In the name of God

LCH
&
HSCT in LCH

BibiShahin Shamsian, MD

- The "L" (Langerhans) group
- LCH includes a broad spectrum of clinical manifestations in children and adults, ranging from self-healing lesions to life-threatening disseminated disease.

- The diagnosis of LCH is based on clinical and radiological findings in combination with histopathological analyses identifying tissue infiltration by histiocytes with **ultrastructural or immunophenotypic characteristics** of LCs.

- **It is recommended that biopsy confirmation of suspected LCH be performed in all cases, especially for patients requiring therapy (grade C2)**

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- **The annual incidence of LCH in children younger than 15 years of age is around 5 to 9/106 and 1/106 in patients older than 15 years of age.**
- **Rare cases of familial LCH have been reported,**
- **No genetic susceptibility has been identified to date.**
- **Lung LCH of the adult is strongly associated with smoking**
- LCH most often is diagnosed in this age group between **0 and 3years of age**
- **LCH appears to be more common in boys than in girls (1.2–2:1).**

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Pediatrics International (2014) 56, 451–461

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

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- **LCH** first appeared in the medical literature around **1900**
- **1950s, Lichtenstein Histiocytosis X : Hand-Sch¨uller-Christian disease,Eosinophilic Granulomas ,Letterer-Siwe**
- 1970s, Nezelof discovered the presence of Birbeck granules, a cytoplasmic structure ultimately associated with langerin (CD207)
- The first classification of histiocytosis, published in 1987 by the Working Group of the Histiocyte Society (HS)

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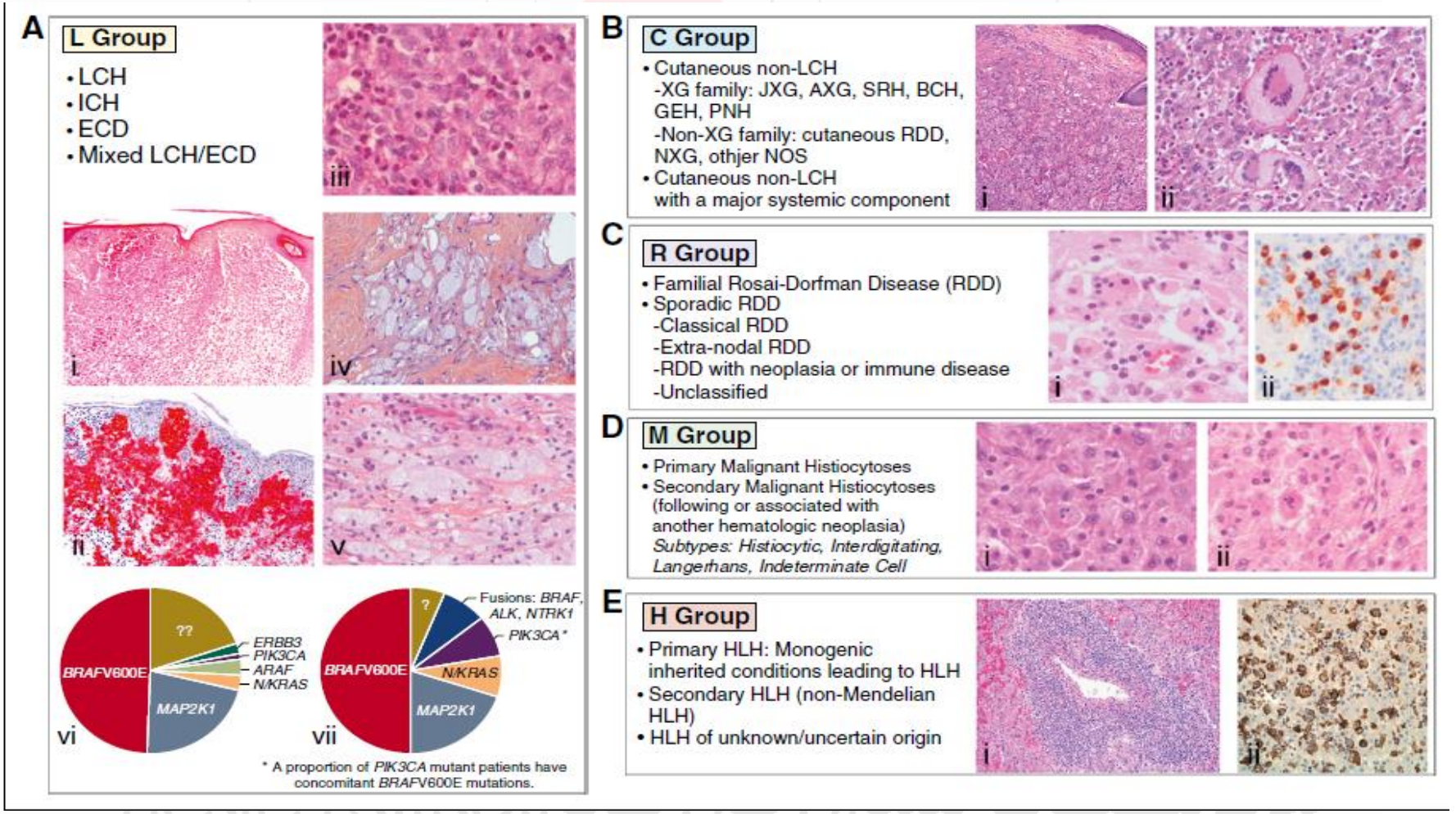
Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages



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

- **5 Groups**
- **A: L Group**
- LCH, ICH, ECD, Mixed LCH/ECD
- B: **C Group** Cutaneous non-LCH -XG family: JXG, AXG, SRH, BCH, GEH, PNH,....
- C: **R Group** Familial Rosai-Dorfman Disease (RDD)
  Sporadic RDD, -Classical RDD, -Extra-nodal RDD,
  -RDD with neoplasia or immune dise
- **D:M Group** Primary Malignant Histiocytoses, Secondary Malignant Histiocytoses
- **E: H Group** Primary HLH: Monogenic inherited conditions leading to HLH, Secondary HLH

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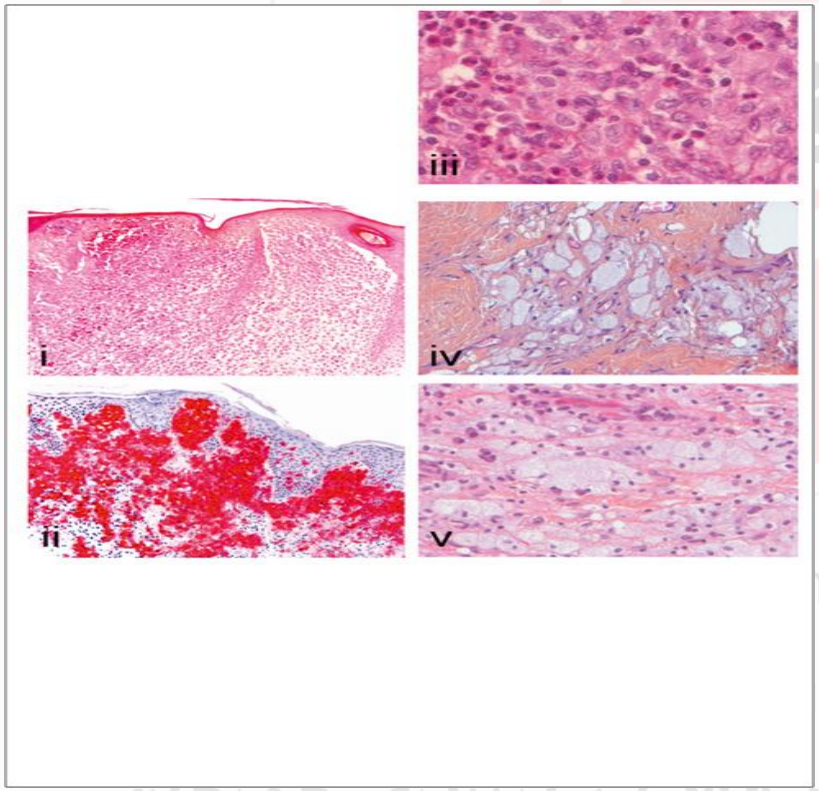
A) L group: Histology of LCH (skin [i-ii] and bone [iii]) and of ECD (perirenal [ivv]).
Pie chart of relative frequencies of activating kinase mutations in LCH (vi) and ECD (vii)

Histology of LCH



L Group

- **LCH** Langerhans cell histiocytosis
- **ICH** indeterminate cell histiocytosis
- **ECD** Erdheim-Chester disease
- **Mixed LCH/ECD**

Presentation in LCH

- LCH may affect any organ of the body, but those more frequently affected in children are
- Bones (80%of cases)
- Skin (33%)
- pituitary gland (25%)
- liver, spleen, hematopoietic system or lungs (15% each)
- lymph nodes (5%-10%),
- Central nervous system (CNS) (2%-4% excluding the pituitary).

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Examples of clinical involvement by histiocytoses.

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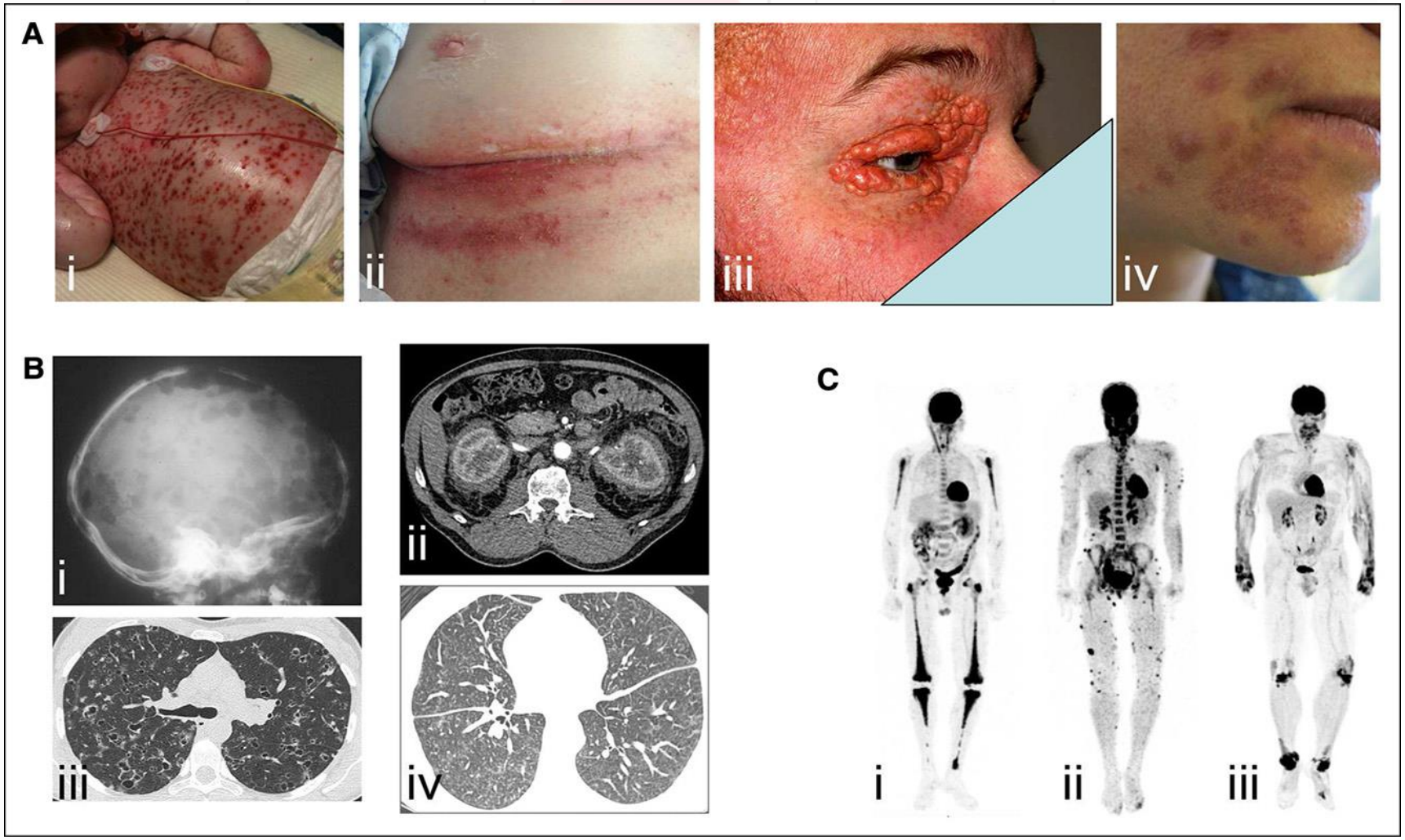
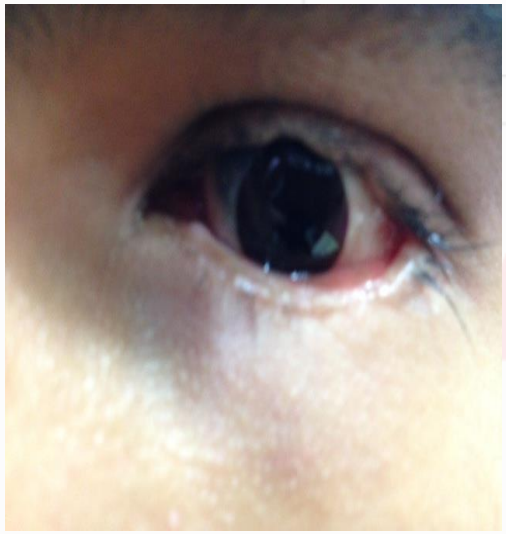
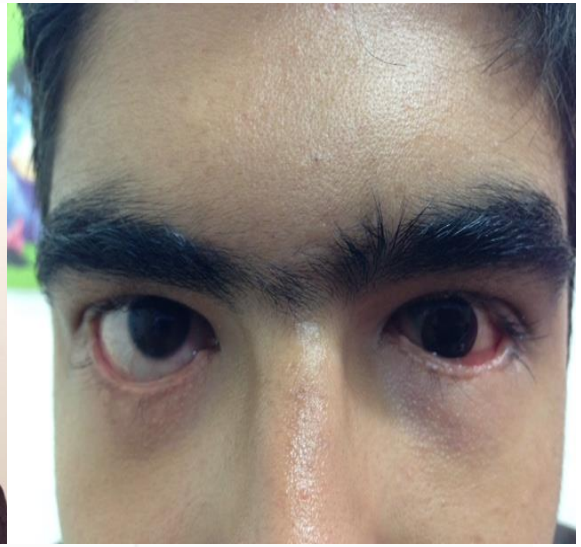


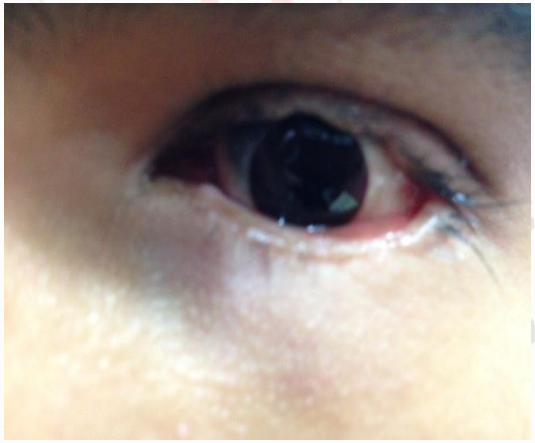
LCH is a rare disorder, which manifests in a wide variety of clinical presentations and courses, ranging from a solitary bone or skin lesion, called a “single-system disease”, to a disseminated, multiple-organ involvement, called a “multisystem disease”

- Vertembral involvement; L1(Observation)
- Vertebral involvement(L4) , and tissue mass, bones lytic lesions(Treatment)
- Vertebral (L4)and tissue mass(Treatment)
- Vertebral involvement L2(observation then 1 year later T6 involvement(Treatment)
- Proptosis, lymphadenopathy, hepatosplenomegaly,
- Pancytopenia,(Treatment)
- ❖ Respiratory symptoms Pneumothorax and bone lesion: (Treatment, expire)
- Pelvis bone involvement and limping (Treatment)
- ❖ Poly dipsia, polyuria(DI)(No treatment undr observe with MRI)
- Mobility of teeth,Teeth loss, (Treatment)
- Occypital swelling , Bone involvement(Treatment)
- Frontal swelling(New case)

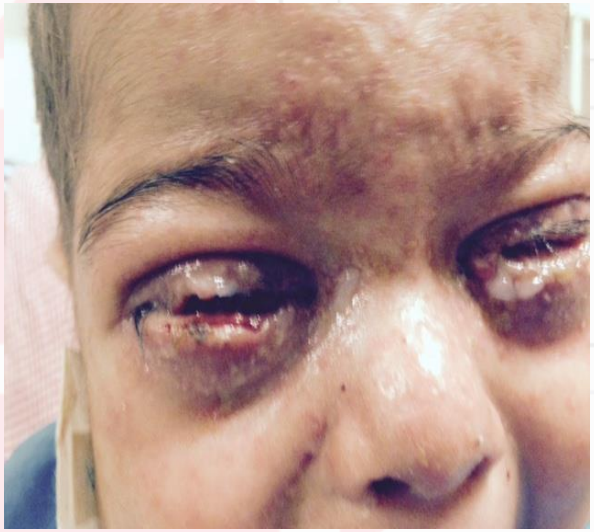
LCH –Case1

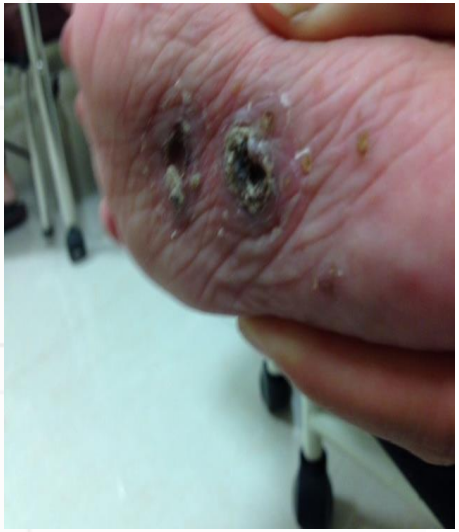


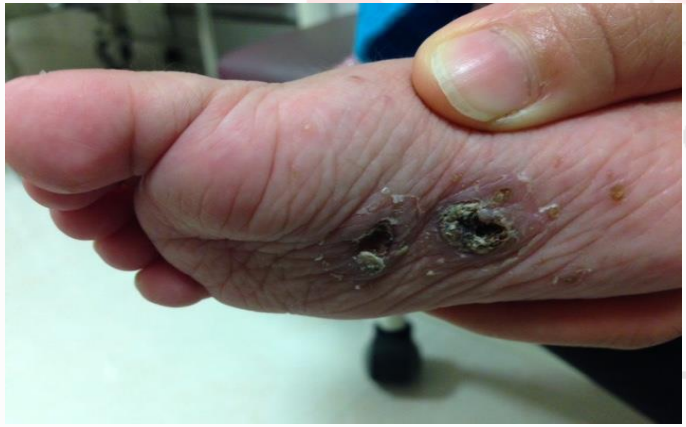


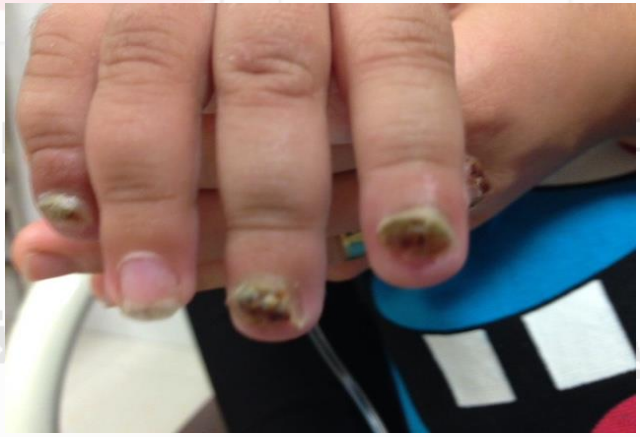


LCH-Case2

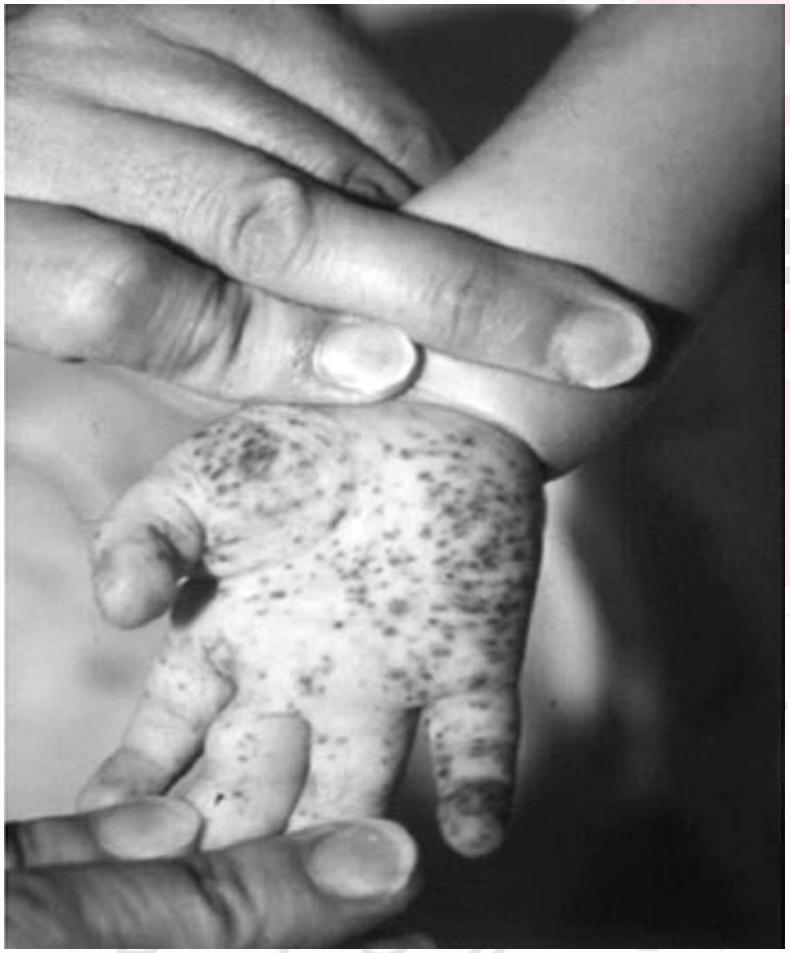


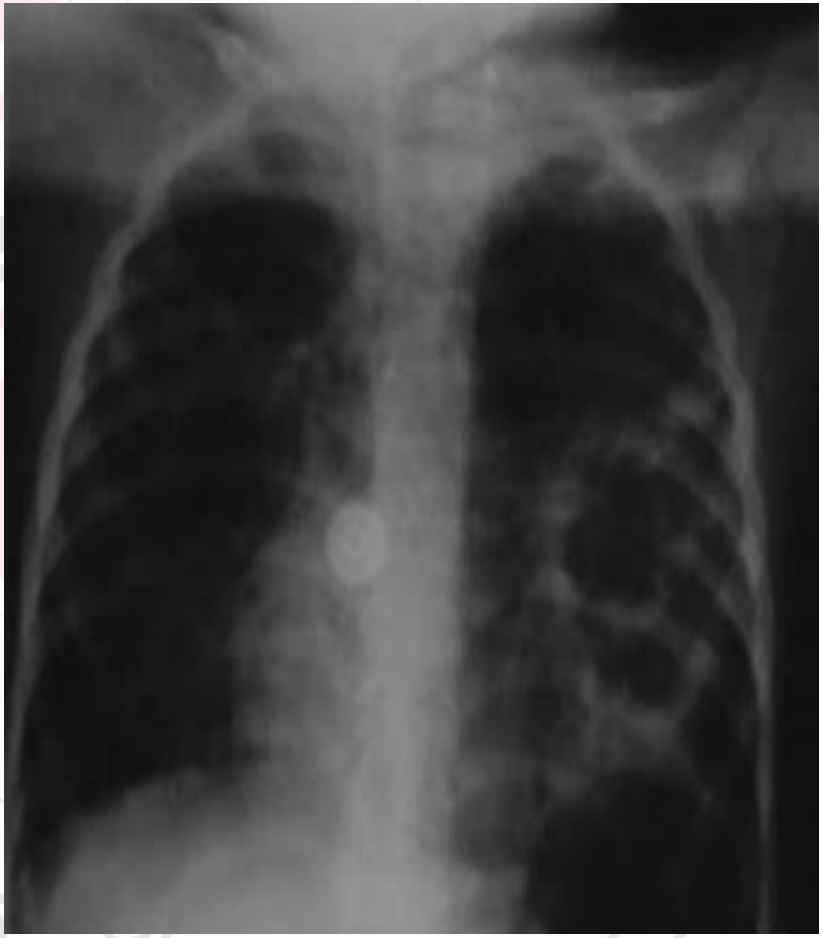






LCH Presentation





Neoplastic transformation vs Dysregulated immune activation of the epidermal LC.

- Langerhans cell histiocytosis (LCH) is a rare proliferative disease of cells that share phenotypic characteristics with Langerhans cells (LC), the primary antigen presenting cell of the epidermis.
- **pathogenesis of LCH ;???**
- LCH is a reactive **inflammatory or a Neoplastic disease**
-
- Blood-derived **CD207+ DCs** distinct from epidermal LCs are detected **in lymphoid and nonlymphoid organs where LCH lesions arise,**Making alternative origins of LCH cells plausible,

- Gene expression profiling is more consistent with the **LCH** cell being a **myeloid precursor than a differentiated epidermal LC.**

British Journal of Haematology, 2015, 169, 711–718
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Molecular analysis in LCH

- Recent molecular analysis of human LCH samples as well as mouse models suggests that the cell of origin may not be the epidermal LC itself, but a myeloid-derived precursor (Berres et al, 2014).
- Genomic screening :
- activating BRAF mutations in the majority of patient specimens
- Recently ARAF mutations (Nelson et al, 2014)
- Somatic MAP2KI mutations (Brown et al, 2014) in BRAF negative LCH patients.
- **Taken together, these observations now point to LCH as a myeloid neoplasm**

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Recurrent activating MAPK mutations in LCH.

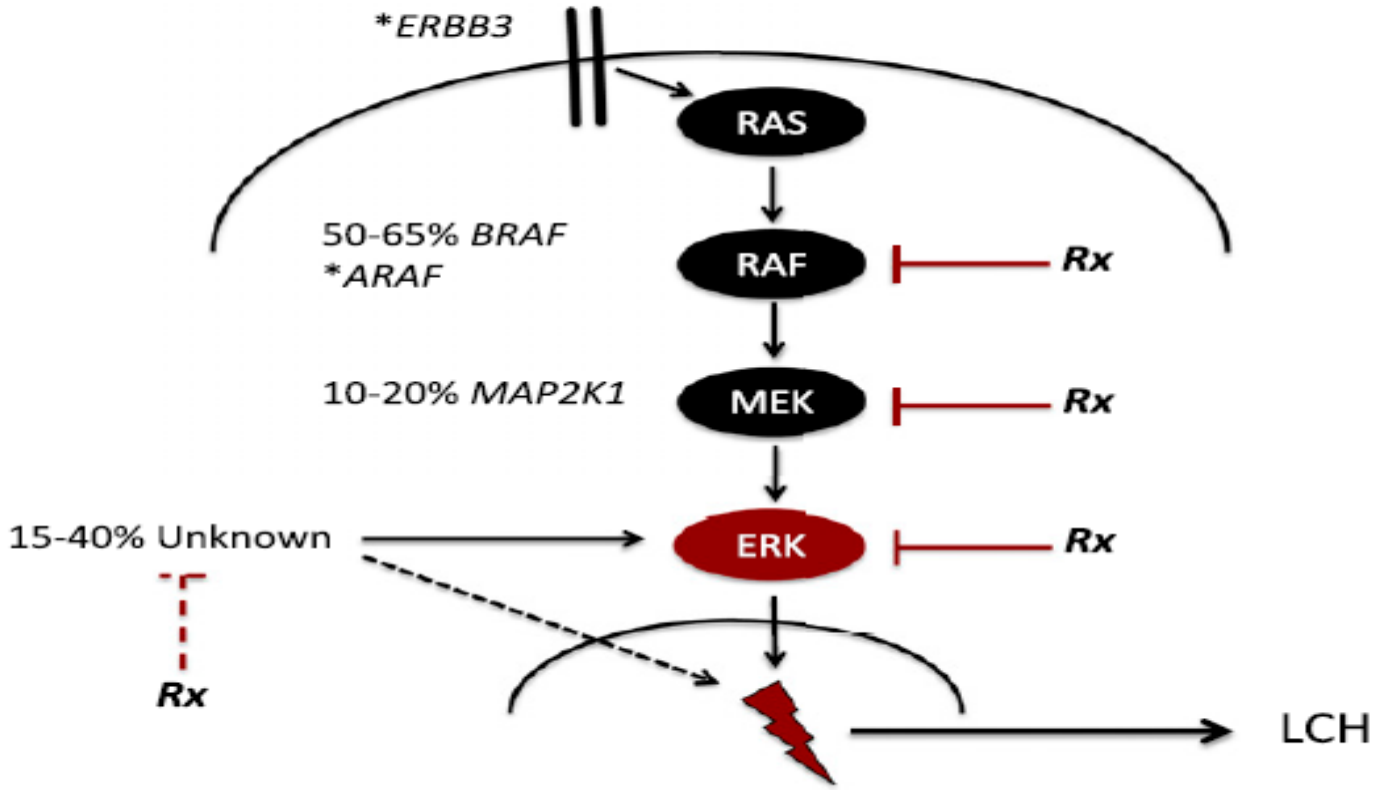
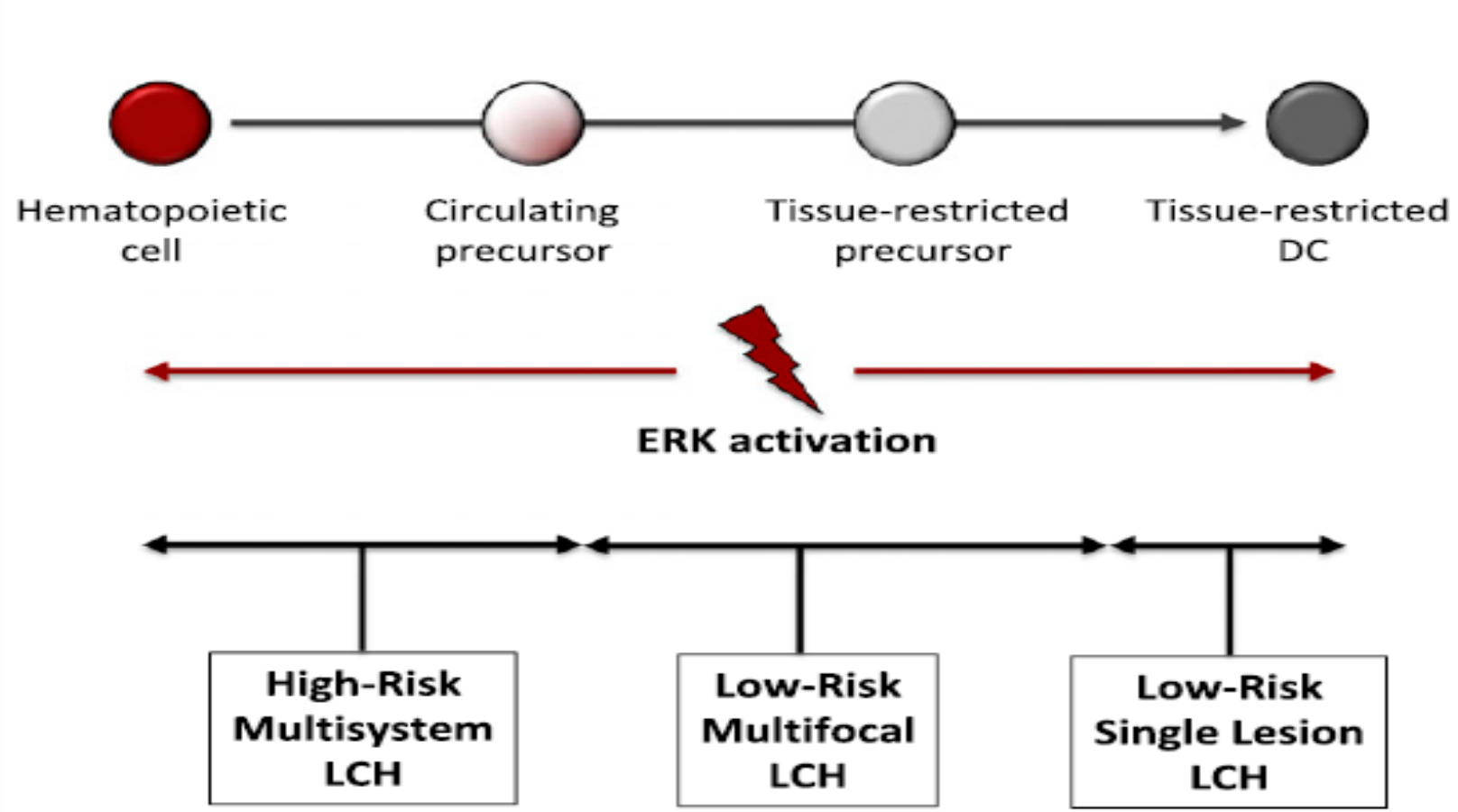


Figure 2. Recurrent activating MAPK mutations in LCH. Known recurrent

Misguided myeloid DC model of LCH pathogenesis



Diagnosis LCH

- LCH is a challenging diagnosis due to the spectrum of clinical manifestations and overlap with more common conditions

- **LCH usually follows a chronic course and reactivations often occur.**

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Pediatrics International (2014) 56, 451–461

Diagnosis/LCH

- **Biopsies** should be fixed in buffered formalin ,**72 hours**, to allow for histopathology, immunohistochemistry, and molecular analyses (gradeB2).
- Pathologic histiocytes in LCH are mononucleated cells with coffee bean– or kidney-shaped nuclei.

- **Detection of LC markers is mandatory to confirm the diagnosis.**

- In routine practice, detection of Birbeck granules by electron microscopy has been widely replaced by detection of CD1a and CD207 expression, which can be performed on formalin-fixed samples.

- LCH cells are often associated with abundant eosinophils and multinucleated giant cells.
- LCH ; association with other hematologic diseases **including RDD, Hodgkin disease, and acute leukemia**

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Malignancies- LCH

- ALL
- AML(Vp16, Radiation ,Alk agents)
- Solid Tumors

❖ **Mlignancy;precede, concurrent, after LCH**

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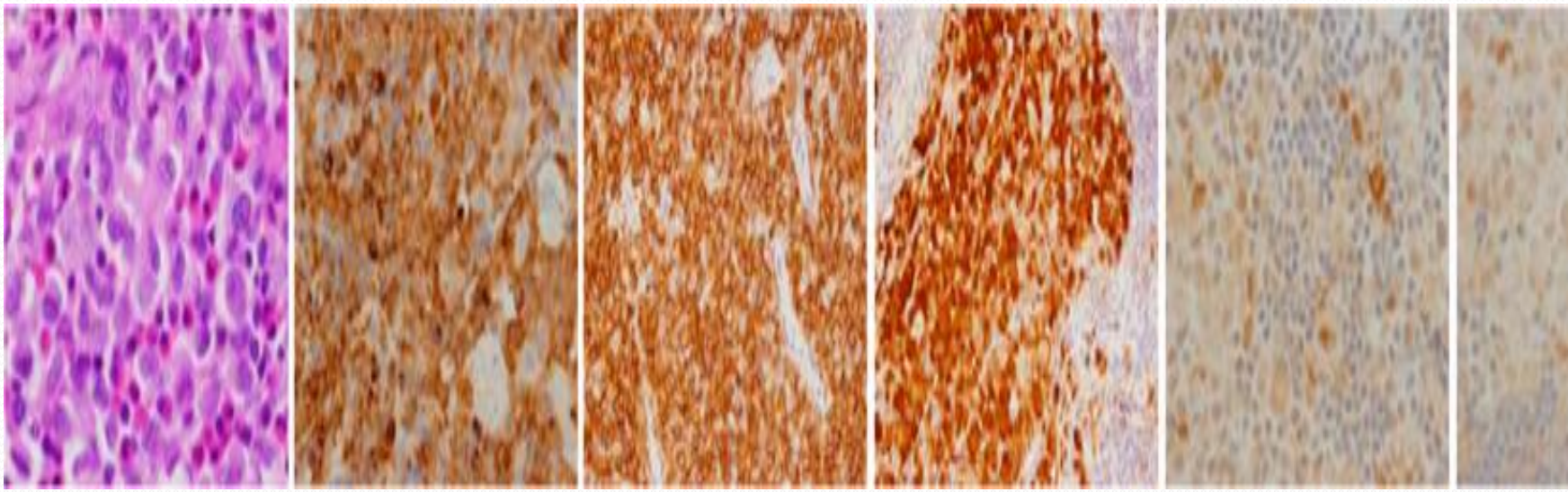
Pathologic "histiocytes" with reniform nuclei and eosinophilic cytoplasm are scattered among an infiltrate of lymphocytes, eosinophils, and macrophages.

The LCH cells react to immunostains for CD207, CD1a, and S100, but not for Fascin or factor XIIIa.

H&E 207 CD1A S100A Fascin FactorXIIIa



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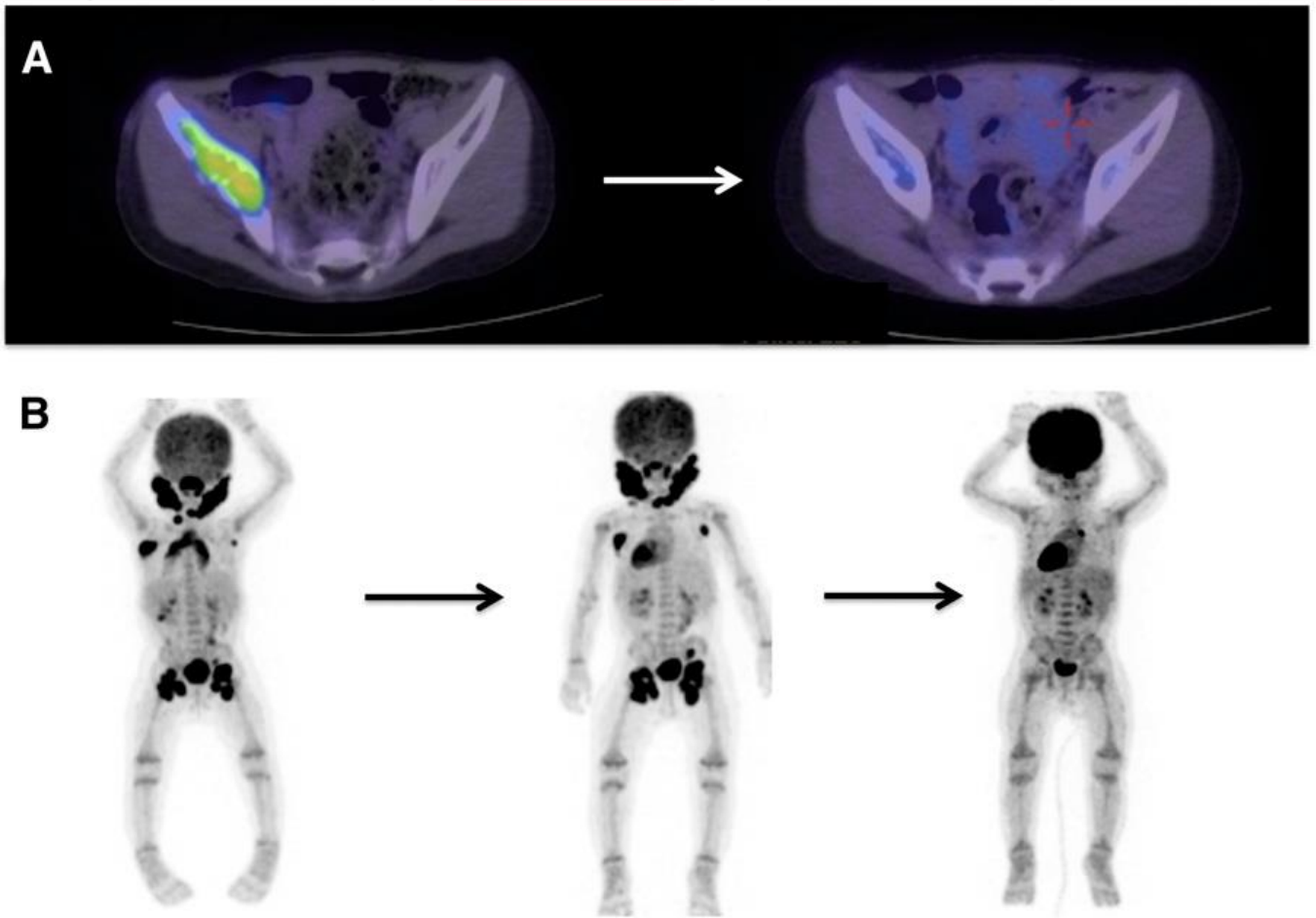
PET/CT scans are effective to stage disease and to evaluate response to therapy



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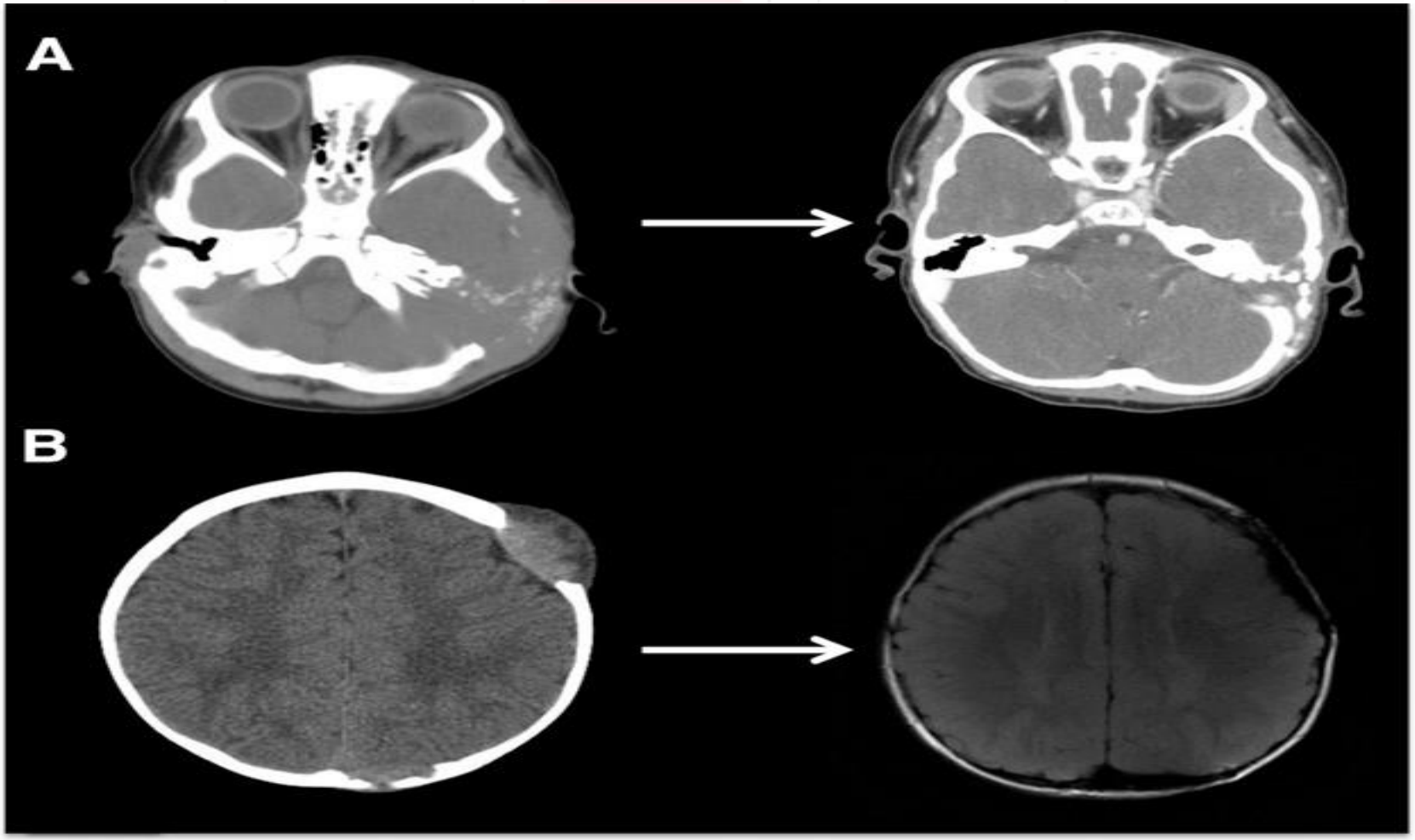
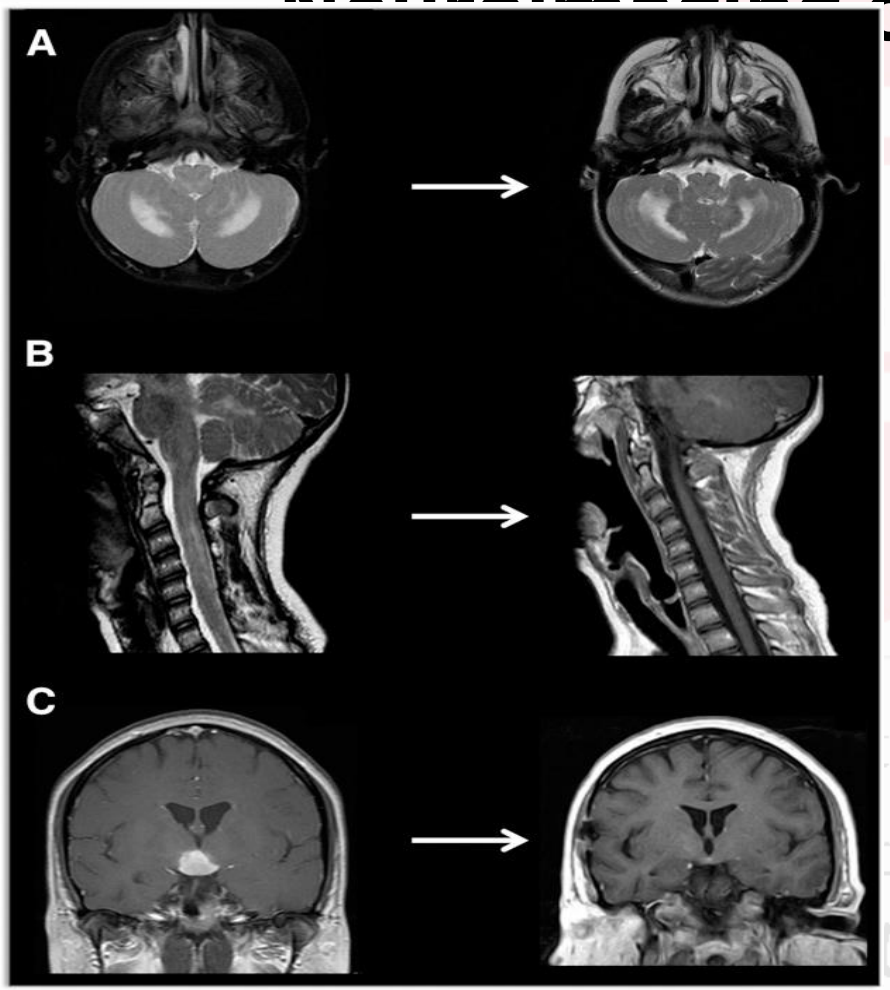
LCH bone lesions may remodel if margins remain intact.

Complete excision of LCH lesion with margins into healthy bone inhibits potential for remodeling. Following resections and successful chemotherapy, skull defects persist.



Neuroimaging of LCH lesions



(A) Brain MRI demonstrates T2- hyperintensity in **cerebellum classic** for LCH neurodegenerative syndrome. In this case, the patient had radiologic and clinical response to treatment with cytarabine.

(B) (B) Spinal MRI demonstrates significant spinal cord lesions. This is a somewhat atypical case of a **13-year-old girl** who had marginal response to **cytarabine**, then **clofarabine. BRAF-V600E was detected in cells from the CSF,** and the patient ultimately had radiologic and clinical response to vemurafenib.

(C) (C) **Brain MRI** demonstrates a pituitary mass classic for LCH, though differential diagnosis also includes **germinoma, lymphoma, and pituitary hypophysitis.** In this case, the lesion was biopsy proven to be LCH, and the patient responded to **cytarabine therapy.**

BMA/ LCH

- Current histologic approaches may be insufficiently sensitive to detect **bone marrow involvement.**

- Based on qPCR of bone marrow aspirate of patients with BRAF-V600ELCH lesions, bone marrow infiltration by BRAF-V600E1 cells is ,1% in most cases, and **half of the cases** reported as **histologically normal** had detectable cells with BRAF-V600E.

- The **relative insensitivity** of histological analysis is likely due to variable differentiation and **low level infiltration of LCH precursor cells**

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Skin

- LCH confined to the skin is rare and accounts for about **5% of the LCH population.**
- **Skin**:at any age, but is most common in **newborns and infants**
- **Most of these cases LCH tends to regress spontaneously, but progression to MS-LCH is common.**

liver

- **Hepatic LCH** is usually associated with elevated liver enzymes,hypoalbuminemia,or hypoproteinemia
- Imaging with **ultrasound or MRI** may show **hypodense areas along the biliary tracts.**
- Biopsy of the liver **rarely** shows **CD1a+ cells**, but more often **lymphocytes and monocytes** which **infiltrate the portal triads**.
- **Rarely, mass lesions with CD1a+** cells may also arise in the liver.
- **PET scans** are helpful in identifying involvement of the **spleen and liver**

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LCH/Liver-Lung

- Diagnostic confirmation may be a challenge in some circumstances (e.g., liver specimens), where **Birbeck granules are not present** and CD1a and/or Langerin may be negative because LCH cells have regressed after having caused **sclerosing cholangitis and Cirrhosis**.
- **Liver. Liver involvement is rare, but can cause serious morbidity**.
- In those with abnormal liver function consider **ultrasound scan, MRI of liver, or cholangiography** as clinically indicated.

- A subset of young children with liver involvement may subsequently **develop sclerosing cholangitis that progresses to cirrhosis**; treatment for these children includes **liver transplantation.**
- The **upcoming clinical trial for LCH in children (LCH-IV), the lung will be no longer considered a risk organ.**

Single system
Bones in LCH /treatment

- **Complete excision** of bone lesions (curettage) may be indicated if the lesion is small (**<2 cm**) and is combined with the diagnostic confirmation.
- **Radical excision of large lesions** (**>5 cm**) is not indicated since it increases the size of the bony defect, could prolong the time to healing, and might result in **permanent skeletal defects**
- For lesions **2–5 cms** in diameter, **a biopsy and partial curettage** is an option
- **Multi focal bones ;Vinblstin + corticosteroids**

Vertebral involvement

- **Vertebra plana**" per se is not an indication for an orthopedic corset, and expert physiotherapy assessment should be considered; however, temporary immobilization may be required for symptomatic relief in the early phases of vertebral involvement.
- certain functionally critical anatomical sites, such as the odontoid peg or other vertebral lesions with intraspinal soft tissue extension there may be an immediate risk to the patient because of the potential for disease progression and the hazards involved in attempting a biopsy; however, these are exceptional situations, and a biopsy should always be considered
- systemic therapy is indicated in patients with lesions involving the skull base, temporal bone, orbits, and vertebral column, where there is also involvement of the adjacent soft tissues.

LCH

- “clean”surgical margins are not required

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Diabetes insipidus /LCH

- IDI is not considered **an indication for systemic therapy per se,**

  when active disease is unequivocally documented by the presence of **thickening of the pituitary stalk** or **a mass lesion** of the hypothalamic-pituitary axis

- DI is with few exceptions uniformly irreversible, although DDAVP needs may vary.

- **Reports suggesting that treatment with :**
- **2-CdA Etoposide**
- **or radiation**
- **soon after DI onset may reverse the condition (evidence: D).**

High-risk patients

- **There are currently two promising treatment strategies for these high-risk patients.**
- combination of **2-chlorodeoxyadenosine and cytarabine inhibition of DNA synthesis** and **cell death**.
- promising approach is allogeneic (HSCT) because of its strong **immunomodulatory effects**

Paul A. Veys. British Journal of Haematology, 2015, 169, 711–718

Salvage therapy

- > 50% of patients with LCH will be refractory to initial therapy or develop recurrent disease,with the majority of reactivations occurring in the first 2 years.
- **Agents used in treatment of acute myeloid leukemia,**including **cytarabine, cladribine, and clofarabine**.

- Lower-dose **cladribine** (5 mg/m2 per day x 5 days per month x 6 months) was effective in achieving a response in patients who were refractory to frontline therapy withr esponse rates of 22% in patients with risk-organ involvement and 62% in patients with out risk-organ involvement ,but only 4% were cured by week24.

- **Intermediate-dose cytarabine(100-170mg/m2** perday)was associated with 41% progression-free survival in an institutional series.
- By comparison, **a salvage strategy ;cytarabine** (**1 g/m2 per day**) and **cladribine**(**9mg/m2 per day x5 day ,** with **extremely high treatment-related toxicity**.

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–Nucleoside analog

Clofarabine

- **Clofarabine** is a second-generation nucleoside analog with activity in refractory acute myeloid leukemia.
- The majority of patients in the LCH series received **25mg/m2** perday (**5days per cycle**) **for 6 cycles** as outpatients

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Clofarabine salvage therapy in refractory multifocal histiocytic disorders, including Langerhans cell xanthogranuloma and Rosai-Dorfman disease. histiocytosis, juvenile .Simko SJ

Pediatr Blood Cancer. **2014** Mar;61(3):479-87.

- **BACKGROUND:**
- **18PATIENTS**
- **LCH (11 patients), systemic JXG (4 patients), and RDD (3 patients).**
- Texas Children's Hospital **2011 -2013**
- **RESULTS:**
- Patients were treated with a median of three chemotherapeutic regimens prior to clofarabine. Clofarabine **25 mg/m(2) /day for 5 days every 28** days for a median of **six cycles** (range: **2-8 cycles**).
- **17/ 18 patients are alive.**
- All surviving patients showed demonstrable improvement after two to four cycles of therapy, with **11 (61%) complete responses**, 4 (22%) partial responses, and 2 patients still receiving therapy.
- Five recurrence, but three of these subsequently achieved complete remission.
- **prolonged neutropenia, severe vomiting, and bacterial infections.**

Response Evaluation

- The evaluation of the disease response is usually classified
- "**Better**" in case of **complete resolution** or **regression of the disease**,
- "**worse**" in case of **progression of the disease**,
- "Intermediate," in case of **stable** or **mixed response with new lesions in one site, and regression in another site.**

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Follow-Up/Duration and Frequency

- All patients should be followed for a sufficient time period, defined as
- (i) at least 5 years after the end of therapy
- ; or
- (ii) 5 years after the last disease reactivation, in those who did not receive systemic therapy; or
- (iii) until final growth and pubertal development have occurred.

Case presentation

- A newborn has a scaly rash diagnosed as “cradle cap.”
- Due to persistence despite topical therapy for 2 months, a skin biopsy is diagnosticofLangerhanscell(LC)histiocytosis(LCH).Evaluation for other sites of disease reveal shehas“skin-only”LCH.
- By 4months,the rash begins to resolve without therapy and by 1 year it disappears.

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Case 2

- A **newborn** has a **scaly rash** diagnosed as "**cradle cap**." The rash persists, but no investigations are done until **22 months** when she develops **dyspnea**
- Chest radiograph shows a diffuse interstitial pattern and computed tomography (CT) scan reveals large pulmonary cysts and nodules.
- Magnetic resonance imaging **(MRI)** of her pituitary shows absence of the posterior bright spot and an **enlarged stalk.**
- (PET) scan : abnormal uptake in **mastoid, liver, spleen, and lungs.**
- **Biopsy mastoid** ;LCH.
- Bone marrow biopsy does not demonstrate CD1a1/CD2071 histiocytes, but quantitative (qPCR) estimates 1% of marrow aspirate cells carry the BRAF-V600E mutation.
- She is treated with vinblastine/ prednisone for **12weeks** with **no response**. She then receives cytarabine for 2 months with little change in the PET scan and her rash persists.
- **Finally**, she is treated with **Clofarabine** and achieves a complete remission

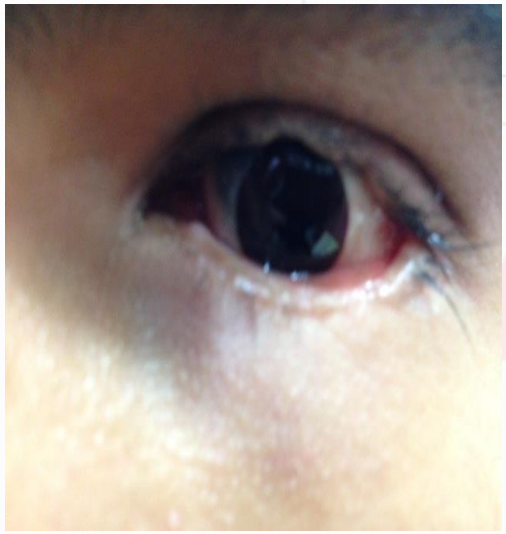
Case 3

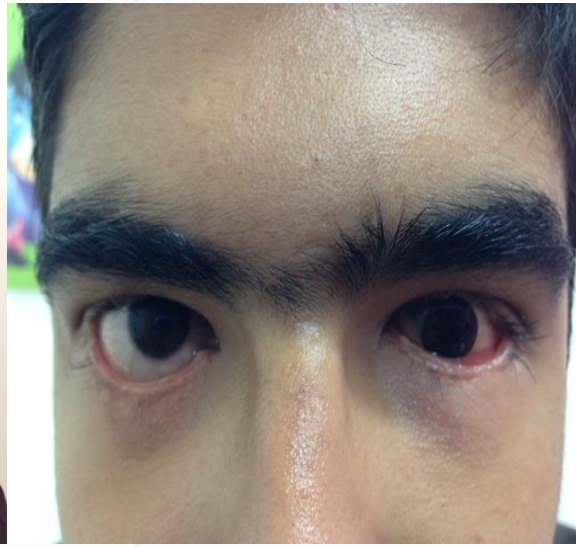
- A 6 month old boy was admitted in our hospital in 1998
- He was 3th child of non cousins parents. He had presentation of macula-papular rash at age of 4 month , then upper and lower palpebral leaions in both eyes including severe blisters and mucopurlent discharges .He had history of vistit by physicians and ophthalmologist which were not helpful
- physical examination he had maculopapular skin rash , palpebral ulserative lesions and left eye cloudiness
- tests results were as below; WBC: 8000/ul, Hb: 11.2gr/dl, Platelet:343,000/ul.
- LDH: iu/ml.FT and urine analysis: normal (SG: 1026).

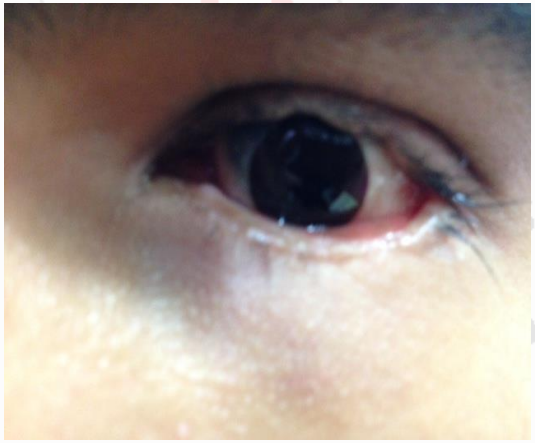
Case 3

- Abdomial sonography,Bone survey and Bone marrow aspiration(BMA);normal.
- CT revealed destructive lesion in left mastoied bone ,but orbital site and other parts of brain were normal.
- Biopsy of skin lesion and immunohistochemistry (IHC-CD1a) was compatible with LCH.
- Patient received treatment including 12 weeks of Vinblastin 6mg/m2 and Prednisone 40mg/m2 for 12 weeks,then oral maintenance therapy with 6MP 50mg/m2 /day and Metothraxate(MTX)20mg/m2/week.
- Surgery was done for palpebral repair and left eye lensectomy duo to cataract . Treatment was discontinued after 1 year of maintenance therapy.
- Now he is an 18 years old young man,He has decrease vision of left eye ,also scars duo to palpebraal lesions, but otherwise he is good.

LCH –Case3







Case 4

- An 18 months old boy ,3th child of first cousins parents, from Iraq was reffered to our hospital in 2016
- **He had history of fever, papulo- vesicular rash especially in head and face, orbital swelling , severe inflamation, ulseration in both upper and lower palpebral and purlent discharges of both eyes since 8 month ago .**
- **He had history of visiting and treatment without response.**
- **In physical examination he had generalized papular rash especially in head and neck, palmar of hand and foot,severe nail involvement, lymphadenopathy , massive hepatomegaly, splenelomegaly and icterus**
- **Evaluations were as below;**
- **WBC: 32,000/ul ,Hb: 9 gr/dl,Platelet: 810,000/ul, Neutrophil:72%, Llymph: 18% ,ESR:80 mm/hr, Retic: 1%,**
- **Direct and Indirect Coombs tests: Negative, Bil T : 7.3mg/dl, Bil D: 5.1mg/dl , SGOT : 295iu/l , SGPT: 310 iu/l, Alk : 2750 iu/ml,**
- **TFT: Nl, Ig level: Normal,Virology tests: Normal.**
- **Bone survey: Ill defined lytic lesions in proximal metaphysysis of right femur , left tibia and distal metaphysis of left femur**

Case 4

- Abdominal Sonography:Hepatomegaly, hypodense lesions about 10-12 mm in liver.
- CT of neck : Bilateral lymphadenopathy , Chest and abdominal CT: lymphadenopathy of right paratracheal, axillary, supraclavicular.
-
- Hepatomegaly with multiple hypodense lesions , retroperitoneal lymphadenopathy .
- Color Doppler of liver: Normal
- BMA :Hyper cellular,BM.
- CD Flowcytometry; Polymorphic population.

Case4

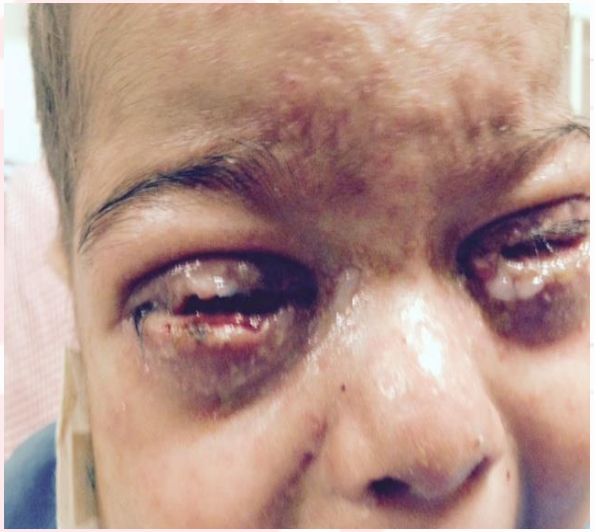
- Cardiac Echo: Normal and EF: 60%.
- Histopathology report of Skin (Face & Sole, Scalp), Cervical Lymph node and Nail biopsy: LCH
- IHC: CD1a, PR S100,CD68: positive.
- Treatment was started ; Vinblastin 6mg/m2/week x 12 times ,prednisone 40 mg/m2 /day for 6 weeks then prednisone 40mg/m2 for 3 days /week for 6 weeks more , Vp16 100 mg/m2 ,IV infusion every 2 weeks(as a whole 4 doses)
- Ophtalmology consult showed no vision problem, he received just local treatment and antibiotic therapy.

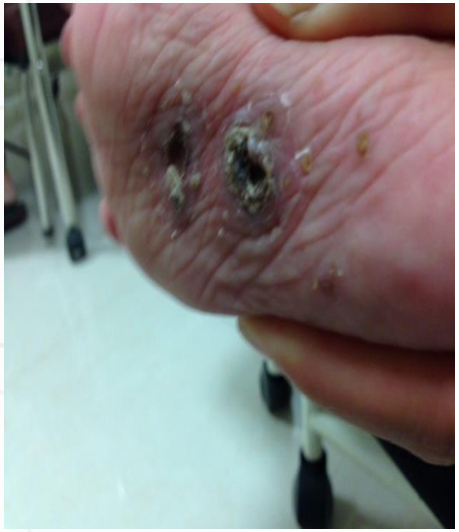
Case 4

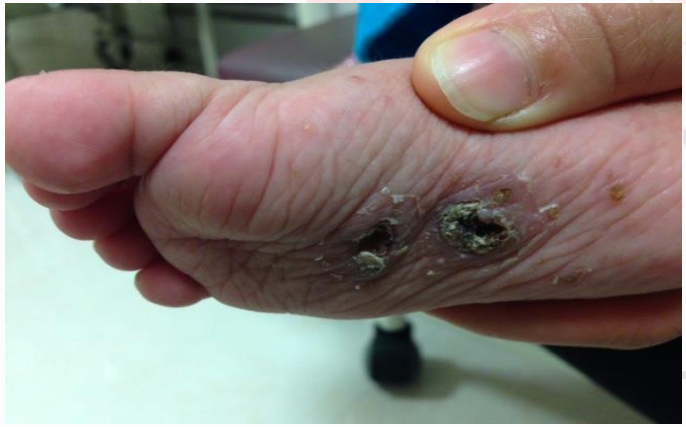
- Evaluation after 3 month showed partial response including very good improvement of skin lesions , nail and palpebral lesions ,
- Still he had persistant massive hepatomegaly.
- Lab tests showed ; WBC:7300/ul, Hb; 11. 3gr/dl, platelet; 900,000/ul, ESR: 20mm/hr ,
- SGOT 59 iu/l, SGPT:81 iu/l , BilT: 1.9mg/dl Bil D:1.3mg/dl , PT and PTT ;Normal.
- LDH : 314 iu/l.
- Treatment of 2-chlorodeoxyadenosine (2CDA) was started
- Now treatment he is in Course 2 with 2 CDA and Cytozar

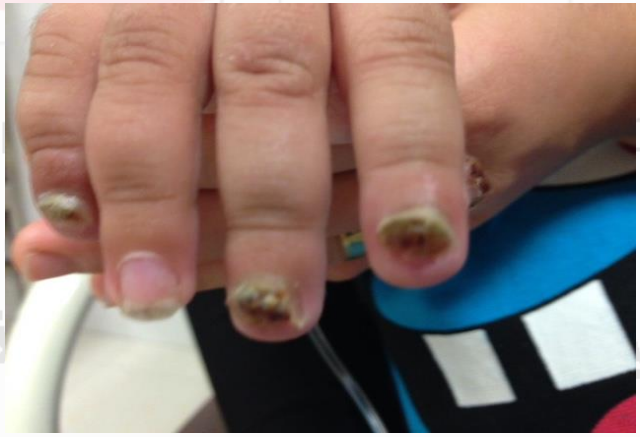
- **He has 2 Sibling**
- **HLA typing was done for HSCT??????**

LCH-Case2

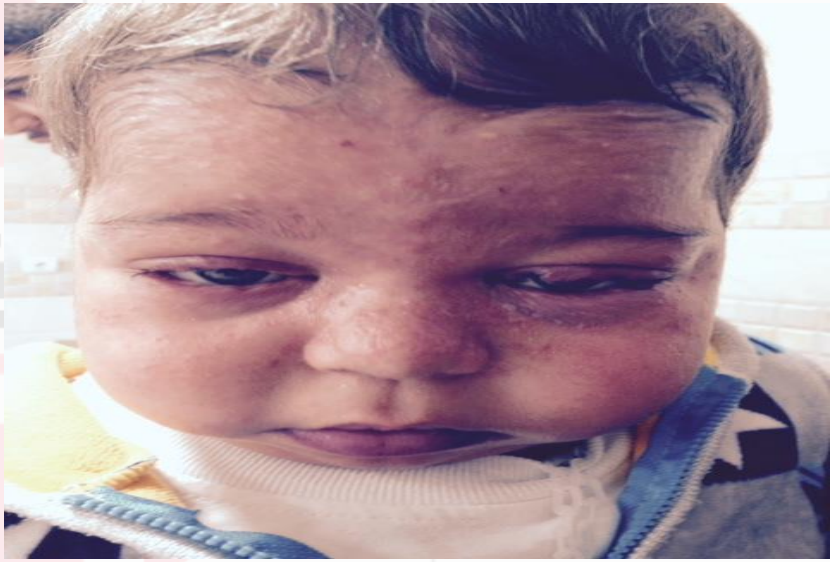


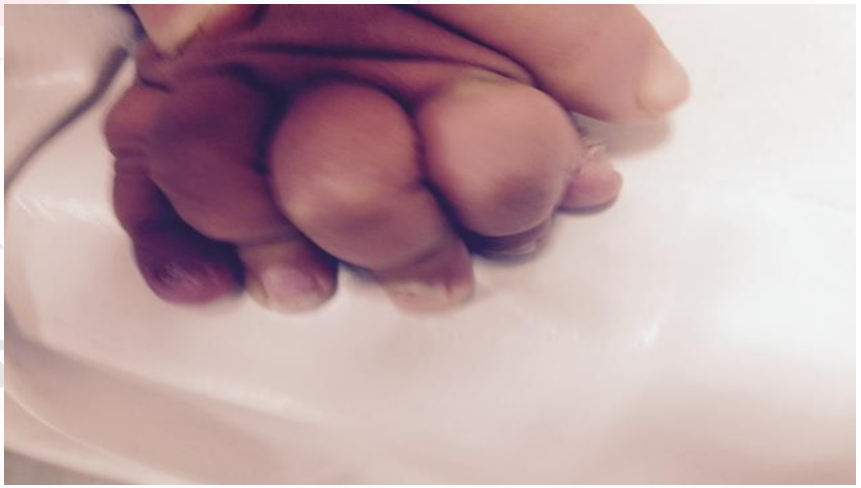






LCH- Case2





Salvage therapy

HSCT in LCH

N Kinugawa.Hematopoietic stem cell transplantation (HSCT) for Langerhans cell histiocytosis Bone Marrow Transplantation, (1999) 24, 935–938 (LCH) in Japan

- 4 Japanese pediatric patients with multisystem LCH disease who underwent HSCT between **1994 and 1997**.
- 2/4 patients are; doing well without any relapse.
- However, **neither of them shows improved sequelae 3 to 4 years after allogeneic HSCT,**
- Graft was rejected in one of the cases.
- The remaining **2 patients died of septic shock**.

- A review of the literature of **11 patients** revealed 4 **fatalities** after the use of HSCT in the treatment of LCH.
- 3 of these were due to active LCH and three deaths occurred within 2 months after HSCT.
- To establish the usefulness of HSCT for refractory LCH, further studies are required

- **11 HSCT cases for refractory LCH were collected from the literature. 7 cases were still alive with remission times ranging from 12 to 168 months**.

Caniglia, M.HEMATOPOIETIC STEM CELL TRANSPLANTATION IS EFFECTIVE CURATIVE TREATMENT IN PEDIATRIC **Italy.**

LANGERHANS CELL HISTIOCYTOSIS. **Biology of Blood and Marrow Transplantation.February 2005**

- 4 children, age 14 months (patient 1), 27 months (patient 2), 96 months (patient 3), and 48 months (patient 4), with **refractory aggressive MS-LCH** who were treated with **A- HSCT in our institution between 2001 and 2003**
- 1 and 3 received **umbilical cord blood transplantation** (UCBT) from HLA **4/6 and 5/6 mismatched unrelated donors**.
- Patients **2 and 4 received bone marrow transplantation (BMT)** from **related HLA-identical donors**.
- **A conditioning regimen ;**
- Busulfan 4mg/kg and Fludarabin30mg/m2 from day-7to day -4 and thiotepa 10 mg/kg on day - 3 was used as preparative regimen.
- All patients received **horse ATG 15 mg/kg from day -6 to day -2, Cyclosporine A** 3 mg/kg from day -1 to day- 180, and **PDN 1 mg/kg until day +30.**

- **After HSCT, all patients are alive with a median follow-up of 30 months**

Cooper.N, The use of reduced-intensity stem cell transplantation in haemophagocytic lymphohistiocytosis and **Langerhans cell histiocytosis**. Bone Marrow Transplantation **Great Ormond** Street Hospital for Children NHS Trust, London, **UK. (2008) 42, S47–S50**

- Allogeneic stem cell transplant is curative for (HLH) and refractory Langerhans cell histiocytosis (LCH). However, patients frequently have significant pre-transplant morbidity and there is high TRM.
- Because HLH is caused by immune dysregulation, we surmised that a reduced-intensity conditioned (RIC) regimen might be sufficient for cure, while decreasing the TRM.
- Here we discuss total of **25 patients treated with RIC SCT for HLH and 3 for LCH.**
- **Twenty-one** of the twenty-five patients with HLH (84%) are alive and well with remission at a median of 36 months from SCT. Mortality included **pneumonitis (n=3) and hepatic rupture (n=1)**.
- **All three patients treated with RIC SCT for LCH remain alive and in remission at a median of 5.1 years from SCT.**
- 7/24 survivors (**one with LCH**) **have mixed chimerism but remain disease-free.**
- **In summary, RIC compares favourably with conventional SCT with long-term disease control in surviving patients with both HLH and LCL, despite a significant incidence of mixed chimerism**

Cooper.N, The use of reduced-intensity stem cell transplantation in haemophagocytic lymphohistiocytosis and Langerhans cell histiocytosis. Bone Marrow Transplantation (**2008)** 42, S47–S50 .Great Ormond Street Hospital for Children NHS Trust, London, UK

- **RIC in LCH**
- 3 patients with LCH with RIC SCT at Great Ormond Street Hospital between 2002 and 2008.
- **2 had failed** to respond to standard chemotherapy and one had an early relapse of LCH
- Patients were **aged 3, 18 and 24 months** and received matched sibling donor-SCT (n=1) or MUD-SCT (n=2).
- All received **Campath-H1 0.2mg/kg/day x4, fludarabine 30mg/m2 x 5 and melphalan 140mg/m2 (day - 2).**

- **All three remain alive and well 6 months, 5.1 and 6 years from transplant.**

- **One patient has mixed chimerism with 70% donor whole blood**, 49% granulocytes, 60% mononuclear cells and 50% DCs and remains in remission.

Jun Y, Haploidentical parental hematopoietic stem cell transplantation in pediatric refractory Pediatr Transplantation 2014: 18: E124–E129 Langerhans cell histiocytosis..China

- **Abstract:** Children with MS-LCH that fail to respond to conventional chemotherapy have poor outcomes
- HSCT represents a potential salvage approach.
- It has been applied in over **56 cases** in recent years.(**35/56 survived**) (21 of the 56 patients **died**)
- **8/56** patients Haploidentical **transplantations**, but unfortunately, **6** /8 died.
- 1 autologous recovery; and 1 second transplantation from a MUD HSCT can achieve greater disease control than chemotherapy, but it carries a high risk of transplant-related mortality; thus, the **haploidentical parental HSCT is used infrequently in pediatric refractory LCH.**
- We report the first successful haploidentical parental HSCT, with no T-cell depletion, in **two girls, aged 26 months and five months**, with **refractory MS-LCH**. The **mothers** :5/6 and 4/6 HLA matches, respectively.

Jun Y, Haploidentical parental hematopoietic stem cell transplantation in pediatric refractory Pediatr Transplantation 2014: 18: E124–E129 Langerhans cell histiocytosis.
China

- Conditioning regimen **included Busulfan + Cyclophosphamide +Etoposid e + antithymocyteglobulin +/-;**
- GVHD prophylaxis was based on ;Cyclosporine + MTX +/- mycophenolate-mofetil +/- **zenapax.** (Daclizumab , Anti Mc Ab CD 25)
- stem cells :peripheral ;PB and BM, which included **CD34+ cells (13.17 x 106/kg and 40.23 x 106/kg, respectively).**
- **Day o : high ose MSC**
- patients survived and showed no signs of disease activity in 54- and 44-month post-HSCT follow-ups.
- **DI improved in Case 1 clinically and imaging ??? (M – SC high doses)**
- Our results indicated that, for patients that fail chemotherapy delivered early in the disease, but do not show organ dysfunction progression, it may be possible to achieve successful haploidentical parental HSCT with a **strong myeloablative regimen**

Haematopoietic stem cell transplantation for refractory Langerhans cell histiocytosis: outcome by intensity of conditioning

- **87 patients** databases CIBMTR and EBMT
- **1990-2013**
- Donors included; human leucocyte antigen (HLA)-matched siblings, HLA-mismatched relatives and HLA-matched or mismatched unrelated donors

- Transplant period **prior to 2000**.
  - 20 patients
  - 18 Mac, 2 RIC.
  - 5 patients who are alive, with a median follow-up of **14.5 years**
  - both patients who received a **RIC,died**

British Journal of Haematology, 2015, 169, 711–718

OS and DFS

- After period 2000 26 RIC/ 41MAC/whole patients 67
- Transplant period 2000; 19/26 RIC alive
- overall and disease-free survival after MAC and RIC transplantation were similar.

- There were no significant differences in terms of TRM, however, relapse rates after RIC transplantation were marginally higher compared to after MAC transplantation

British Journal of Haematology, 2015, 169, 711–718

Discussion

- Reasons: better supporticve care
- Electetion to treat higher risk patients with RIC procedures
- Behaviour of myeloid malignancy with an increased relapse rate after RIC transplantation (so may be???- myeloablative but reduced toxicity protocols, such as the addition of thiotepa to fludarabine and melphalan…

- **4/6 patients who relapsed after RIC HSCT attained a further remission with chemotherapy, implying these patients are relatively easy to salvage.**

British Journal of Haematology, 2015, 169, 711–718

Discussion

- The observed lower incidence of acute GVHD in the setting of RIC transplantation despite the higher number of patients receiving peripheral blood progenitor cells reflects the increased use of serotherapy with RIC regimens.
- The use of serotherapy might also explain the trend to higher infectious-related deaths in the RIC regimen

British Journal of Haematology, 2015, 169, 711–718

Discussion

- Most patients achieved 100% donor chimerism; amongst those with mixed donor chimerism, there was a significant increase in disease progression or relapse; this is again reminiscent of the behaviour of a malignant disease

British Journal of Haematology, 2015, 169, 711–718

Discussion

- At several of the institutions represented by the authors of this manuscript the current policy is to treat refractory LCH with 2-chlorodeoxyadenosine and cytarabine.
- At the same time a search is initiated for potential HSCT donors.
- If there is no response after 2 courses of salvage chemotherapy and a donor has been identified, patients proceed to HSCT

British Journal of Haematology, 2015, 169, 711–718

Late effects

- vertebral lesions
- LCH causes **extensive damage to the bile ducts**, progressive **sclerosing cholangitis** may develop, most often resulting in **liver failure with** the need for **liver transplantation**
- **DI**
- Neuropathy, learning difficulties, and growth and development abnormalitie

Target Therapy

- **Inhibition of MAPK activation**
- In melanoma trials, **vemurafenib** is associated with a complex toxicity profile, **including secondary squamous cell carcinoma** in over **30% of patients**, and case reports of more serious adenomas.

Conclusion

HSCT may be a curative therapy in three out of four children with high risk LCH that is refractory to chemotherapy, however the optimal choice of conditioning intensity remains uncertain.

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Risk Stratification

- **Disseminated disease**
- **Liver dysfunction with coagulopathy,together with refractory thrombocytopenia** and sometimes a secondary HLH, is associated with a **high risk of lethal haemorrhage**.
- **Neutropenia and a poor nutritional status due to malabsorption and enteral protein loss contribute to the increased risk of sepsis**

Paul A. Veys. British Journal of Haematology, 2015, 169, 711–718

THANK YOU