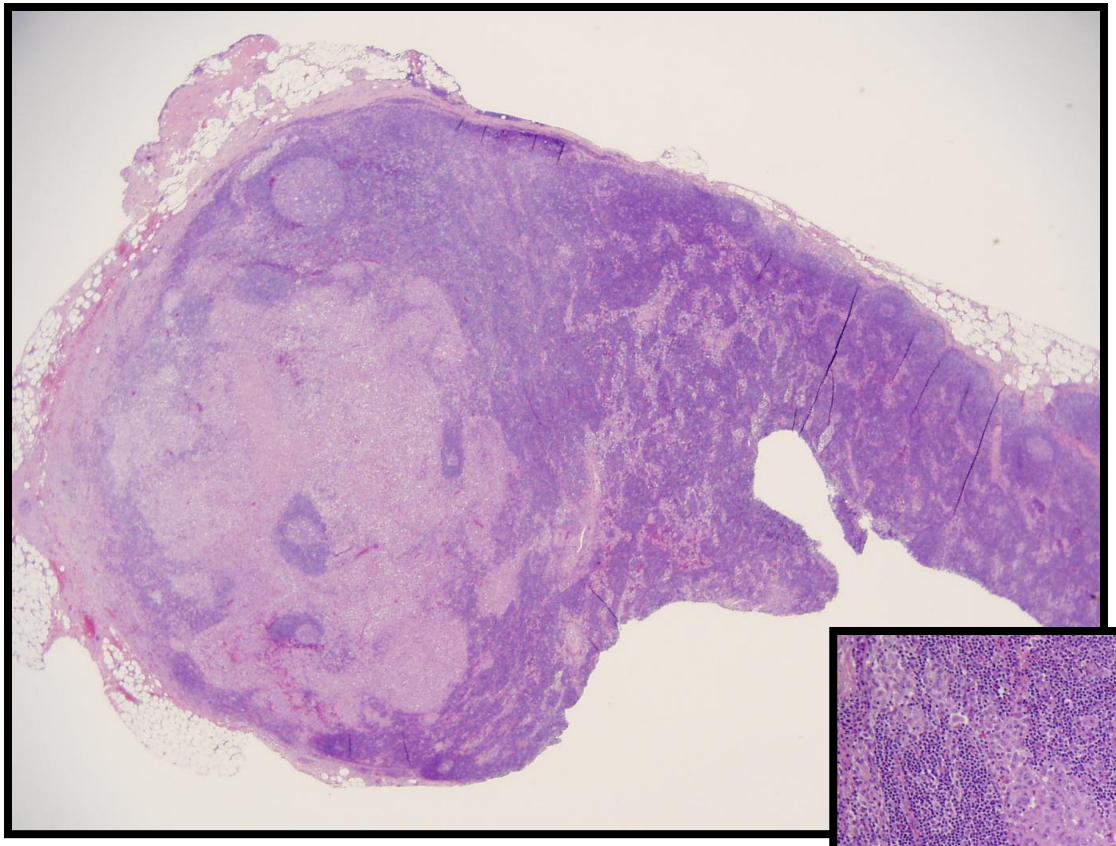
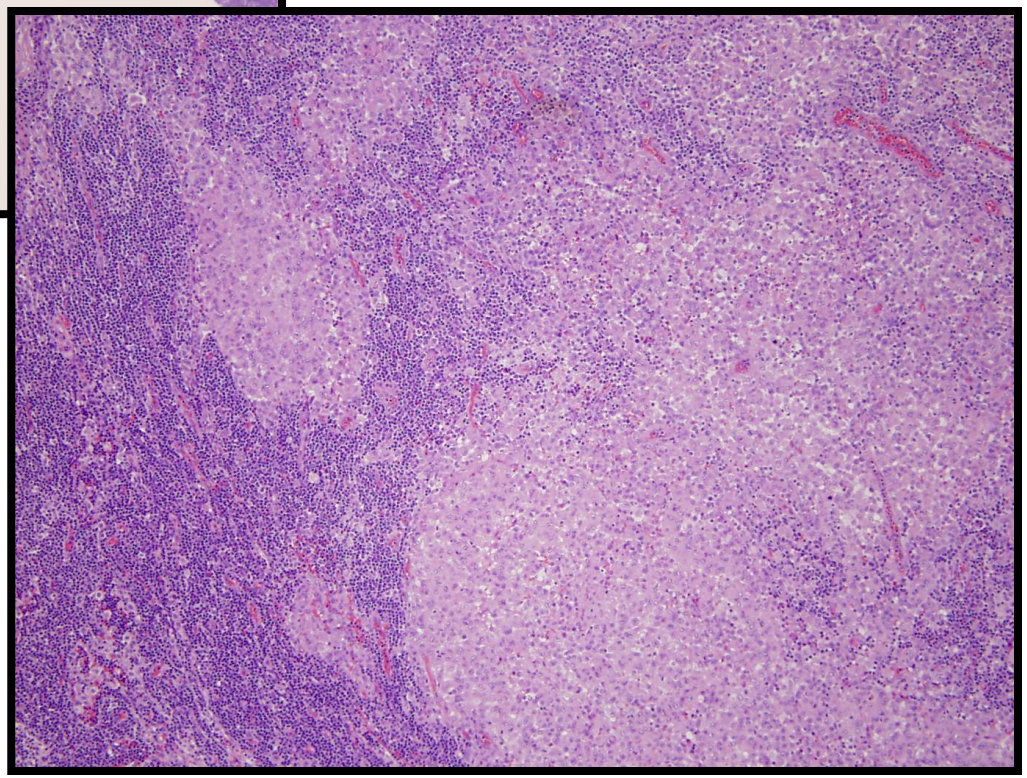
CASE 9

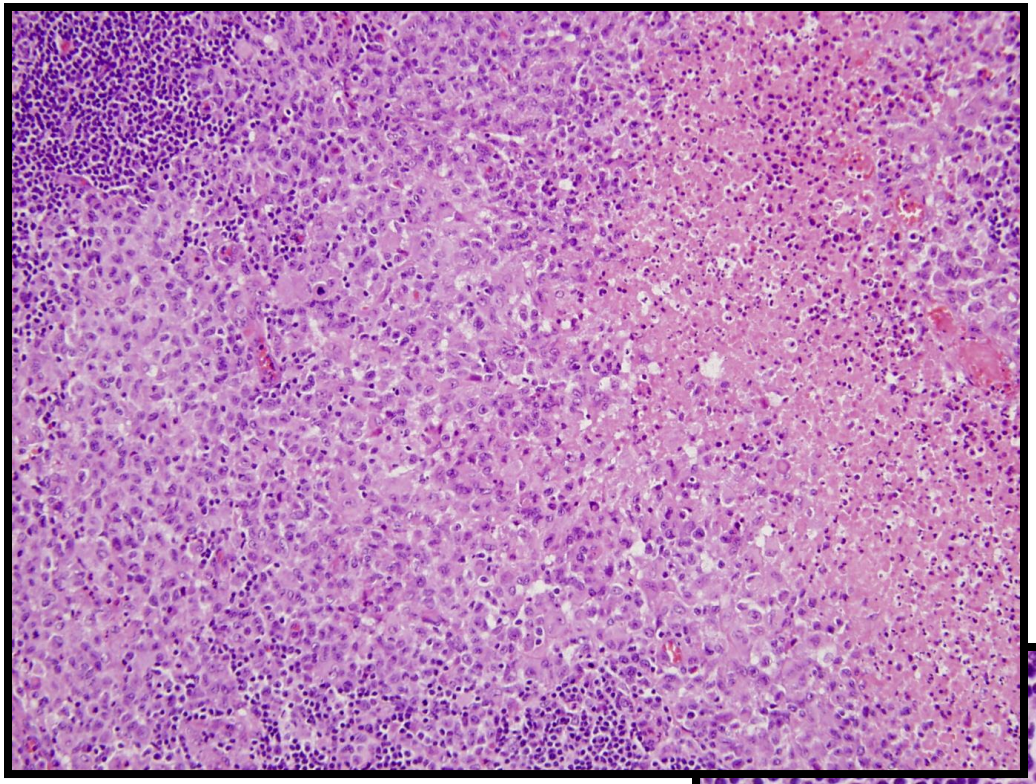
A 48-year-old woman presented with hoarseness and wa found to have T2 N0 squamous cell carcinoma of the right voval cord. She was treated with cisplaytin and radiation therapy. One year later she developed a level II left neck lymph node whch was biopsied.

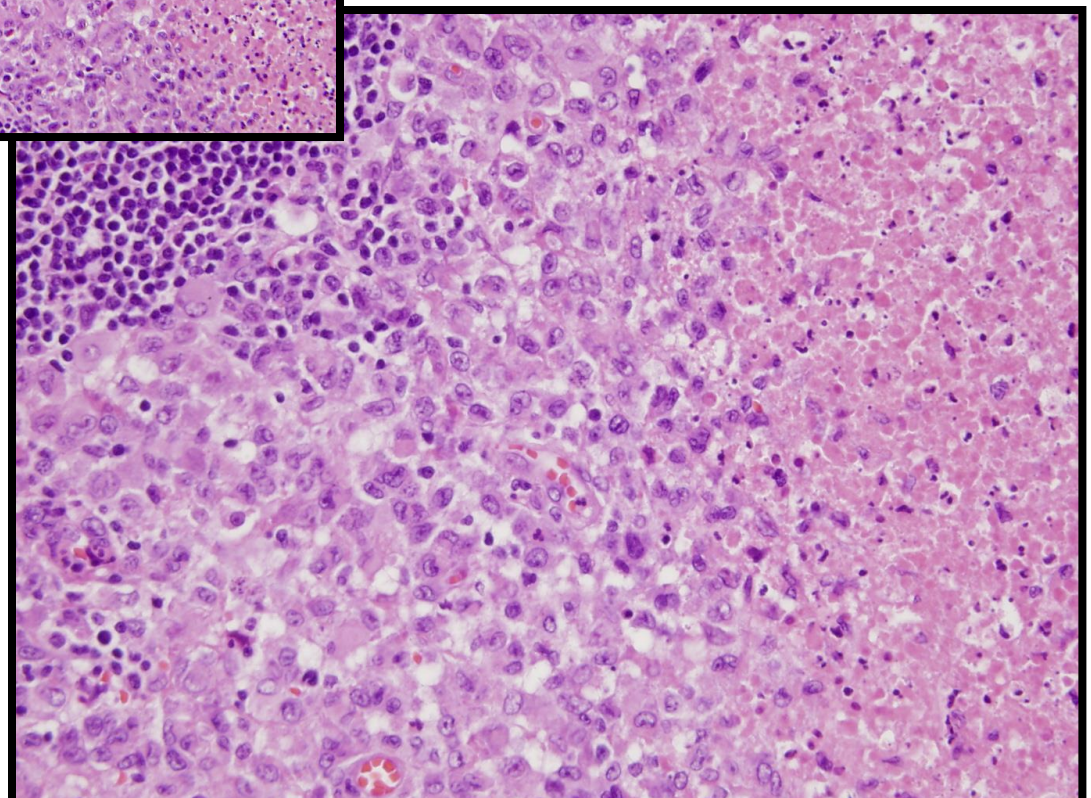
Case 9



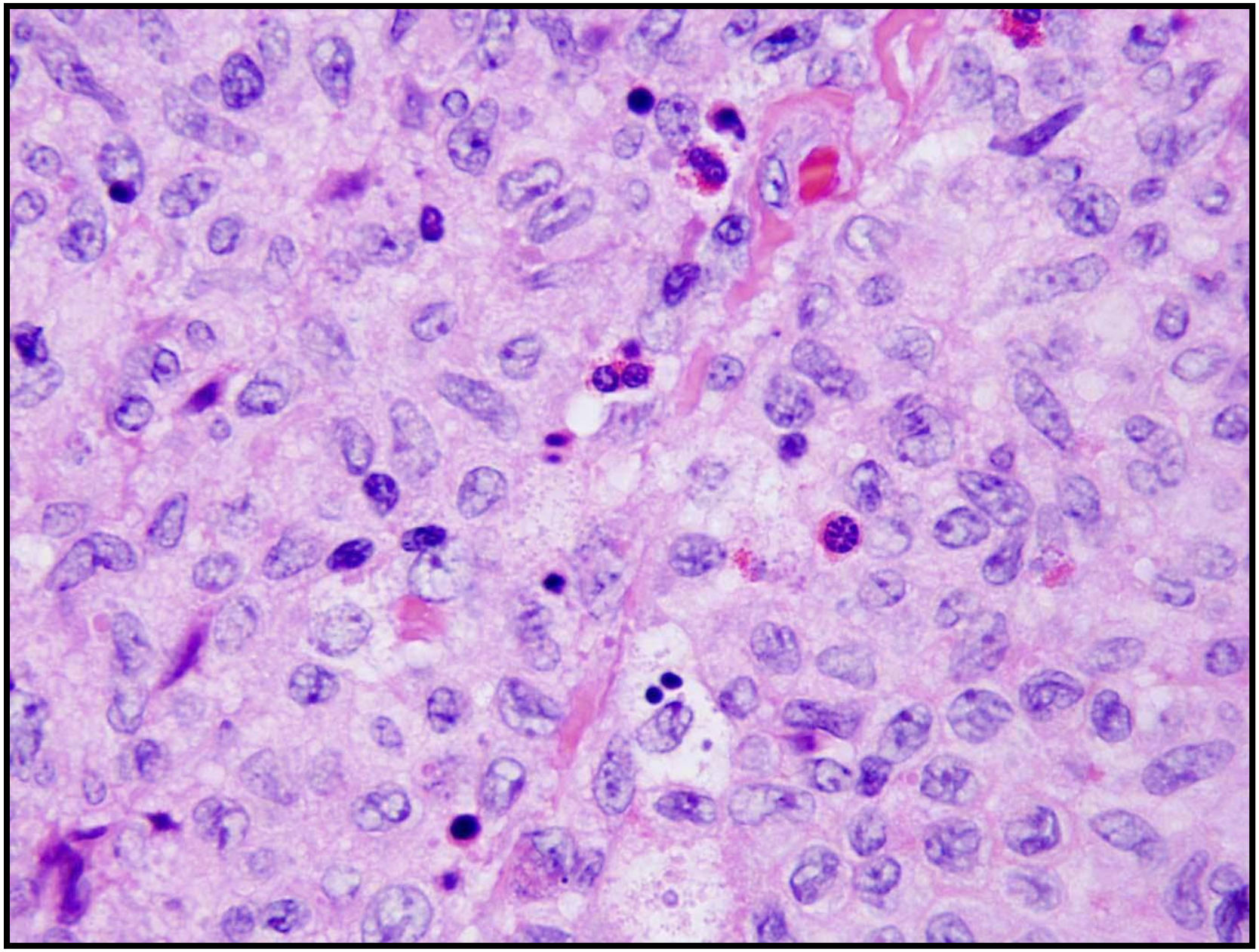


Case 9

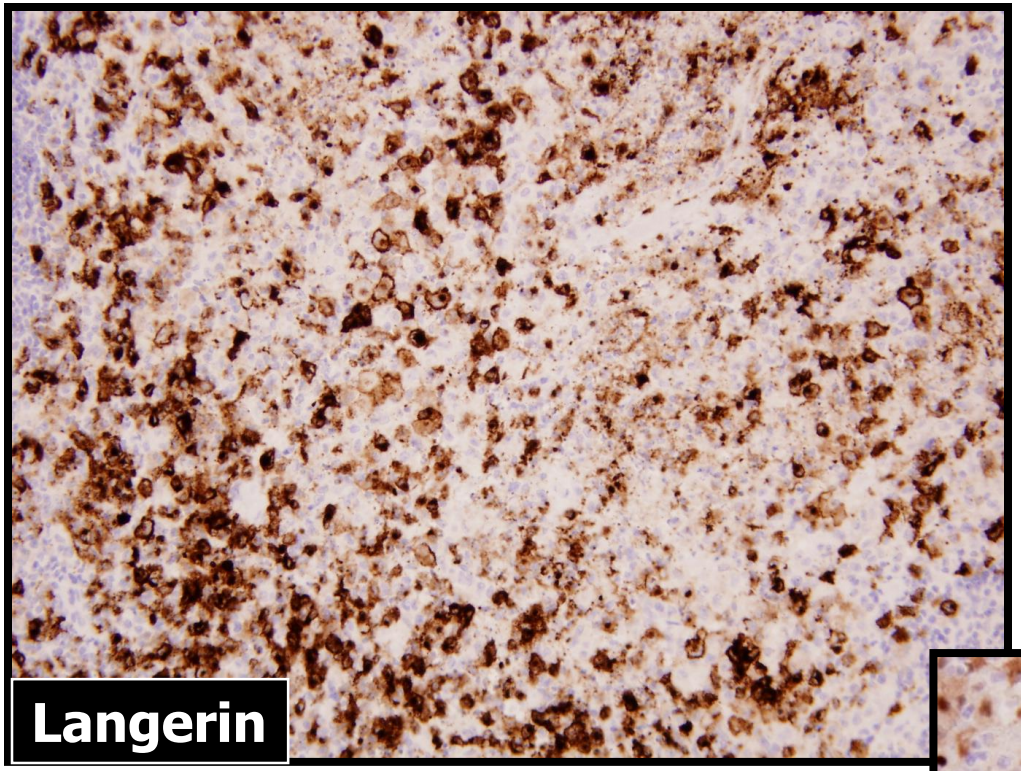


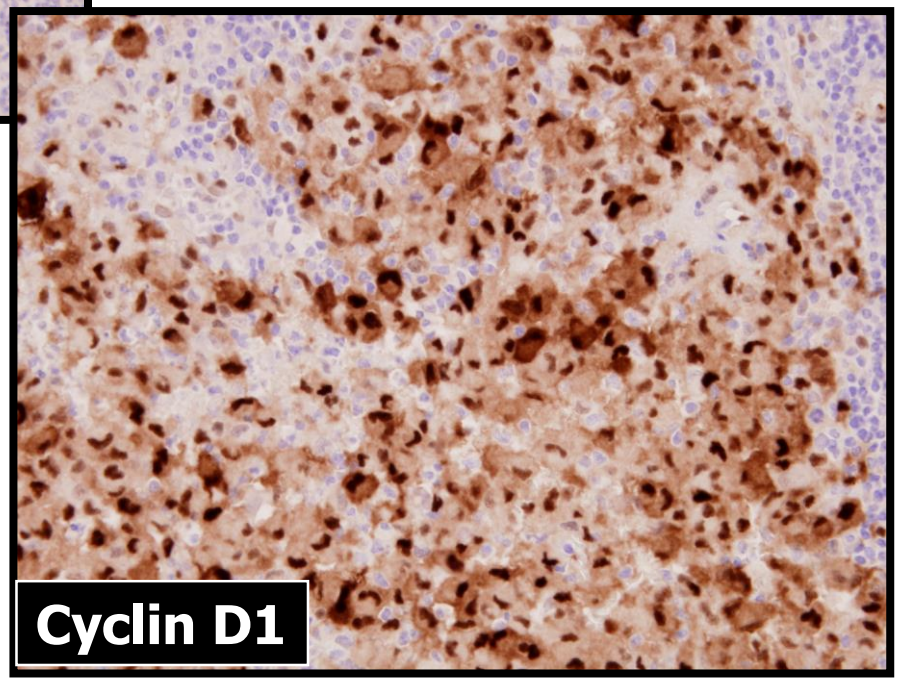


Case 9



Case 9





DIAGNOSIS (CASE 9)

Langerhans cell histiocytosis

Langerhans Cell Histiocytosis
"Old" Terminology

Eosinophilic granuloma

Single lesion of bone, LN, or skin

Hand-Schuller-Christian disease

Lytic lesions of skull, exopthalmos, and diabetes insipidus

Letterer-Siwe disease

Widespread visceral disease involving liver, spleen, bone marrow, and other sites

Histiocytosis X

Umbrella term proposed by Sidney Farber and then Lichtenstein in 1953

Sidney Farber
1903-1973

Louis Lichtenstein
1906-1977

Langerhans Cell Histiocytosis
Incidence and Disease Distribution

Incidence

Children:	$5\text{-}9 \times 10^6$
Adults:	1×10^6

Sites of Disease

Bones	80%
Skin	30%
Pituitary gland	25%
Liver	15%
Spleen	15%
Bone Marrow	15%
Lymph nodes	10%
CNS	<5%

Poor Prognosis

Liver
Spleen
Bone marrow

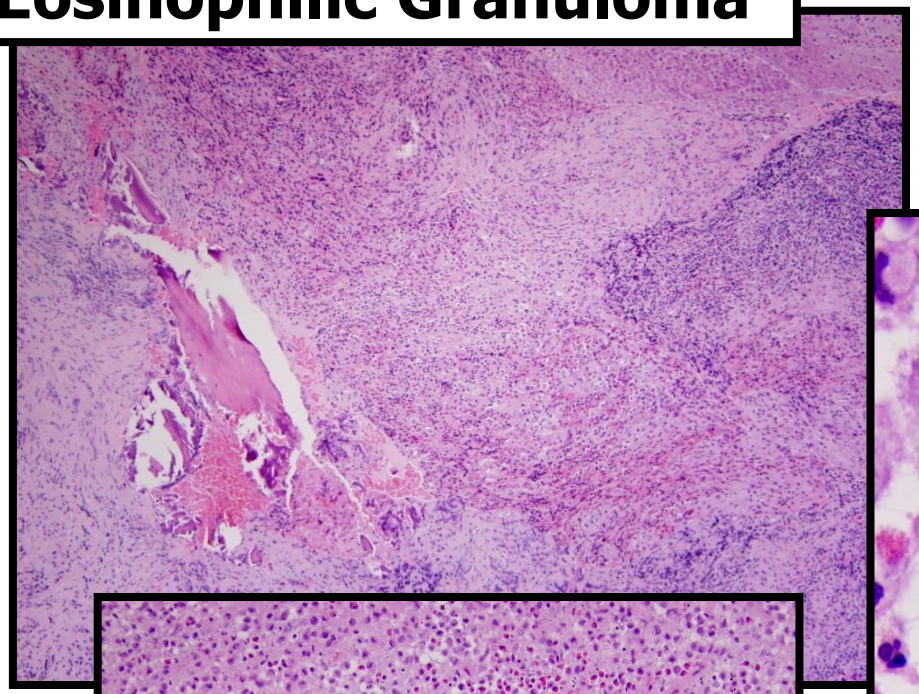
High-risk organs

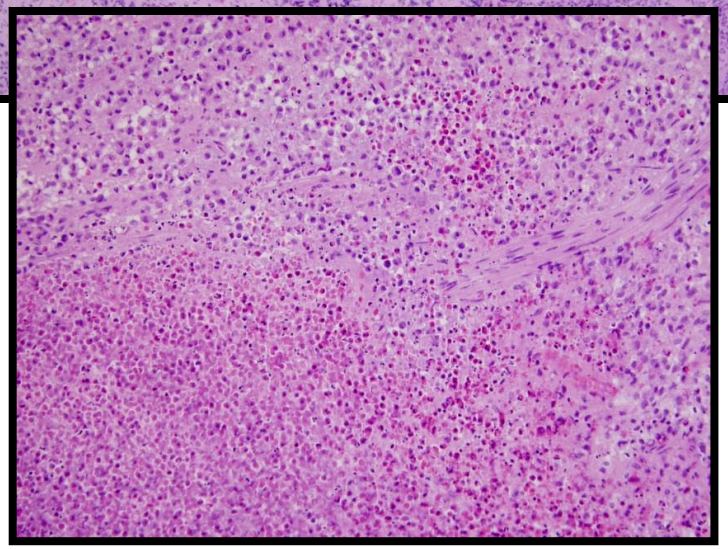
Blood 127: 2672, 2016
N Engl J Med 379: 856, 2018

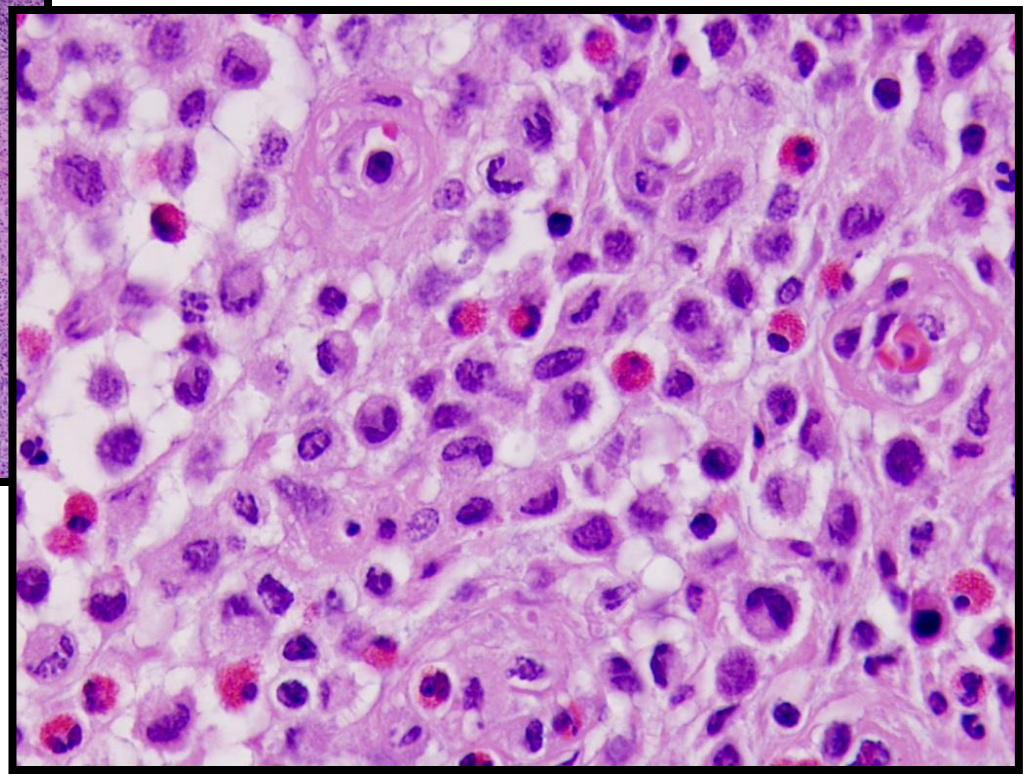
Langerhans Cell Histiocytosis

Solitary lesion of bone

Eosinophilic Granuloma

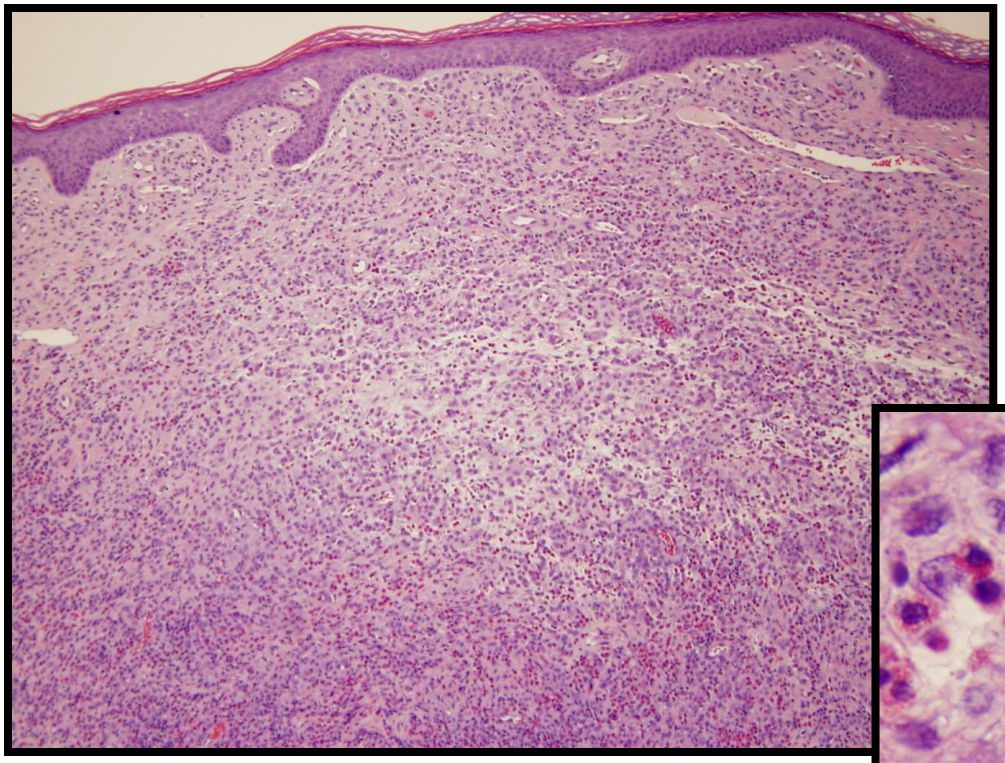


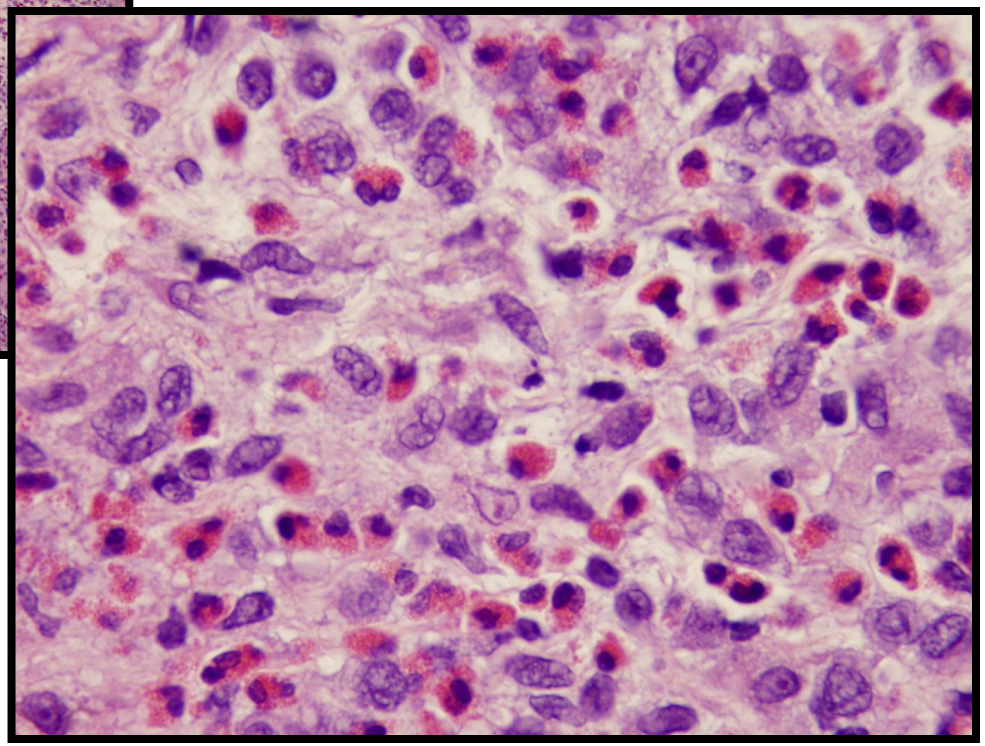




Langerhans Cell Histiocytosis

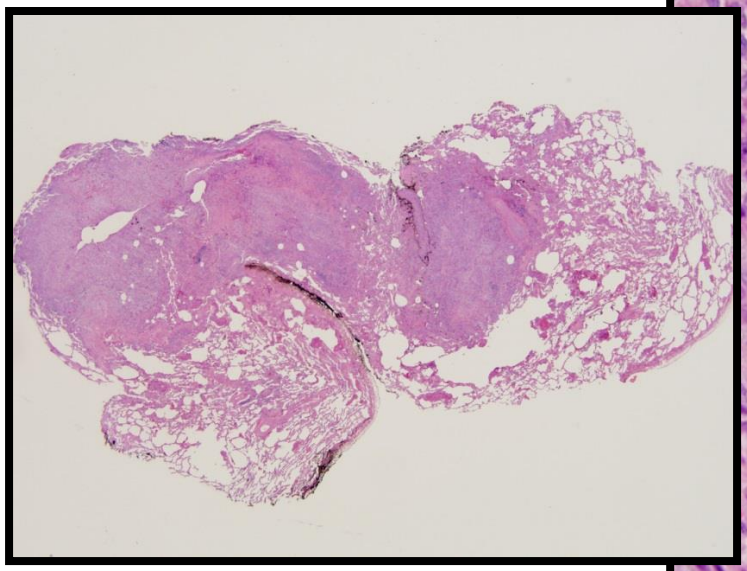
Skin

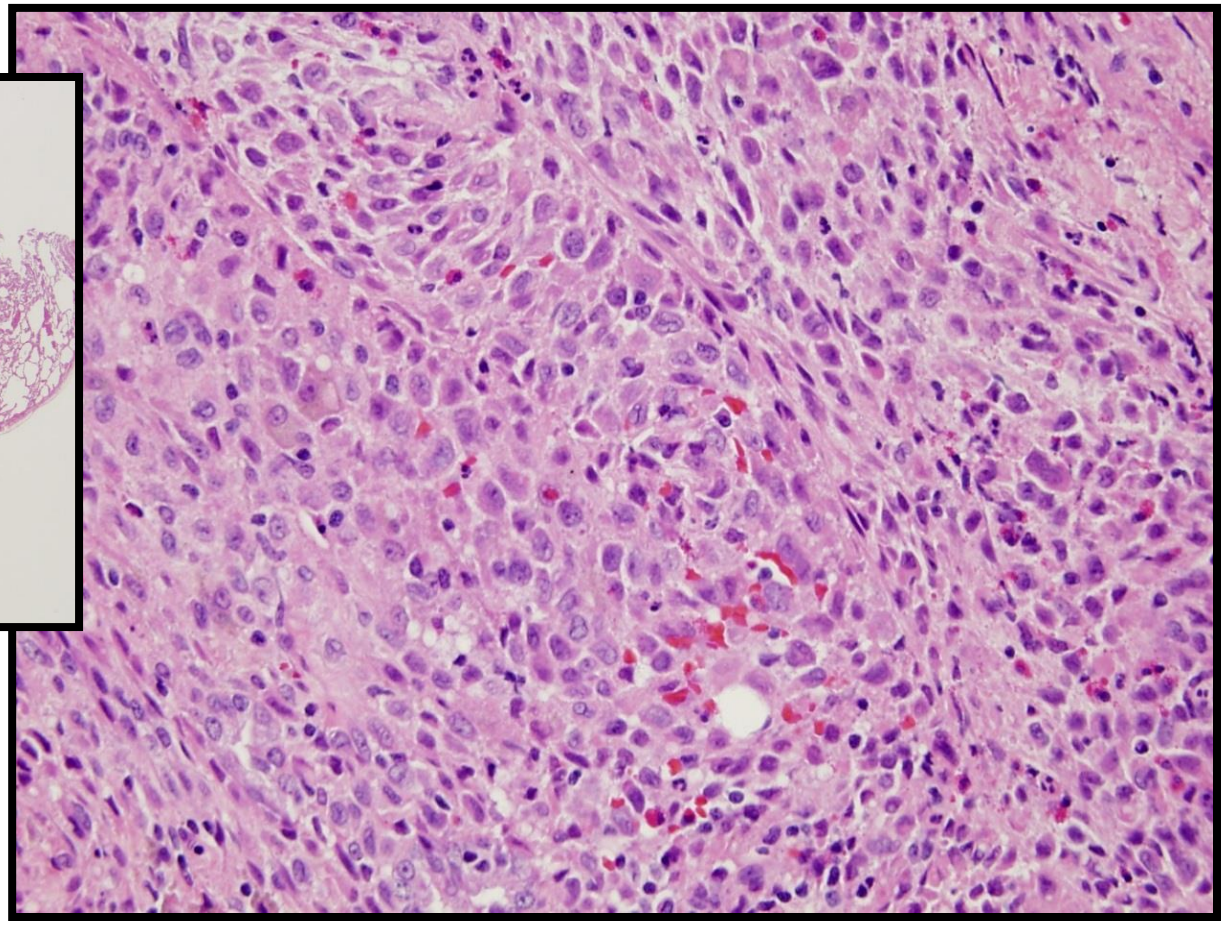




Langerhans Cell Histiocytosis

Lungs



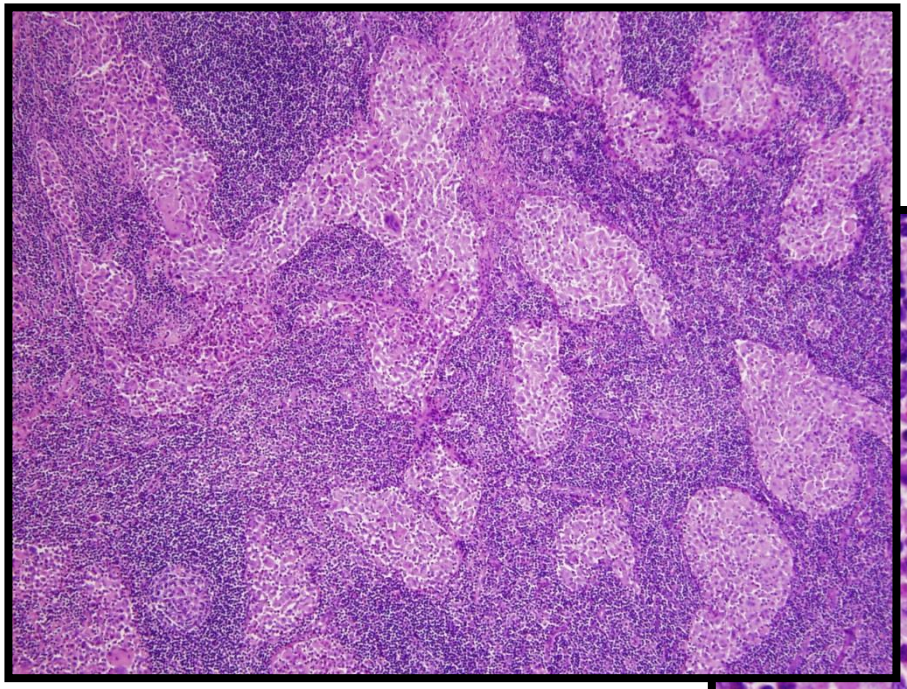


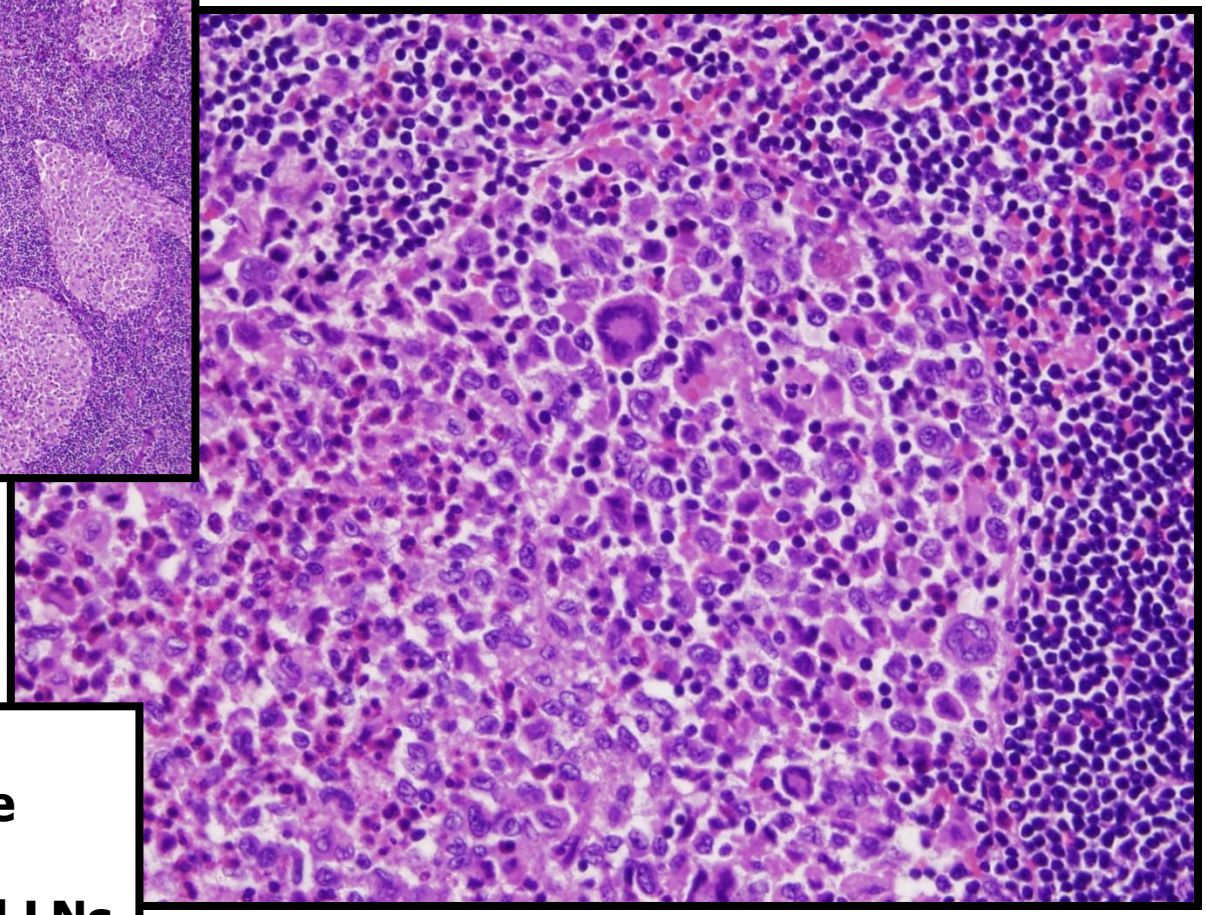
Associated with smoking
May resolve if smoking stopped

CD207

Langerhans Cell Histiocytosis

Lymph Nodes





LNs can be localized or a part of disseminated disease

This patient had generalized LNs

Langerhans Cell Histiocytosis
Morphologic Features

Frequency	Feature
100%	Langerhans cells (<5-75%)
92%	Eosinophils
84%	Multinucleated giant cells
75%	Small lymphocytes
61%	Necrosis
49%	Neutrophils
29%	Foamy histiocytes

Mild atypia (reactive type) in ~50% of cases

Mitotic rate: 0-23/10 high power fields

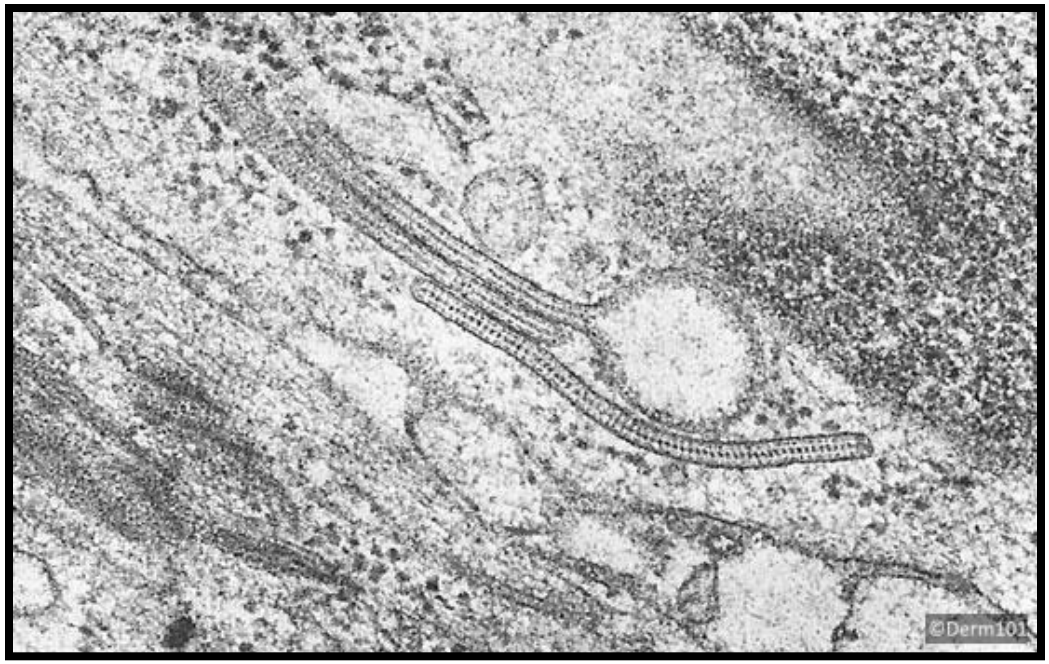
Arch Pathol Lab Med 107: 59, 1983

Langerhans Cell Histiocytosis

Birbeck Granules

Also known as X bodies or Langerhans bodies

Birbeck granules are characteristic (but not unique to) Langerhans cells
Presence is a reflection of membrane activity; function debated
Contain langerin = a type II transmembrane lectin receptor



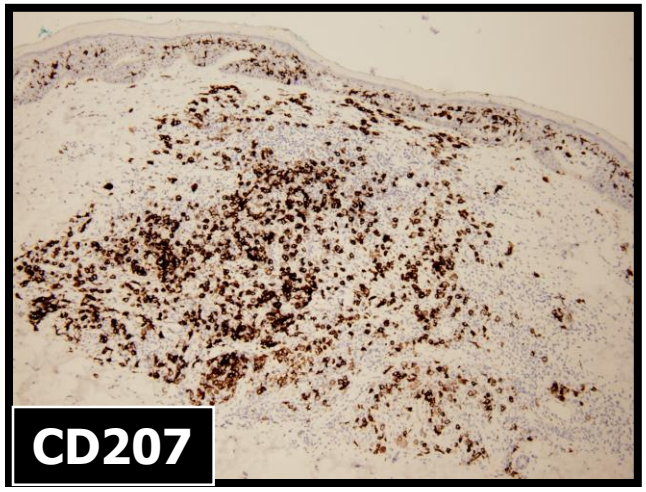
J Invest Dermatol 37: 51, 1961
CR Acad Sci (Paris) 261:5719, 1965

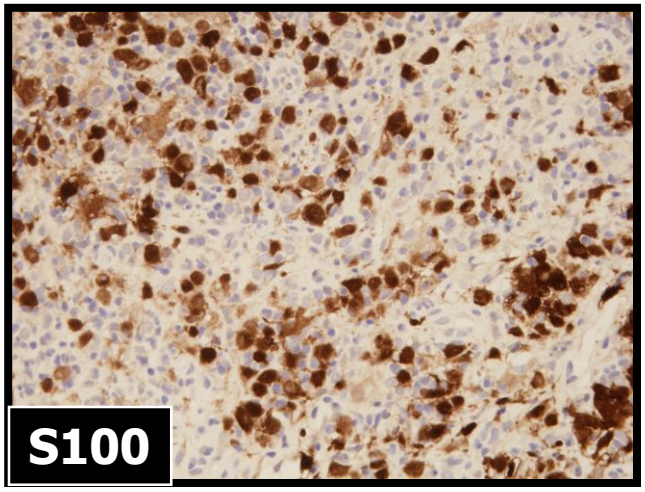
Francoise Basset, PhD

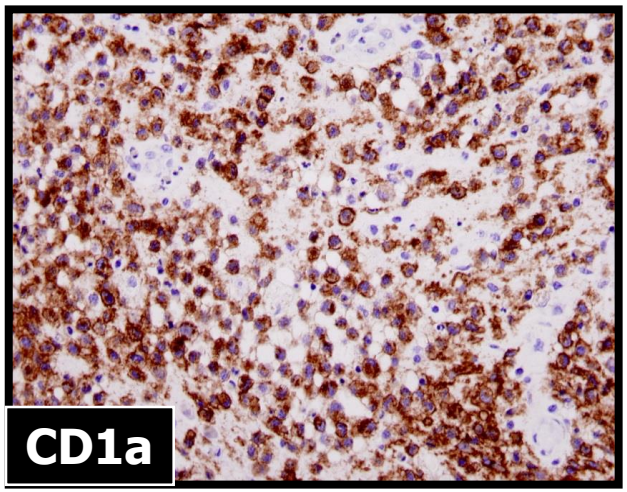
Michael S. C. Birbeck, PhD
1925-2005

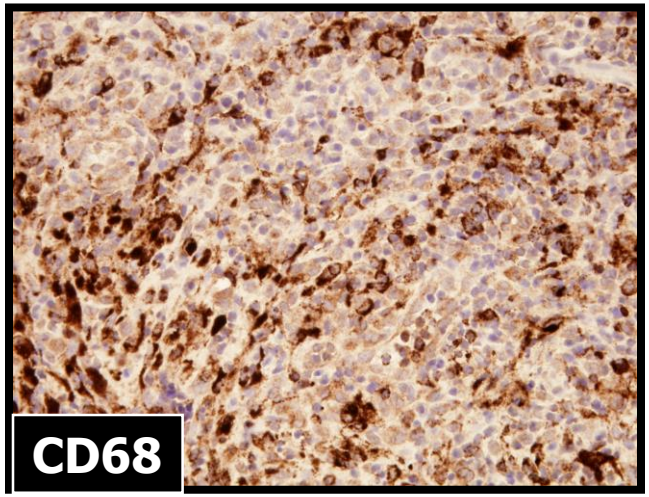
Langerhans Cell Histiocytosis

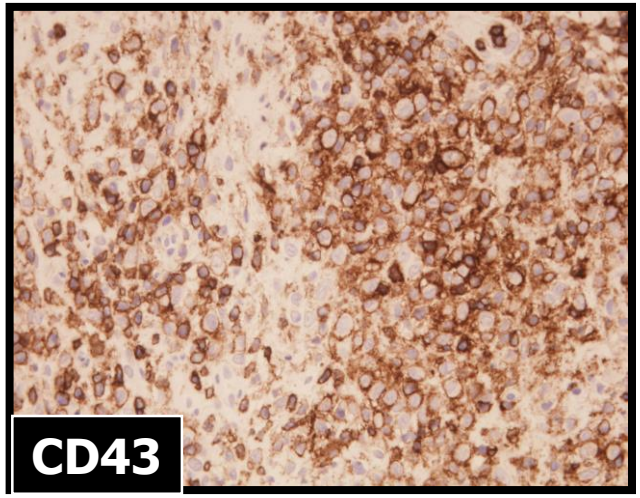
Immunophenotype











Positive

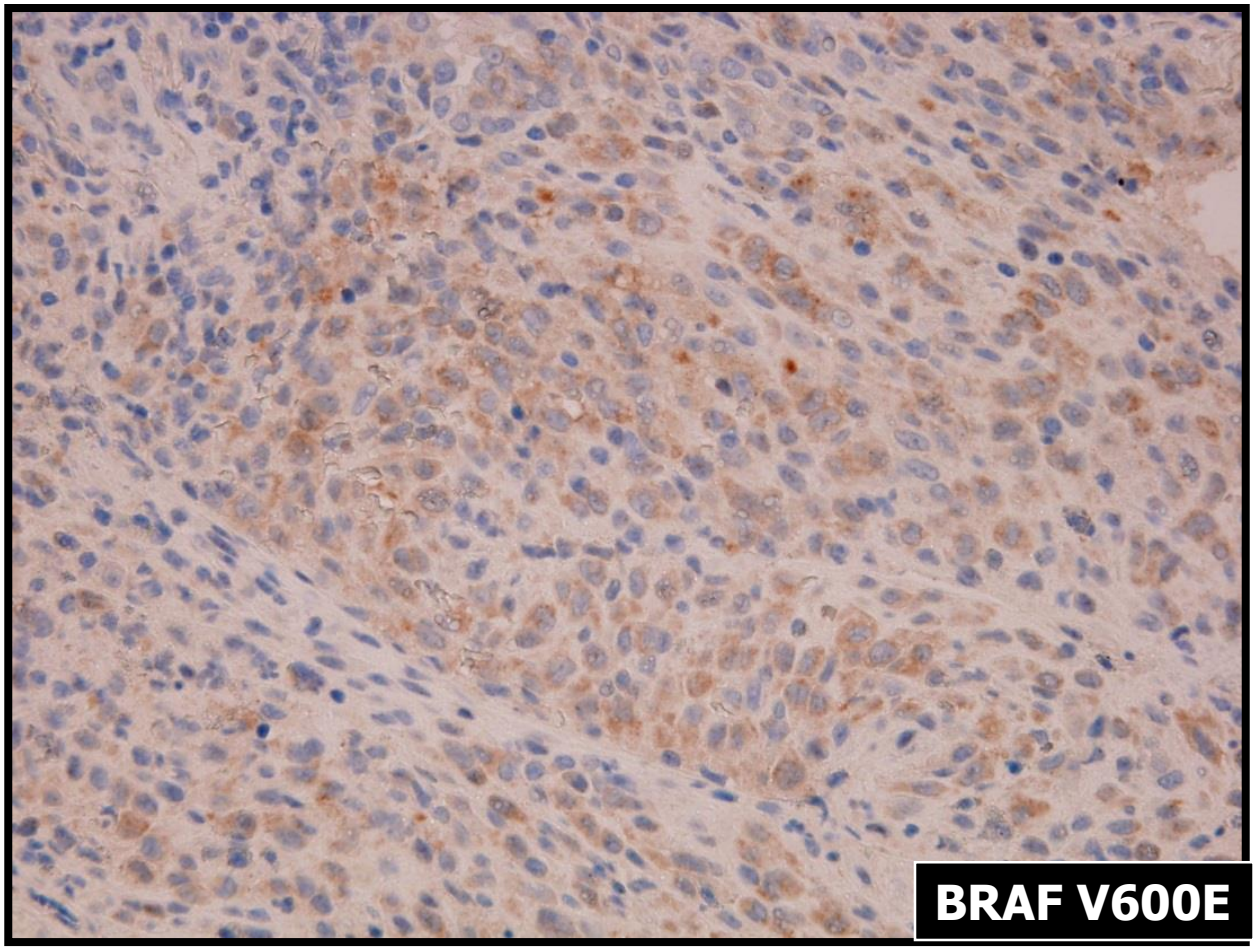
CD1a, CD207, S100

Variable

CD4, CD11c, CD14, CD43, CD68, CD163 lysozyme

Langerhans Cell Histiocytosis

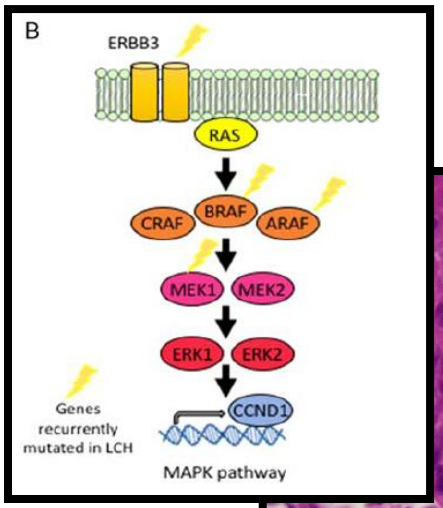
Immunophenotype

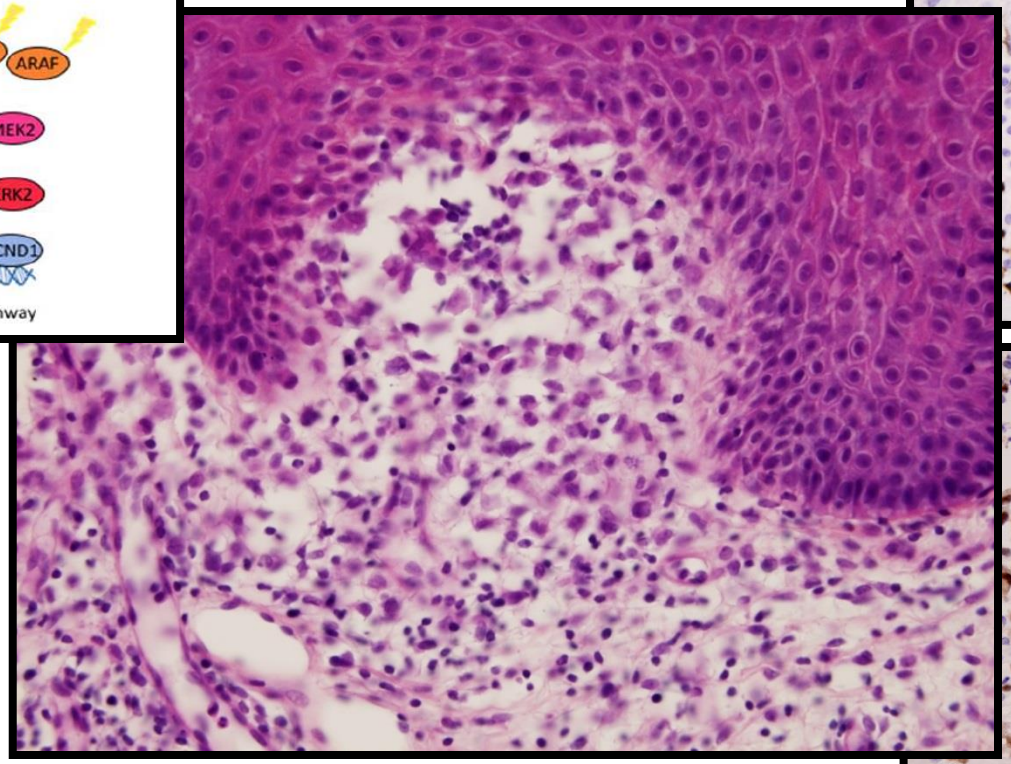


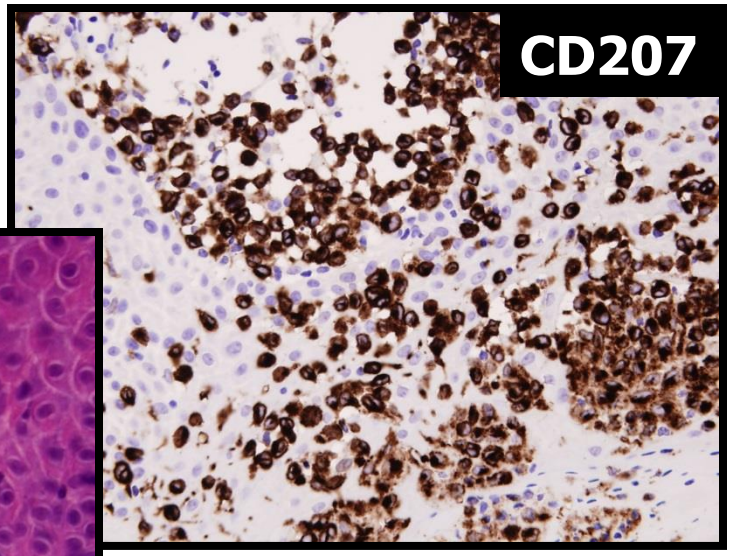
We use VE-1 antibody from Ventana/Roche (790-5095)

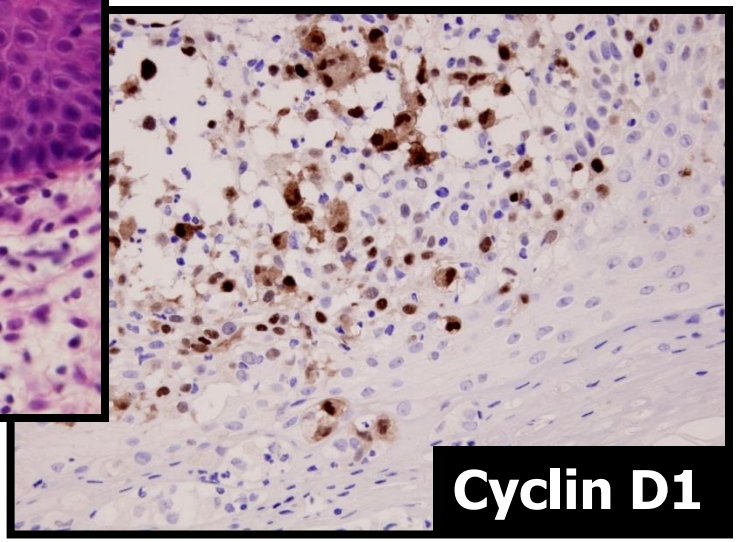
Cyclin D1 Is Expressed in Neoplastic Cells of Langerhans Cell Histiocytosis but Not Reactive Langerhans Cell Proliferations

Vignesh Shanmugam, MD, Jeffrey W. Craig, MD, PhD, Jason L. Hornick, MD, PhD, Elizabeth A. Morgan, MD, Geraldine S. Pinkus, MD, and Olga Pozdnyakova, MD, PhD









Am J Surg Pathol 41: 1390, 2017

Langerhans Cell Histiocytosis
Mutations in BRAF/MAP2K1 Are Common

Brief report

Recurrent *BRAF* mutations in Langerhans cell histiocytosis

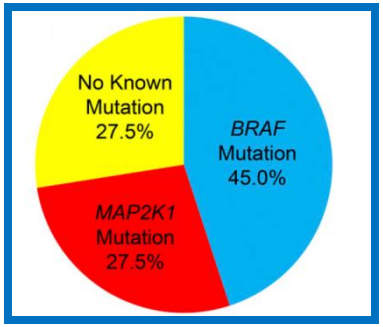
Gayane Badalian-Very,[1-3] Jo-Anne Vergilio,[4,5] Barbara A. Degar,[6-8] Laura E. MacConaill,[9] Barbara Brandner,[1-3] Monica L. Calicchio,[4] Frank C. Kuo,[5,10] Azra H. Ligon,[5,10,11] Kristen E. Stevenson,[12] Sarah M. Kehoe,[9] Levi A. Garraway,[1-3,9,13] William C. Hahn,[1-3,9,13] Matthew Meyerson,[1,2,9,13] Mark D. Fleming,[4,5] and Barrett J. Rollins[1-3]

Blood 116: 1919, 2010

High prevalence of somatic *MAP2K1* mutations in *BRAF* V600E–negative Langerhans cell histiocytosis

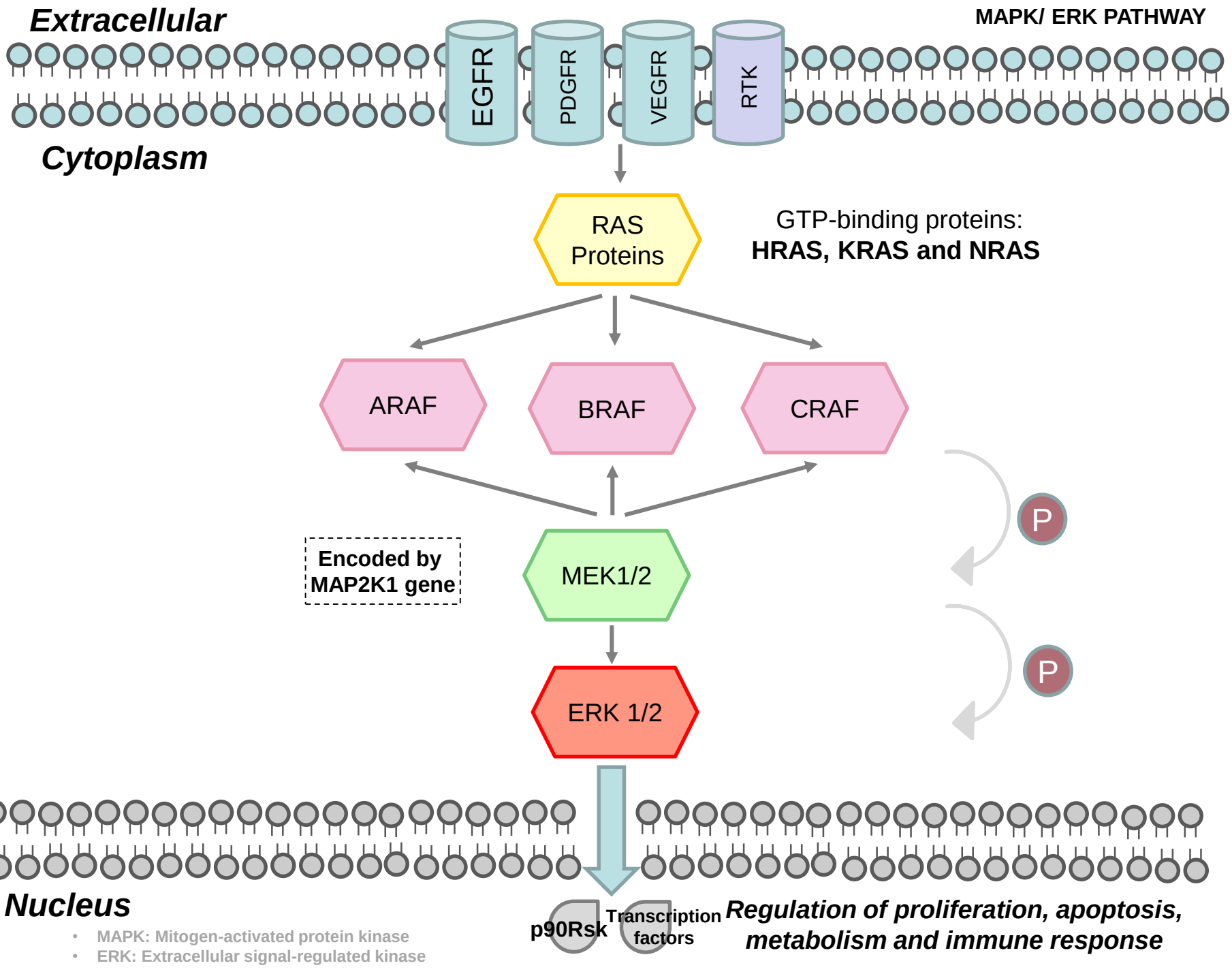
Noah A. Brown,[1] Larissa V. Furtado,[2] Bryan L. Betz,[1] Mark J. Kiel,[1] Helmut C. Weigelin,[1] Megan S. Lim,[1] and Kojo S. J. Elenitoba-Johnson[1]

[1]Department of Pathology, University of Michigan Medical School, Ann Arbor, MI; and [2]Department of Pathology, University of Chicago, Chicago, IL



BRAF V600E	**18/40 (45%)**
MAP2K1	**11/40 (27.5%)**

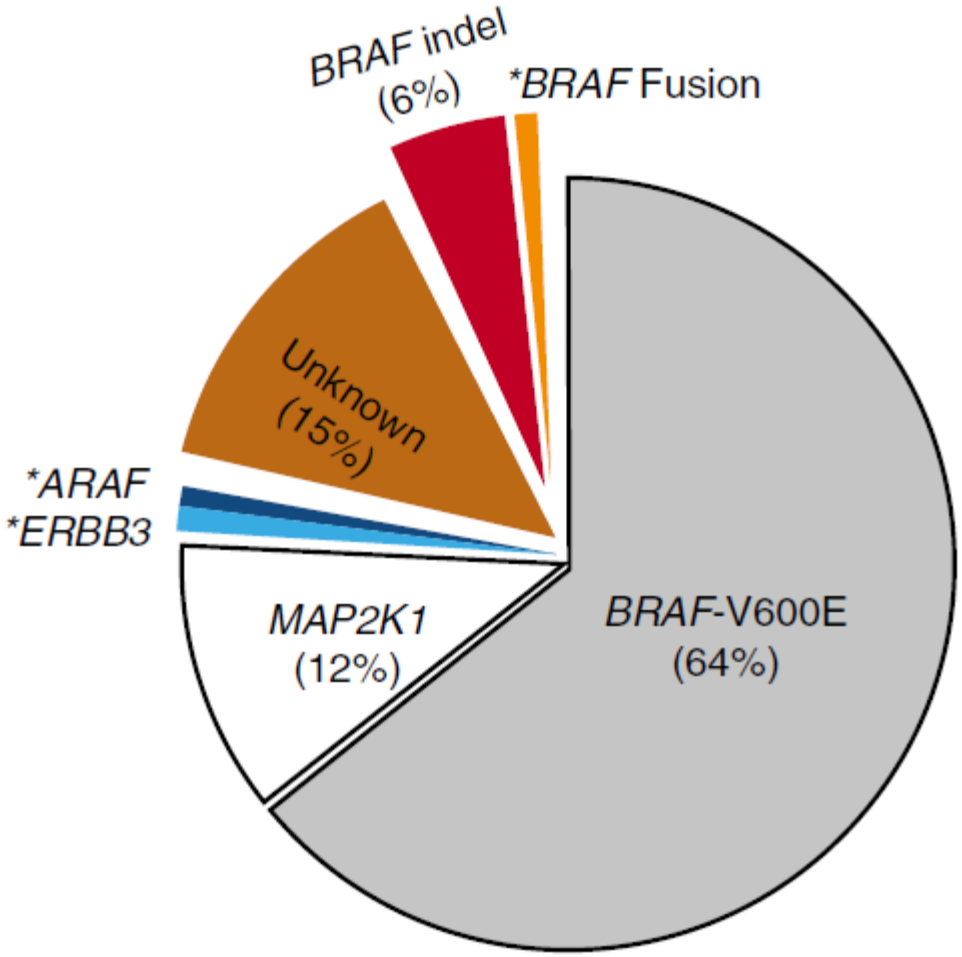
Blood 124: 1655, 2014



- MAPK: Mitogen-activated protein kinase
- ERK: Extracellular signal-regulated kinase

Alternative genetic mechanisms of BRAF activation in Langerhans cell histiocytosis

Rikhia Chakraborty,[1,2,*] Thomas M. Burke,[1-3,*] Oliver A. Hampton,[4,5,*] Daniel J. Zinn,[1,2] Karen Phaik Har Lim,[1,3] Harshal Abhyankar,[1] Brooks Scull,[1] Vijetha Kumar,[6] Nipun Kakkar,[4] David A. Wheeler,[4,5] Angshumoy Roy,[2,6] Poulikos I. Poulikakos,[7] Miriam Merad,[7] Kenneth L. McClain,[1,2] D. Williams Parsons,[1-5] and Carl E. Allen[1-3]



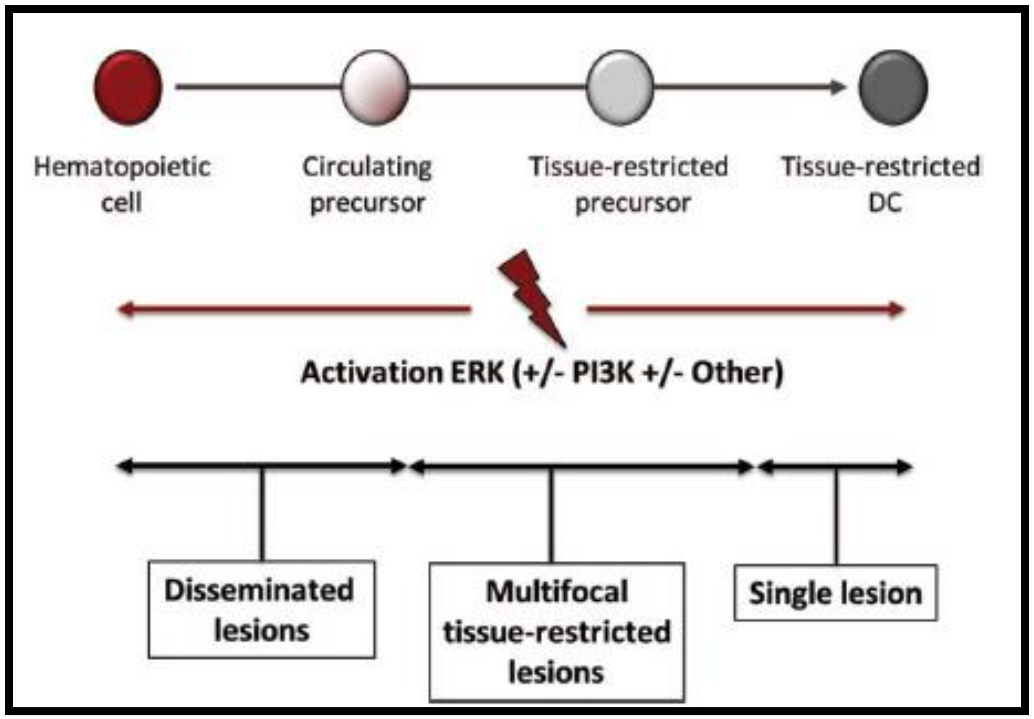
85% of LCH cases have genetic abnormalities of the MAPK pathway

They likely all do

Blood 128: 2533, 2016

Langerhans Cell Histiocytosis

Misguided Myeloid Dendritic Cell Model



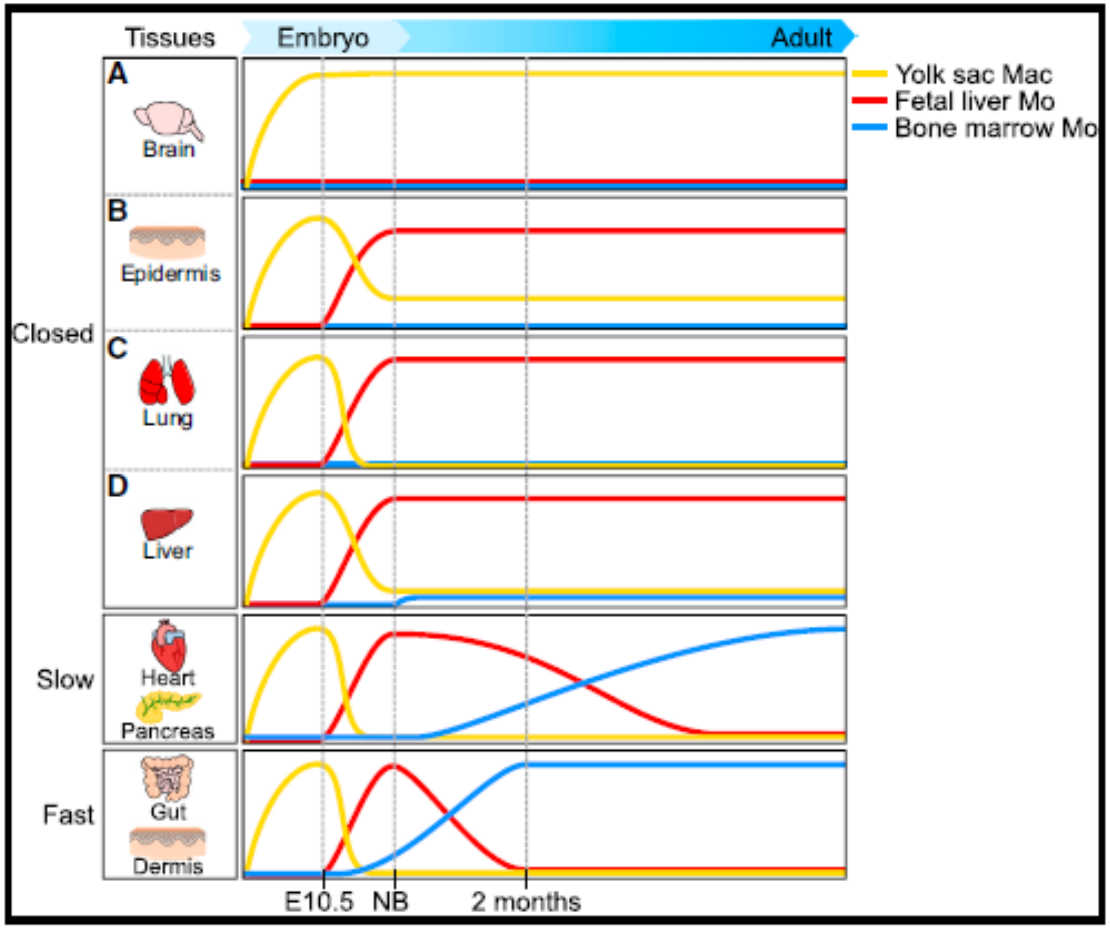
Model to explain the widely disparate presentations of LCH

Distribution of disease depends on the cell in which mutation/ERK activation occurs

Hematology Am Soc Hematol Educ Program 2015;2015:559-564

Tissue-Resident Macrophage Ontogeny and Homeostasis

Florent Ginhoux[1,2,*] and Martin Guilliams[3,4,*]
[1]Singapore Immunology Network (SIgN), A*STAR, 8A Biomedical Grove, Immunos Building, Level 3, Singapore 138648, Singapore
[2]Shanghai Institute of Immunology, Shanghai JiaoTong University School of Medicine, 280 South Chongqing Road, Shanghai 200025, China
[3]Unit of Immunoregulation and Mucosal Immunology, VIB Inflammation Research Center, Ghent 9052, Belgium
[4]Department of Biomedical Molecular Biology, Ghent University, Ghent 9000, Belgium
*Correspondence: florent_ginhoux@immunol.a-star.edu.sg (F.G.), martin.guilliams@irc.ugent.be (M.G.)
http://dx.doi.org/10.1016/j.immuni.2016.02.024



Immunity 44: 439, 2016

Histiocytosis X
(Langerhans' Cell Histiocytosis)

Prognostic Role of Histopathology

Robert J. Risdall, MD; Louis P. Dehner, MD; Paul Duray, MD;
Nathan Kobrinsky, MD; Leslie Robison, MPH; Mark E. Nesbit, Jr, MD

Louis Dehner, MD

"Histiocytosis X (HX) has the advantage of widespread use, although it has been applied to other types of histiocytosis. The generally recognized Langerhans cell derivation of HX makes Langerhans cell histiocytosis and attractive alternative."

Arch Pathol Lab Med 107: 59, 1983

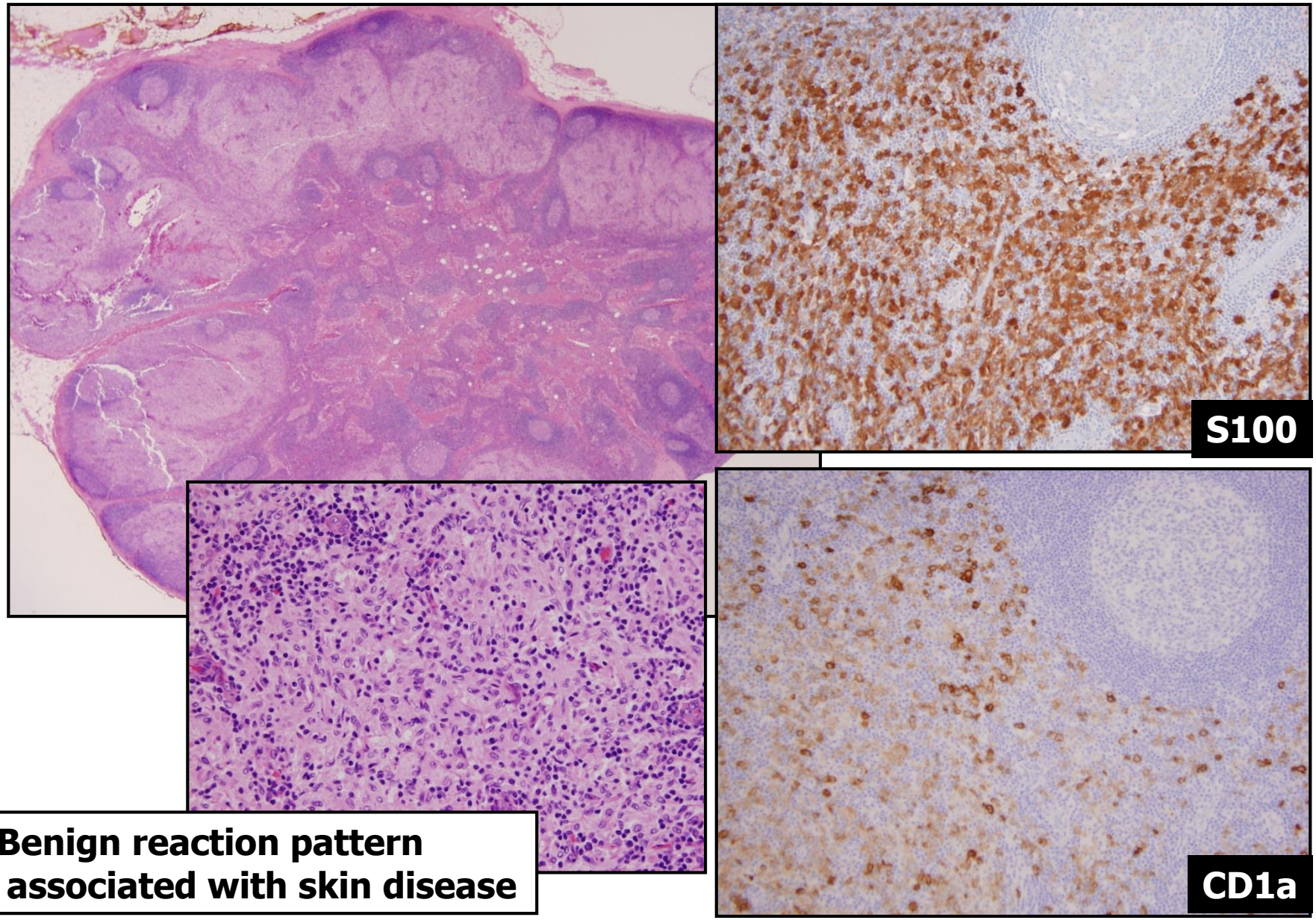
Langerhans Cell Histiocytosis
Differential Diagnosis

Dermatopathic lymphadenopathy

Indeterminate dendritic cell tumor

Langerhans cell sarcoma

Dermatopathic Lymphadenopathy



Benign reaction pattern associated with skin disease

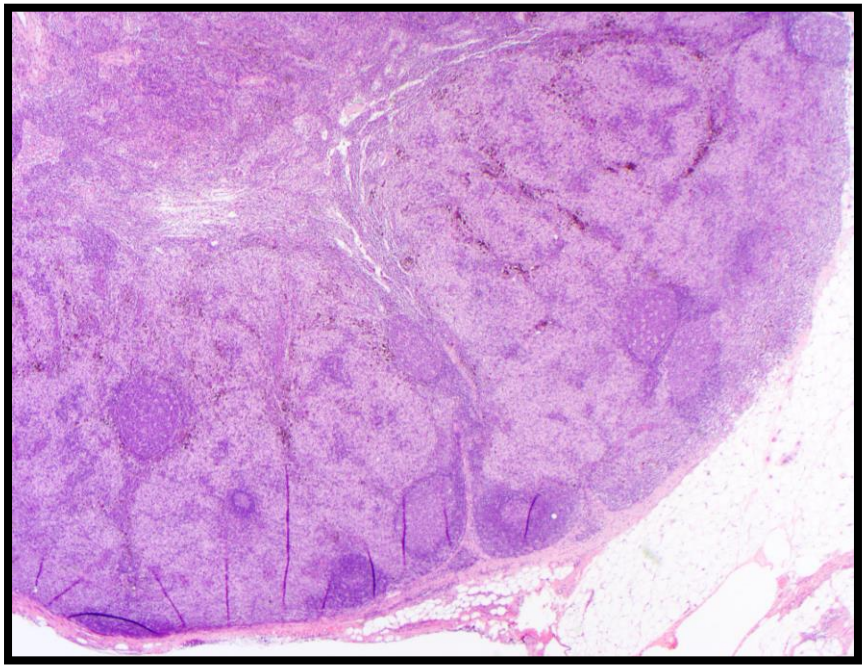
Dermatopathic Lymphadenopathy vs LCH

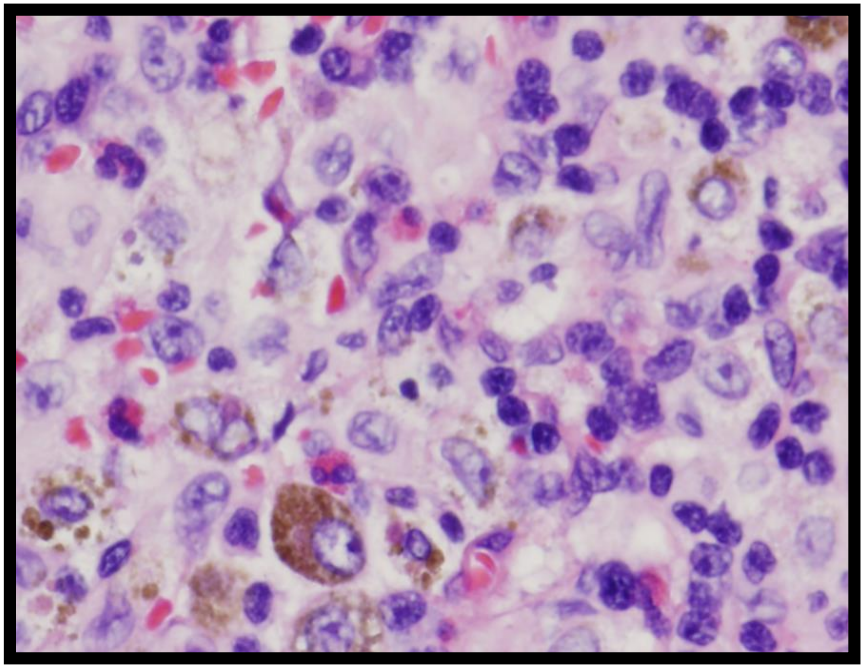
Differential Diagnosis

	Dermatopathic Lymphadenopathy	Langerhans Cell Histiocytosis (LCH)
Age	Adults > children	Chidren > adults
Lymph node	Always	Uncommon
Infiltration pattern	Paracortical	Sinus
Eosinophils	Few	Numerous
Necrosis	Absent	Often present
Multinucleated giant cells	Absent	Common
Melanophages	Present	Absent
BRAF V600E	Absent	Often present
Cyclin D1	Absent	Present
MUM1/IRF4	Present	Absent
BRAF/ERK pathway mutations	Absent	Present

Dermatopathic Lymphadenopathy

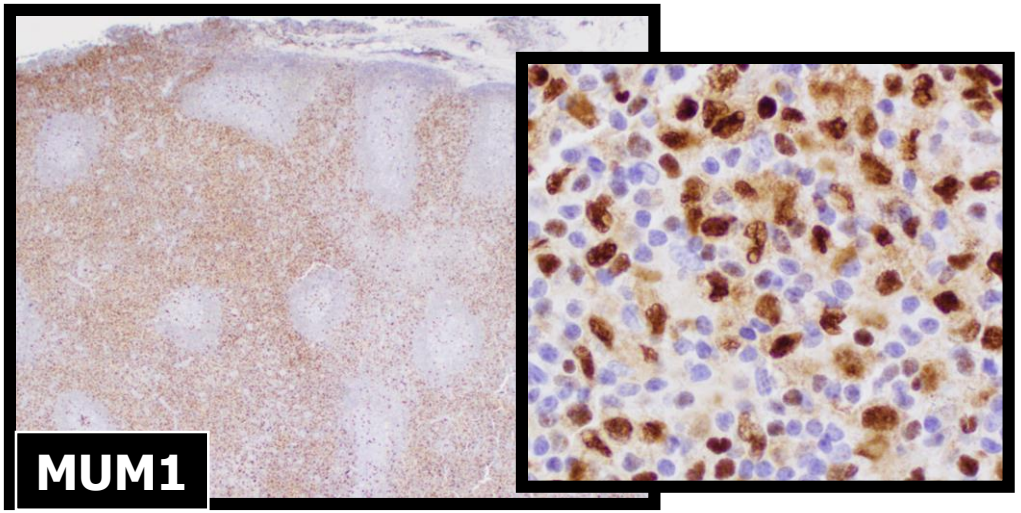
Utility of MUM1/IRF4



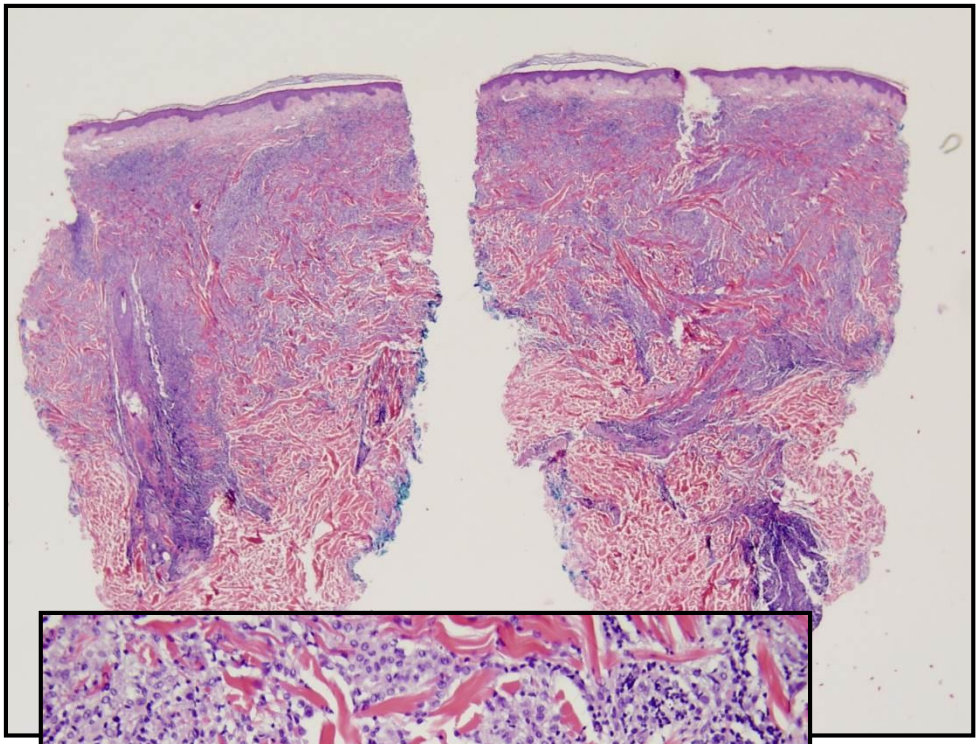


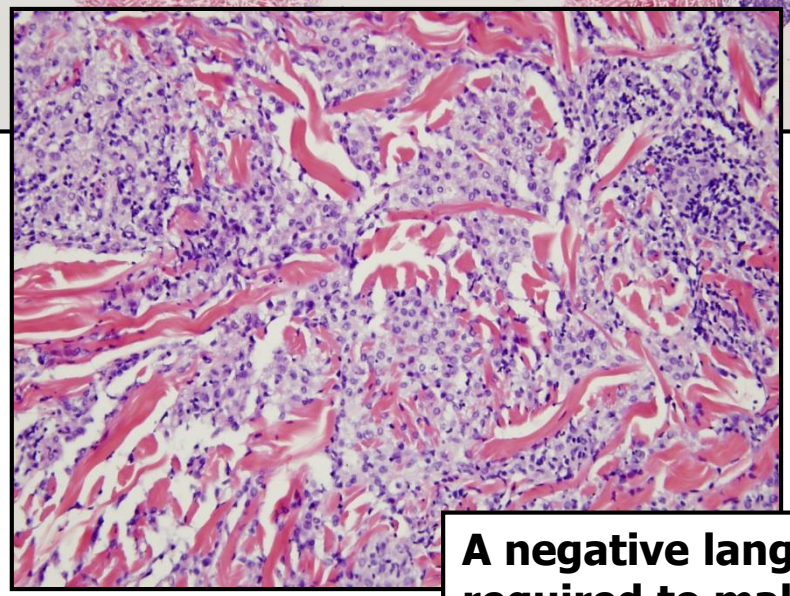
MUM1/IRF4

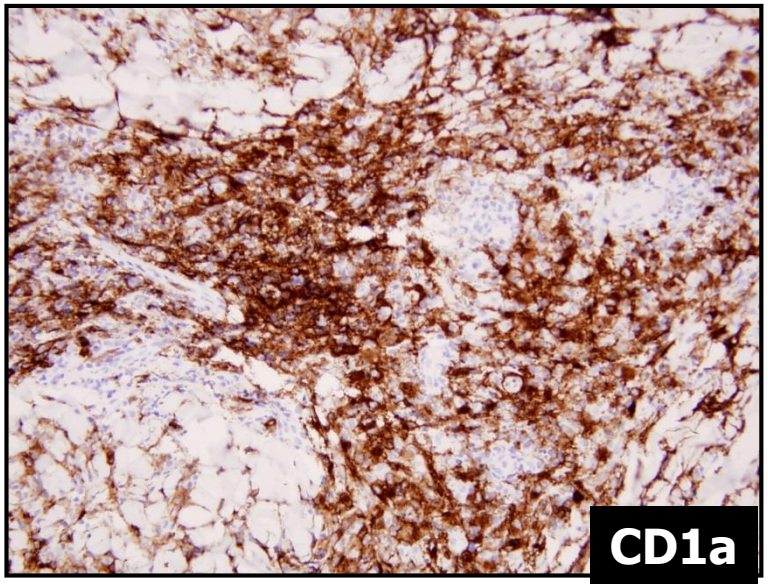
DL	**22/22**
LCH	**0/24**

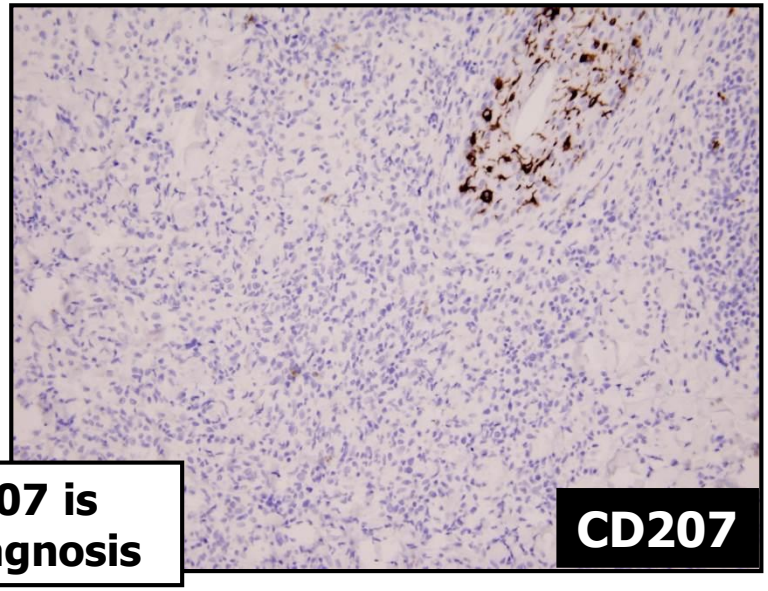


Indeterminate Dendritic Cell Tumor









A negative langerin/CD207 is required to make this diagnosis

Indeterminate Dendritic cell Tumor

Thought to be derived from normal precursors of Langerhans cells (so-called indeterminate cells)

Patients present with ≥ nodules, papules or plaques on skin

Dermis-based disease that can extend into subcutaneous fat

Histologically looks like Langerhans cells histiocytosis

But often no eosinophils

Immunophenotype: CD1a+, S100+, CD207-

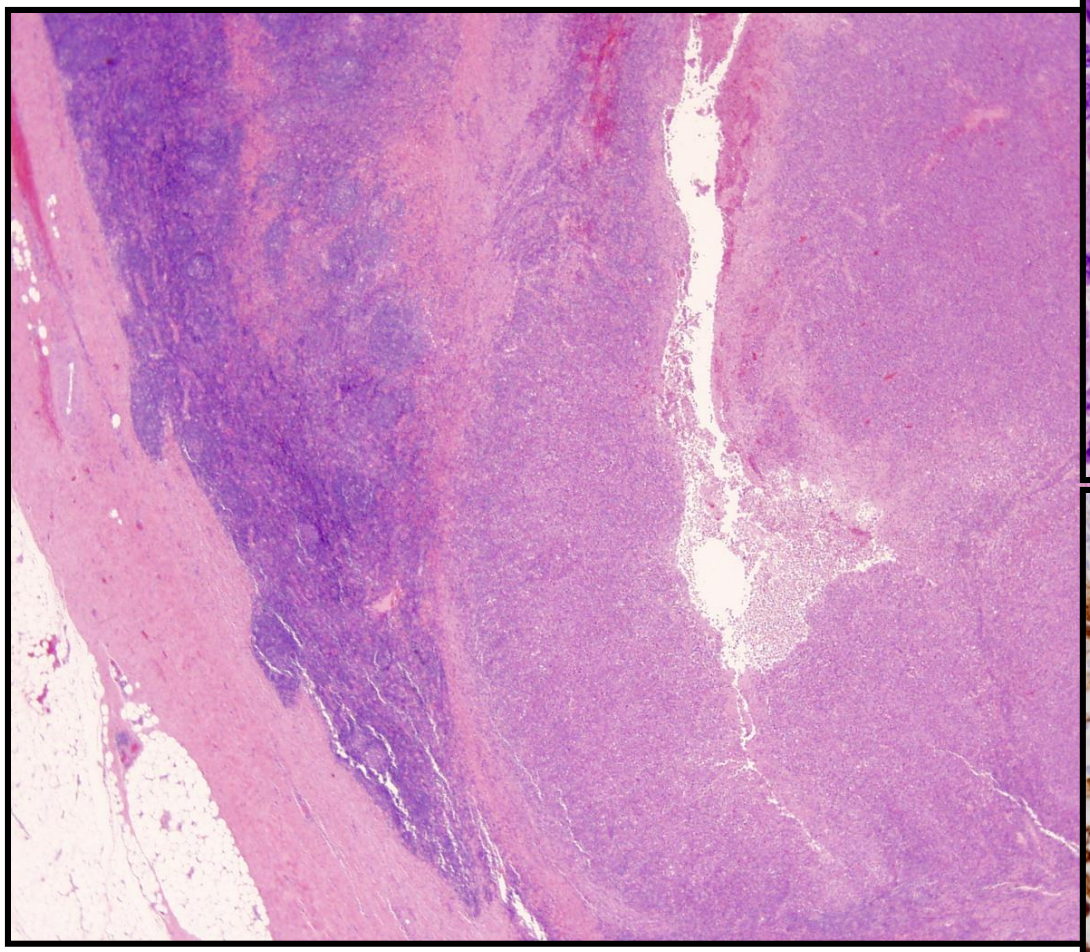
Electron microscopy: No Birbeck granules

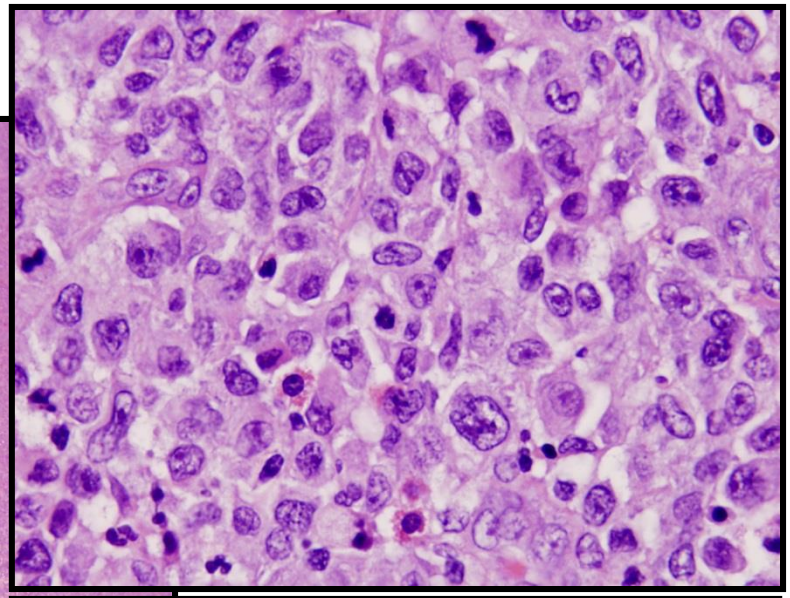
Genetics: *ETV3-NCOA2*/t(1;8)(q23.1;8q13.3) reported in 3 cases

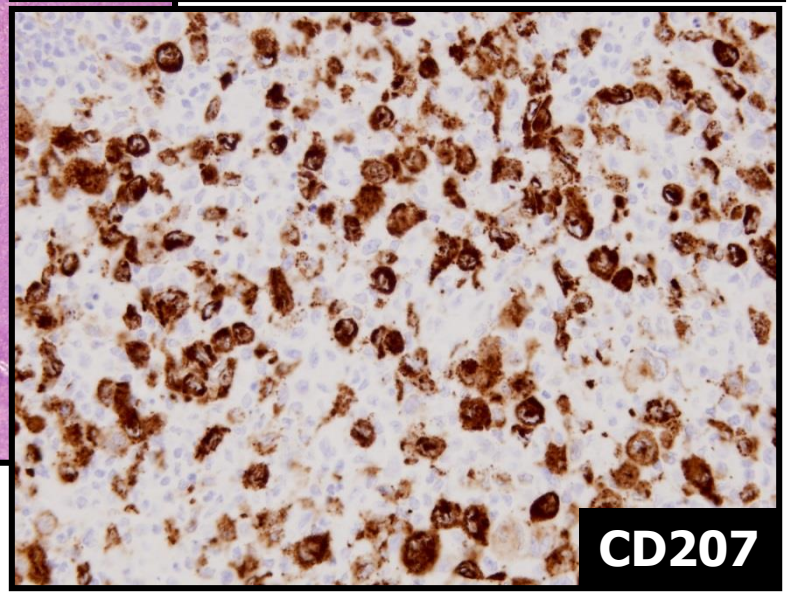
Highly variable clinical course:

Spontaneous regression or progression

Langerhans Cell Sarcoma







Langerhans Cell Sarcoma

Definition

A high-grade neoplasm with overt malignant cytologic features and Langerhans cell phenotype

History

Rarely preceded by typical LCH (in my experience)

Age and Sites of Disease

Median 41 yrs (10-72yrs)
Extranodal ~ 80% (most often skin); nodal ~ 20%

Ancillary Support for Diagnosis

Immunohistochemistry: S-100+, CD1a+, CD207/langerin+
Electron microscopy: Birbeck granules

Genetics

Rare cases with monoclonal *IGH* rearrangements

Prognosis

~50% mortality as a result of progressive disease

Review Article

Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages

Jean-François Emile,[1,2] Oussama Abla,[3] Sylvie Fraitag,[4] Annacarin Horne,[5] Julien Haroche,[6,7] Jean Donadieu,[1,8] Luis Requena-Caballero,[9] Michael B. Jordan,[10] Omar Abdel-Wahab,[11] Carl E. Allen,[12] Frédéric Charlotte,[7,13] Eli L. Diamond,[14] R. Maarten Egeler,[3] Alain Fischer,[15,16] Juana Gil Herrera,[17] Jan-Inge Henter,[18] Filip Janku,[19] Miriam Merad,[20] Jennifer Picarsic,[21] Carlos Rodriguez-Galindo,[22] Barret J. Rollins,[23,24] Abdellatif Tazi,[25] Robert Vassallo,[26] and Lawrence M. Weiss,[27] for the Histiocyte Society

[1]Research Unit EA4340, Versailles University, Paris-Saclay University, Boulogne, France; [2]Pathology Department, Ambroise Paré Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Boulogne, France; [3]Division of Hematology/Oncology, Department of Pediatrics, The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada; [4]Pathology Department, Necker Hospital, Paris, France; [5]Department of Women's and Children's Health, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden; [6]Department of Internal Medicine and French Reference Center for Rare Auto-immune and Systemic Diseases, Institut E3M, AP-HP, Pitié-Salpêtrière Hospital, Paris, France; [7]Université Pierre et Marie Curie University Paris 6, Paris, France; [8]Pediatric Hematology, Trousseau Hospital, APHP, Paris, France; [9]Fundación Jiménez Díaz, Universidad Autónoma, Madrid, Spain; [10]Department of Pediatrics, Cincinnati Children's Hospital Medical Center and the University of Cincinnati College of Medicine, Cincinnati, OH; [11]Leukemia Service, Human Oncology and Pathogenesis Program, Memorial Sloan Kettering Cancer Center, New York, NY; [12]Feigin Center, Texas Children's Cancer Center, Houston, TX; [13]Pathology Department, Pitié-Salpétrière Hospital, Paris, France; [14]Department of Neurology, Memorial Sloan Kettering Cancer Center, New York, NY; [15]Necker Enfants Malades Hospital, AP-HP, Paris, France; [16]Institut Imagine, Sorbonne Paris Cité, Université Paris Descartes, Paris, France; [17]Division of Clinical Immunology, Hospital General Universitario and Health Research Institute "Gregorio Marañón," Madrid, Spain; [18]Childhood Cancer Research Unit, Department of Women's and Children's Health, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden; [19]Department of Investigational Cancer Therapeutics (Phase I Clinical Trials Program), The University of Texas MD Anderson Cancer Center, Houston, TX; [20]Mount Sinai School of Medicine, New York, NY; [21]Pathology Department, University of Pittsburgh School of Medicine, Children's Hospital of Pittsburgh of University of Pittsburgh Medical Center, Pittsburgh, PA; [22]Dana-Farber Cancer Institute, Boston, MA; [23]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA; [24]Department of Medicine, Brigham & Women's Hospital, Harvard Medical School, Boston, MA; [25]Division of Pulmonary, Saint Louis Hospital, Paris, France; [26]Division of Pulmonary and Critical Care Medicine, Mayo Clinic College of Medicine, Rochester, MN; and [27]Clarient Pathology Services, Aliso Viejo, CA

The histiocytoses are rare disorders characterized by the accumulation of macrophage, dendritic cell, or monocyte-derived cells in various tissues and organs of children and adults. More than 100 different subtypes have been described, with a wide range of clinical manifestations, presentations, and histologies. Since the first classification in 1987, a number of new findings regarding the cellular origins, molecular pathology, and clinical features of histiocytic disorders have been identified. We propose herein a revision of the classification of histiocytoses based on histology, phenotype, molecular alterations, and clinical and imaging characteristics. This revised classification system consists of 5 groups of diseases: (1) Langerhans-related, (2) cutaneous and mucocutaneous, and (3) malignant histiocytoses as well as (4) Rosai-Dorfman disease and (5) hemophagocytic lymphohistiocytosis and macrophage activation syndrome. Herein, we provide guidelines and recommendations for diagnoses of these disorders. (*Blood*. 2016;127(22): 2672-2681)

Introduction

The histiocytoses are rare disorders characterized by the accumulation of cells thought to be derived from dendritic cells (DCs) or macrophages. Their clinical behavior ranges from mild to disseminated and, sometimes, life-threatening forms. The first classification of histiocytosis, published in 1987 by the Working Group of the Histiocyte Society (HS),[1] consisted of 3 categories: Langerhans cell (LC) or non-LC-related, and malignant histiocytoses (MH). In light of recent insights, we propose to parsimoniously gather the large number of categories of histiocytic disorders into 5 groups (Figure 1; supplemental Methods, available on the *Blood* Web site) based on clinical, radiographic, pathological, phenotypic, genetic, and/or molecular features.

Histiocyte and dendritic cell lineages

DCs, monocytes, and macrophages are members of the mononuclear phagocyte system,[2] whereas a histiocyte is a morphological term referring to tissue-resident macrophages. Macrophages are large ovoid cells mainly involved in the clearance of apoptotic cells, debris, and pathogens. In contrast, DCs are starry cells that present antigens on major histocompatibility complex molecules and activate naive T lymphocytes.[3] Human DCs are classified into 2 main groups: plasmacytoid and myeloid (mDC). mDCs have been further subdivided into 2 subsets on the basis of their expression of CD141 (mDC1) and CD1c (mDC2). LCs are DCs localized within the epidermis,

Writing Group of the Histiocyte Society

Major Groups of Histiocytic Lesions

Group	Name
L	Langerhans-related
C	Cutaneous and mucocutaneous
M	Malignant histiocytosis
R	Rosai-Dorfman disease
H	Hemophagocytic lymphohistiocytosis

Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages

Jean-François Emile,[1,2] Oussama Abla,[3] Sylvie Fraitag,[4] Annacarin Horne,[5] Julien Haroche,[6,7] Jean Donadieu,[1,8] Luis Requena-Caballero,[9] Michael B. Jordan,[10] Omar Abdel-Wahab,[11] Carl E. Allen,[12] Frédéric Charlotte,[7,13] Eli L. Diamond,[14] R. Maarten Egeler,[3] Alain Fischer,[15,16] Juana Gil Herrera,[17] Jan-Inge Henter,[18] Filip Janku,[19] Miriam Merad,[20] Jennifer Picarsic,[21] Carlos Rodriguez-Galindo,[22] Barret J. Rollins,[23,24] Abdellatif Tazi,[25] Robert Vassallo,[26] and Lawrence M. Weiss,[27] for the Histiocyte Society

Blood 127: 2672, 2016

Rosai-Dorfman Disease

History

Described by Rosai and Dorfman in 1969

Designated as sinus histiocytosis with massive lymphadenopathy

Arch Pathol Lab Med 87: 63, 1969

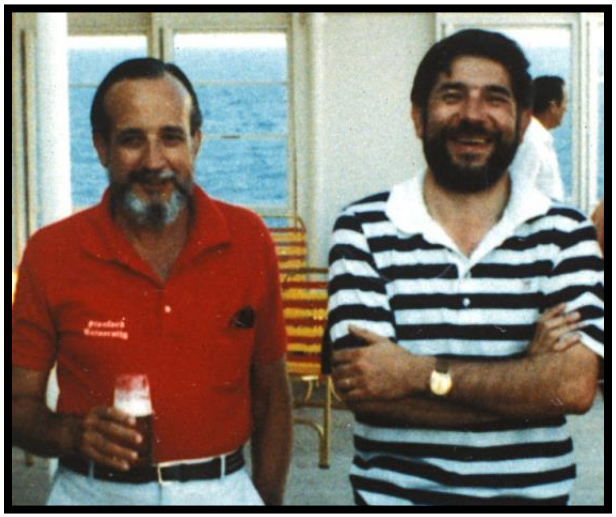
Also described by two other groups:

Destombes et al. (Bull Soc Pathol 58:1169, 1965)

Azoury and Reed (N Engl J Med 274: 928, 1966)

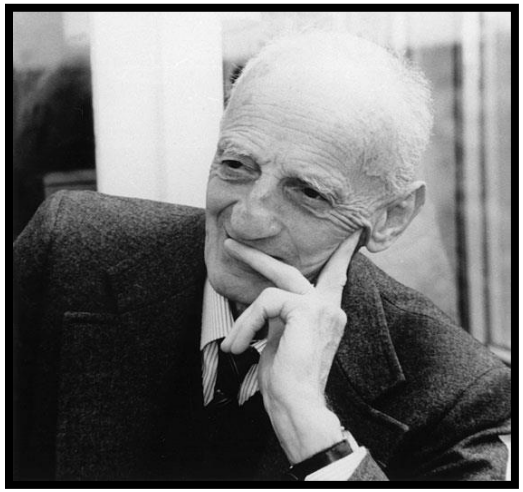
Juan Rosai, MD

Ronald F. Dorfman, MD



Circa 1970

Destombes-Rosai-Dorfman Disease

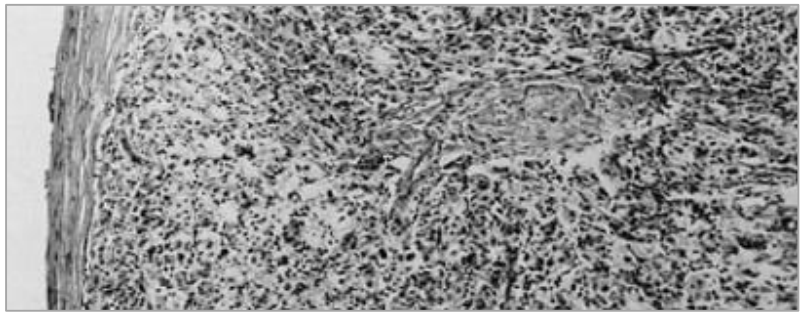


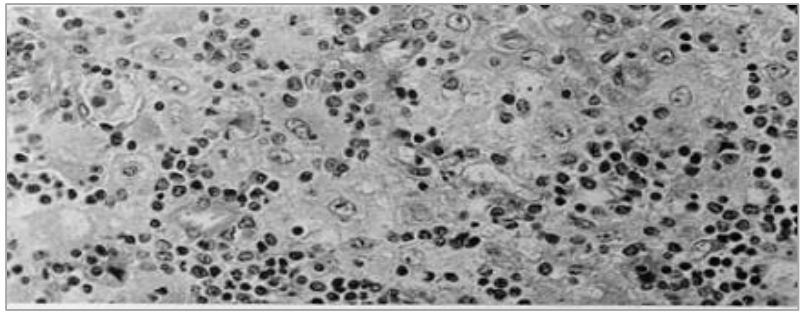
Pierre-Paul Destombes

* ADÉNITES AVEC SURCHARGE LIPIDIQUE, DE L'ENFANT OU DE L'ADULTE JEUNE, OBSERVÉES AUX ANTILLES ET AU MALI

(Quatre observations).

Par P. DESTOMBES (*)





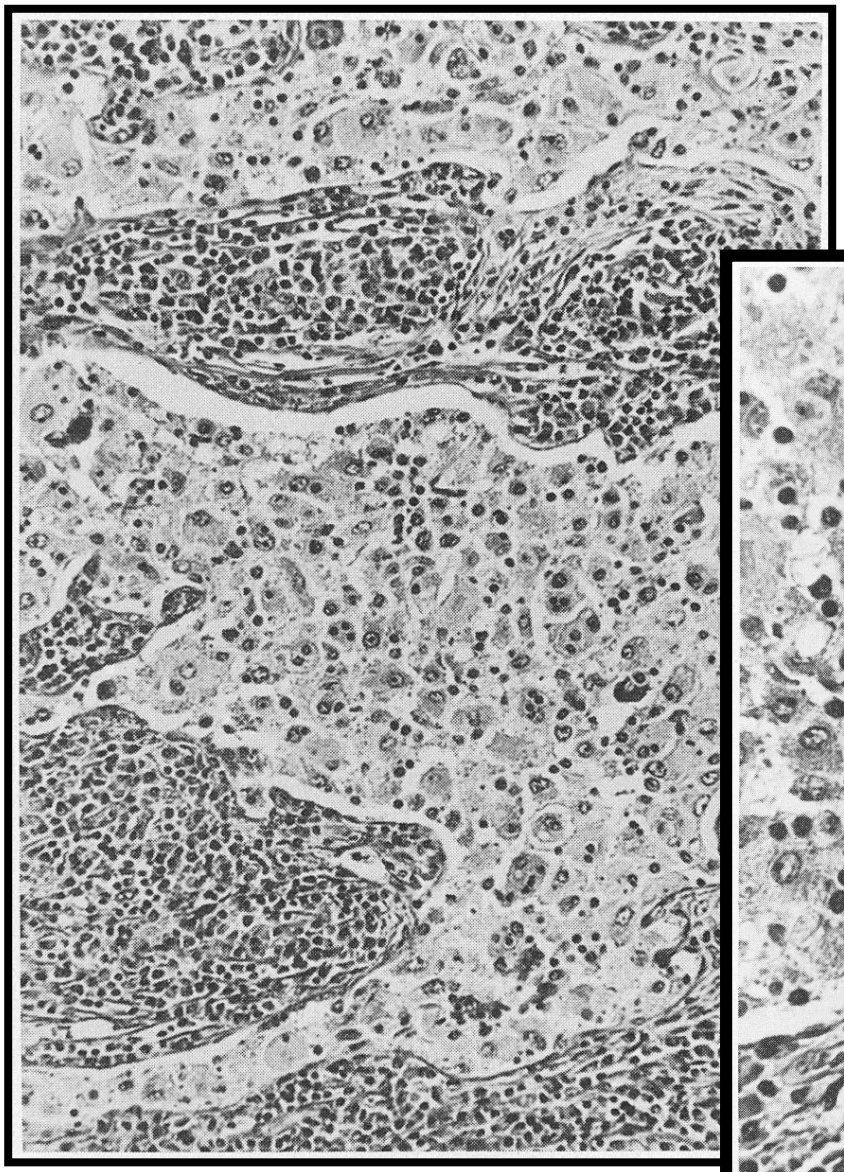
Bull Soc Pathol. (1965);58(6):1169-75.

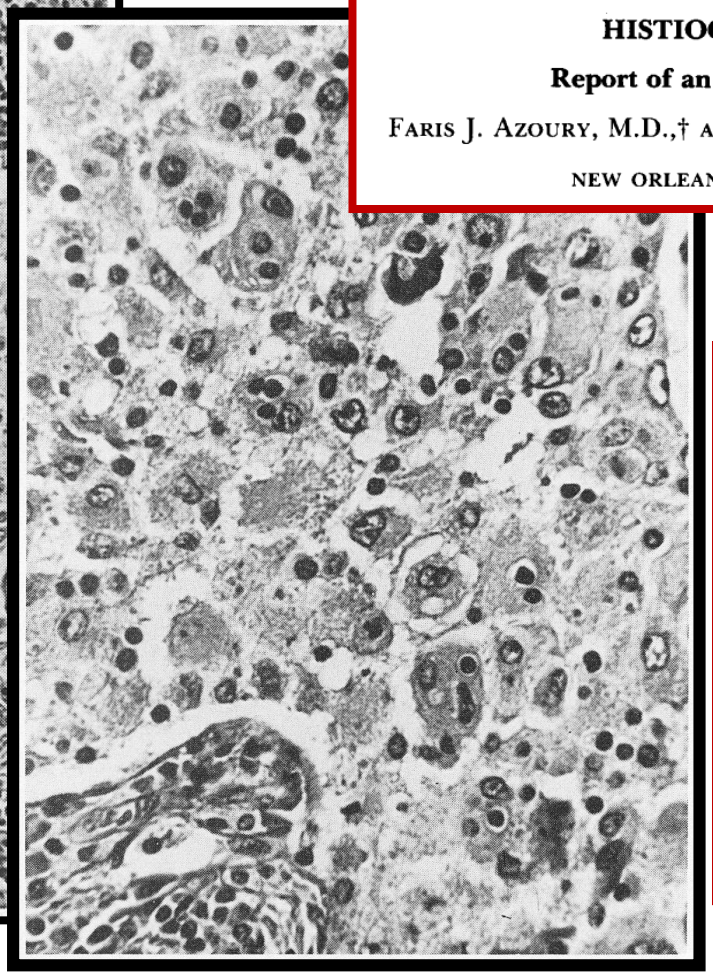
***Adenitis with lipid excess**

Derm 101 Vol 6, No 3, 2000

Rosai-Dorfman Disease

Case Report in 1966





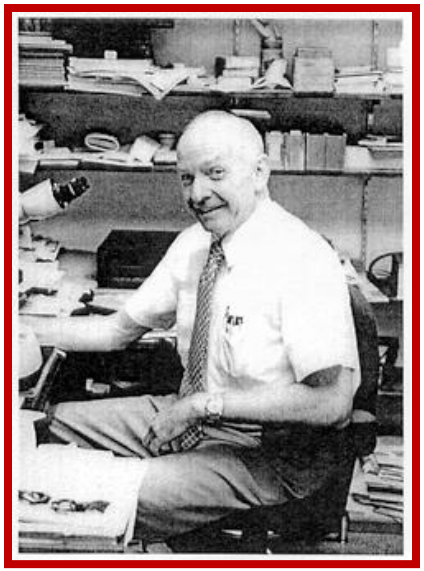
THE NEW ENGLAND JOURNAL OF MEDICINE

HISTIOCYTOSIS*

Report of an Unusual Case

FARIS J. AZOURY, M.D.,† AND RICHARD J. REED, M.D.‡

NEW ORLEANS, LOUISIANA



Richard J. Reed, MD
1928-2021

Azoury FJ, Reed RJ. N Eng J Med 274:928-930, 1966

Rosai-Dorfman Disease
Clinicopathologic Features

Most cases are sporadic

Rare familial forms

H (Faisalabad) syndrome

SLC29A3 mutation

Autoimmune lymphoproliferative syndrome

***TNFRSF6* mutation**

Presentation

~60% Lymphadenopathy

Bilateral large, painless cervical LNs

Other lymph node groups can be involved

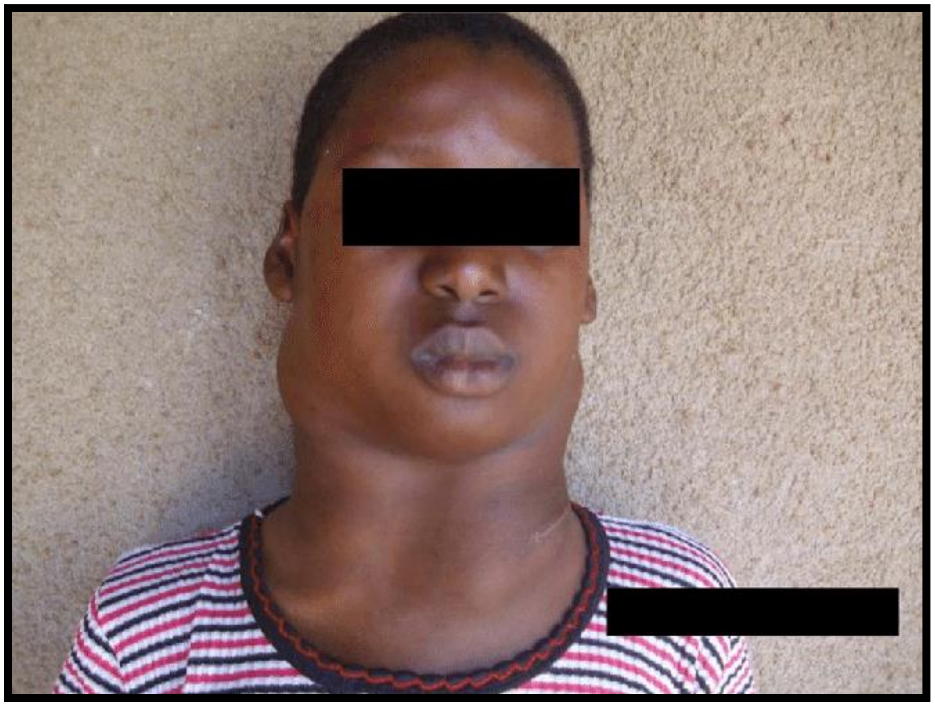
+/- fever, night sweats, weight loss, fatigue

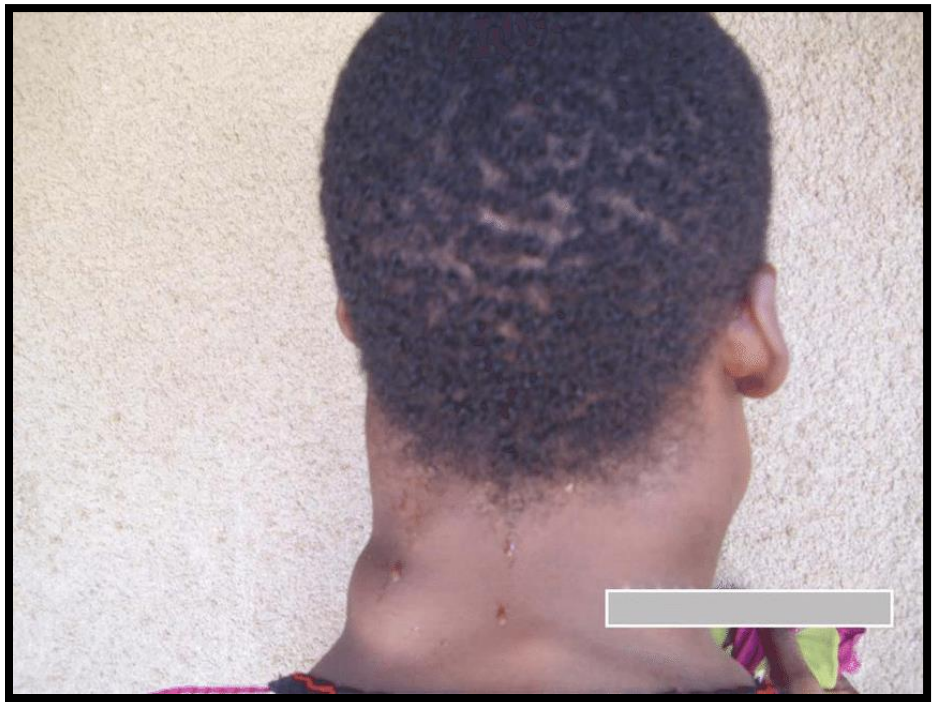
~40% Extranodal sites of disease

Sem Diagn Pathol 33:244, 2016

Rosai-Dorfman Disease

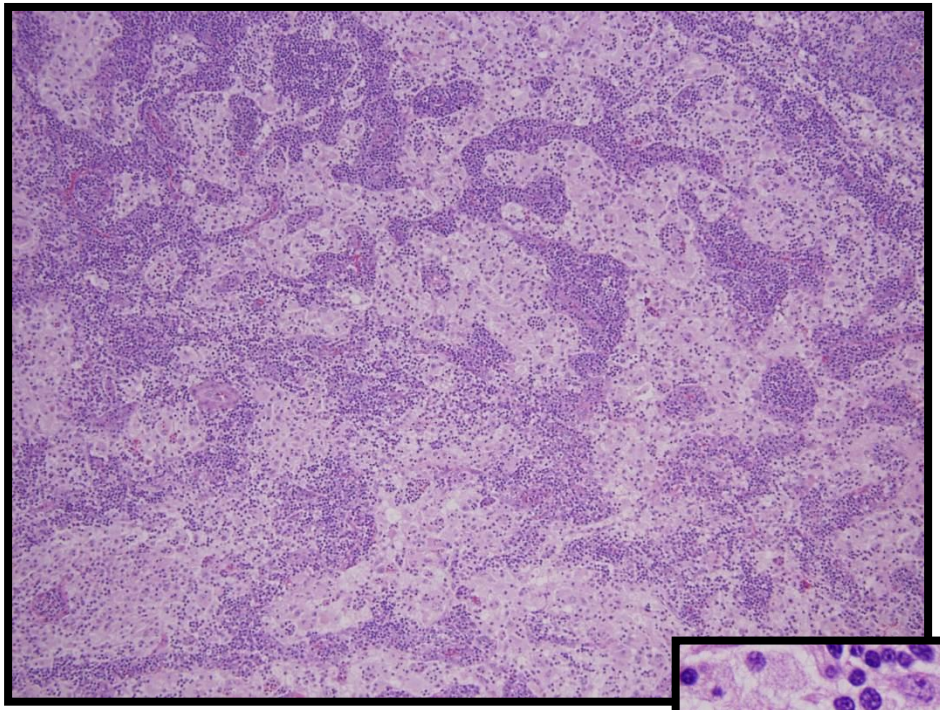
Bilateral Cervical Lymphadenopathy is Common

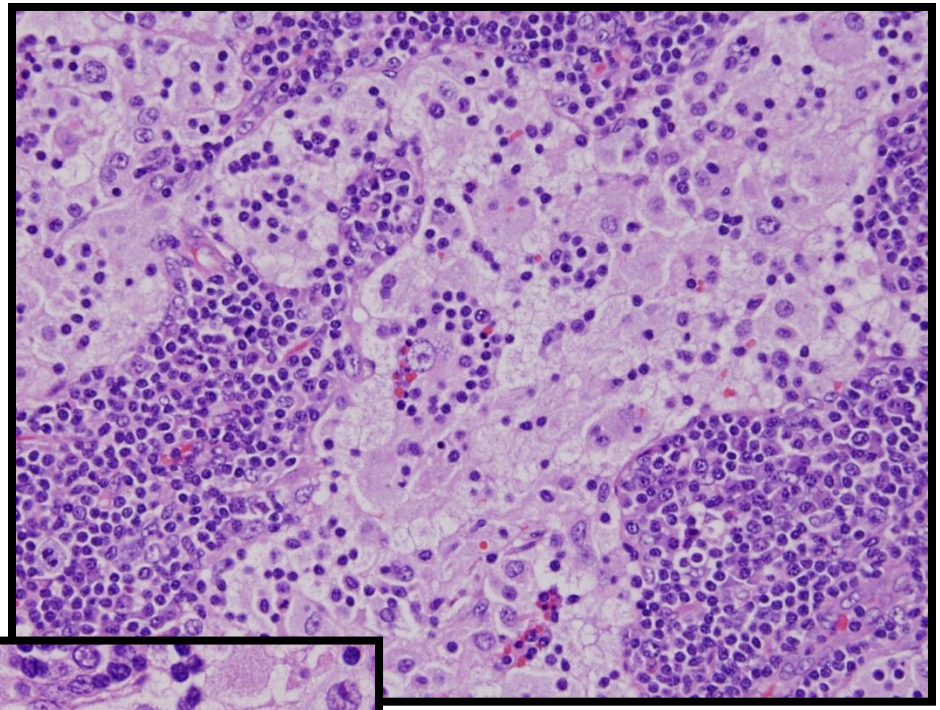


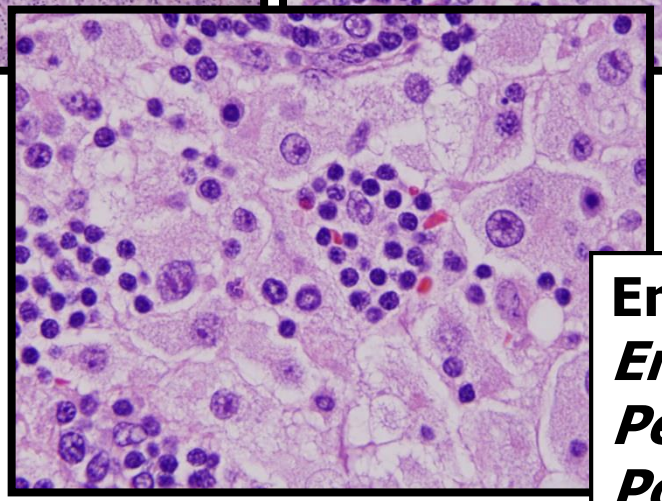


Rosai-Dorfman Disease

Lymph Node



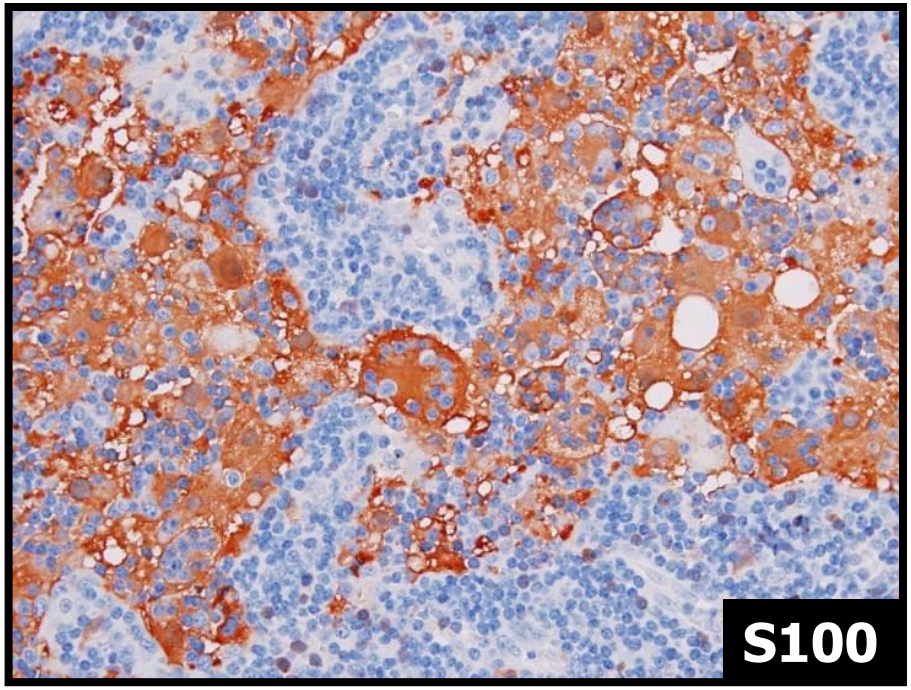




Emperipolesis (greek)
Em **= inside**
Peri **=around**
Polesis **= going about**

Rosai-Dorfman Disease

Immunophenotype



Positive

S100 protein

CD68

CD163

Fascin

OCT2

Cyclin D1

Negative

CD1a

CD207/langerin

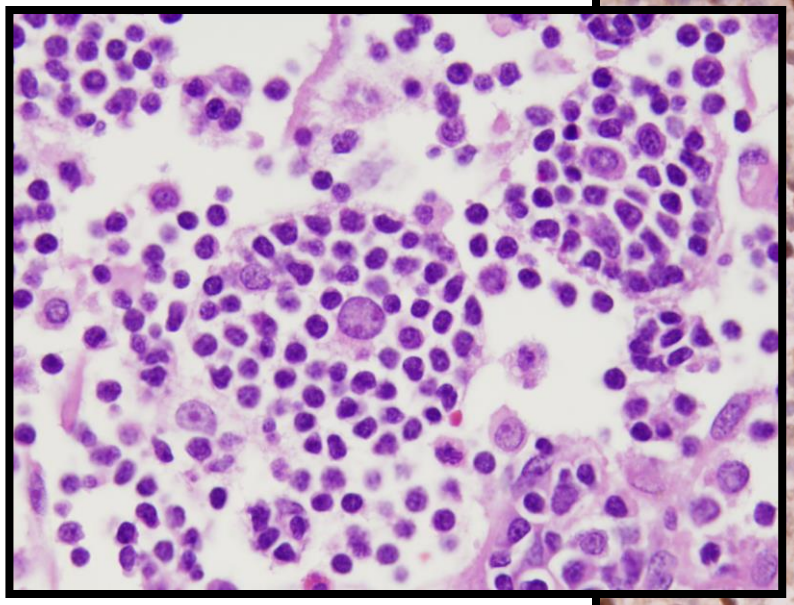
CD3, CD20

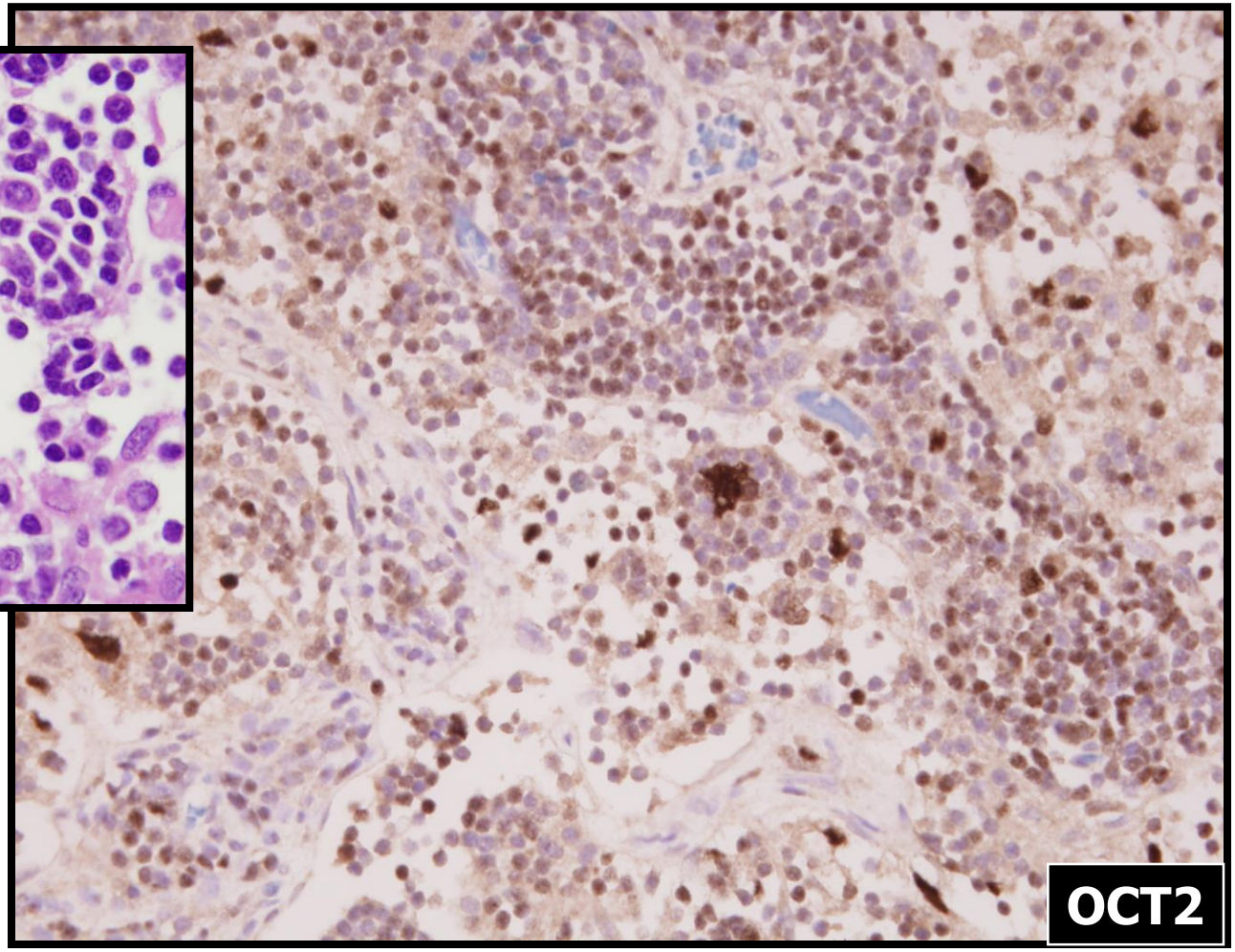
Beware

IgG4 plasma cells can be numerous in RDD

Rosai-Dorfman Disease Displays a Unique Monocyte-Macrophage Phenotype Characterized by Expression of OCT2

Aishwarya Ravindran, MBBS, Gaurav Goyal, MD,†‡ Ronald S. Go, MD,† and Karen L. Rech, MD;* On Behalf of the Mayo Clinic Histiocytosis Working Group*





Am J Surg Pathol
45: 35, 2021

Cyclin D1 is Positive in Rosai-Dorfman Disease

bjh research paper

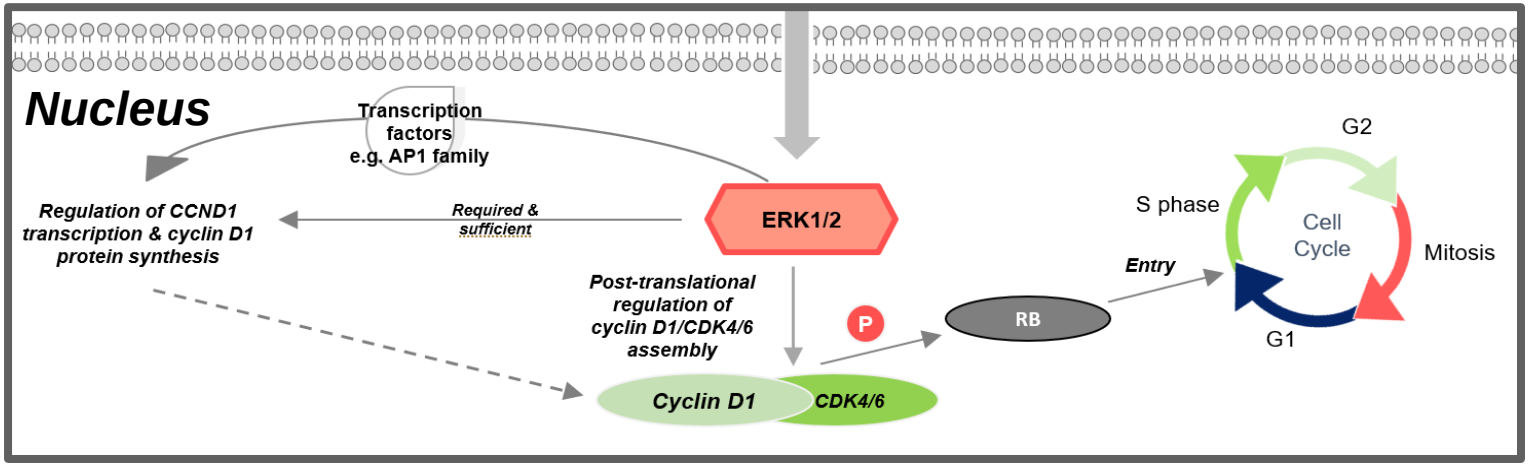
Cyclin D1 expression and novel mutational findings in Rosai-Dorfman disease

Ezra Baraban, Sam Sadigh, Jason Rosenbaum, John Van Arnam, Agata M. Bogusz, Chelsea Mehr and Adam Bagg

Department of Pathology and Laboratory Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA, USA

Cyclin D1 expression in Rosai-Dorfman disease: a near-constant finding that is not invariably associated with mitogen-activated protein kinase/extracellular signal–regulated kinase pathway activation ☆

Sofia Garces MD [a,*], L. Jeffrey Medeiros MD [a], Mario Luiz Marques-Piubelli MD [a,c], Sheila Aparecida Coelho Siqueira MD [c], Roberto N. Miranda MD [a], Branko Cuglievan MD [b], Vathany Sriganeshan MD [d], Ana Maria Medina MD [d], Juan Carlos Garces MD [e], Karan Saluja MD [f], Meenakshi B. Bhattacharjee MD [f], Joseph D. Khoury MD [a], Shaoying Li MD [a], Jie Xu MD, PhD [a], Fatima Zahra Jelloul MD [a], Beenu Thakral MD [a], C. Cameron Yin MD, PhD [a]



Br J Haematol 186: 837, 2019
Hum Pathol 121: 36, 2022

Extranodal Sites Involved by RDD

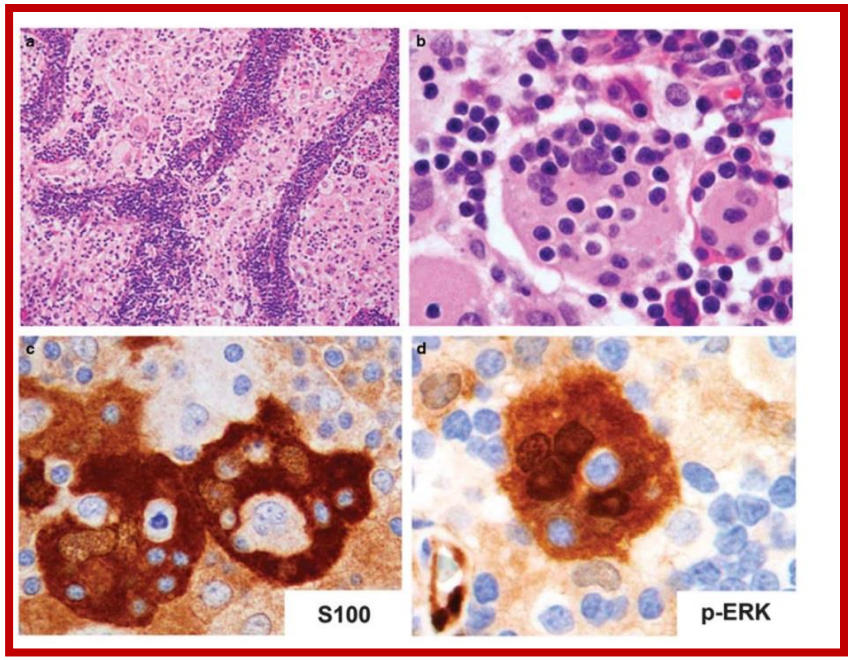
Anatomic Site	Frequency
Nasal cavity and paranasal sinuses	11.3%
Soft tissue	8.9%
Orbit/eyelid	8.5%
Bones	7.8%
Skin	6.8%
Genitourinary system	6.4%
Major salivary glands	5.2%
Central nervous system	4.7%
Oral cavity	2.6%
Lungs, larynx, liver, tonsil, breast, GI tract, thyroid, heart	Each $\leq$ 2%

E. Foucar et al. Semin Diagn Pathol 7:19, 1990

Mutually exclusive recurrent *KRAS* and *MAP2K1* mutations in Rosai–Dorfman disease

Sofia Garces[1], L Jeffrey Medeiros[1], Keyur P Patel[1], Shaoying Li[1], Sergio Pina-Oviedo[1], Jingyi Li[1], Juan C Garces[2], Joseph D Khoury[1] and C Cameron Yin[1]

Sofia Garces, MD



MAP2K1 c.157 T>G p.F53V

7/21 (33%) cases with *KRAS* or *MAP2K1* mutation

All point mutations

KRAS exon 2 (n=2) or exon 4 (n=2)
MAP3K1 exon 1 (n=1) or exon 3 (n=2)

VAF ~ 5%

Mutations correlated with

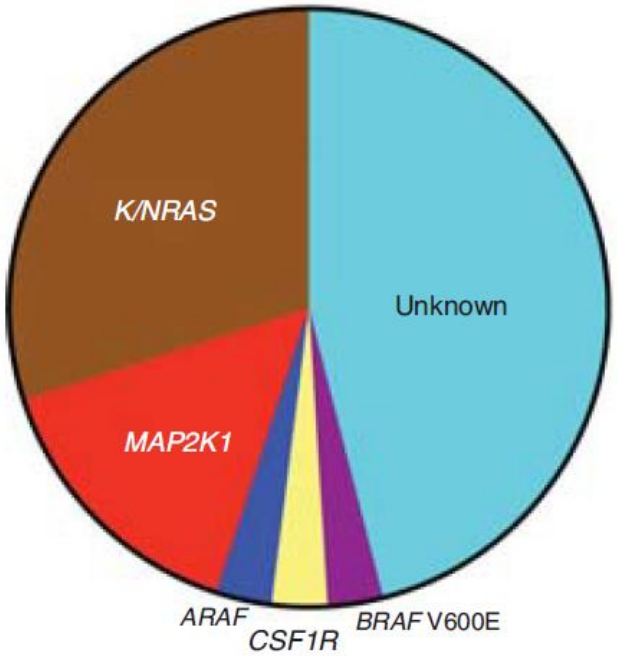
- Head and neck site
- Younger age
- Multifocal disease

No correlation with outcome

Mod Pathol 30: 1367, 2017

MAP-Kinase-Driven Hematopoietic Neoplasms: A Decade of Progress in the Molecular Age

Rikhia Chakraborty,[1,2] Omar Abdel-Wahab,[3,4] and Benjamin H. Durham[3,5]



Rosai–Dorfman–Destombes disease

Cold Spring Harbor Perspect Med 11: a034892, 2021

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Rosai–Dorfman Disease with Activating *KRAS* Mutation — Response to Cobimetinib

Before **After**

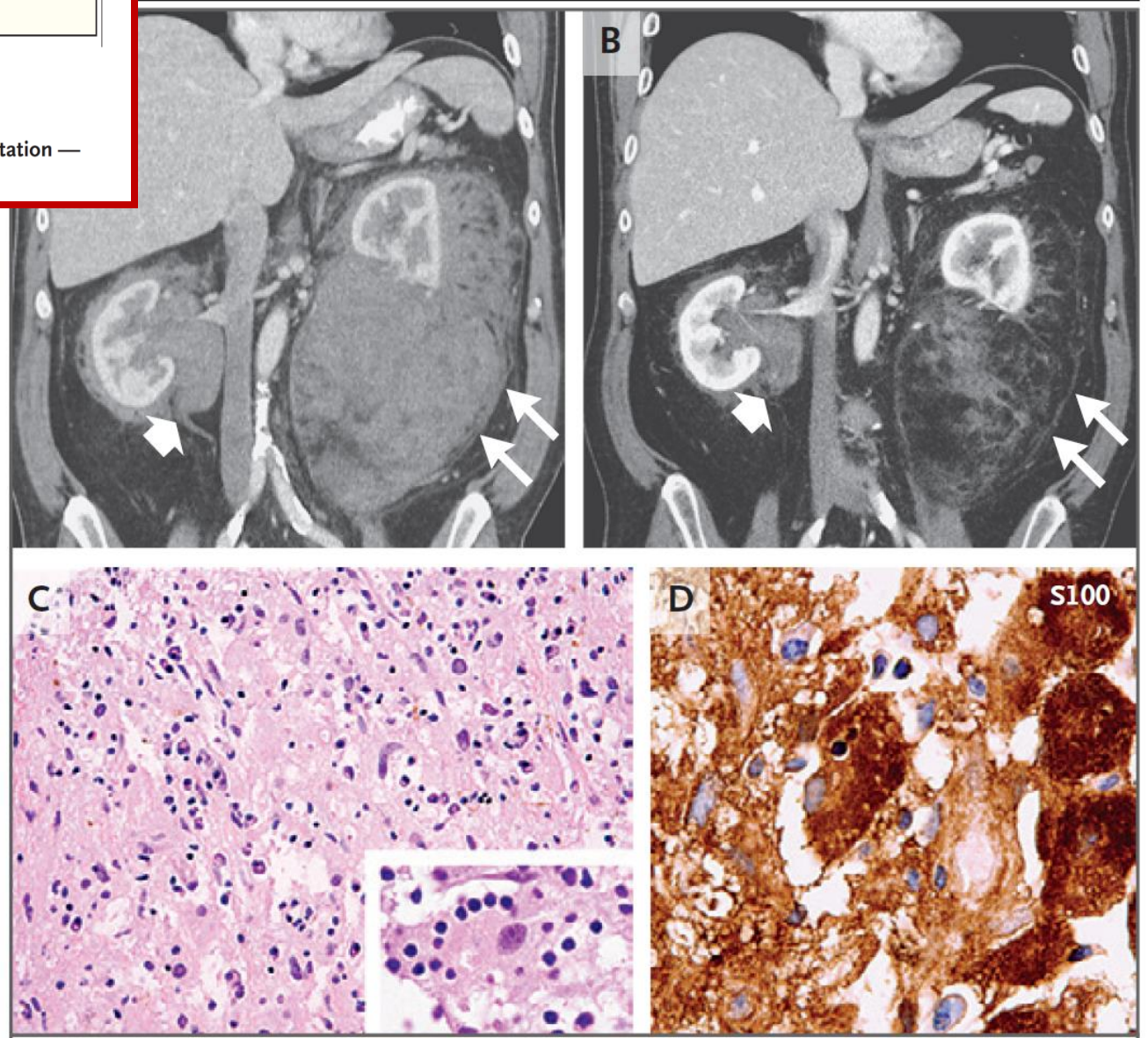
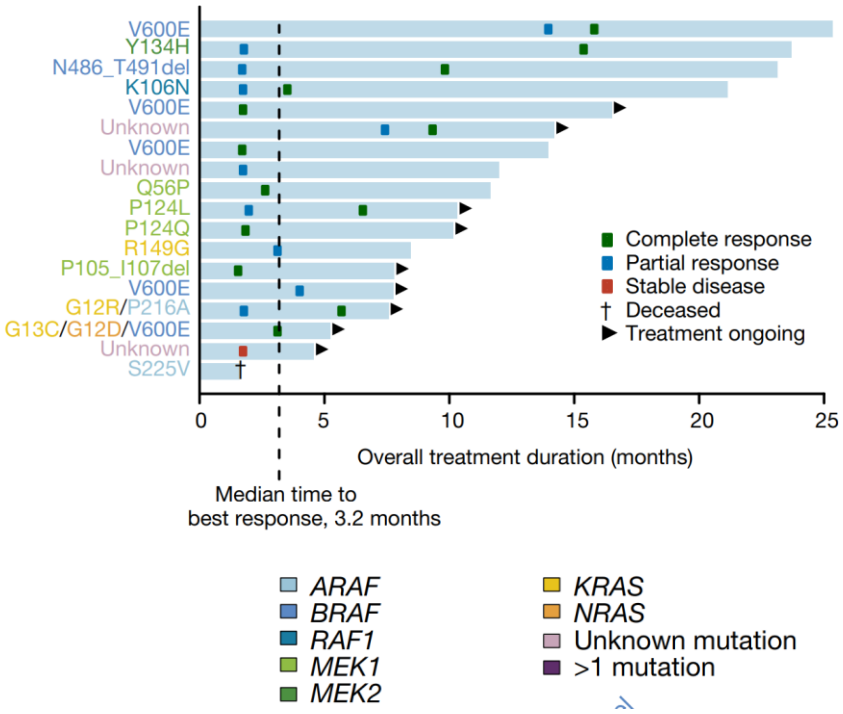
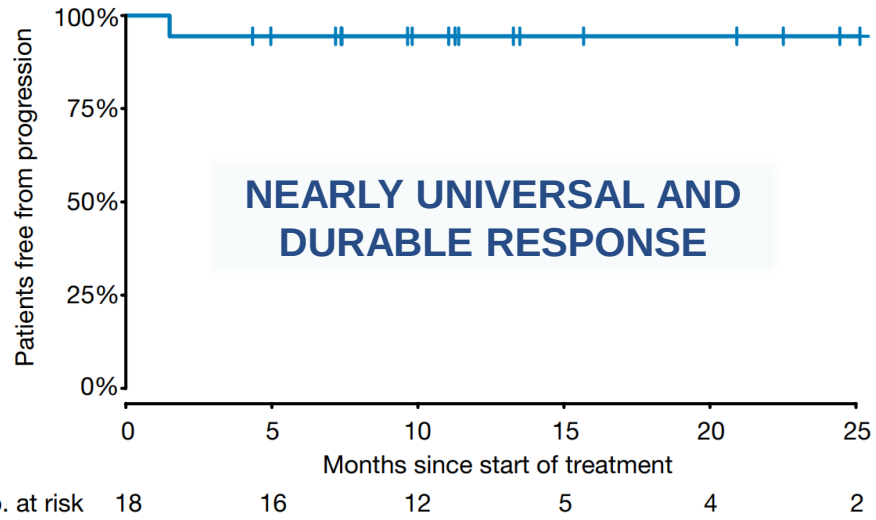


Figure 1. Rosai–Dorfman Disease Associated with a *KRAS* Mutation.

N Engl J Med 377: 2398, 2017

Cobimetinib Granted "Breakthrough Therapy" Designation for Histiocytic Neoplasms by FDA





Nature 567(7749):521, 2019

www.clinicaltrials.gov/ct2/show/NCT02649972