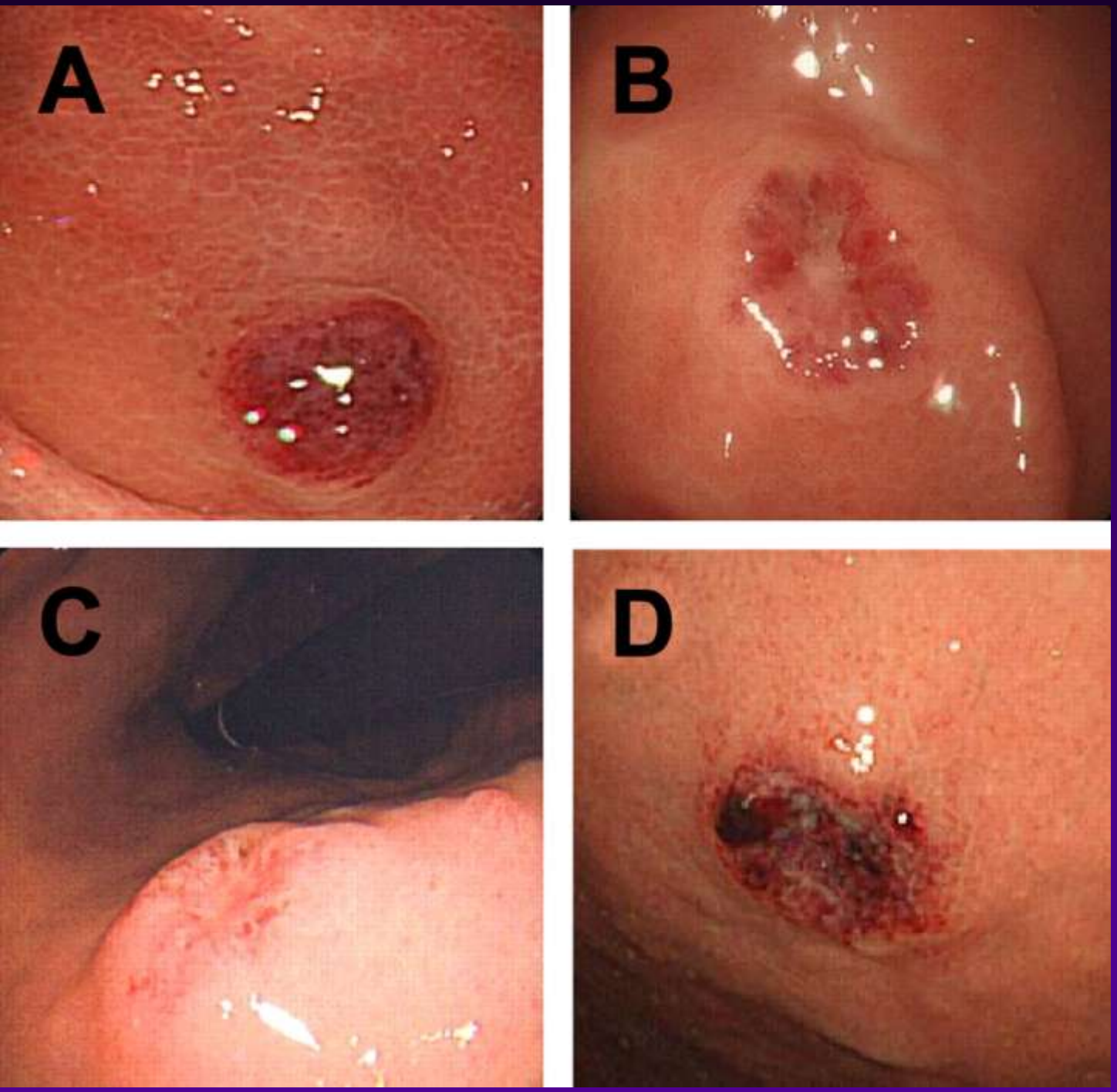
Blood 2011;117:1447-1452

NK lymphomatoid gastroenteropathy

- A self-limiting, pseudomalignant NK cell proliferation affecting the stomach or intestines
- Sex: F > M
- Age: Adults (27-75 years)
- Presentation
  - Asymptomatic
  - Vague gastrointestinal symptoms

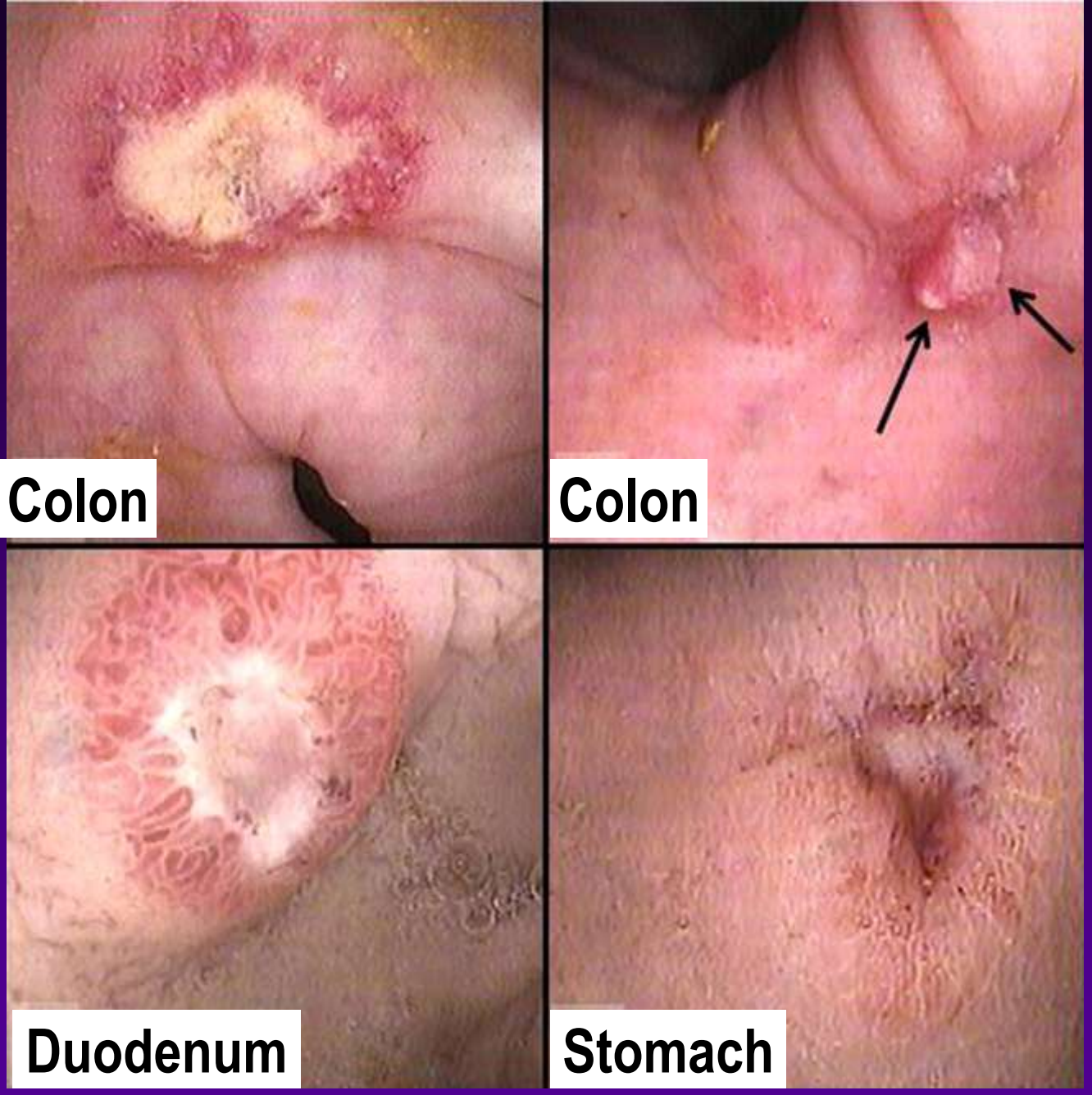
NK lymphomatoid gastroenteropathy

- Endoscopic findings
  - Superficial small lesions (~1 cm)
  - Ulcer, erosion, elevated lesion, often with hemorrhage and edema
- Single or multiple sites in gastrointestinal tract
- Imaging work-up: No other sites of disease
- Follow-up information (without cytotoxic therapy)
  - Spontaneous resolution
  - Persistence
  - Recurrence



are shown.

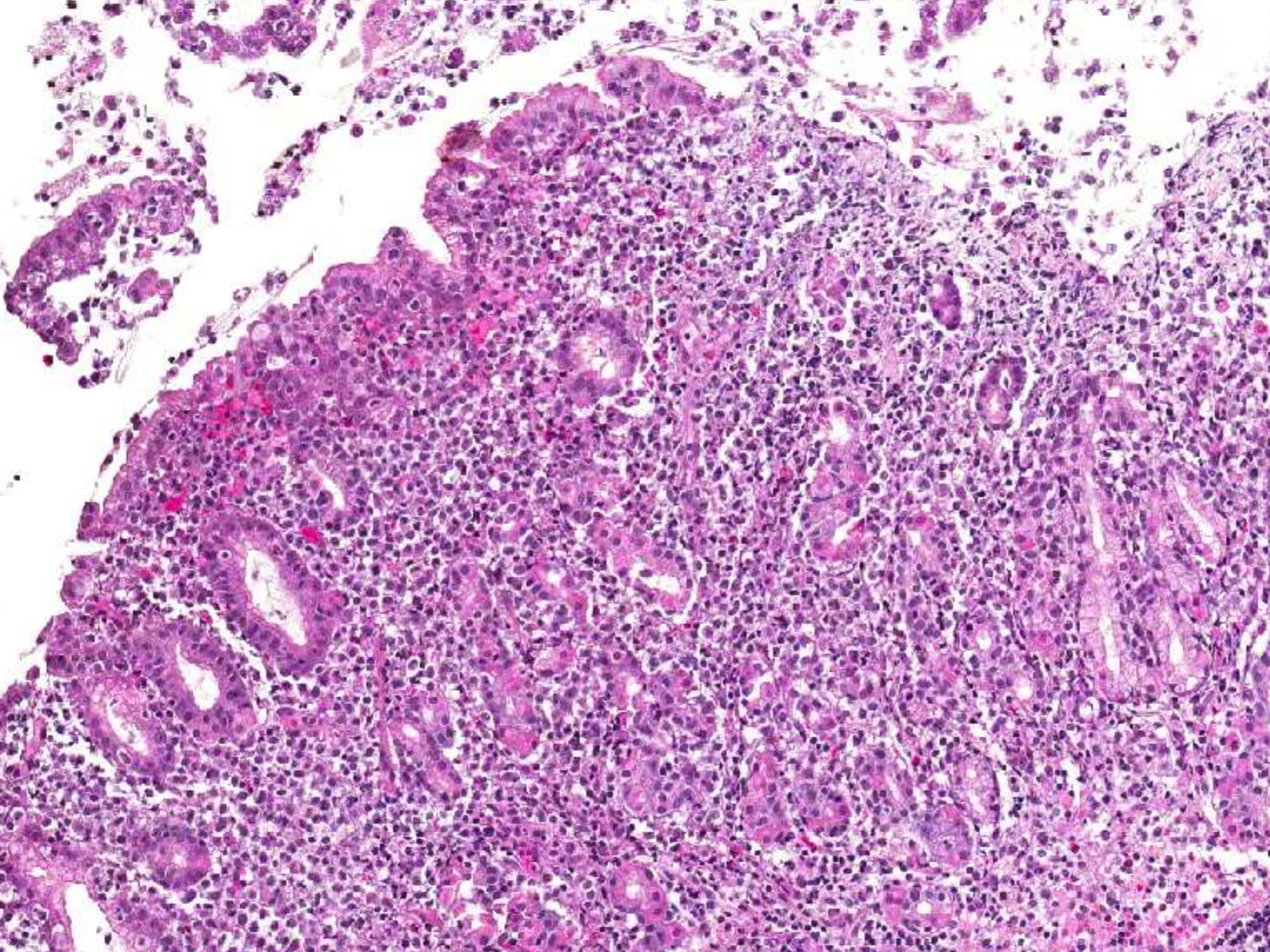
Takeuchi K et al.
Blood 2010;116:5631-5637

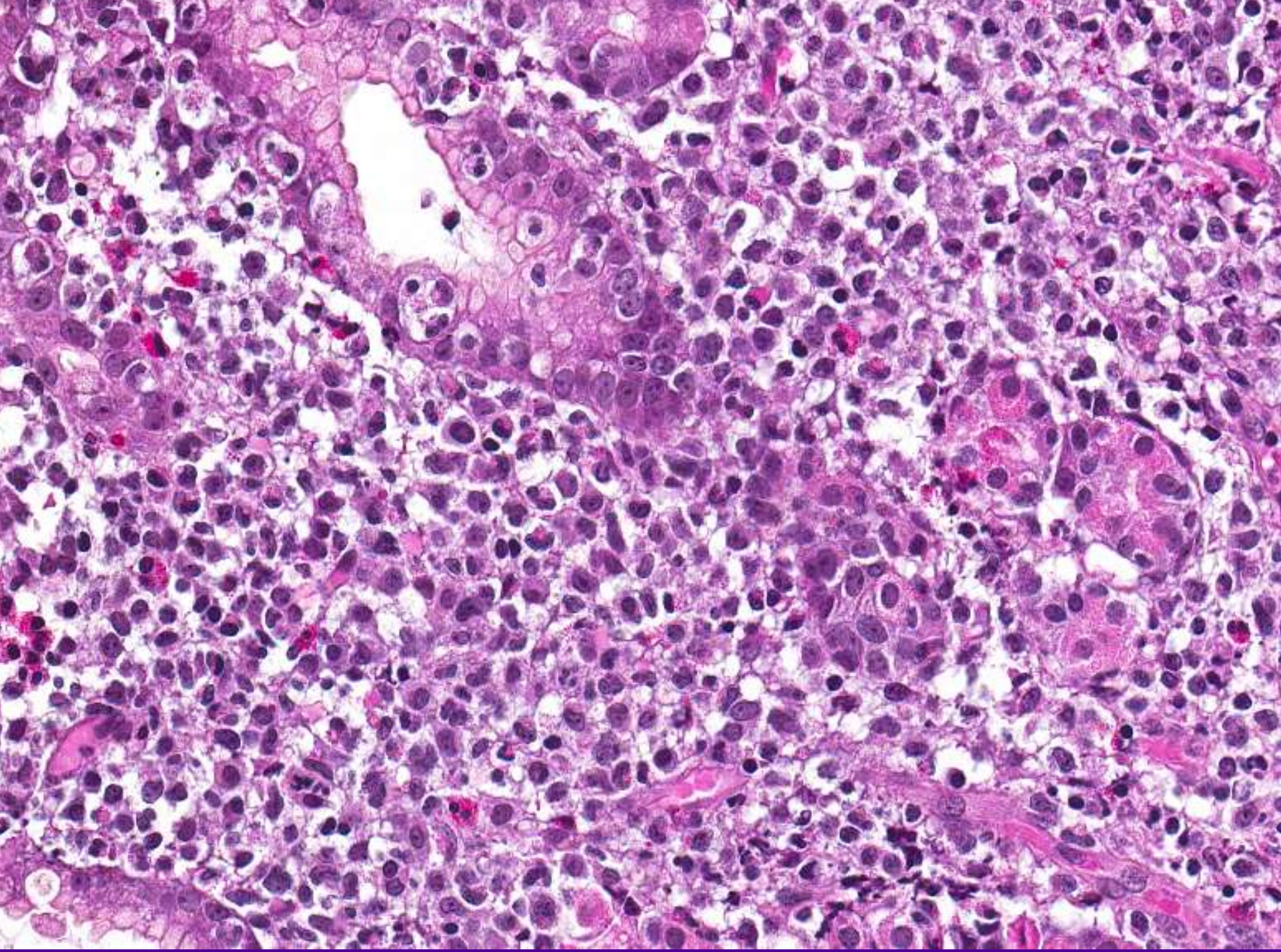


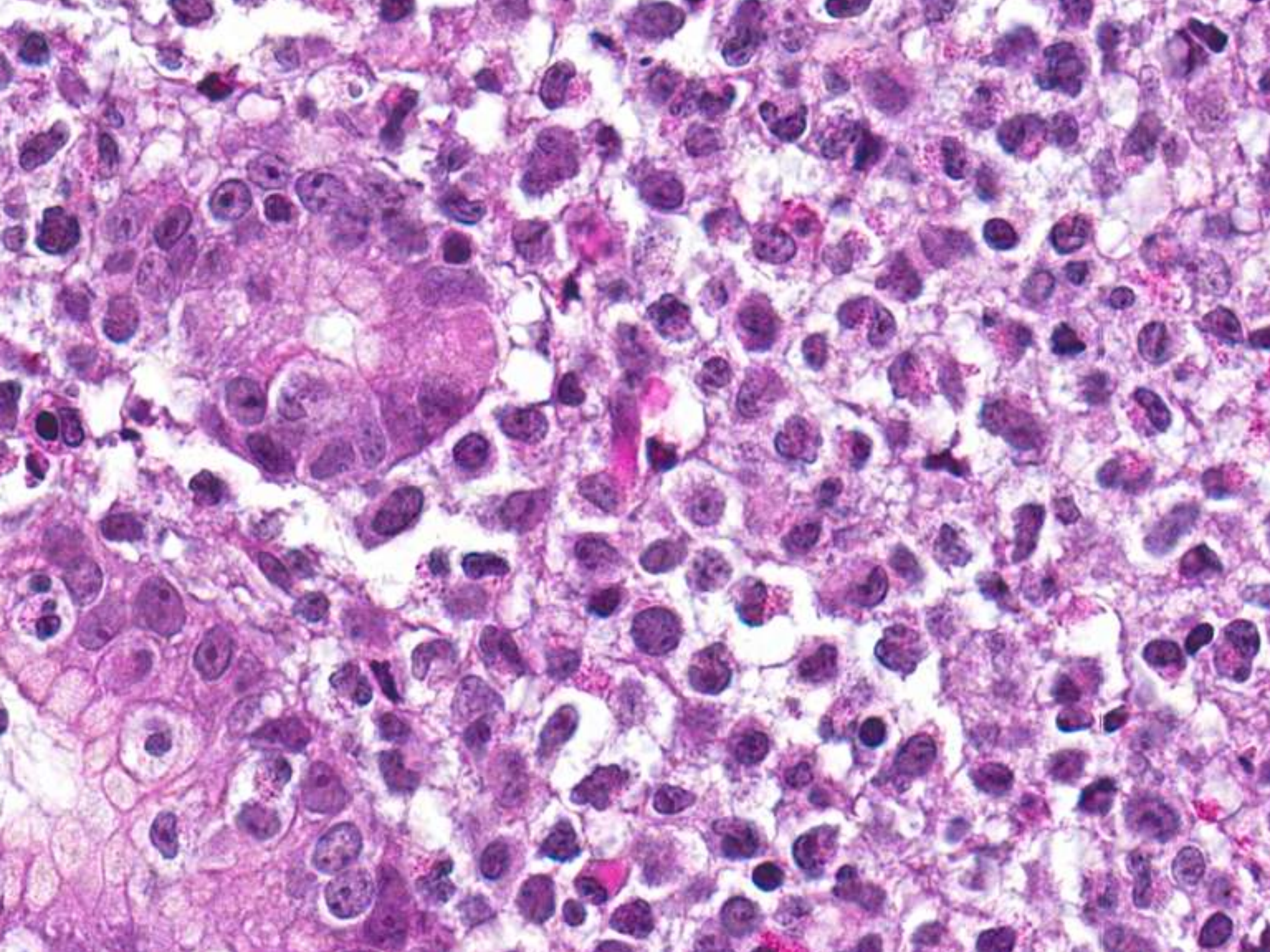
Mansoor A et al. Blood 2011;117:1447-1452

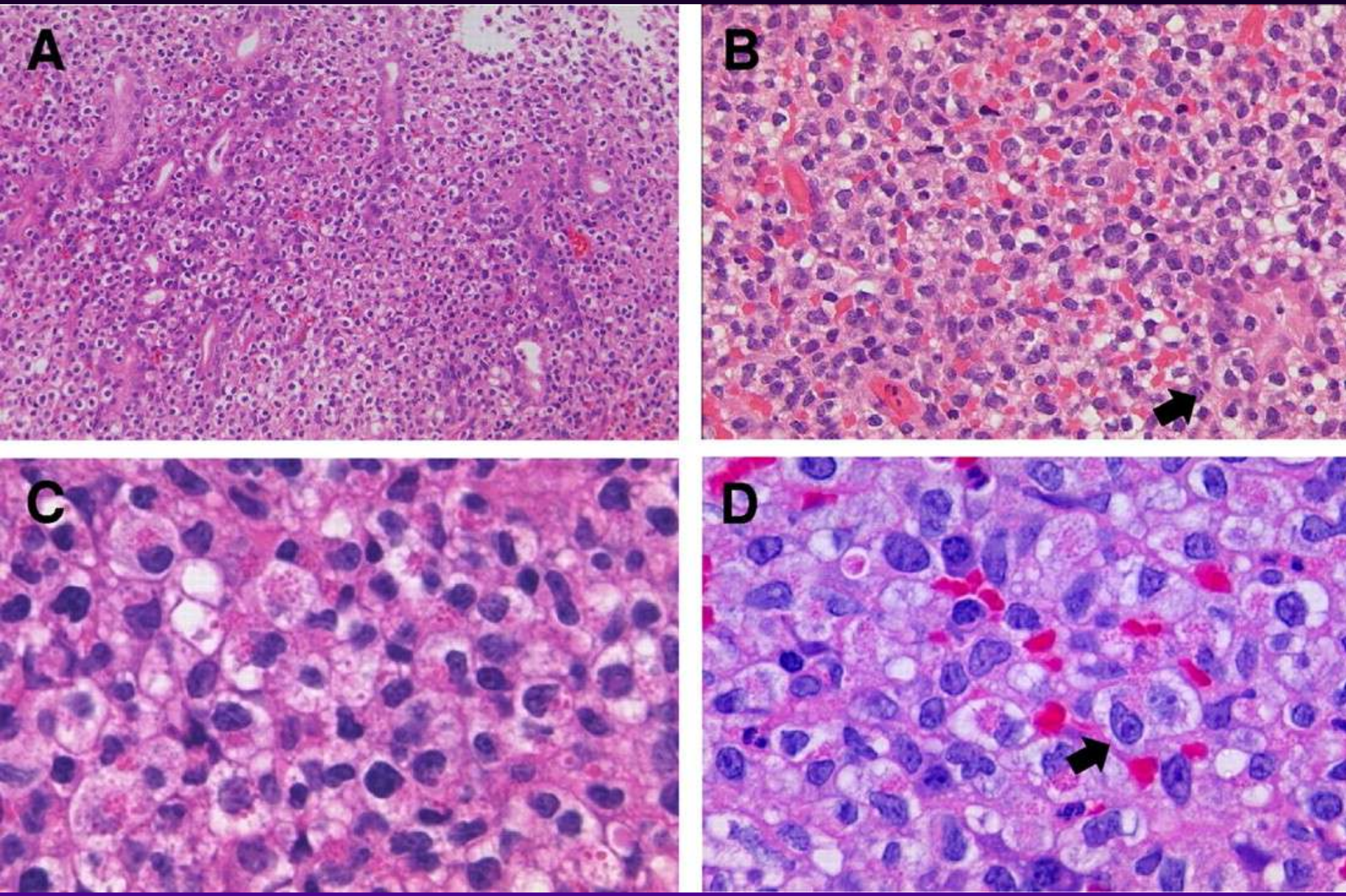
NK lymphomatoid gastroenteropathy

- Histology:
  - Mucosa shows expansion by atypical lymphoid infiltrate
  - May show epithelial invasion
  - Medium-sized or large cells with indented or irregular nuclei +/- nucleoli
  - Many cells have brightly eosinophilic granules
  - No angioinvasion; usually no necrosis





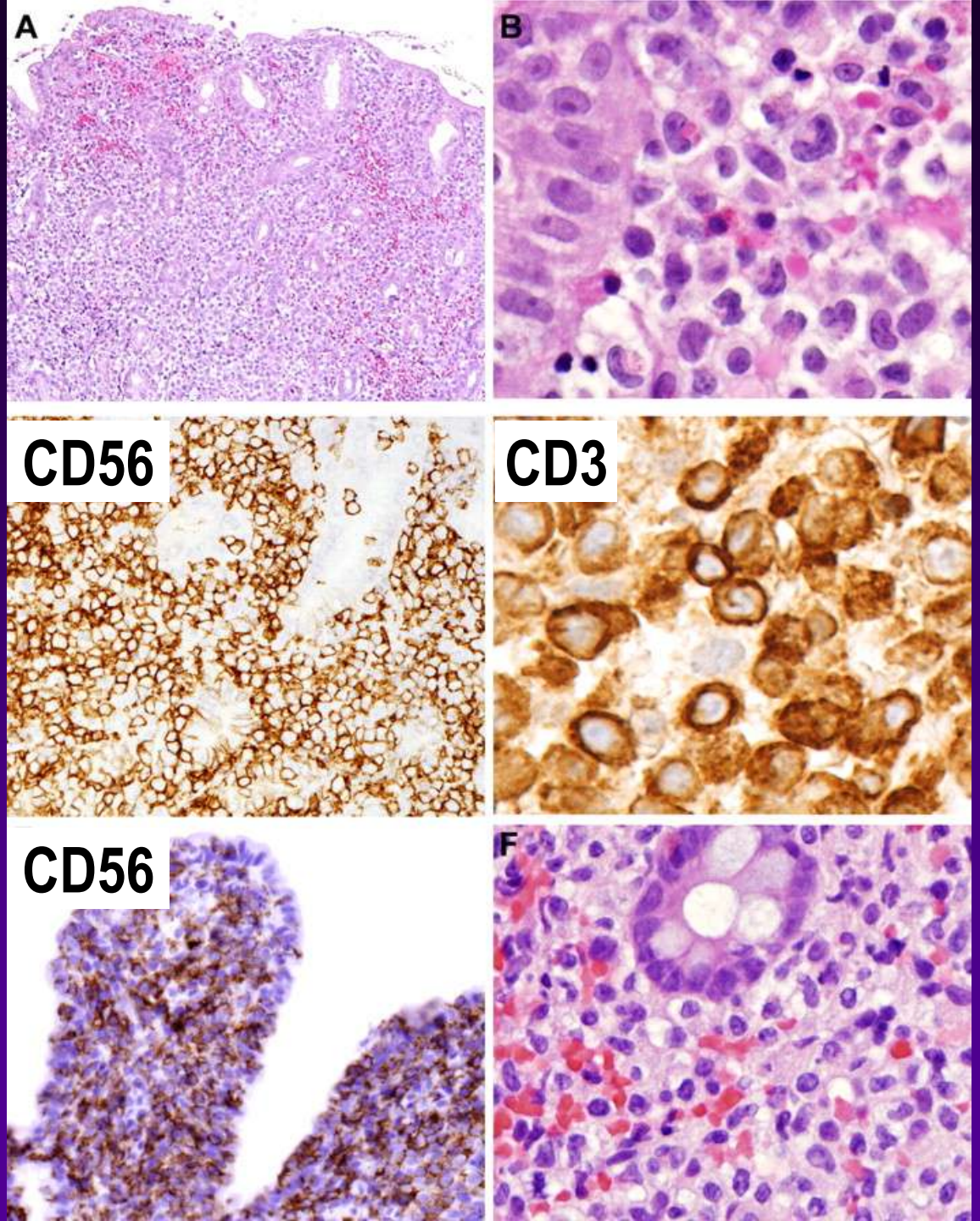




Takeuchi K et al. Blood 2010;116:5631-5637

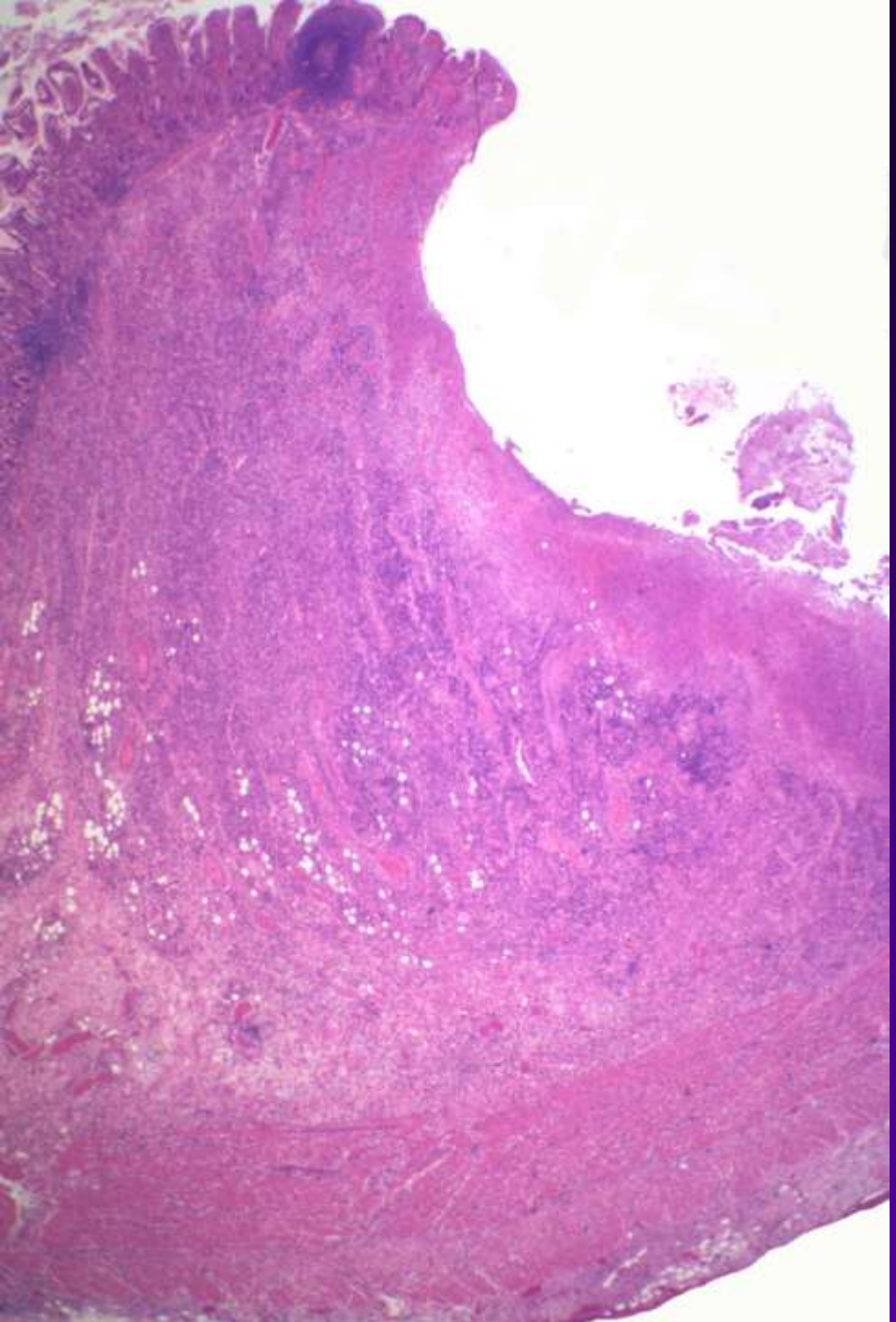
NK lymphomatoid gastroenteropathy

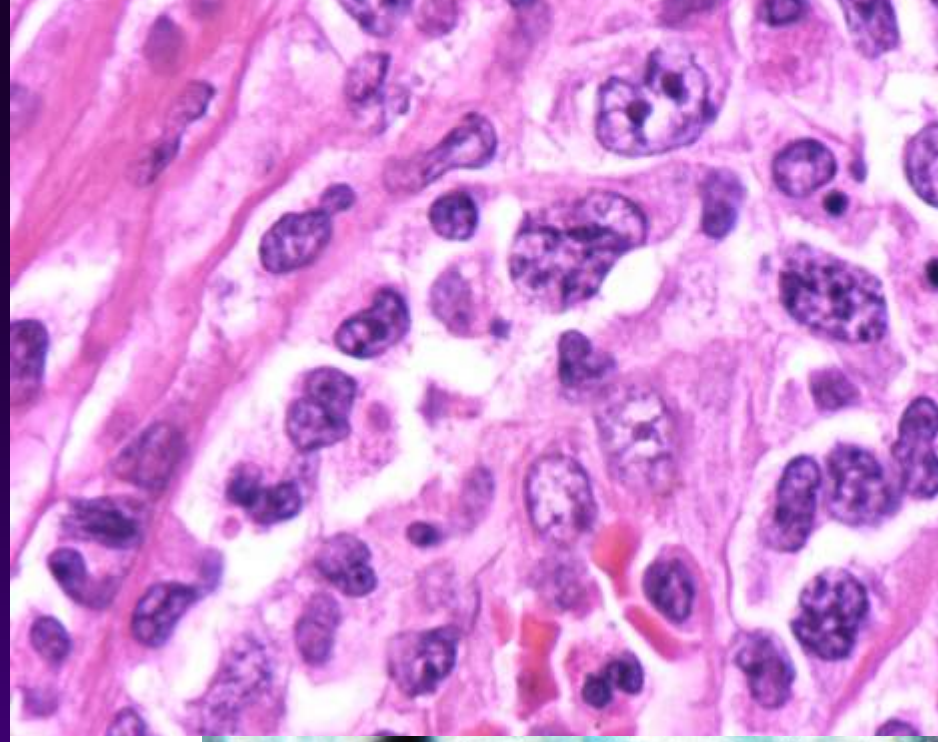
- Immunohistochemistry:
  - CD3+ (cytoplasmic); surface CD3 negative
  - CD56+
  - CD5-
  - TIA1+
- EBER: Negative
- TCR gene rearrangements: Negative

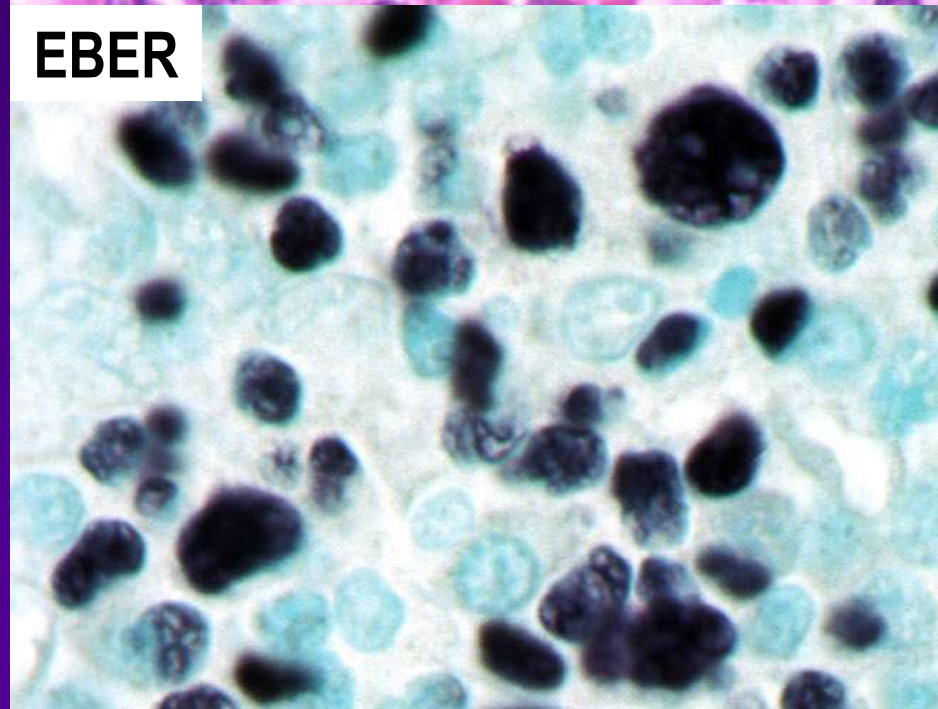


Mansoor A et al. Blood 2011;117:1447-1452

	NK lymphomatoid gastroenteropathy	Extranodal NK/T-cell lymphoma
Endoscopic or gross appearance	Small and superficial (erosion, ulcer, raised, hemorrhagic) lesions	Large and deep mass lesions
Histology	Brightly eosinophilic granules commonly seen in lymphoid cells (H&E)	Granules rarely ever seen in H&E section
EBV	Negative	Positive






EBER

- Seroma-associated ALCL adjacent to breast implant
- Indolent CD8+ lymphoid proliferation of the ear
- NK lymphomatoid gastroenteropathy