Histiocytosis and the nervous system: from diagnosis to targeted therapies

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Introduction

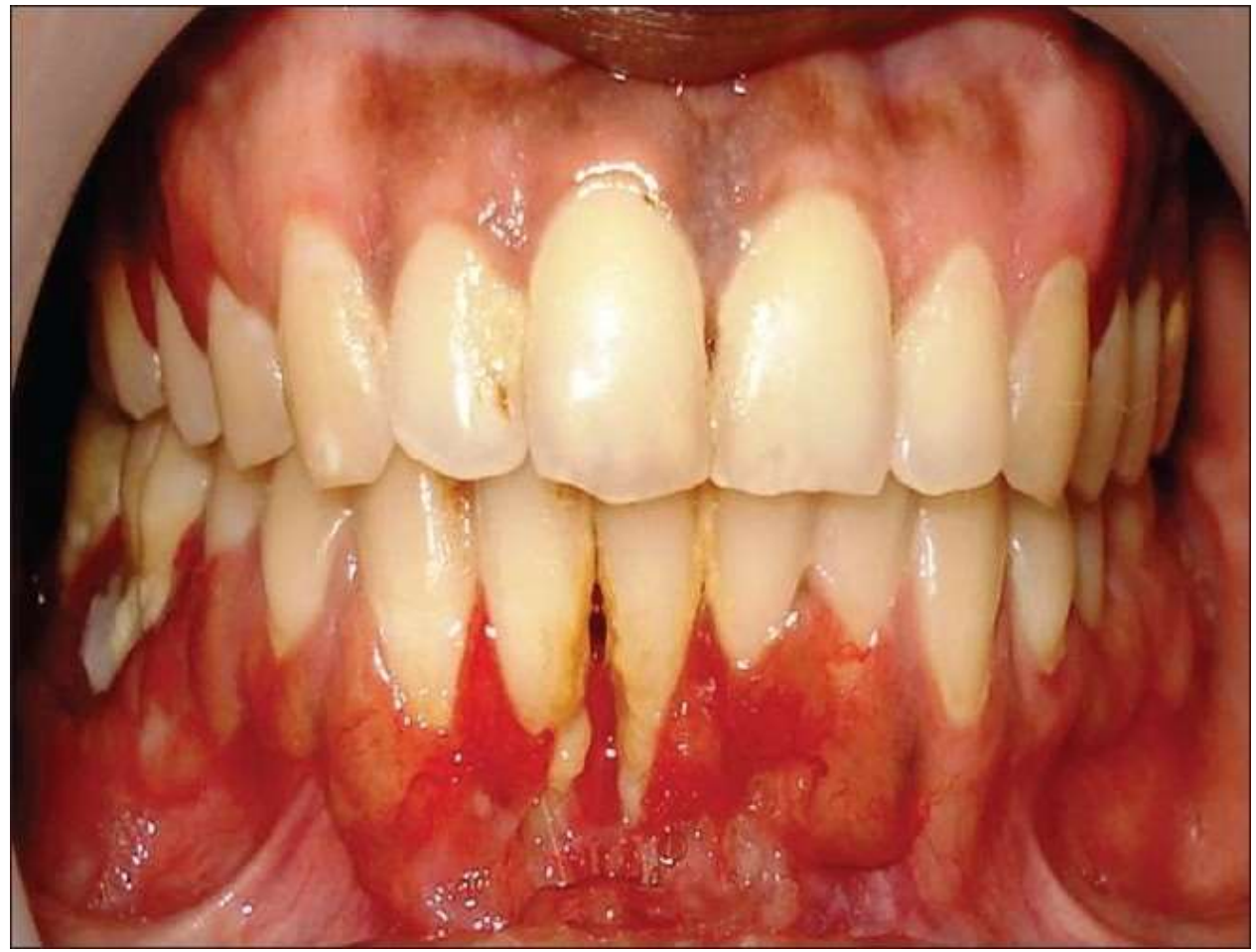
- Histiocytosis are heterogeneous hematopoietic diseases characterized by the accumulation of CD68(+) cells with various admixed inflammatory infiltrates
- The identification of the pivotal role of the mitogen-activated protein kinase (MAPK) pathway has opened new avenues of research and therapeutic approaches.
- Central nervous system (CNS) manifestations occur in 10%-25% of LCH cases, with both tumorous or neurodegenerative forms.

Introduction

- Tumorous or degenerative neurologic involvement occurs in 30%-40% of ECD patients and affects the hypothalamic-pituitary axis,meninges, and brain parenchyma.
- RDD lesions are typically tumorous with meningeal or parenchymal masses with strong contrast enhancement.
- Unlike LCH and ECD, neurodegenerative lesions or syndromes have not been described with RDD.
- Familiarity with principles of evaluation and treatment both shared among and distinct to each of these 3 diseases is critical for effective management.
- Refractory or disabling neurohistiocytic involvement should prompt the consideration for use of targeted kinase inhibitor therapies.

Case presentation

- A 24-year-old male patient was reported to the Department of Periodontics, , with a chief complaint of pain, burning sensation, swelling, and bleeding of the gums.
- Dental and family history were no significant.
- Medical history revealed the previous diagnosis of empty sella and panhypopitutarism and patient was treated with testosterone ,hydrocortisone , fludrocortisone ,levothyroxine, and DDAVP .
- Patient was severe and morbid obesity (170 Kg) and nourished.
- No signs of pallor, icterus, clubbing, cyanosis, and edema were observed.
- No facial asymmetry or temporo mandibular joint (TMJ) abnormalities were detected.
- On clinical examination, the right and left submandibular lymph nodes were palpable and were nontender.
- Gingiva was erythematous and fragile, with missing interdental papilla.



Nikfar Sina,
ID 1400/08/08 - 90

Parto Oral & Maxillofacial Radiology

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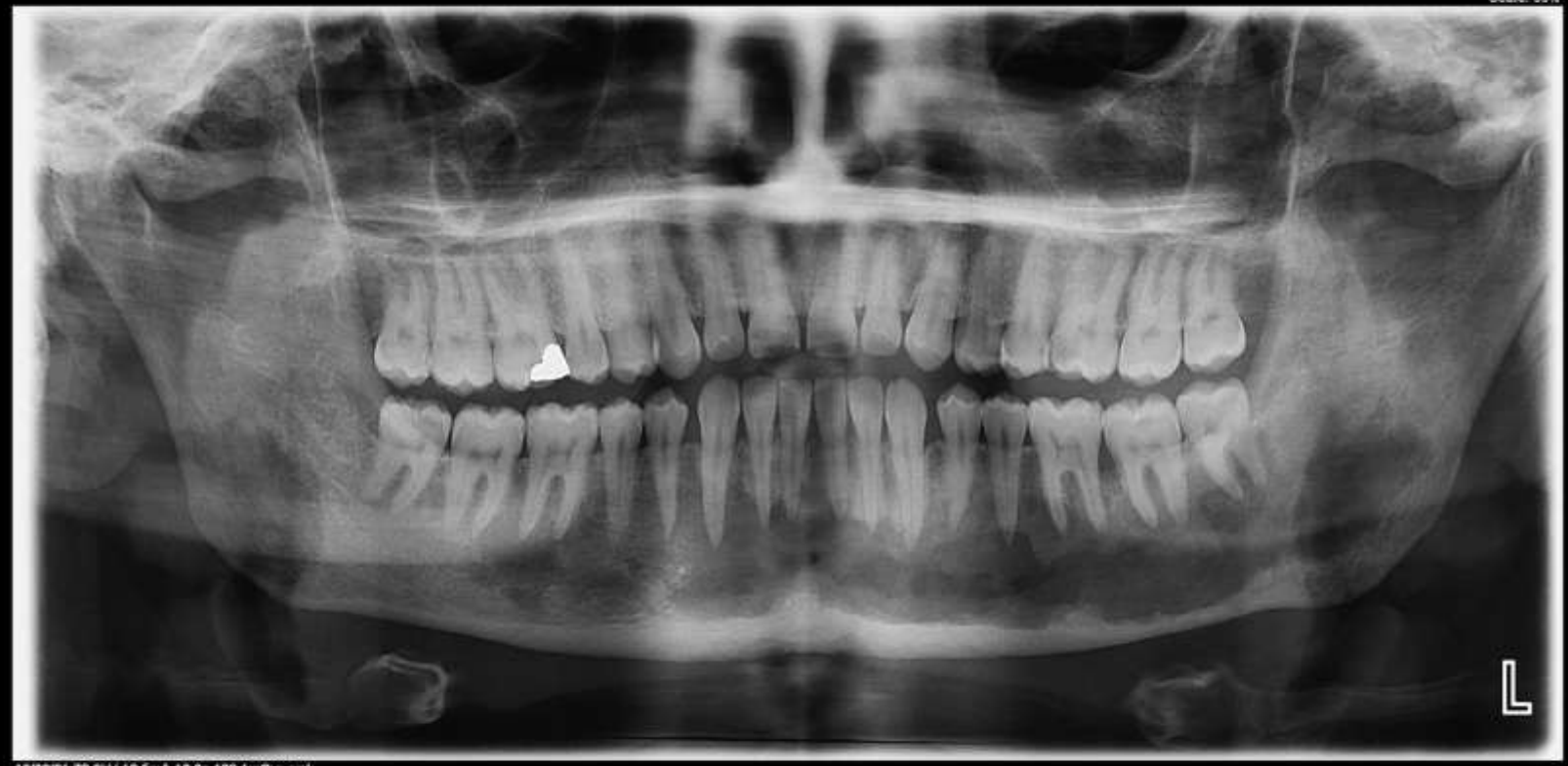

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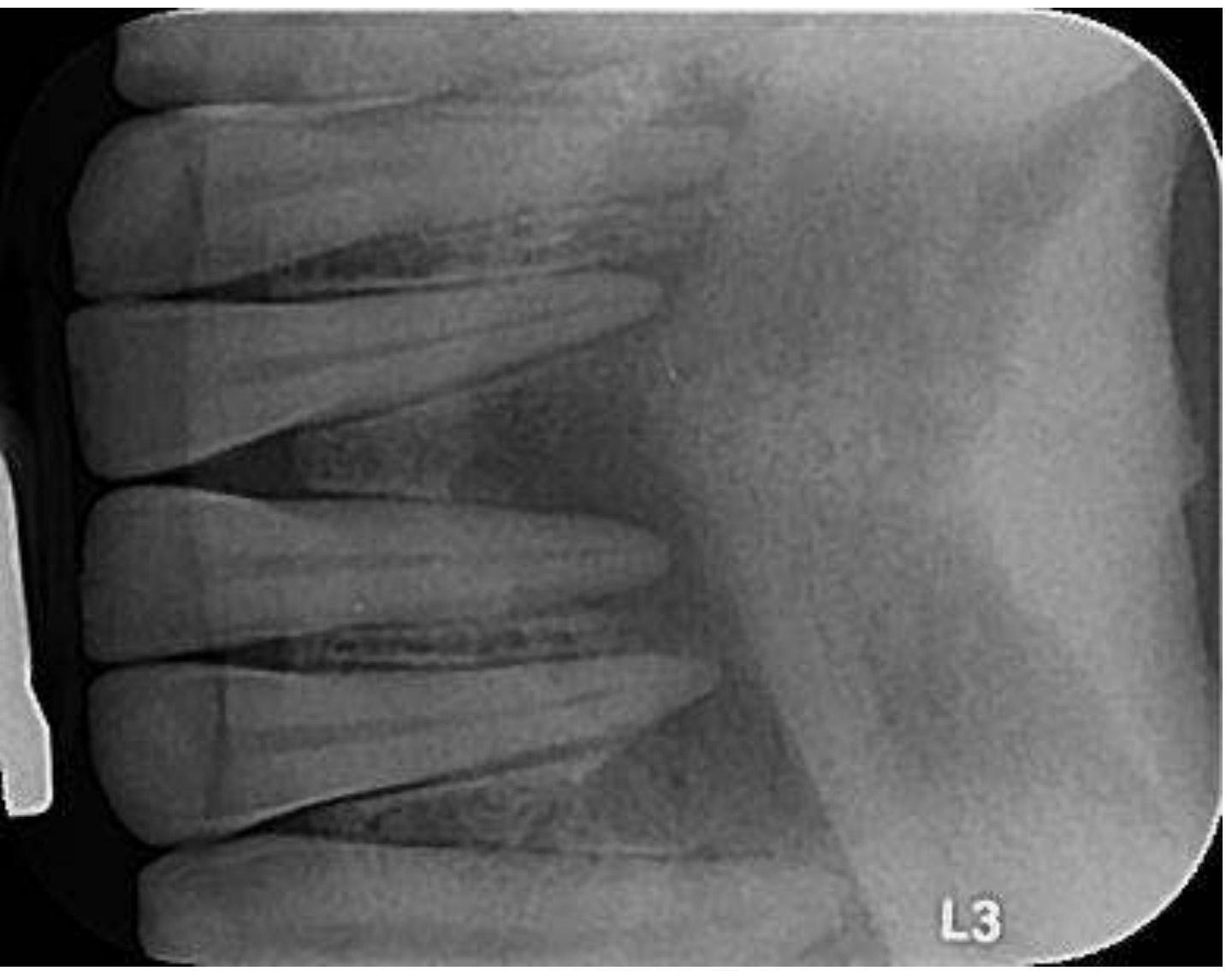
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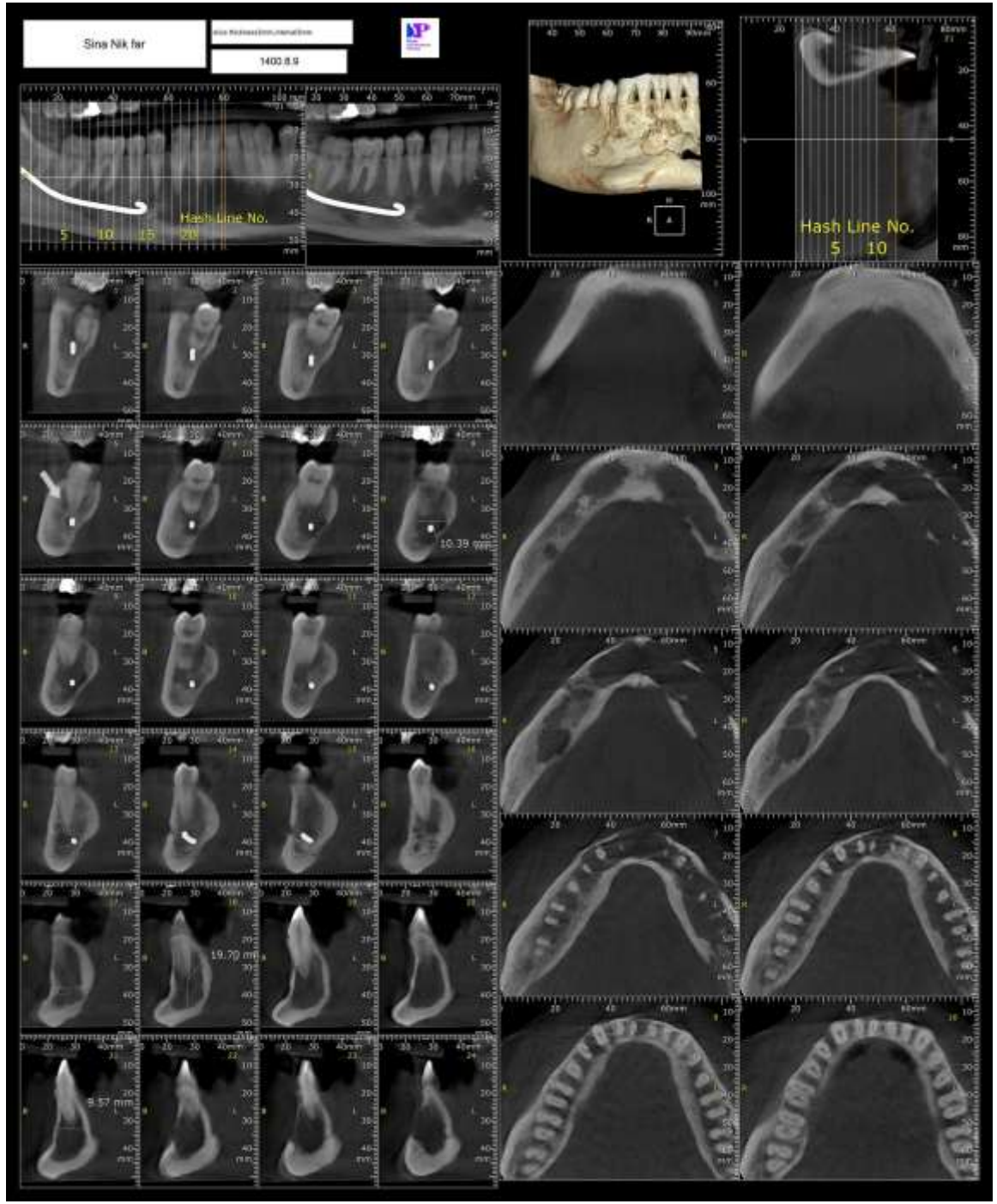
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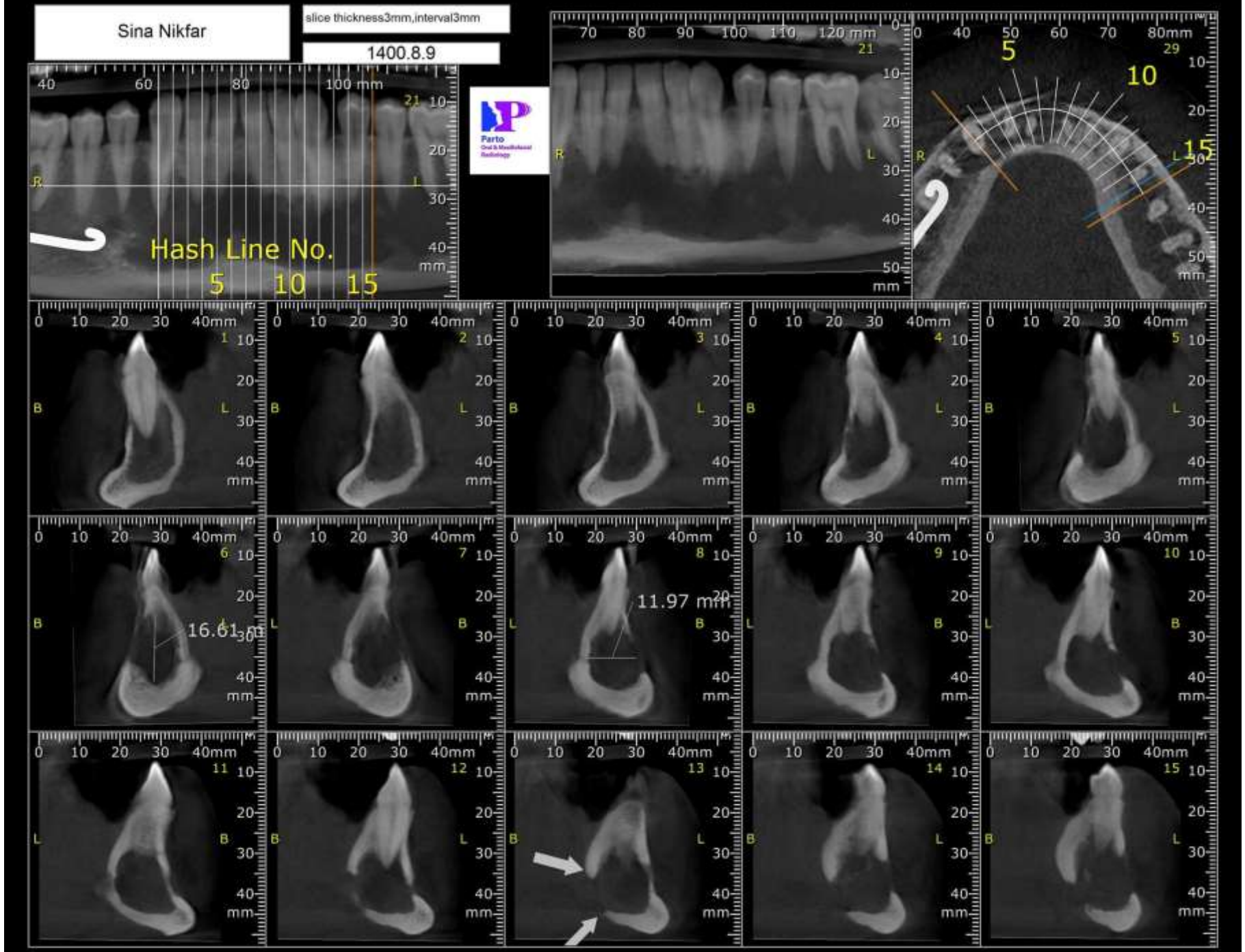
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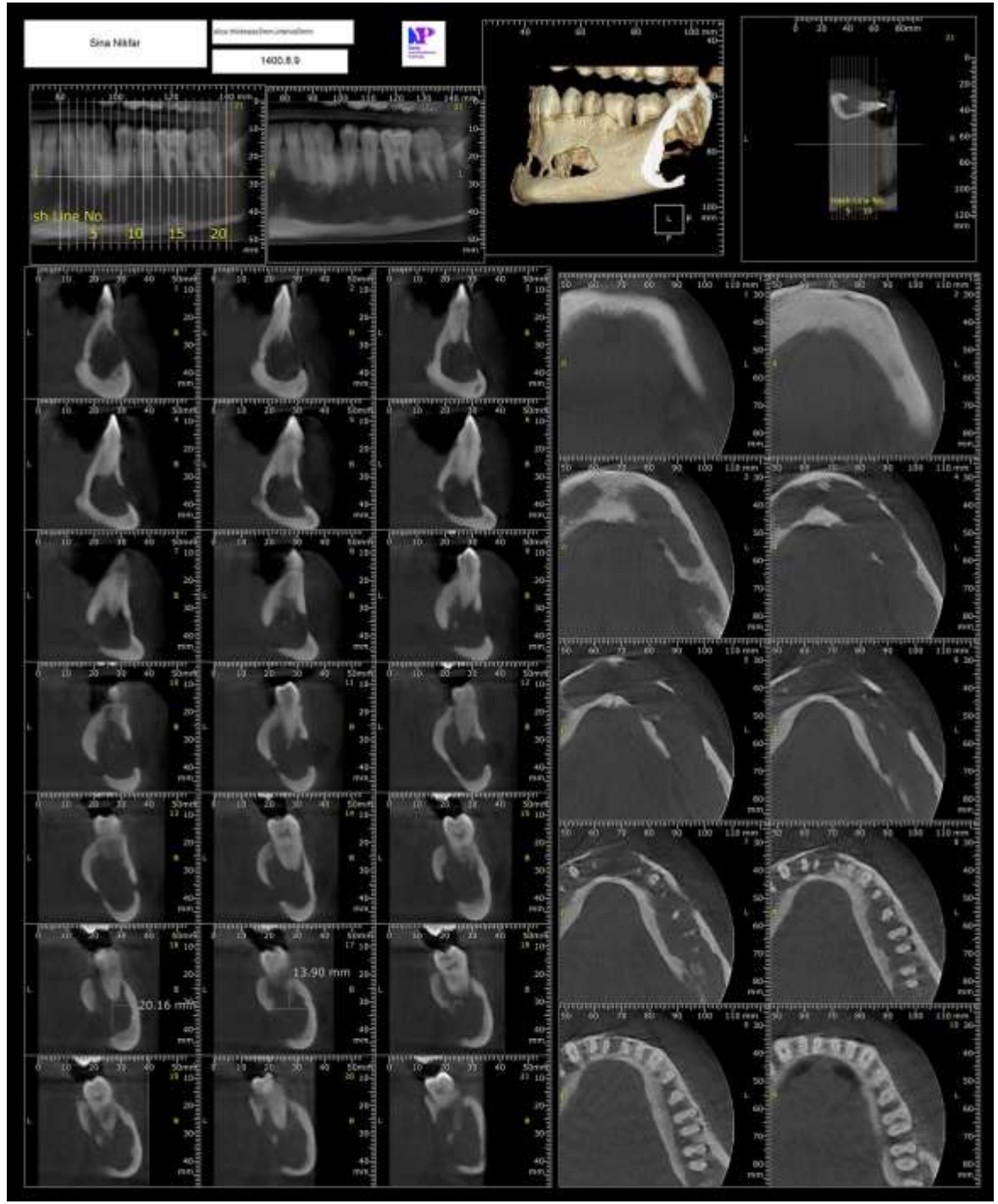
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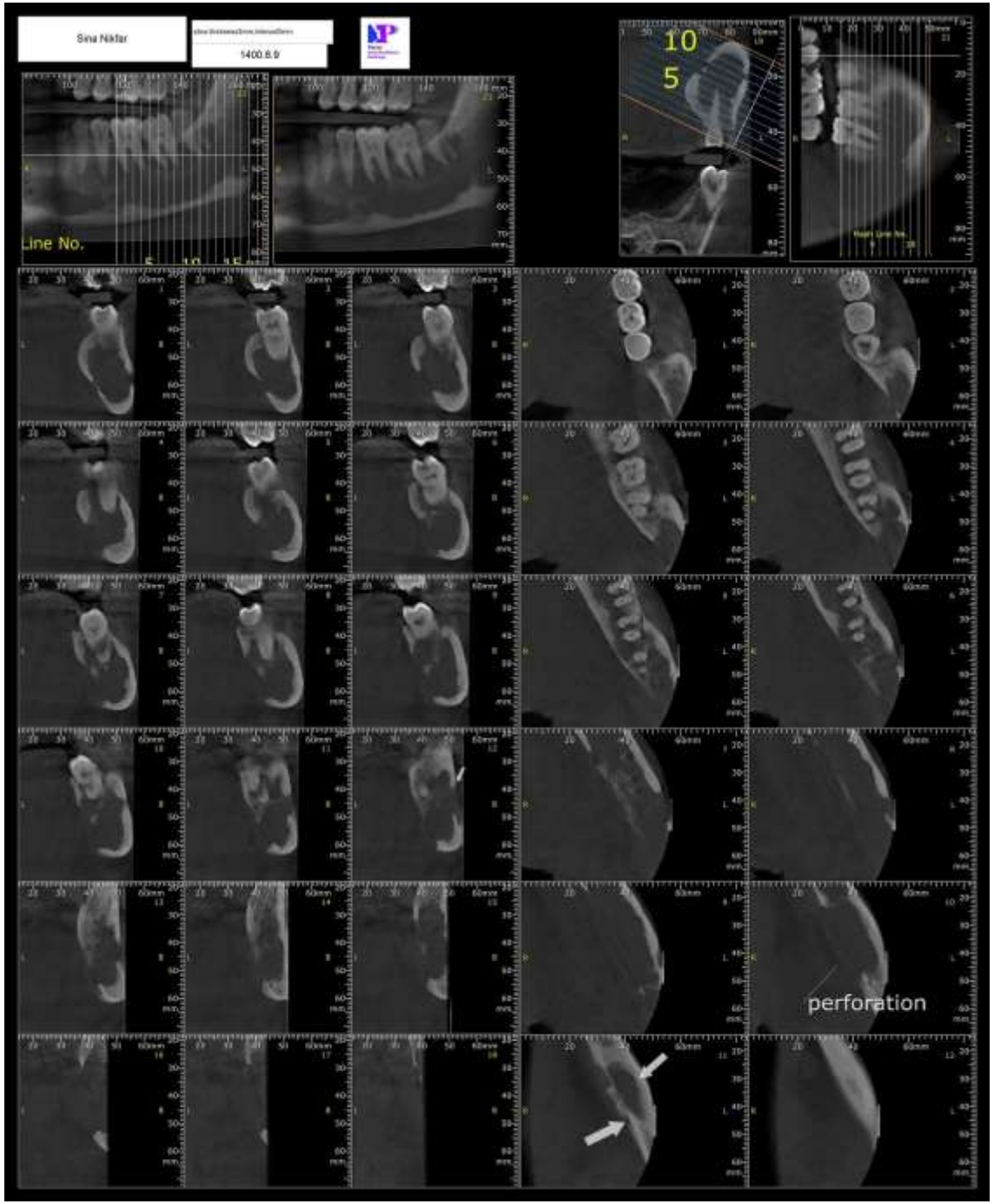
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perforation

Oral examination

- Root surface denudation with grade II furcation involvement .
- On palpation of external surface of gingiva, a yellowish cheesy material was expressed.
- Patient had poor oral hygiene, particularly in the lower anteriors and molar region where the lesions were more inflamed and painful.
- Radiographic examination revealed generalized angular bone loss and furcation involvement

Clinical diagnosis and dental treatment

- Excisional biopsy was performed following administration of local anesthesia.
- Gingival biopsy was sent for histopathological examination
- On the basis of the clinical, general morphology, and the immunohistochemical results, a diagnosis of LCH was made.

دانشکده دندانپزشکی دانشگاه علوم پزشکی شهید بهشتی	فرم جواب ۱.	کد : DS-SAA-FM-20/00 تاریخ بازنگری :

Department of Oral and Maxillofacial Pathology

Patient's Name	سینا نیک فر	Lab. No	1400-171	Physician's Name	دکتر محمد میر صادقی
Patient Record No	67580	Date of report	1400/08/29	Referring Department	خصوصی
Age	24	Received Date	1400/08/24	Site of Biopsy	mandible
Sex:	M■ F□				

Clinical Diagnosis

1 .Ameloblastoma
2 .Myxoma

x-ray features

A well- defined radiolucent lesion with scalloped borders in mandible, extended 7 to left ramous which caused root resorption ,thinning of buccal and lingual cortex and perforation of lingual cortex in left side.

Gross Description

Specimen received in formalin consists of multiple pieces of irregular creamy-gray elastic tissue, totally measuring 1x0.9x0.3cm. In cut surface is solid ,homogeneous and creamy.
S.O.S:M/1 T.S.S

Microscopic Description

Sections show a diffuse infiltration of large pale staining cells like histiocytes with indented and numerous number of eosinophils in fibrous background . chronic cells infiltration , sections of nerve bundles, muscle fibers, hemorrhage and curetted bone are also evident.
IHC study demonstrated:
CD-207:strongly positive (+++)
CD-1a:scattered positive (++)
S-100:patchy positive (+)

Dx

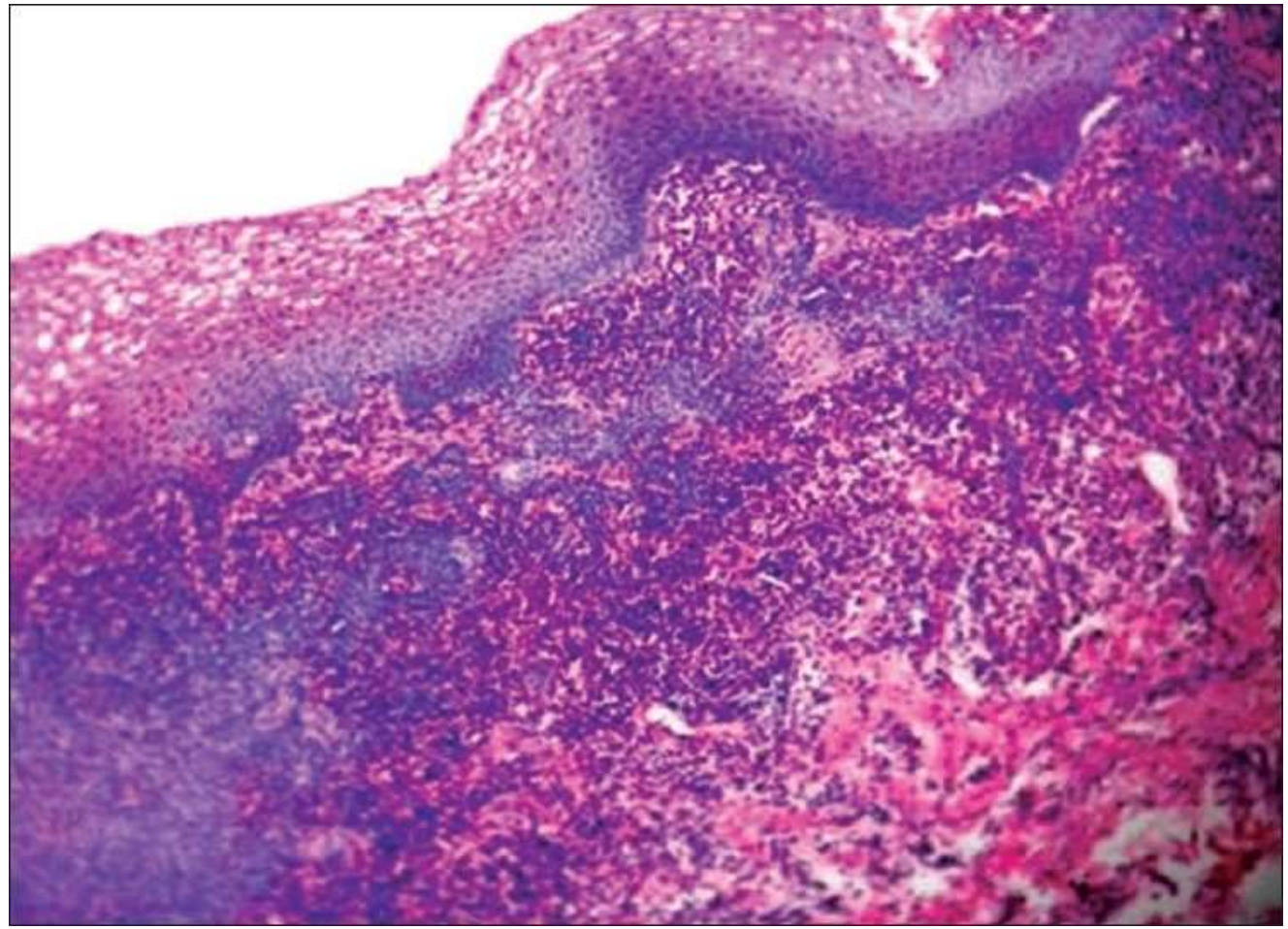
Mandible ,area of 7 to left ramus ,incisional biopsy:
Due to IHC staining:
Langerhans cell histiocytosis

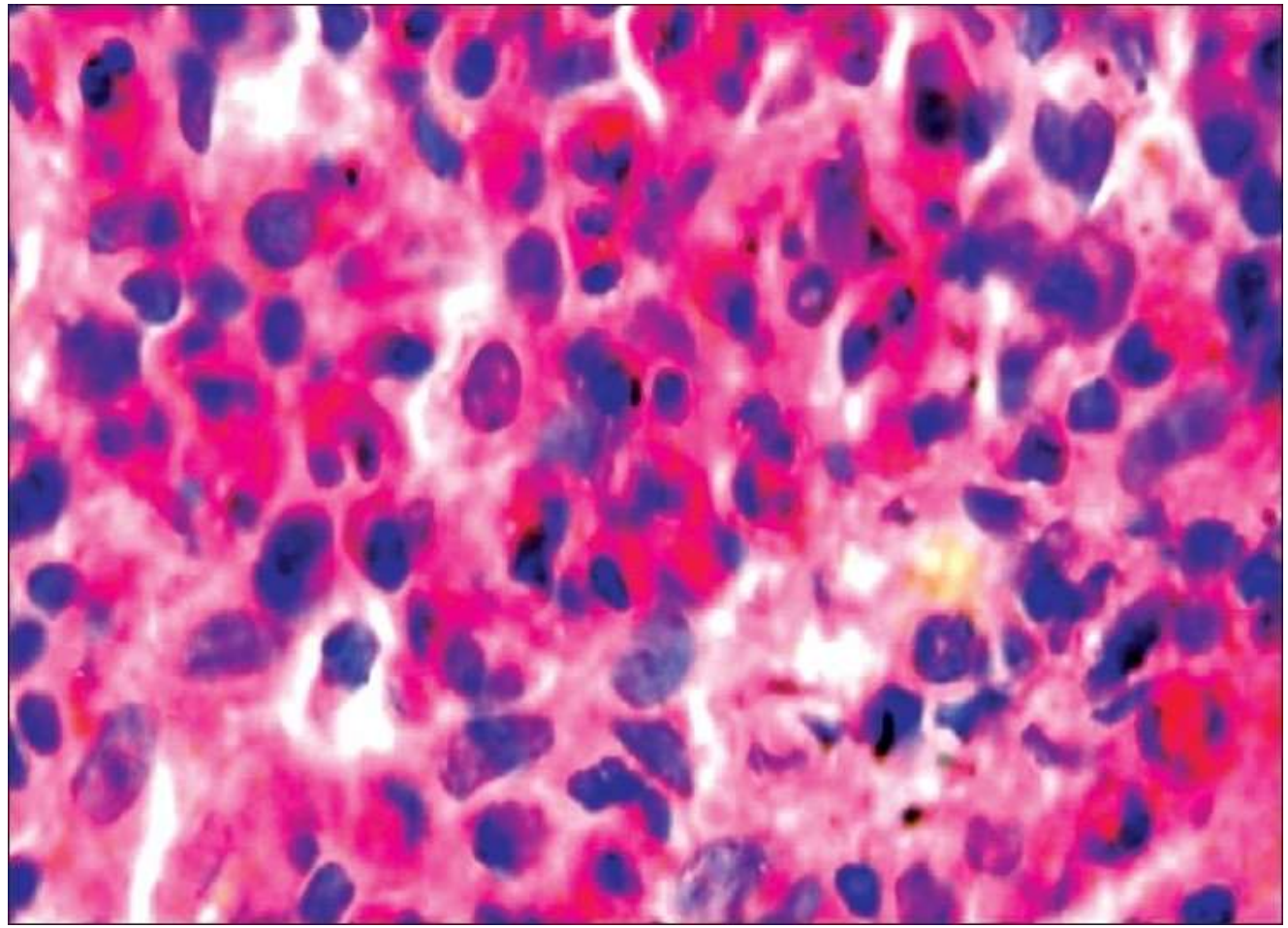
Note

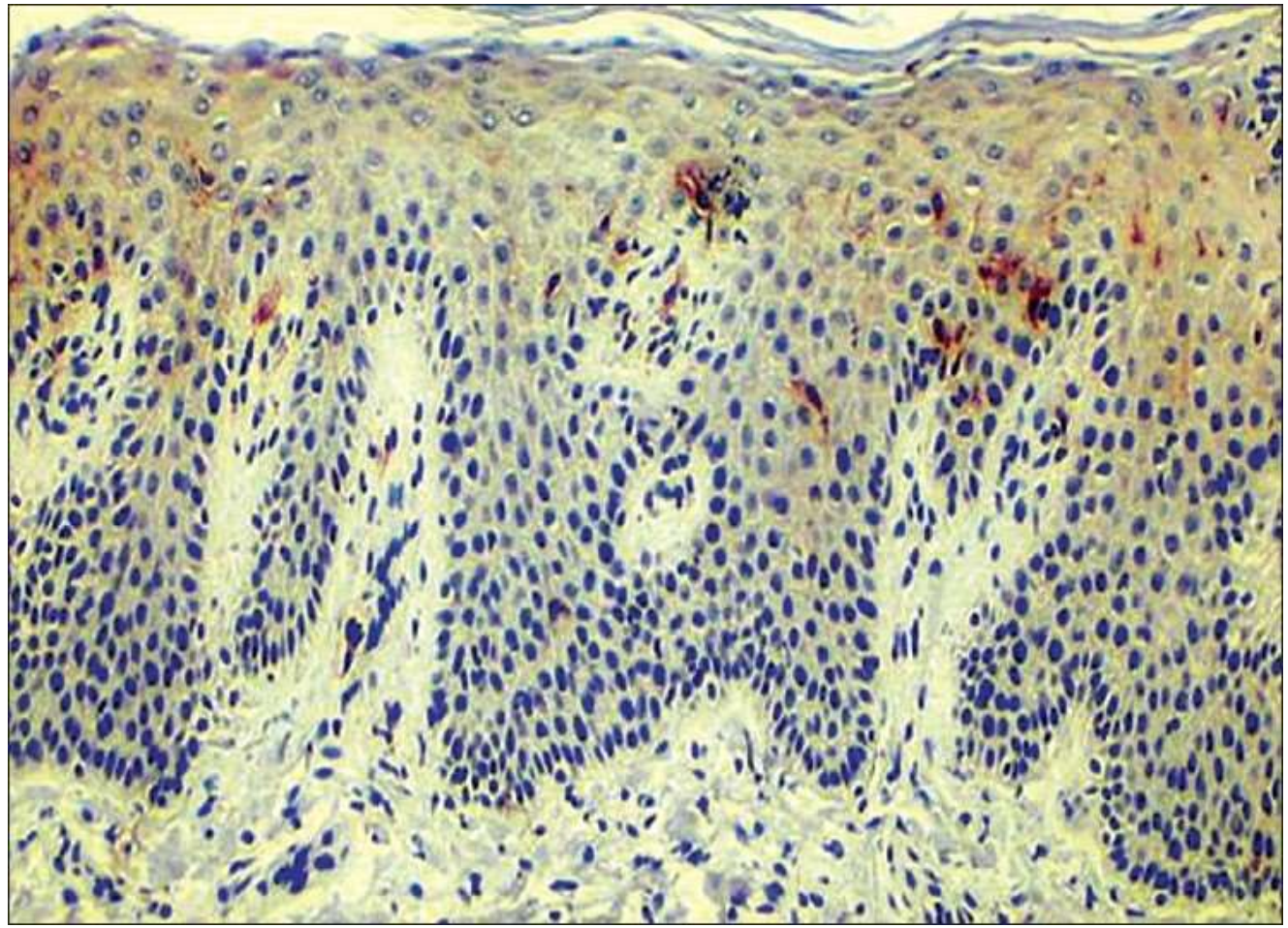
پاتولوژیست: دکتر غلامی

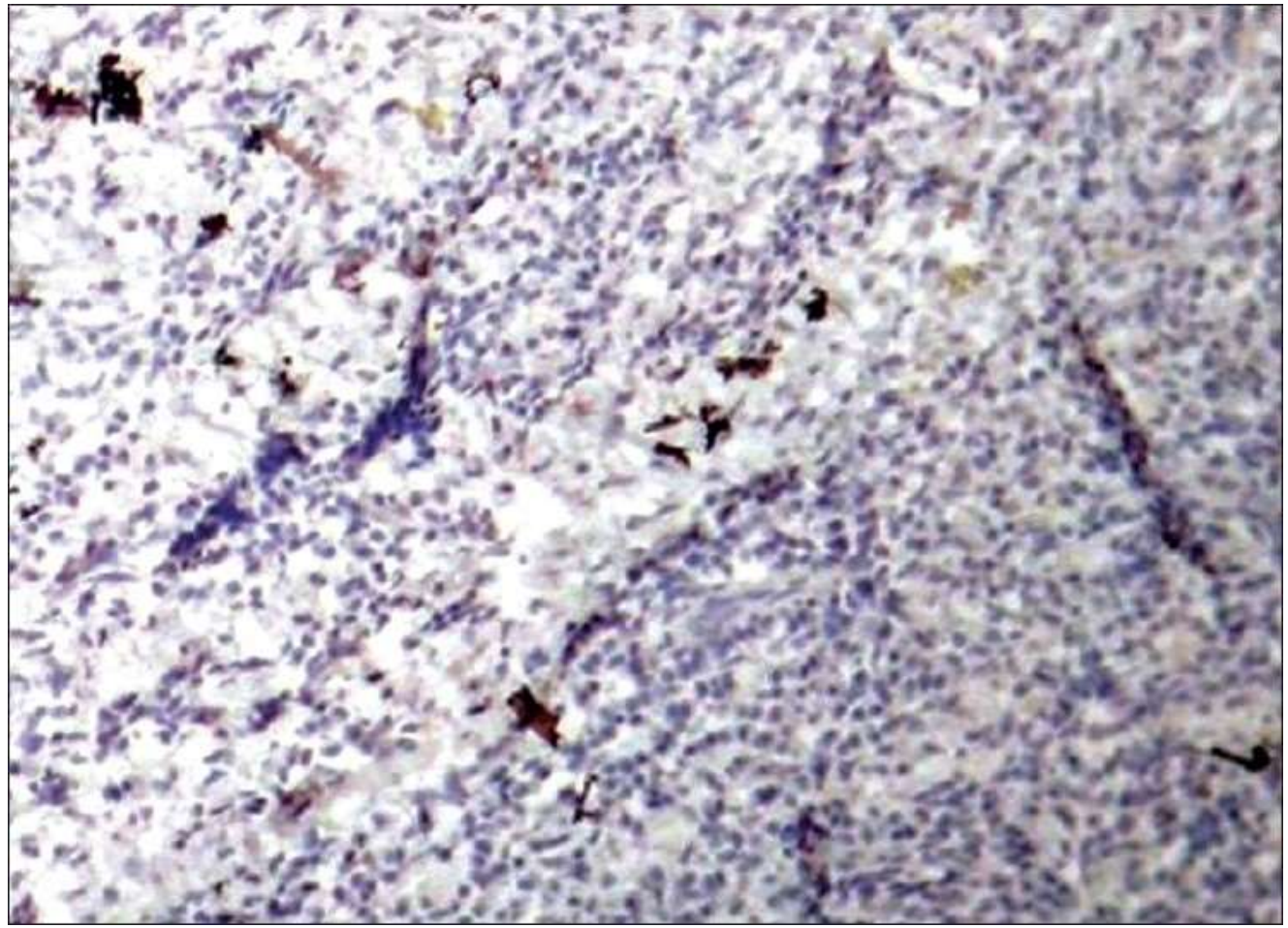
پاتولوژیست: دکتر مشهدی عباس

رزیدنت :









Work-Up

- Laboratory parameters were hypochromic microcytic blood picture with neutrophilia.
- Chest X-ray and skull-PA showed lytic lesions and ultrasound test of the abdomen showed normal-sized spleen and fatty liver grade III.

موسسه تحقیقات پزشکی هسته ای
و تصویر برداری مولکولی

Research Institute for Nuclear Medicine and Molecular Imaging

Shariati Hospital

دانشگاه علوم پزشکی و خدمات
بهداشتی درمانی تهران

Patient Name : Mr.S.Nikfar
Age : 24 Y
Ref Physician :
Date of exam : 1400/09/03

WHOLE BODY BONE SCAN

Procedure :

Three hours after IV injection of 20 mCi Tc-99m-MDP, whole body scintigraphy was performed on the anterior and posterior projections.

Description :

SPECT/CT and planar images show multiple lytic lesions with increased tracer uptake in the mandible, bilateral frontal, and parietal bones, as well as right temporal, orbital, zygomatic and the right side of the sphenoid bones. There is also evidence of sphenoid and mastoid sinuses involvement. Additionally, there is increased uptake in the distal parts of both femora and along bilateral tibiae and fibulae. No other remarkable abnormality is noted in the rest of the skeleton.

Interpretation :

- Osteoblastically active tumoral bone lesions in the skull, facial bones, mandible and bilateral lower extremities.
- The scan pattern is suggestive of Erdheim chester disease. For evaluation of the visceral involvement FDG-PET/CT is recommended.

R.Manafi-Farid,MD

N.Yavari,MD

Ferdous
مرکز پزشکی هسته ای فردوس
Nuclear Medicine Center
PET/ CT Unit

Patient's Name: SINA NIKFAR
Gender: Male
Age: 24 Y/O
Exam Date: 12/01/2021(m/d/y)

شماره پذیرش: [illegible]
نام بیمار: نیکفر سینا
جنسیت: مرد
سن: ۲۴
تاریخ اسکن : ۱۴۰۰/۰۹/۱۰ ۰۰:۲۴
جناب دکتر : میرمحمدصادقی - حسن

PET/CT FROM VERTEX TO MID-THIGH
With Discovery 690 GE (General Electric), 64 Slice CT & Time-of-flight (ToF)

HISTORY: Others (histiocytosis)
QUESTION: Initial Staging

TECHNIQUE:

Sixty minutes following administration of 370 MBq of FDG intravenously a partial body integrated PET-CT scan from vertex to proximal thighs was acquired. Sections were reconstructed in three standard orthogonal planes.
For anatomic referencing and for transmission correction purposes an unenhanced low dose CT was acquired and fused images were also generated.

BRAIN:

Mildly hypermetabolic lytic lesions in the right parietal and left frontal and sphenoid bones are seen.
Communicating hydrocephaly is noted.
Increased metabolic activity in the sellar region is seen. Correlation with MRI is recommended.
There is no midline shift or intracranial hemorrhage. The lateral ventricles are normal. The cerebellum and brainstem are intact. The basal cisterns are patent.

NECK:

Prominent hypermetabolic palatine tonsils are seen.
Mildly hypermetabolic bilateral cervical adenopathies are noted.
Bilateral hypermetabolic lytic lesions in the mandible are seen (SUV max up to 12.8). Please refer to the images.
Hypermetabolic opacity in left ethmoid sinus is also detected.
The major salivary glands of the neck are normal. The epiglottis & aryepiglottic folds, true & false vocal cords, and supra & subglottic airways are intact. The thyroid lobes have normal size & texture.

Patient's Name: SINA NIKPAR
Gender: Male
Age: 24 Y/O
Exam Date: 12/01/2021(m/d/y)

نام بیمار: نیکفر_سینا
جنسیت: مرد
سن: ۲۴
تاریخ اسکن : ۱۴۰۰/۰۹/۱۰ ۰۰:۲۴
جناب دکتر : میرمحمدصادقی - حسن

CHEST:

Lung fields are clear and no parenchymal infiltration is noted. No evidence of hilar or mediastinal adenopathy is seen. No mass lesion is detected. No evidence of pleural effusion is seen. Chest wall is unremarkable. Heart size is normal. Physiological FDG-uptake of the heart is noted.

ABDOMEN & PELVIS:

The liver has normal size. There is no intra or extrahepatic bile duct dilatation.
The spleen and pancreas are intact. The kidneys and adrenal glands are normal.
The abdominal aorta is normal in caliber.
There is no lymphadenopathy within the abdomen.
The visible genital organs are normal. Rectum & pararectal fossa are intact. The visualized bowel loops are normal.
There is no lymphadenopathy within the pelvis.
Physiological FDG-uptake of the kidneys and the bladder are seen.

MUSCULOSKELETAL:

Mildly hypermetabolic lytic lesions in the right parietal and left frontal and sphenoid bones are seen.

Bilateral hypermetabolic lytic lesions in the mandible are seen (SUV max up to 12.8). Please refer to the images.

Heterogenous increased metabolic activity in bilateral tibia and femurs are seen. Given the history of langerhans histiocytosis findings can be related to histiocytic infiltration.

CONCLUSION:

- **Hypermetabolic lytic lesions in the mandible, right parietal, left frontal and left sphenoid bones**
- **Hypermetabolic opacity in left ethmoid sinus**
- **Increased metabolic activity in the sellar region. Correlation with MRI is recommended.**
- **Heterogenous increased metabolic activity in bilateral tibia and femurs. Given the history of langerhans histiocytosis findings can be related to histiocytic infiltration.**

ed by: --1400/09/10 10:07

yam Mehrian M.D
sociate Professor of Radiology
T-CT Fellowship

Abtin Doroudi-Nia M.D
Assistant Professor of Nuclear Medicine
PET-CT Fellowship

M.R.I
SEMNAN MEDICAL IMAGING CENTER
مرکز تصویربرداری پزشکی سمنان

نام بیمار: سینا نیکفر
کد پذیرش: 93352
تاریخ جواب: 1399/06/15
نام پزشک: دکترهادي نجمی
سن بیمار: 23 سال

Axial Spiral CT-Scan of Brain without contrast media **demonstrates :**

In axial sections obtained from brain in soft tissue window, parenchymal pattern is normal.
Left lateral ventricle is dilated.
3th and both lateral ventricle are dilated (more prominent in left side). no obstructing agent in ventricular system is seen.
There is evidence of small mass like lesion isointense with CSF about 2.5 cm in diameter in left temporal lobe which could be due to arachnoid cyst . correlation with clinical and MRI finding is recommended.
No mid line shift is seen.
Posterior fossa and cerebellar hemisphere appear normal bilaterally.
There is evidence of about 2 cm in diameter a bony lesion in skull bone in right temporoparietal area .

Axial Spiral CT-Scan of Orbit without contrast **demonstrates :**

Left eye proptosis is evident. clinical correlation is recommended.
There is no evidence of mass lesion in left orbit. ais muscle and optic nerves appear normal bilaterally.
There is no evidence of bony lesion in both orbits .

yours sincerely
B.movasseghi M.D Radiologist

دکتر بهزاد موثقی
متخصص رادیولوژی و سونوگرافی
فلوشیپ فوق تخصصی اینترونشن و ام آر آی
نظام پزشکی ۴۳۹۱۱

Code : 776770 Age : سال 55

Name : مستخدمين حسيني ليلا Date : 1397/04/20 17:42

مرکز تصویربرداری پزشکی
دکتر محمد اطهری
DR.ATHARI medical imaging center

Dear Dr. SANAEIHA

Coronal Spiral CT-Scan of Paranasal sinuses without contrast media

Findings :

Evidence of mild mucosal thickening is seen at maxillo-ethmoidal sinuses .
Both osteomeatal complexes are open .
Nasal septal deviation is seen with concavity toward right side .
Nasal turbinates are normal .
Nasal spur is seen at left side

YOURS SINCERELY
B.SHEKARCHI , CONSULTANT RADIOLOGIST

Shekarchi.babak@Yahoo.com

دکتر بابک شکارچی
رادیولوژیست
متخصص MRI، سی تی اسکن و رادیولوژی

تهران ، خیابان استاد مطهری ، خیابان فجر ، روبروی بیمارستان جم
No. 35-33 , Nazari Alley , Fajr St , Motahari St .Tehran . Iran

ofoq
medical imaging center

مرکز جامع تصویربرداری پزشکی افق

شماره: ۱۳۹۵/۰۵/۲۴
تاریخ: _____
پیوست: _____

نام بیمار : آقای سینا نیکفر

همکار گرامی - -

BRAIN MRI (with and without contrast):

MR study of brain with axial T1,T2,Flair w and sagittal T2/w and coronal T2/w were Performed.

There is cerebral atrophy for his age.

There is dislocation of cisterns and ventricles.

There is not space occupying lesion in supra and infratentarial structures.

White and gray matter signal intensity, basal ganglia and cerebral ventricles are normal without mass lesion.

Brain stem, posterior fossa and C.P angles structures are seen in normal appearances.

Orbit and chiasma are unremarkable.

Interhemispheric line is shown in midline and undisplaced.

In POST GD-DTPA T1/W images, any abnormal enhancement was not seen.

DYNAMIC PITUTARY MRI (WITH & WITHOUT CONTRAST):

MR study of pituitary gland with dynamic injection were obtained in Sagittal and coronal T1, T2/w images.

There is empty sella.

Any focal abnormality is not seen.

The pituitary stalk lies in midline and optic chiasm is undisplaced.

Other structures are of normal appearance.

After GD-contrast media (IV), any abnormal enhancement is not seen.

Dr.Vahedi

مرکز جامع تصویربرداری پزشکی افق
دکتر محمد ابراهیم واحدی
۲۶۷۷۵
متخصص رادیولوژی - سونوگرافی - ۶۰ سی تی اسکن
تهران

نارمک - خ شهید آیت - بالاتر از چهارراه تلفنخانه - بعد از خ چمن - پ ۴۰۹ ط همکف
تلفن : ۷۷۹۱۱۷۶۰ تلفکس : ۷۷۹۰۱۵۸۱ پست الکترونیکی : ofoqtp86@yahoo.com

Code : 776768 Age : 21 سال

Name : نیکفر سپنا Date : 1397/04/20 17:46

مرکز تصویربرداری پزشکی
دکتر محمد اطهری
DR.ATHARI medical imaging center

Dear Dr. GHOLI POOR

MRI OF BRAIN WITH AND WITHOUT CONTRAST INJECTION:

Multiplanars and multisequentials images reveal:

Dilatation of ventricular system mainly involving both lateral ventricles is seen.
Gray and white matter differentiation is normal.
Brain stem and cerebellum appear normal.
CP angles are normal.
No evidence of infarct or demyelinating disease process is seen.

MRI OF PITUITARY GLAND WITH AND WITHOUT CONTRAST MEDIA

Technique: *Sag T1WI. Post Gd Sag and Coronal T1WI.*

Findings:
Sign of partially empty of sella is seen.
Enlargement of sella is seen contains CSF intensity material.
Thin layer of adenohypophysis is seen along roof of sella.

YOUR SINCERELY
SHEKARCHI.M.D.RADIOLOGIST
Shekarchi.babak@Yahoo.com

دکتر بابک شکارچی
رادیولوژیست
MRI، سی تی اسکن، سونوگرافی

تهران ، خیابان استاد مطهری ، خیابان فجر ، روبروی بیمارستان جم
کوچه نظری ، پلاک های ۳۳ و ۳۵ (شرکت نسیم سحر اطهر)
تلفن : ۶ - ۸۸۸۳۲۸۶۴ و ۸۸۸۳-۳۲۶ فکس : ۸۸۸۲۷۵۶۱ تلگرام : ۰۹۰۱۳۷۲۵۲۵۲

No. 35-33 , Nazari Alley , Fajr St , Motahari St .Tehran .
(Naseem Sahar Athar Co.) Tel : + 9821 888326
Fax : + 9821 88827561 Telegram : + 98 901 374
www.atharimd.c

Partolab
PATHOLOGY & GENETICS

پرتولب

Patient: آقاي سينا تيک فر Sex: Male Age: 24 Y	Referred By: دکتر عزيزي محمدرضا Lab. Ref. No.: M-1400-2807 - Lab Receipt: O-16674	Date Received: 1400/09/16 Date Reported: 1400/09/20

Clinical data

Requested for BRAF mutation.

Specimen

FFPE tissue block including 30% tumor (ID: 00-171)

Method

Genomic DNA was extracted by QIAGEN FFPE DNA kit and V600E mutation of BRAF gene was checked by PCR-Pyrosequencing method.

Test Result

Mutation has been identified in BRAF oncogene.

Cautions

Test results should be interpreted in context of clinical findings, sampling, and other laboratory data. If results obtained do not match other clinical or laboratory findings, please contact the laboratory for possible interpretation. Misinterpretation of results may occur if the information provided is inaccurate or incomplete. Every molecular test has a 0.5-1 % error rate. This is due to rare molecular events and factors related to the preparation and analysis of samples.

If specimen has not been collected in Partolab we won't accept any responsibility of patient's identity because improper labeling, handling and storage or delayed delivery may cause inaccurate or false results.

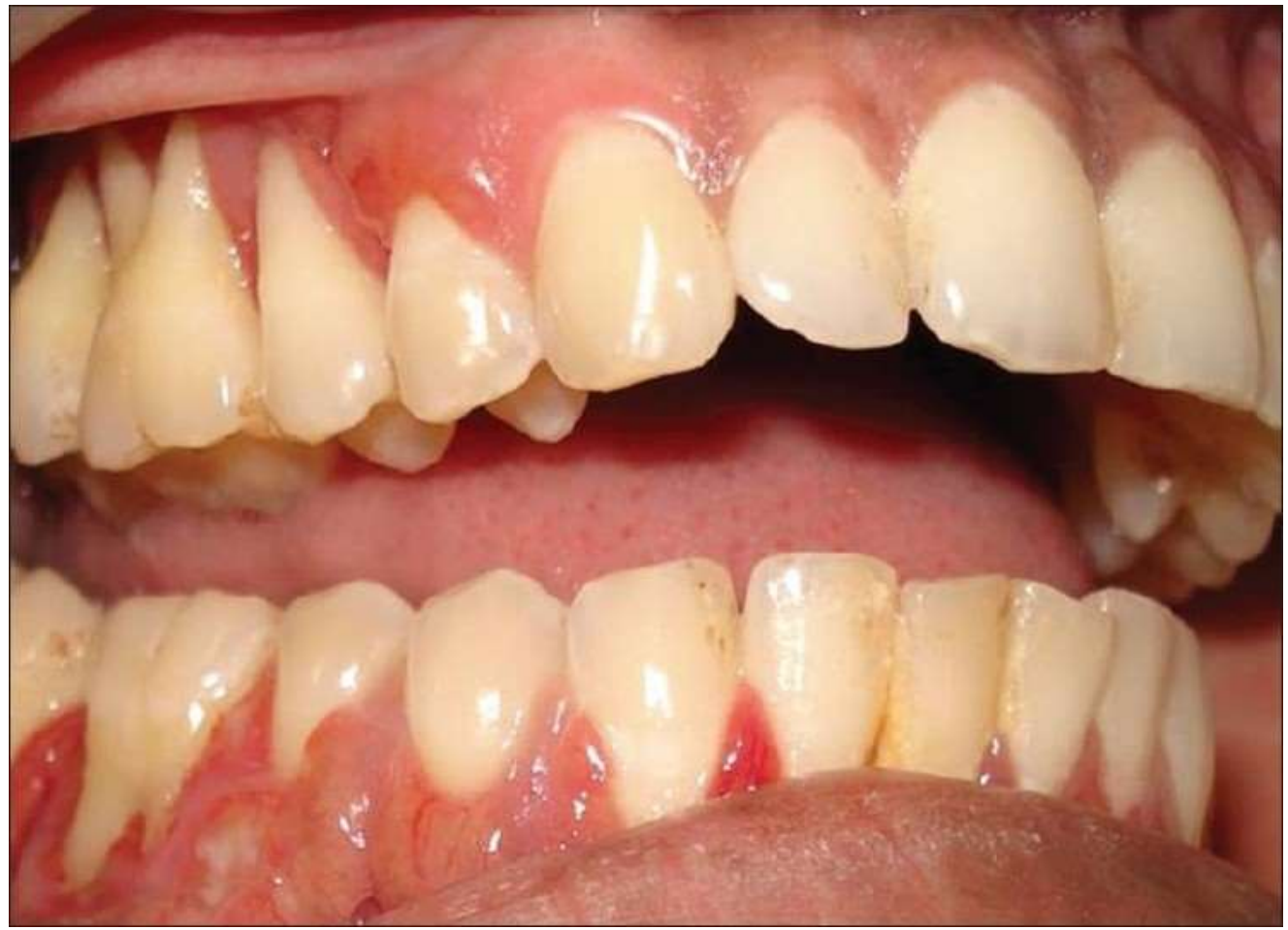
S.SEYYEDI

Medical Geneticist, PhD

پرتولب
دکتر سعاد سیدی
متخصص ژنتیک پزشکی

Periodontal treatment

- It has been reported that periodontitis-like lesion in LCH may respond at least partially to treatment when evaluated by periodontal parameters alone.
- It was reported that there was recurrence of periodontal lesion refractory to conventional therapy, which included scaling, root planning, modified Widman flap, and local application of antiseptic agents.
- The present case is an LCH of Multi-system involvement.
- A conservative palliative treatment was performed which included Scaling and Root planning
- Oral hygiene was reinforced with proper brushing habits and mouth rinse.
- Patient was reevaluated after one month and the pain and the burning sensation had reduced, gingival inflammation was reduced with gingival recession at the treated areas .



Systemic Therapy

- Bibi-
- can you get trametinib? If you can and you think he would continue to have access indefinitely then that is what we would treat with.
- He is at risk for CNS neuro- degeneration which is not reversible.
- All LCH responds to inhibitors.
- The only problem is that you can’t stop the treatment. - mike
-

Introduction

- Langerhans cell histiocytosis (LCH) is a disease characterized by clonal expansion of myeloid precursors that differentiate into $CD1a^{+}/CD207^{+}$ in lesions.
- It presents at all ages with various degrees of systemic involvement, and although cure rates are high, severe long-term neurological or endocrine complications may affect quality of life.

Incidence

- Ranges from 2.6 to 8.9 cases per million children younger than 15 years per year, with a median age at diagnosis of 3 years
- The exact incidence of LCH in adults is much less defined:
    - ***The only available data are for disseminated disease, with 0.07 cases per million per year***

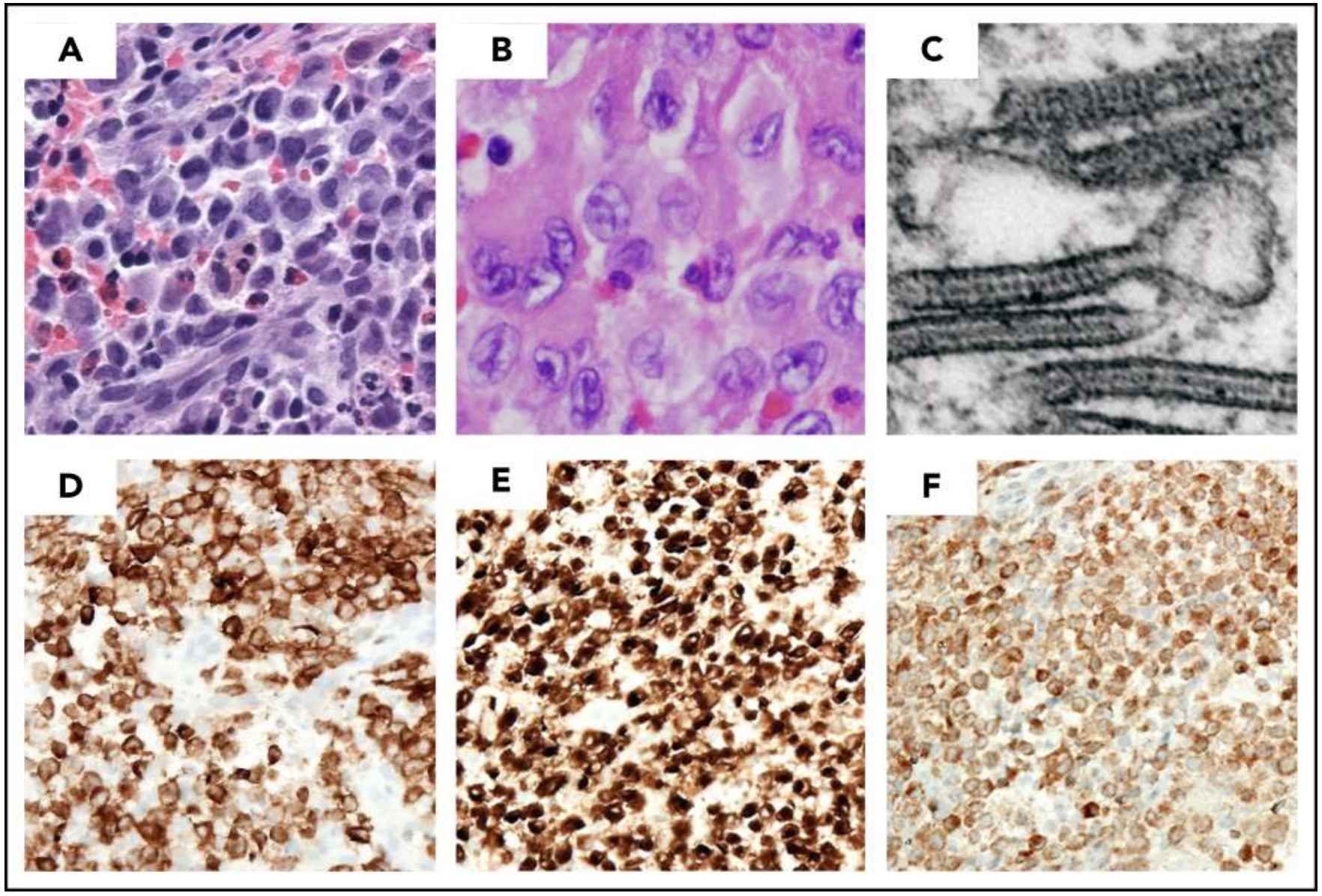
LCH & Malignancy

- The association between LCH and other malignancies has been described, with frequencies varying from 2.6% in children to 32% in adults.
- Solid malignancies :
  - ***Lung carcinoma***
  - ***Thyroid carcinoma***
- Hodgkin and non-Hodgkin lymphomas
- The most common hematologic malignancy reported is acute myeloid leukemia, often occurring years after LCH.
- In contrast, LCH in association with acute lymphoblastic leukemia (ALL) commonly occurs during treatment.

Pathology

- The histopathological examination revealed an intense and mixed infiltrate of eosinophils and histiocytes.
- Immunohistochemical analysis was performed with both anti-S100 and anti-CD1a primary antibodies.
- These cells, mainly organized in sheets, groups, or single elements, showed brown immunohistochemical positivity for both S100 and CD1a proteins

Langerhans cell histiocytosis



Diagnosis

- Clonal neoplastic proliferation with expression of CD1a, CD207 (Langerin), and S100
- The cells are generally large, round to oval in shape, with a coffee-bean nuclear grove, and without the branching that characterizes inflammatory $CD1a^+$ dendritic cells.
- On electron microscopy, pentalaminar cytoplasmic rod-shaped inclusions (Birbeck granules) can be identified, although electron microscopy is no longer required for diagnosis in the presence of $CD207^+$ staining.
- Because LCH cells activate and recruit other immunologic cells, microscopic examination shows an inflammatory pattern consisting of eosinophils, neutrophils, lymphocytes, and macrophages in addition to the LCs; this appearance is what is described as eosinophilic granuloma.[22]

	Langerhans Cell Histiocytosis	Erdheim-Chester Disease	Rosai-Dorfman-Destombes Disease
Distinctive clinical manifestations	• Constitutional symptoms (fatigue, night sweats), bone pain, skin lesions, anemia, and lymphadenopathy. • Cough, dyspnea, and apical-predominant nodular and/or cystic lung disease with interstitial changes. • Lytic lesions in the calvarium, base of skull, and axial skeleton. • Variable disease course (from slowly progressive to acute or subacute presentations).	• Osteosclerosis in the legs (96% of cases). May be asymptomatic and only detected by radiotracer uptake in the distal ends of the femurs and the proximal and distal tibia. • Dense infiltration of perinephric fat, described as a "hairy kidney" on computed tomography, is a highly prevalent (68% of cases) finding. • Other organs involvements vary depending on *BRAF* status.[19] Right atrium pseudo-tumor and cardiac involvements are more prevalent in *BRAF*-mutated patients. • The disease course is usually slow (over several years), but some symptoms and signs may be not clinically detected.	• Bilateral, massive, and painless cervical lymphadenopathy with or without intermittent fevers, night sweats, and weight loss. • Extranodal involvement (skin, head, and neck, CNS, soft tissues, kidneys, ophthalmic manifestations) is present with or without lymphadenopathy. • Association with autoimmunity (eg, cytopenia, lupus). • The disease course is usually slow, over several months or years.
Distinctive pathological features	• Histopathological analysis demonstrates inflammatory lesions containing abundant CD68(+), CD163(+), CD1a+ Langerin+ S100+ histiocytes.	• Tissues are infiltrated by foamy CD68(+), CD163(+), Factor XIIIa(+), CD1a(−), and Langerin(−) histiocytes with fibrosis. • Touton giant cells are often present. • Positivity for S100 and emperipolesis have been rarely observed (2).	• Typical findings include large pale histiocytes with cytoplasmic and nuclear S100 and fascin positivity, CD68 positivity, and variable CD163 and CD14 positivity. The cells are CD1a−/CD207− in contrast to LCH. • Emperipolesis is frequently present but may be variable, especially in extranodal sites.
Molecular features	• *BRAF*^{V600E} mutation is present in 50% of cases. And can be detected in lesional tissue or cell-free DNA extracted from plasma. • *BRAF*^{V600} wild-type cases are characterized by activating mutations in the MAPK pathway.	*BRAF*^{V600E} mutation is present in 50% of cases. The presence of *BRAF* mutation is useful to confirm ECD in ambiguous cases. *BRAF*^{V600E} mutations can be detected in lesional tissue cell-free DNA extracted from plasma. Ultrasensitive techniques are often needed for *BRAF*^{V600E} determination because of low VAF in tissues.[20] *BRAF*^{V600} wild-type cases are characterized by activating mutations in the MAPK pathway as well as *ALK*, *NTRK*, and others.	Typically *BRAF*^{V600} wild type although few cases of *BRAF*^{V600E} reported. *NRAS*, *KRAS*, *MAP2K1*, and *ARAF* mutations may be found in a subset of cases.[15]

Abbreviations: CNS, central nervous system; ECD, Erdheim-Chester disease; LCH, Langerhans cell histiocytosis; RDD, Rosai-Dorfman-Destombes disease.

Clinical presentation

- Systemic involvement:
    - ***Solitary eosinophilic granuloma to widespread disseminated disease with organ dysfunction***
- The current classification system is based on the site of lesions, number of involved sites (single or multisystem/local or multifocal), and whether the disease is involving risk (of mortality) organs (hematopoietic system, liver, or spleen;)
- Multisystem disease, approximately 15% of them had involvement of a risk organ.
- The skeleton is the most commonly affected system, as bone lesions are present in approximately 80% of patients with LCH, and in half of them, lesions are single.
- The most common site of bone involvement is the skull, followed by spine, limbs, and pelvis.

Clinical Manifestation

- Skin involvement is also common, particularly in infants, where it presents as seborrheic eczema, and in adults, where it may present as refractory eczema in intertriginous and genital areas
- Isolated skin involvement usually carries a good prognosis, with an approximately 60% chance of regression with topical treatments
- The lesions of congenital self-healing LCH are often present at or shortly after birth; can appear as eroded or ulcerated papules, pustules, or vesicles with hemorrhagic crusting; and may masquerade as diffuse neonatal hemangiomatosis or blueberry muffin rash.
- Close monitoring is required in infants, as reactivation or progression to multisystem involvement has been observed in up to 40% of cases.
- In adults, cutaneous involvement commonly presents as papules and intertrigo, with significant scaling and crusting, most commonly in the scalp, although mucosal involvement of the genitalia or oral cavity is also common.[37]

Clinical Manifestation

- In children, lung involvement usually occurs in the context of multisystem disease, where it has been reported to occur in up to 35% of patients.
- Radiographic findings are typical for the presence of a reticulonodular pattern with bullae formation
- In the absence of other risk organ involvement, pulmonary disease is not a predictor of adverse outcome.
- Isolated pulmonary involvement is a rare presentation that is almost exclusive of adults with a smoking habit
- The presence of hematopoietic dysfunction in the form of cytopenias is a poor prognostic sign.
- It occurs in the context of multisystem involvement, usually in very young children. Its pathophysiology is multifactorial, including direct involvement of the bone marrow as well as peripheral destruction resulting from hypersplenism from LC infiltrates in the spleen.[45]
- Liver involvement also carries a very poor prognosis.
- Patients present with hypoalbuminemia, hepatomegaly, or conjugated hyperbilirubinemia. A well-described but rare complication in young children and in adults is the development of sclerosing cholangitis and hepatic fibrosis, which commonly evolve to end-stage liver failure

Clinical Classification

Clinical group	Description
Multisystem	Two or more systems involved
With risk organ involvement	Involvement of liver, spleen or bone marrow
Without risk organ involvement	Without involvement of liver, spleen or bone marrow
Single-system	Only 1 system involved
Single site	Skin, bone, lymph node, other (thyroid, thymus)
Multiple sites	Multifocal bone disease
Special site	Skull-base lesion with intracranial extension or vertebral lesion with intraspinal soft tissue extension
Pulmonary LCH	Isolated lung disease
CNS LCH	Tumorous lesions
	Neurodegenerative disease
	LACI
	LACS

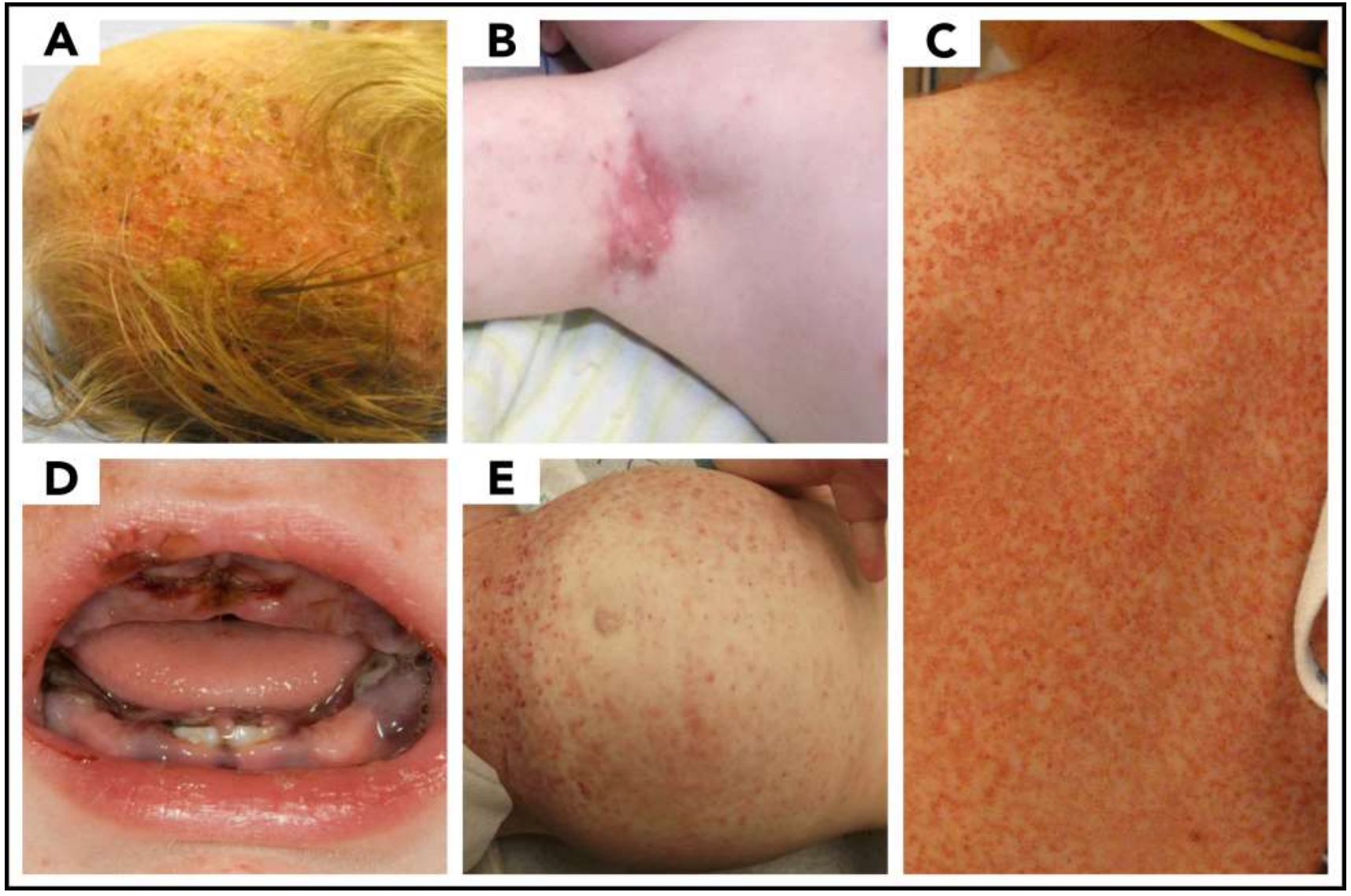
Hematopoietic Involvement

Hematopoietic involvement (with or without bone marrow involvement*), at least 2 of the following:
Anemia: hemoglobin <100 g/L (<10 g/dl), infants <90 g/L (<9.0 g/dL), not a result of other causes (eg, iron deficiency)
Leukocytopenia: leukocytes <4.0 × 10^9/L (4000/μL)
Thrombocytopenia: platelets <100 × 10^9/L (100 000/μL)
Spleen involvement enlargement:
>2 cm below costal margin in the midclavicular line†
Liver involvement, one or more of the following:
Enlargement >3 cm below costal margin in the midclavicular line†
Dysfunction (ie, hypoproteinemia <55 g/L, hypoalbuminemia <25 g/L, not as a result of other causes)
Histopathological findings of active disease

LCH in Adults

- Adult LCH usually presents after the fourth decade, and approximately two-thirds of patients have multisystem involvement at diagnosis.
- Its association with other neoplastic diseases is common, especially other myeloproliferative neoplasms.
- In a significant proportion of patients, LCH and Erdheim-Chester lesions may coexist.
- In general, the clinical presentation and organs involved are similar to pediatric patients, with the more frequent involvement of the genitalia, particularly in females.
- The rarity of LCH in adults, combined with the nonspecific and varied clinical presentations, typically result in missed and delayed diagnosis

Langerhans cell histiocytosis



Pulmonary LCH

- Isolated pulmonary LCH (PLCH) is primarily a disease of young adult smokers, with more than 90% of patients endorsing a smoking history.
- PLCH presents with respiratory symptoms, mainly cough and dyspnea on exertion, in approximately two-thirds of the cases.
- Less frequently, patients may present with spontaneous pneumothorax or with asymptomatic lesions on routine chest X-ray.
- Extrapulmonary organ involvement occurs in 10% to 15% of patients.[54] High-resolution CT shows a pattern of bilateral reticulonodular and cystic changes, with apical and midlung predominance, sparing the bases and costophrenic angles.
- Transbronchial lung biopsies may be diagnostic of PLCH in expert centers; however, because of the focal nature of the disease, the diagnostic yield varies between 15% and 40%, and a thoracoscopic lung biopsy is usually recommended.
- Pathology of PLCH shows nodular lesions with the typical histology.
- In late disease, nodules are replaced by advanced bullous and cystic lesions, often in association with hyperinflation and honeycombing.
- *BRAF*V600E and *MAP2K1* mutations have been reported at similar frequency as in extrapulmonary LCH, although lower mutation rates are identified in the more fibrotic lesions.[58,5]

LCH of the central nervous system

- Central nervous system (CNS) involvement in LCH (LCH-CNS) represents a spectrum of diseases ranging from active infiltration by LCH to long-term effects.
- Its prevalence has been noted to range from 3.4% to 57%.
- LCH-CNS can be divided in focal mass lesions and lesions associated with progressive neurodegeneration.
- Mass lesions tylically present in meninges, choroid plexus, and brain parenchyma.
- Characteristic neuroimaging findings include hypothalamic-pituitary involvement, often with diabetes insipidus, infundibular thickening, and absent bright spot in posterior pituitary; enlargement and enhancement of the pineal gland; thickening and enhancement of choroid plexus; or intraparenchymal masses.
- Among patients with anterior pituitary dysfunction, the most common deficiency is in antidiuretic hormone, followed by growth hormone (which occurs in up to 50% of patients with diabetes insipidus), gonadotropin, and thyrotropin.

LCH of the central nervous system

- Anterior pituitary dysfunction is more common in childhood-onset patients and in those with multisystem disease.
- Diabetes insipidus, the hallmark of this dysfunction, has been reported to occur in up to 24% of patients with LCH, but in half of patients with multisystem disease ; in one third of cases, the diabetes insipidus precedes or is concurrent with the diagnosis of LCH, and in the remaining two-thirds of the cases, it is diagnosed later.
- With the use of more comprehensive risk-adapted management of LCH, the incidence of endocrinopathies has decreased to 10% to 15% in recent large cohort studies.
- Neurodegenerative LCH (LCH-ND) is characterized by progressive radiologic and clinical abnormalities.
- separate clinical forms are identified: LCH-associated abnormal CNS imaging (LACI), which includes asymptomatic patients with radiologic findings, and LCH-associated abnormal CNS symptoms (LACS), which describes patients with abnormal cognitive and psychological findings.
- LACI and LACS are associated with increased T2-weighted MRI signal in the dentate nucleus of the cerebellum, basal ganglia, and pons

Lesion type and site	Pathology	MRI characteristics
Tumorous lesions		
Cerebral white and gray matter	Typical LCH morphology with CD1a/CD207 + histiocytes	Nodular or space-occupying lesions; T2 hyperintensity and T1 iso- or hypointensity; variably contrast enhancing; can present mass effect
LACI		
Dentate nuclei of the cerebellum	Loss of Purkinje cells with gliosis in the cerebellar cortex	Bilateral and symmetrical slight T1-w hyperintensity, followed by development of T1-w hypointensity and/or T2-w hyperintensity
Infratentorial white matter (cerebellum, brainstem)	Neuroaxonal loss with secondary demyelination; pronounced inflammatory process dominated by $CD8^+$ T-lymphocytes and microglial activation; $BRAFV600E^+$ perivascular myeloid cells and increased frequency of *BRAF*V600E $^+$ peripheral blood mononuclear cells (for patients with $BRAFV600E^+$ systemic LCH)	Bilateral and symmetrical abnormalities (T2-w hyperintensity, T1-w isointensity or hypointensity)
Basal ganglia	—	Bilateral and symmetrical leukoencephalopathy-like abnormalities, or confluent lesions in a vascular pattern, with T2 hyperintensity and T1 hypointensity
Supratentorial white matter	Reactive gliosis and microglial activation decreased *BRAF*V600E $^+$ cells compared with cerebellum/brainstem	Bilateral and symmetrical leukoencephalopathy-like abnormalities, or confluent lesions in a vascular pattern, with T2 hyperintensity and T1 hypointensity
Prominent, dilated perivascular spaces		
Cerebral white matter	—	Bilateral and symmetrical punctate lesions in a vascular pattern. T2-w hyperintensity, and T1 iso- or hypointensity; variable contrast enhancement and mass effect

Neurodegenerative LCH

- LACS is a neurodegenerative syndrome of variable severity and course.
- The incidence of long-term neurodegeneration has been estimated to be between 1.9% and 11%, and it seems to be higher in patients with multisystem disease, diabetes insipidus, history of involvement of bones of the skull base and orbit,or *BRAF*V600E-mutated LCH.
- Of particular therapeutic relevance are the skull-based lesions (CNS-risk lesions), as this risk association has been considered an indication for the use of systemic therapy, rather than local control measures only.
- The appearance of clinical and radiographic signs of LCH-ND can occur with the initial LCH diagnosis, although it commonly occurs years later.
- Symptoms may initially include tremors, abnormal reflexes, gait disturbance, motor spasticity, ataxia, dysarthria, dysphagia, behavioral changes, learning disorder, or psychiatric problems. Some patients develop a progressive cerebellar syndrome, with spastic tetraparesis, pseudobulbar palsy, and cognitive deterioration.
- Magnetic resonance imaging shows a characteristic infratentorial predilection, with symmetric abnormalities of the dentate nuclei and of the white matter of the cerebellum and pons
- Outside the infratentorial compartment, abnormalities of the basal ganglia, optic nerves, and tracts; dilatation of the Virchow-Robin spaces; or diffuse abnormalities of the hemispheric white matter consistent with leukoencephalopathy are also common.
- Serial imaging and neurocognitive evaluations are recommended when the disease is suspected.

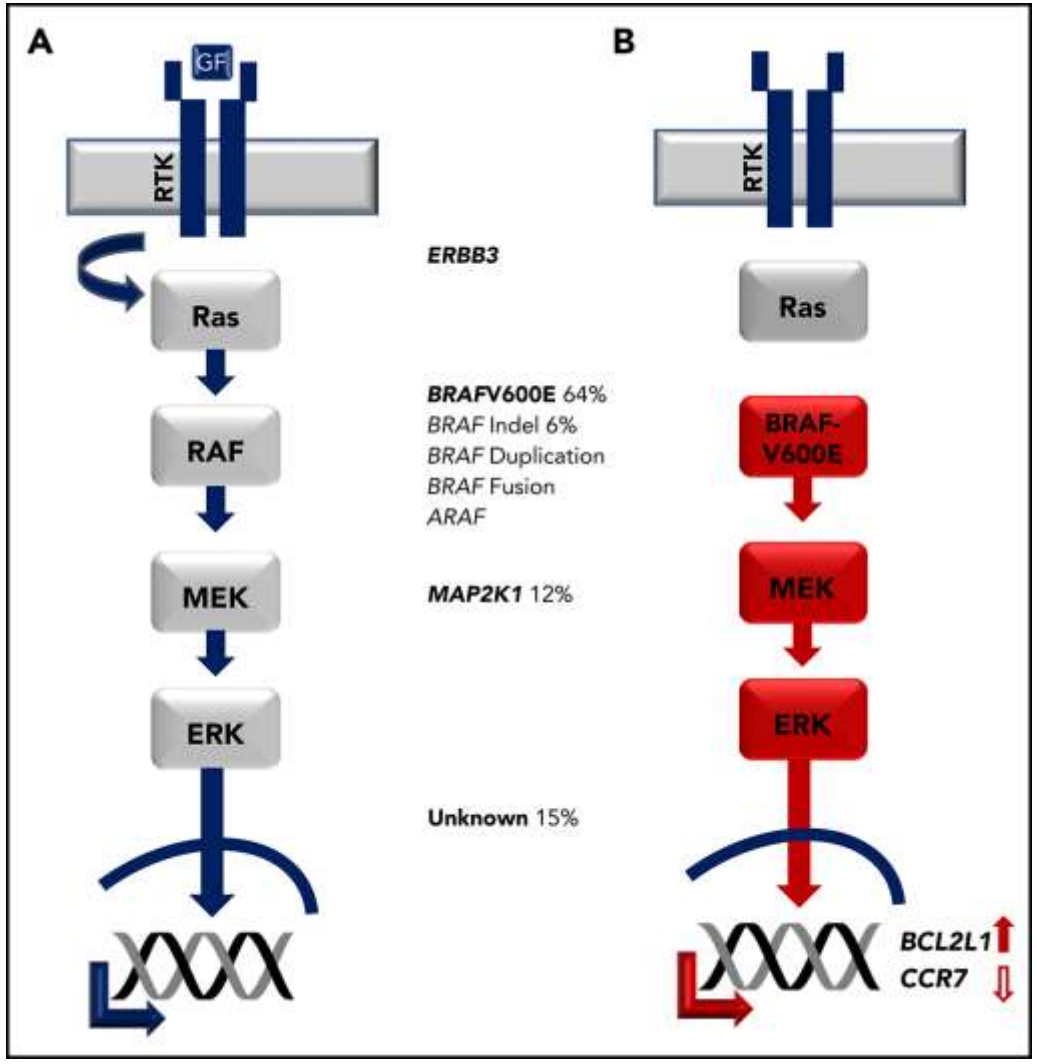
Neurodegenerative LCH

- Whether CNS involvement with degeneration represents active disease or a radiologic scar remains undefined.
- Until recently, the only histologic study of LACS reported absence of $CD1a^+$ histiocytes, an inflammatory collection of $CD8^+$ lymphocytes with neuronal and axonal degeneration, and extensive myelin loss, supporting the view of a late consequence of an inflammatory phenomenon.
- Recent study supports hematopoietic origin of myeloid cells that share precursors with LCH lesion $CD207^+$ cells.
- Clinical and radiological responses to BRAF inhibitors further support this view.

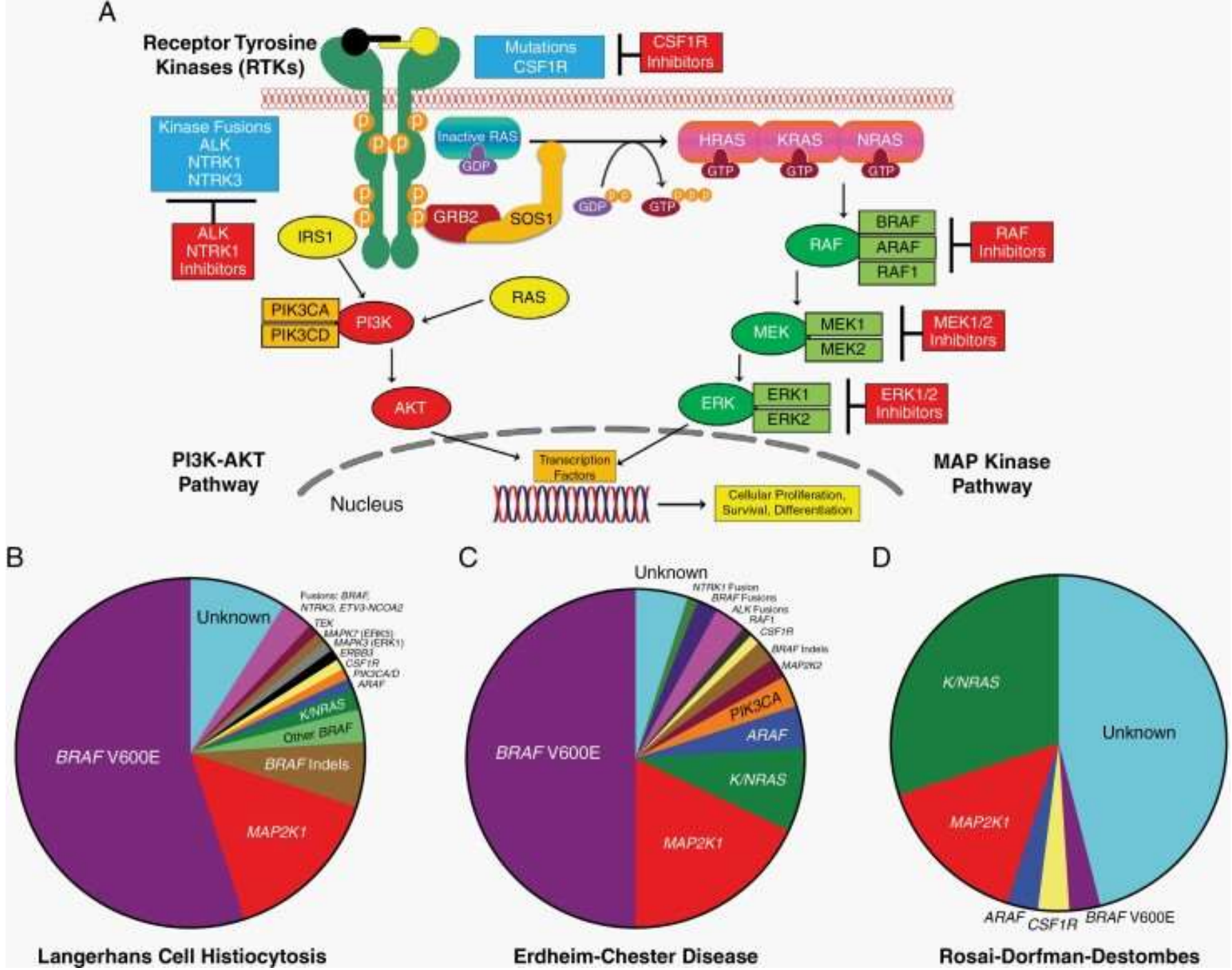
Biology

- **Ontogeny and function of epidermal LCs**
- During development, a wave of LCs arises from yolk sac progenitors and fetal liver-derived monocytes and seeds the epidermis.
- This population is maintained locally, with tissue-resident precursors during steady state.

Langerhans cell histiocytosis



Carlos Rodriguez-Galindo,Carl E. Allen, Langerhans cell histiocytosis, Blood, 2020,


A
Receptor Tyrosine Kinases (RTKs)
Mutations CSF1R
CSF1R Inhibitors
Kinase Fusions ALK NTRK1 NTRK3
ALK NTRK1 Inhibitors
Inactive RAS
GDP
GTP
HRAS
KRAS
NRAS
GRB2
SOS1
IRS1
RAS
RAF
BRAF
ARAF
RAF1
RAF Inhibitors
PIK3CA
PIK3CD
PI3K
MEK
MEK1
MEK2
MEK1/2 Inhibitors
AKT
ERK
ERK1
ERK2
ERK1/2 Inhibitors
PI3K-AKT Pathway
MAP Kinase Pathway
Transcription Factors
Nucleus
Cellular Proliferation, Survival, Differentiation
B
Unknown
Fusions: BRAF, NTRK3, ETV3-NCOA2
TEK
MAPK7 (ERK5)
MAPK3 (ERK1)
ERBB3
CSF1R
PIK3CA/D
ARAF
K/NRAS
Other BRAF
BRAF Indels
BRAF V600E
MAP2K1
Langerhans Cell Histiocytosis
C
Unknown
NTRK1 Fusion
BRAF Fusions
ALK Fusions
RAF1
CSF1R
BRAF Indels
MAP2K2
PIK3CA
ARAF
K/NRAS
BRAF V600E
MAP2K1
Erdheim-Chester Disease
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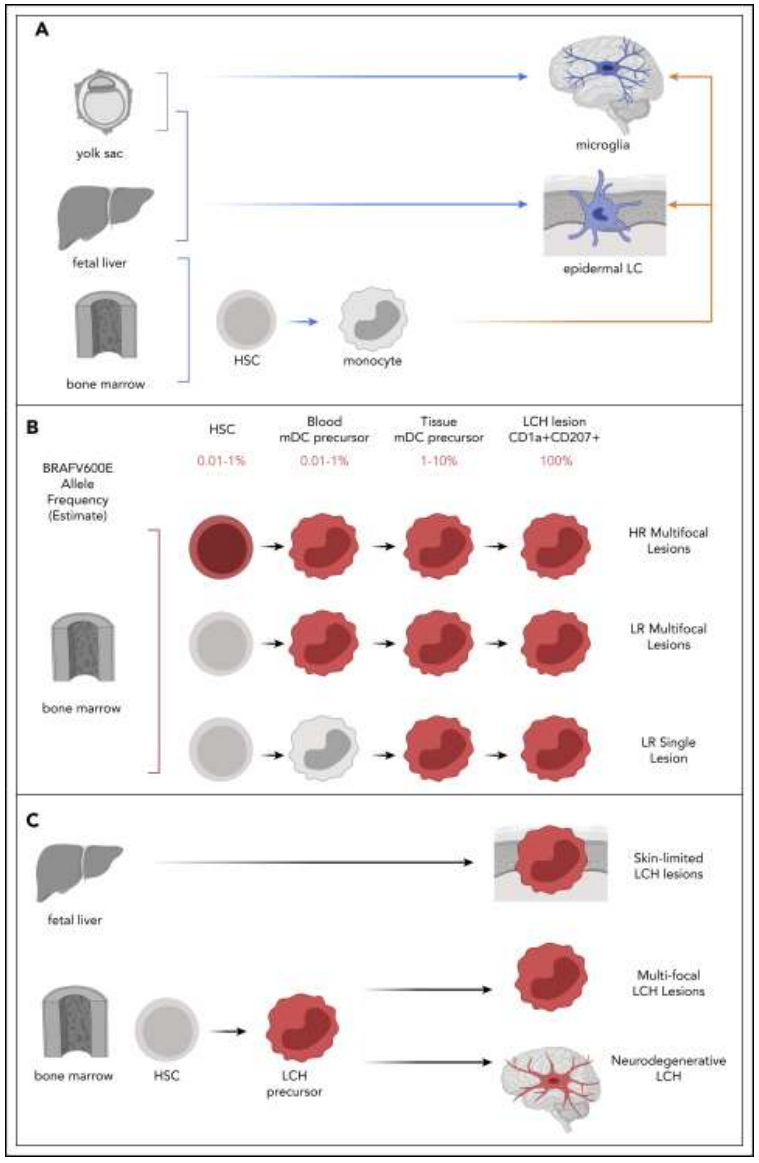
Unknown
MAP2K1
ARAF
CSF1R
BRAF V600E
Rosai-Dorfman-Destombes

Langerhans cell histiocytosis



Inflammation and LCH

- Histologic similarities between LCH cells and epidermal LCs set the stage for a long-standing debate about LCH as a disorder of pathologic activation of epidermal LCs vs neoplastic transformation.
- The pathologic $CD207^{+}$ dendritic cells (LCs) constitute a median of 8% of LCH lesion cells.The remainder of the lesion is composed of inflammatory infiltrate, including a significant population of T cells (enriched for activated $CD4^{+}$ regulatory suppressor T cells) and abundant inflammatory cytokines.
- The LCs of an LCH lesion express high levels of the programmed cell death ligand 1, and infiltrating T cells express the programmed cell death protein.

Recurrent somatic activating MAPK pathway gene mutations in LCH

- In a long-standing cancer vs inflammation debate, nonrandom X-inactivation of $CD1a^+$ cells supported clonality of LCH lesion LCs.
- LCH lesion biopsies identified recurrent *BRAF*V600E mutations in more than 50% of the cases.
- Several groups subsequently found that *BRAF*V600E or alternative activating MAPK pathway gene mutations are nearly universal in LCH, including other *BRAF* mutations and mutations in *MAP2K1* (encoding MEK1)

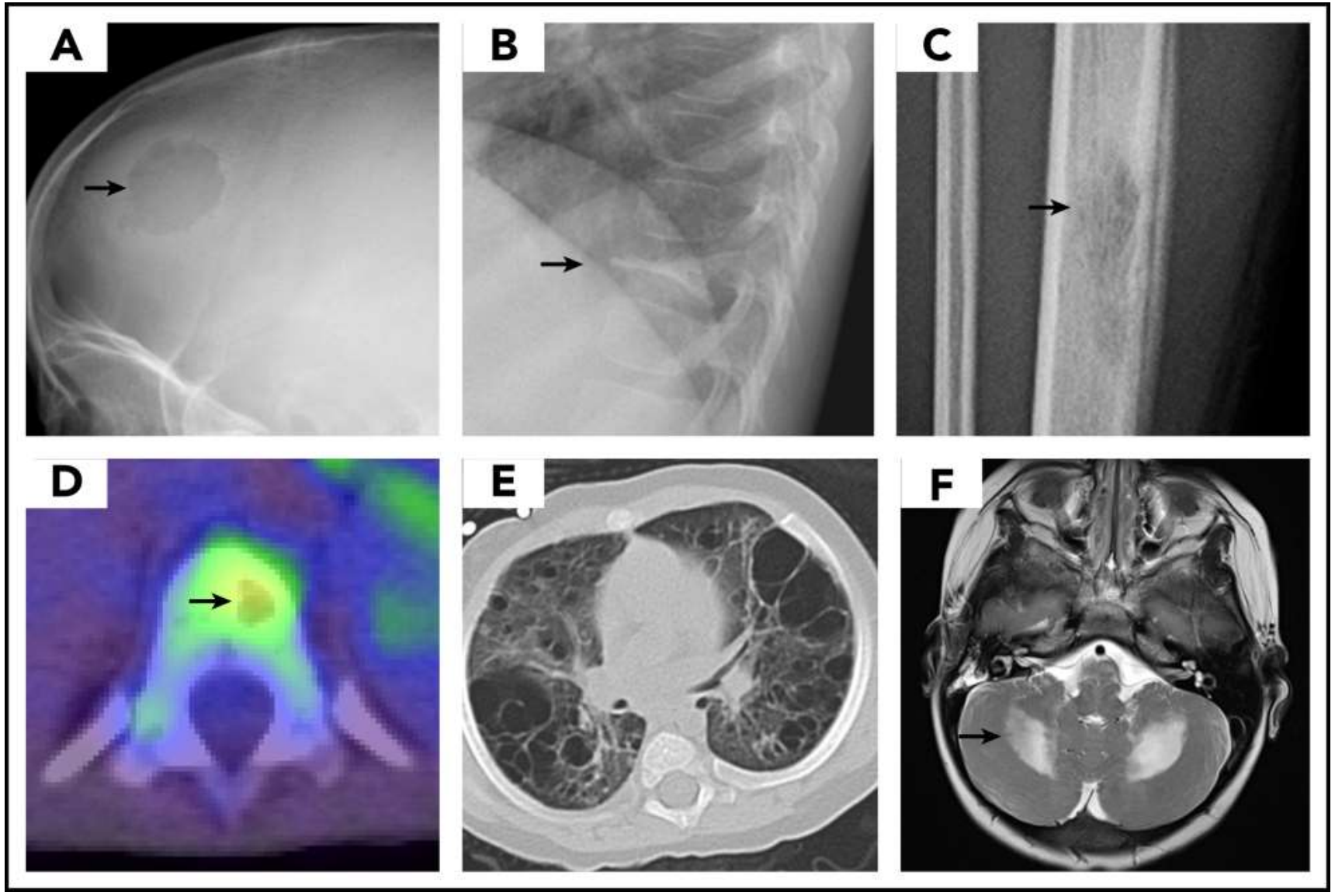
Beyond BRAF

- The MAPK pathway transduces extracellular signals that regulate transcriptional programs of cell growth, differentiation, and survival.
- The MAPK pathway is the most common dysregulated pathway in cancer, and *BRAF*V600E is identified in ~8% of all cancers. It is infrequently associated with hematologic malignancies with the notable exception of hairy cell leukemia, and ERK activation affects myeloid cell differentiation and maturation.
- Identifying mutation-specific pathogenic mechanisms may inform opportunities for clinical risk stratification and precision therapy

Work-Up

- Most organs can be affected by LCH, and therefore a comprehensive evaluation is indicated.
- Bone imaging studies reveal a lytic lesion without marginal sclerosis, with or without periosteal reaction
- Radio-isotope imaging is recommended to assess the number of bone lesions; fluorodeoxyglucose–positron emission tomography scans can be useful in defining the extent of the disease and the response to therapy.
- The skull, including the skull base, is very commonly involved; typical locations include the bones of the orbit or the temporal bone (typically the mastoid).
- Involvement of the vertebral bodies is also common, and the presence of a vertebra plana is frequent.
- Pain and tumor formation in a localized area of bone is a very common presentation of LCH.

Langerhans cell histiocytosis



Treatment of LCH

- The difficulties in developing effective therapies for LCH are linked to the deficiencies in the understanding of its pathogenesis.
- Patients are now stratified into different risk categories based on the disease extent and the degree of organ dysfunction; patients with single-system disease confined to a single site usually require only local therapy or observation, whereas patients with more extensive disease require systemic therapy.
- These advances in risk-adapted treatment have resulted in better characterization of the natural history of the disease and an overall improvement in outcomes.
- Population-based studies have documented a significant increase in survival for patients with disseminated LCH, although these improvements appear to have favored children over adults, with 5-year relative survival rates of 90% vs 70%,
- Multifocal LCH or unifocal disease in CNS-risk sites is vinblastine/prednisone for 1 year, with the potential addition of mercaptopurine for high-risk LCH.
- LCH responds to increasing doses of nucleoside analogs with efficacy in other myeloid malignancies (cytarabine, cladribine, and clofarabine).
- For patients with low-risk disease recurrence, including patients with reactivation of single-system or multifocal bone disease or multisystem disease without risk organ involvement, less toxic regimens have proven to be effective, including oral 6-mercaptopurine and methotrexate,[107] indomethacin,[108] bisphosphonates,[109] and hydroxyurea.
- The international LCH-IV protocol (ClinicalTrials.gov identifier: NCT02205762) represents a comprehensive effort to address the most relevant clinical and therapeutic challenges, including the management of upfront and relapsed LCH and the treatment of CNS disease.

MAPK Inhibitors

- Early-phase trials in adults with LCH and Erdheim-Chester disease support near-universal responses in patients treated with MAPK pathway inhibitors.
- High-risk LCH, patients with multiple previous treatment failures, and patients with LCH-ND.
- However, rapid reactivations occur in the majority of patients after discontinuation of therapy, and reintroduction of the BRAF inhibitor is usually effective.

Special treatment considerations

- **Treatment of adult LCH**
- Treatment of LCH in adults follows similar guidelines to those recommended for children, with some modifications.
- The more severe skin manifestations have shown to respond well to phototherapy, low-dose methotrexate, and thalidomide or lenalidomide.
- For patients requiring systemic therapy, vinblastine-based regimens remain quite effective in the adult population, with similar outcomes to children.
- However, given the diminished tolerance of adults to corticosteroids and vinblastine, treatment with cytarabine or cladribine is generally preferred, although BRAF inhibitors are being increasingly used in this population.
- For adults with pulmonary LCH, smoking cessation is critical for stabilization and improvement of symptoms, and a trial of observation after discontinuing smoking is recommended.

Treatment of LCH CNS disease

- There are no standard guidelines for treatment of LCH CNS disease.
- For tumorous lesions and new-onset diabetes insipidus, treatment with a standard LCH regimen is indicated; vinblastine and prednisone or single-agent cladribine have been shown to be effective.
- Treatment of LCH-ND is less defined.
- Improvement in the neurological condition has been reported with the use of cytarabine,intravenous-immunoglobulins, rituximab, infliximab, and *cis*-retinoic acid.
- BRAF inhibitors

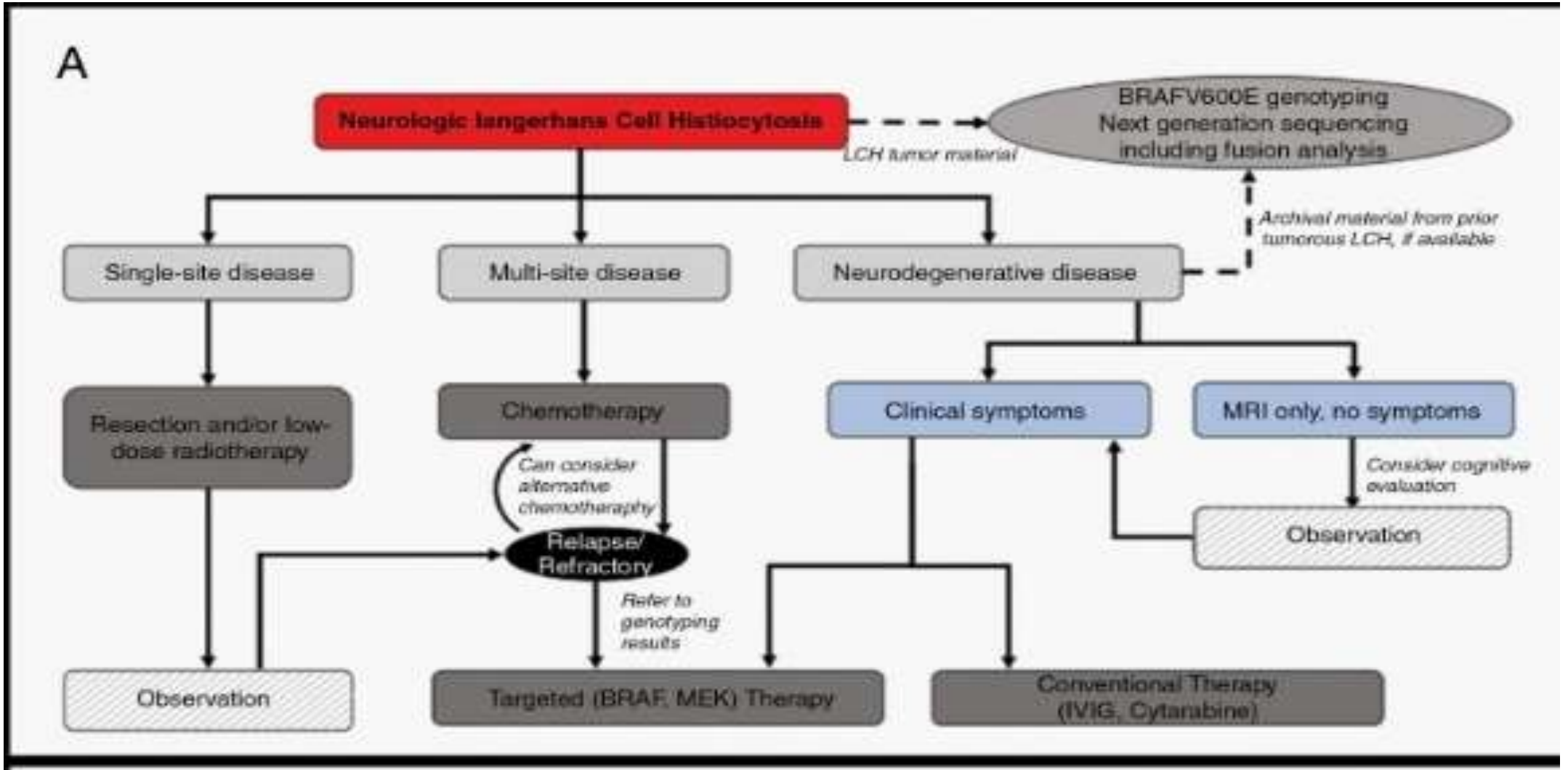
Targeted Therapy

Targeted therapy						
Vemurafenib	480-960 mg twice daily	+	+	+	NR	Recommended for refractory or clinically severe symptomatic *BRAF*^{V600E}-mutated disease[a]
Dabrafenib	75-150 mg twice daily	+	+			
Cobimetinib	20-60 mg daily for 21 of the 28-day cycle	+	+	+	+/–	Recommended for refractory or clinically severe *BRAF*^{V600} wild type or *BRAF*^{V600E}-undefined disease
Trametinib	1-2 mg daily					

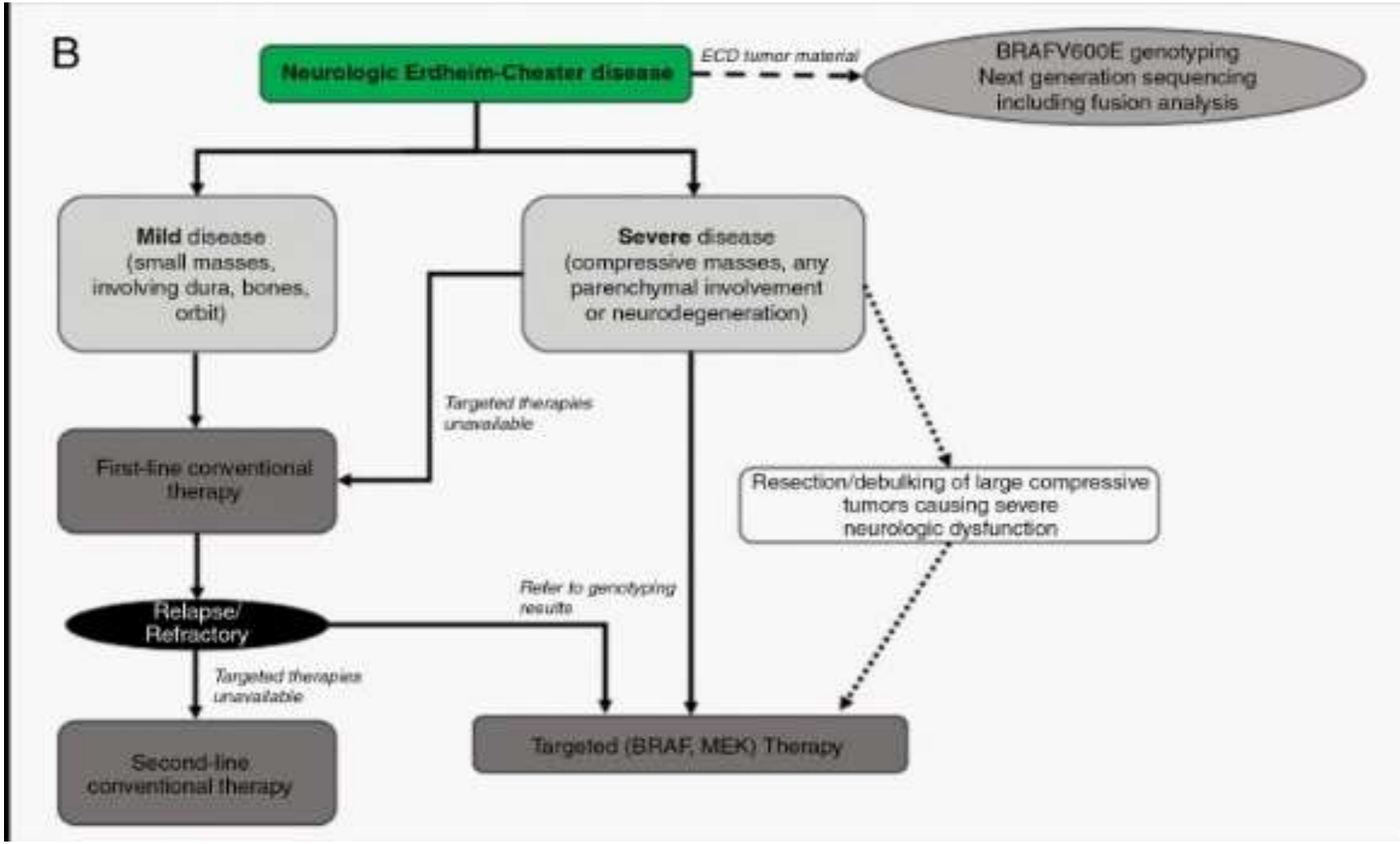
Late effects

- Up to 50% of survivors have at least 1 permanent consequence.
- Long-term effects have been reported to be more frequent among patients with multisystem disease and patients with multiple reactivations.
- The most commonly reported late effects are diabetes insipidus and orthopedic abnormalities, which may occur in up to or slightly above 20% of patients, followed by growth retardation, hearing loss, and neurodegeneration in approximately 10% of the patients, and biliary cirrhosis, and respiratory insufficiency in less than 5% of patients.
- Of particular relevance is the neurodegenerative syndrome that usually occurs years after the original diagnosis

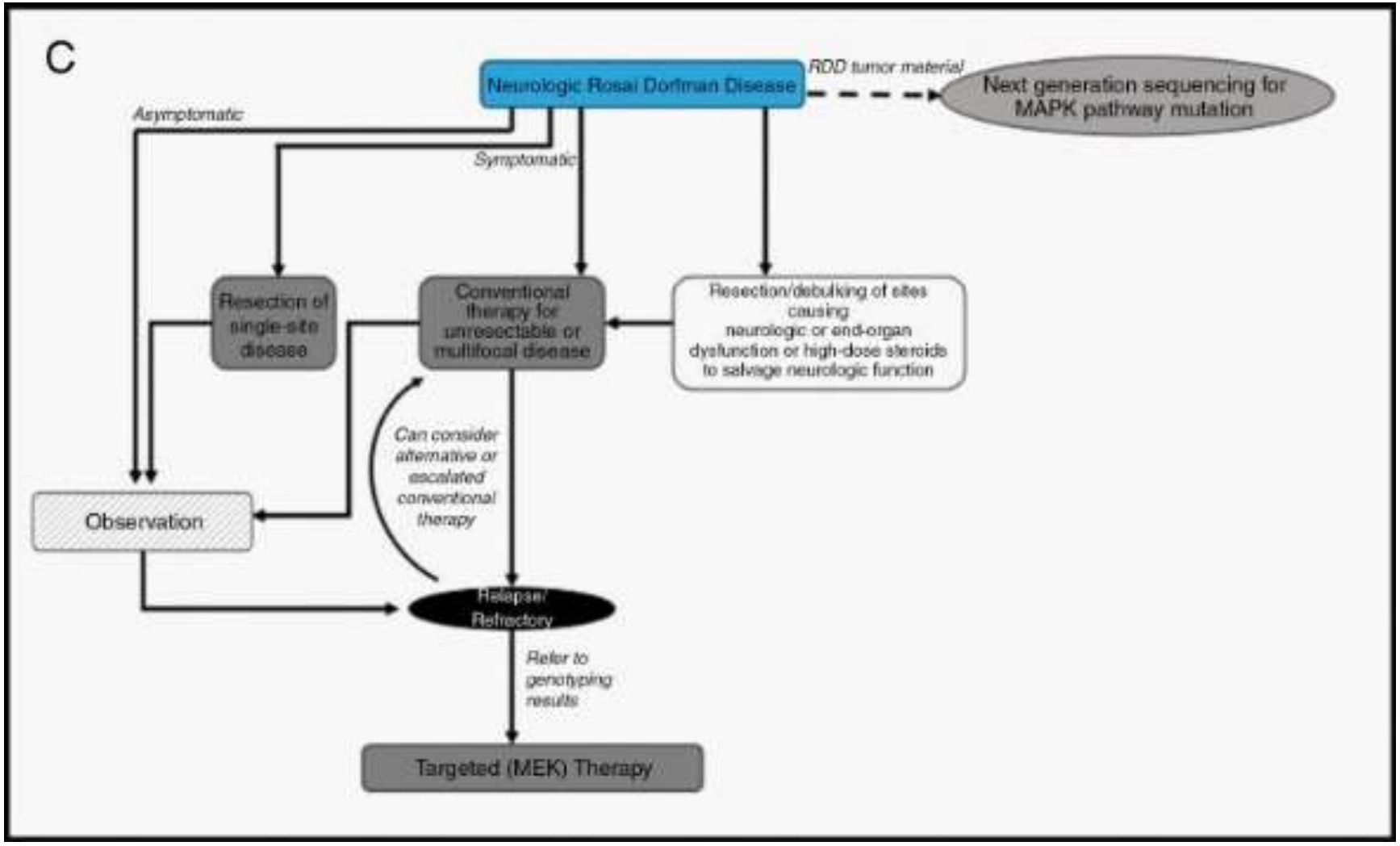
LCH


A
Neurologic Iangerhans Cell Histiocytosis
LCH tumor material
BRAFV600E genotyping
Next generation sequencing
including fusion analysis
Archival material from prior
tumorous LCH, if available
Single-site disease
Multi-site disease
Neurodegenerative disease
Resection and/or low-
dose radiotherapy
Chemotherapy
Can consider
alternative
chemotherapy
Relapse/
Refractory
Refer to
genotyping
results
Clinical symptoms
MRI only, no symptoms
Consider cognitive
evaluation
Observation
Observation
Targeted (BRAF, MEK) Therapy
Conventional Therapy
(IVIG, Cytarabine)

Erdheim-Chester



Rosai-Dorfman



Future perspectives

- Further research in the biology of LCH and its correlation with clinical presentation and outcomes will be required for better refinement of treatment of the disease and its complications, such as LCH-ND.
- Although the universal activation of the MAPK pathway provides a strong rationale for the use of pathway inhibitors, their role, including indications, optimal duration of treatment, and combination with standard chemotherapy, needs to be investigated.

Summary

Clonal expansion of myeloid precursors that differentiate into $CD1a^{+}/CD207^{+}$ cells in lesions that leads to a spectrum of organ involvement and dysfunction.

The pathogenic cells are defined by constitutive activation of the MAPK signaling pathway.

Treatment of LCH is risk-adapted: patients with single lesions may respond well to local treatment, whereas patients with multisystem disease require systemic therapy.

Although survival rates for patients without organ dysfunction is excellent, mortality rates for patients with organ dysfunction may reach 20%.

Summary

- Despite progress made in the treatment of LCH, disease reactivation rates remain above 30%, and standard second-line treatment is yet to be established.
- Treatment failure is associated with increased risks for death and long-term morbidity, including LCH-associated neurodegeneration.
- Early case series report promising clinical responses in patients with relapsed and refractory LCH treated with BRAF or MEK inhibitors, although potential for this strategy to achieve cure remains uncertain.

Thank You
Any Questions