HSCT for Congenital neutrophil Disorders

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Introduction

- divides neutrophil disorders into four broad categories:
- Congenital neutropenia associated with syndromic disease
- Congenital neutropenia associated without syndromic disease, and
- functional neutrophil defects with syndromic disease
- functional neutrophil defects without syndromic disease

Usual Clinical manifestations

- Affected patients can present with variable symptoms including
  - recurrent infections,
  - failure to thrive, and
  - overwhelming septic episodes leading to high morbidity and mortality.
- CGD
  - Early and severe respiratory infections
    - (e.g., Burkholderia cepacia, Aspergillus spp.),
  - visceral abscesses,
  - cellulitis,
  - lymphadenitis, and
  - granulomatous lesions

Complications

- Some patients develop severe autoinflammatory complications
  - underlining the role of neutrophils in autoinflammatory processes beyond microbial defense
- In many of these diseases there is a recognized risk of progression to myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML)

Management

- Treatment for neutrophil disorders classically comprises
- anti-microbial therapy,
- granulocyte-colony stimulating factor (G-CSF), and
- allogeneic hematopoietic stem cell transplantation (allo-HSCT)

Syndrome-Associated Neutropenia

Disease	Main Clinical Manifestations	G-CSF responsive	MDS/AML risk progression	HSCT successful evidence
SDS	Bone marrow failure, Exocrine pancreas dysfunction, Malabsorption, Skeletal abnormalities, Neurocognitive deficit, Recurrent infections	Yes	Yes (15-30%)	Yes
G6PC3 deficiency	SCN, thrombocytopenia, CHD, Urogenital anomalies, Dysmorphism, G & D delay, Crohn's, steatorrhea	Yes	Yes	Yes
Glycogen storage disease type 1b	Neutropenia, Hypoglycemia, Recurrent infections, IBD, Liver diseases and hepatosplenomegaly, ↑TG	Yes	Yes	Yes
Cohen syndrome	↓fetal activity and lBW, Neutropenia/SCN, Obesity, Hypotonia, Dysmorphisms, dental anomalies, poor vision, limb abnormalities, Intellectual disability	Yes	None reported	No
Barth syndrome	Neutropenia, Dilated cardiomyopathy and rhythm abnormalities, Skeletal myopathy, Growth delay, Developmental delay, Hypoglycemia, Early death	Yes	None reported	No
Clericuzio syndrome (Poikiloderma with neutropenia	Eczema, Poikiloderma, Nail dystrophy, palmar/plantar hyperkeratosis, Reactive airway disease Hypogonadotropic hypogonadism, infection	Yes	Yes	No

Syndrome-Associated Neutropenia

Disease	Main Clinical Manifestations	G-CSF responsive	MDS/AML risk	HSCT successful evidence
VPS45 deficiency	***Neutropenia non-responsive to G-CSF,*** Extramedullary hematopoiesis with organomegaly, Nephromegaly	No	Unknown	Yes
P14/LAMTOR2	SCN, Partial albinism, B-cell deficiency, CD8 deficiency Coarse facial features	Yes	None reported	No
JAGN1	SCN, Recurrent infections, Bone, dental, pancreatic insufficiency, Failure to thrive, Developmental delay	Variable	Yes	Yes
3-methylglutaconic acid	SCN, Recurrent infections, Progressive brain atrophy with intellectual disability, Movement disorder, Cataracts, Movement disorder	Yes	Yes	No
SMARCD2	Neutropenia, Delayed separation of the umbilical cord Recurrent infection, Chronic diarrhea, Developmental delay, Dysmorphic features	No	Yes	No
WDR1	Neutropenia with impaired lymphoid function, Mild learning disability, Aphthous stomatitis and skin ulcers, Pneumonia, Gout, Pancreatitis, Glioblastoma	Unclear	Yes	No
HYOU	Neutropenia, Recurrent oral herpes infection, Hypoglycemia, Autoimmunity	Yes	None reported	No

Neutropenia Without Syndromic Disease

Disease	Main Clinical Manifestations	G-CSF responsive	MDS/AML risk progression	HSCT successful evidence
SCN1 (ELANE, AD)	Neutropenia, Recurrent bacterial skin infections, Abscess formation, Gingivitis, FTT, Can cause cyclic neutropenia	Yes	No	Yes (indicated if high doses of GCSF needed)
SCN2 (GFI1, AD)	Recurrent bacterial skin infections, Abscess formation Gingivitis, FTT, Mild lymphopenia	Yes	None reported	Not reported
SCN3 (HAX1, AR)	Neutropenia, Recurrent skin infections, Gingivitis, FTT, Abscess formation, Neurological impairment	Yes	Yes	Yes
X-linked neutropenia (WAS)	Neutropenia, Bacterial infections, Lymphopenia and monocytopenia, Autoimmune enteropathy	Yes	Possible	Not reported
G-SCF receptor Deficiency (CSF3R)	Cases of acquired somatic mutation in AML/MDS	Yes	Yes	HSCT for mutation detected
Neutropenia with combined immune deficiency	Severe bacterial and fungal infections, BCG-related disease, Abscess formation, Mild thrombocytopenia FTT	Not reported	Not reported	Not reported

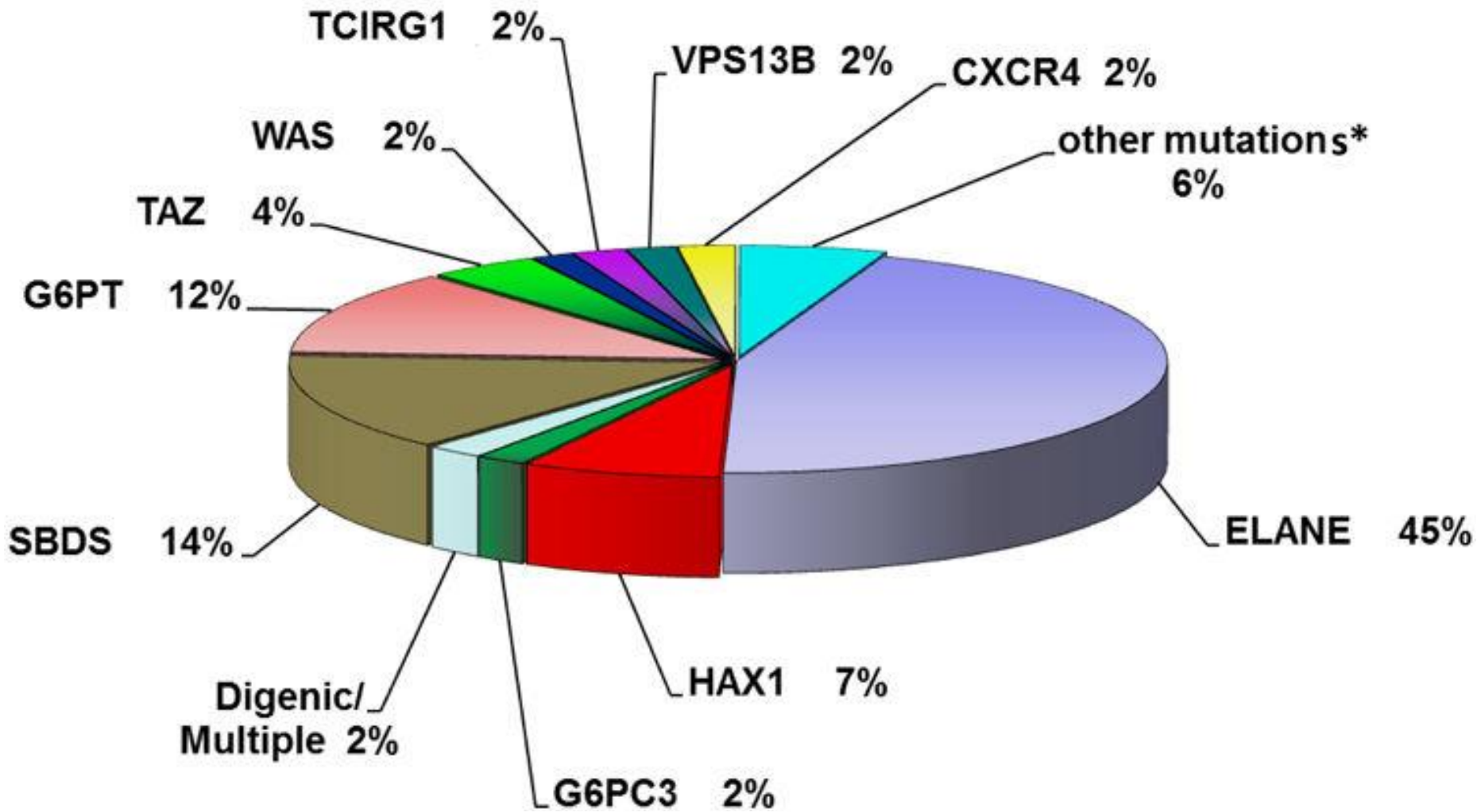
Phagocyte Function With Syndromic Disease

Disease	Main Clinical Manifestations	G-CSF responsive	MDS/AML risk progression	HSCT successful evidence
CFTR--dependent LAD type IV	**Clinical features of cystic fibrosis**	No	No	No
Papillon-Lefevre	Palmoplantar keratoderma, Periodontitis, Premature loss of dentition, Liver abscesses, Pneumonia	Unknown	No	No
Localized juvenile periodontis	Palmoplantar keratoderma, Periodontitis, Premature loss of dentition, Liver abscess	Yes	No	No
ß-ACTIN	Developmental delay, Recurrent infections, Photosensitivity, Thrombocytopenia, Stomatitis	Unknown	Unknown	No
LAD type I	leucocytosis, recurrent bact. infections, impaired pus formation, Delayed wound healing, ***Delay UCB detachment***	No	No	Yes
LAD type II	leucocytosis, Recurrent bact. Infection, psychomotor retardation, dysmorphism, Impaired neutrophil motility, ***Bombay blood group***	No	No	No
LAD type III	leucocytosis, Recurrent bacterial infection ***Bleeding tendency***	No	No	Yes

Phagocyte Dysfunction Without Syndromic Disease (Excluding CGD)

Disease	Main Clinical Manifestations	G-CSF responsive	MDS/AML risk progression	HSCT success eviden
MonoMac	Infections, Cytopenia, Lymphedema, Pulmonary alveolar proteinosis, Deafness, Predisposition to mycobacteria	No	Yes	Yes
Specific granule deficiency	Recurrent infections, neutropenia, Dysmorphic features, developmental delay	No	Yes	No
Neutrophil immune deficiency Syndrome	Severe bacterial infection Poor wound healing Absence of pus	Unclear	No	No
G6PD deficiency class I	Severe hemolytic anemia in response to specific medications and fava beans Chronic anemia	No	No	No

Genes with germline mutations associated with severe congenital neutropenia



Case Presentation

- A 13-yr old boy
- Congenital severe Neutropenia
- Hx of recurrent infections
- Admitted two times due to severe infection
- Genetically confirmed
- Her sister with similar problem was corrected by HSCT

Case Presentation

Type of request **نوع درخواست:**

Mono (patient) Whole Exome Sequencing Test Followed by Mutation Confirmation by Direct Sanger Sequencing

Clinical Indication **دلایل کلینیکی:**

بیمار با تشخیص Neutropenia

Pedigree/Family Genetic Information **شجره/شرح سابقه بیماری در فامیل:**

بیمار حاصل ازدواج خویشاوندی بوده و دو برادر بزرگتر دارد.

Test Result Summary **خلاصه نتایج:**

Primary/Diagnostic Sequence Variant(S) Detected:

- موتاسیونهای دارای اهمیت تشخیصی بیشتر (اولیه):

Gene	Variant coordinates	dbSNP rsID[a]	Associated disease	Phenotype MIM number	Inheritance[b]	Zygosity[c]	ACMG/ClinVar Classificatio[d]
HAX1	Chr1- 154245888 154245888 – A: NM_006118: exon2: c.130_131insA: p. W44_G45delinsX	-	Neutropenia, severe congenital 3, autosomal recessive	610738	AR	Patient: Hom Father: Het Mother: Het Brother1: Hom Brother2: Hom WT	Likely Pathogenic/NR

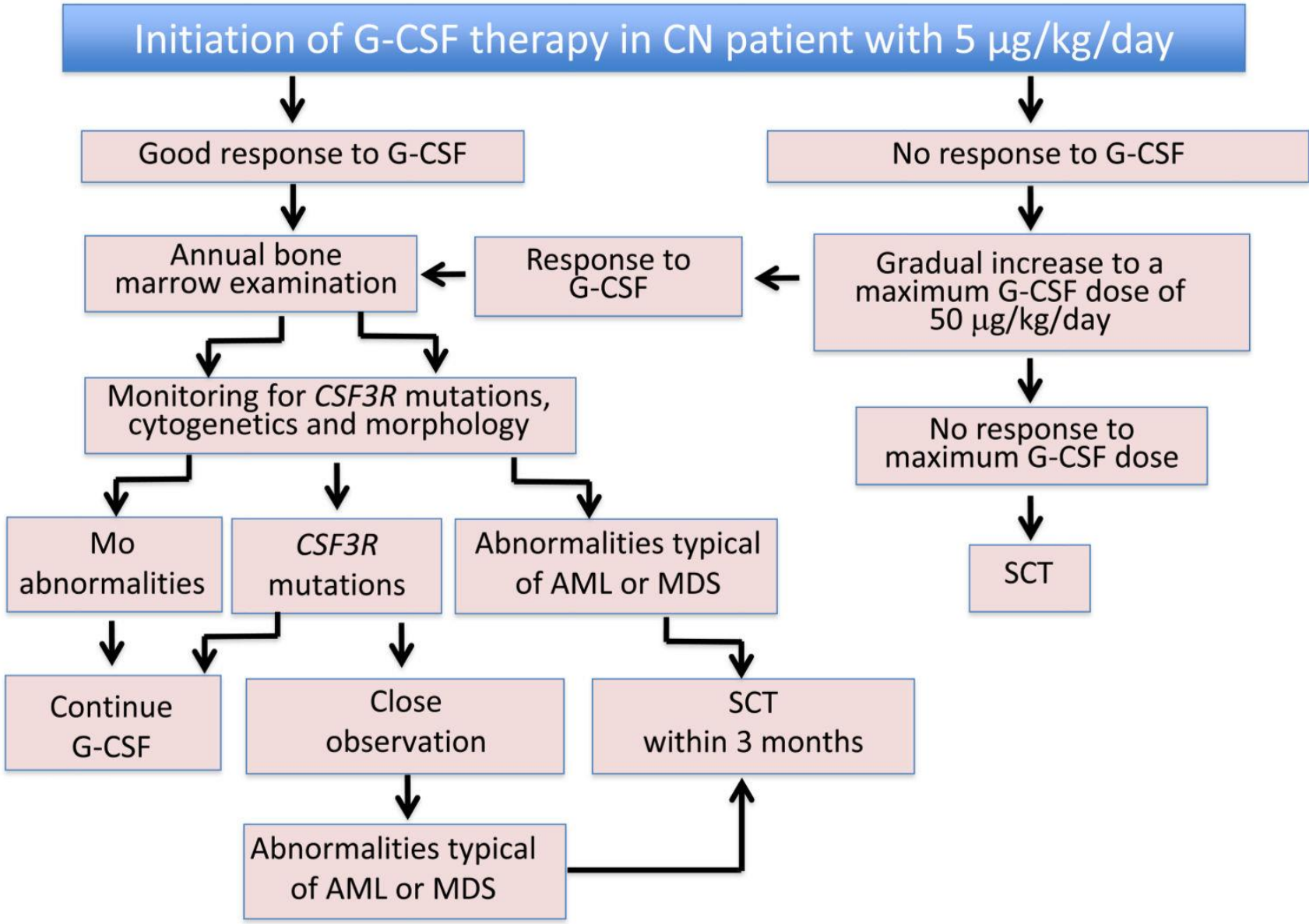
Case Presentation

- GCSF 5 µ/kg/wk
- ANC > 1500/µl
- Without any infection problem
- Without any monocyte increase
- Without any GCSF side effects

HSCT Indications

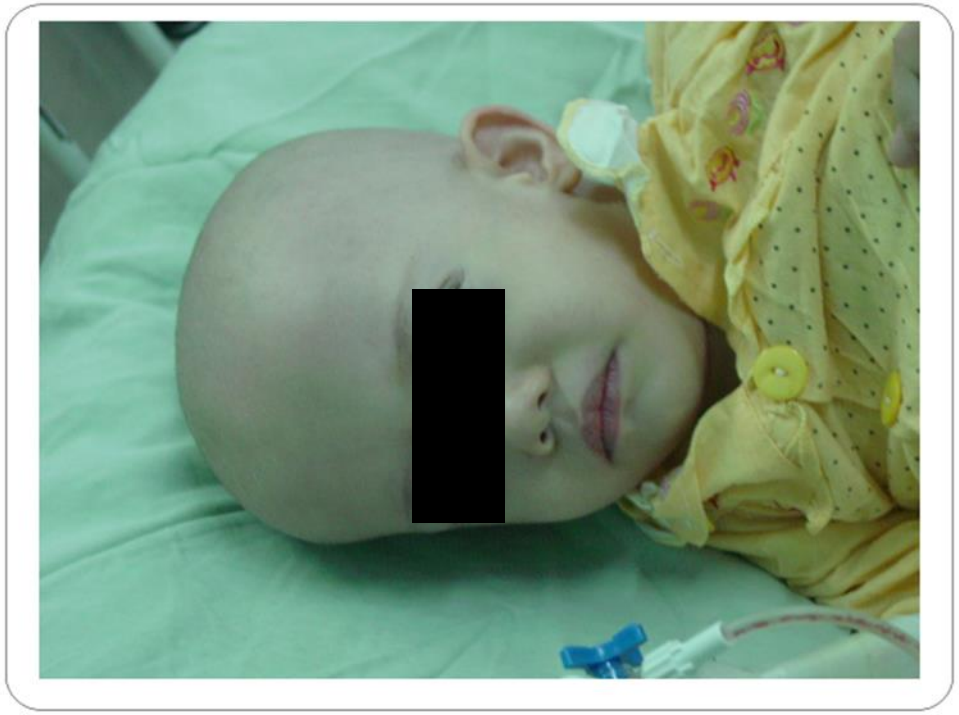
- In 2015, the EBMT and SCETIDE released the findings of the largest retrospective cohort of patients with severe congenital neutropenia to undergo alloHSCT.
- The 136 patients in that study demonstrated an overall 3 years survival of 82%, with transplant related mortality at 17%.
- It concluded that transplantation should be considered in patients with
  - ***severe infections or***
  - ***unresponsiveness to G-CSF or***
  - ***requiring high doses of G-CSF (over 8 mcg/kg/day to maintain an ANC over 0.5 × 109/L)***
- Both MAC and RIC conditioning was effective
- transplant outcomes were improved if
  - ***were transplanted before 10 years of age***
  - ***and before the development of MDS/AML***

Algorithm for the management of patients with severe congenital neutropenia based on response to G-CSF therapy



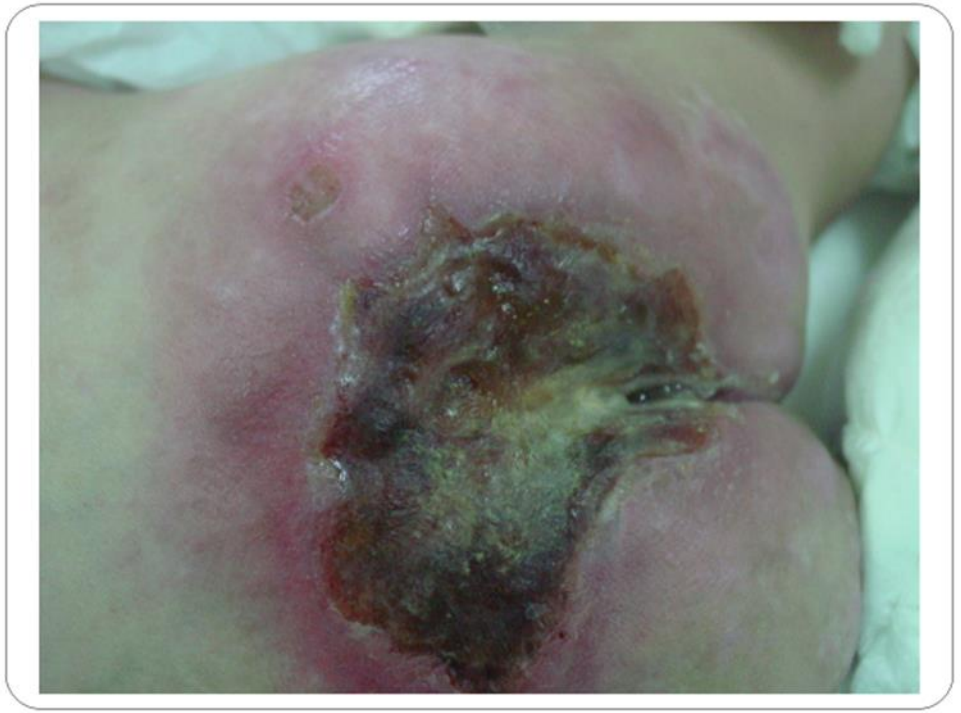
Case presentation

- 30-month-old girl with LAD-I
- Afghanian parents
- her umbilical cord separated 26 days after birth
- omphalitis from birth and in the first five months of life had multiple pulmonary tract infections
- Marked leukocytosis was persistently observed from birth (up to 140 · 109 WBC/L)
- leukocyte CD11/CD18 expression of <1%



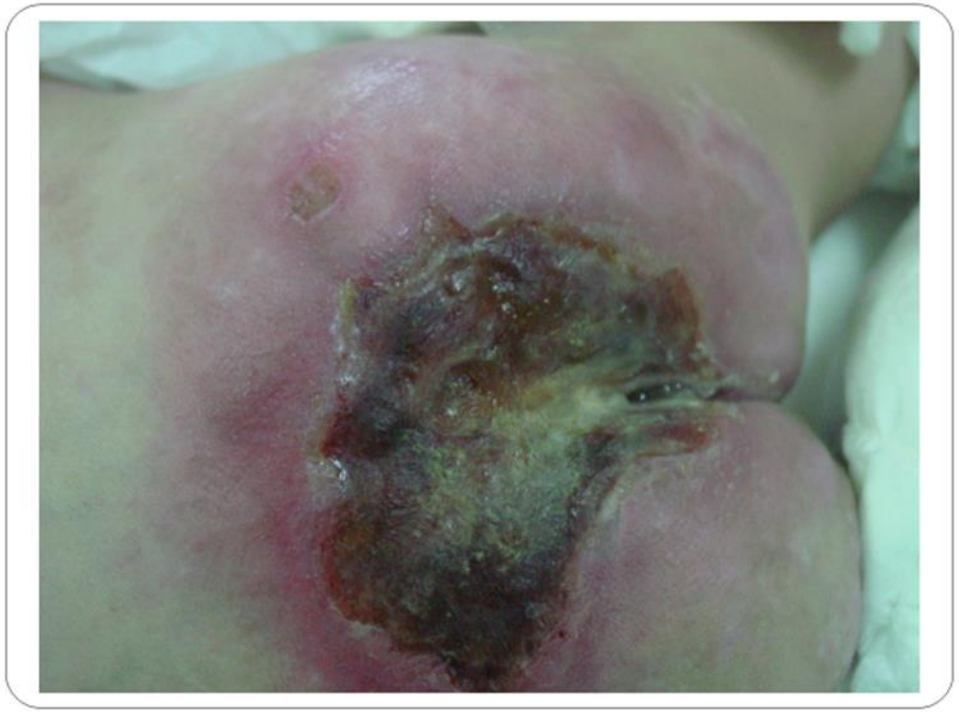
Case Presentation

- Until 24 months of age, she was admitted multiple times due to recurrent infections in the lumbosacral and perianal regions.
- Her ulcers were refractory to medical treatment and she required surgical debridement, skin grafting, and ultimately a diverting colostomy.
- failure to thrive and a 12 x 12 cm^2 necrotic wound of lumbosacral and perianal area in admission.

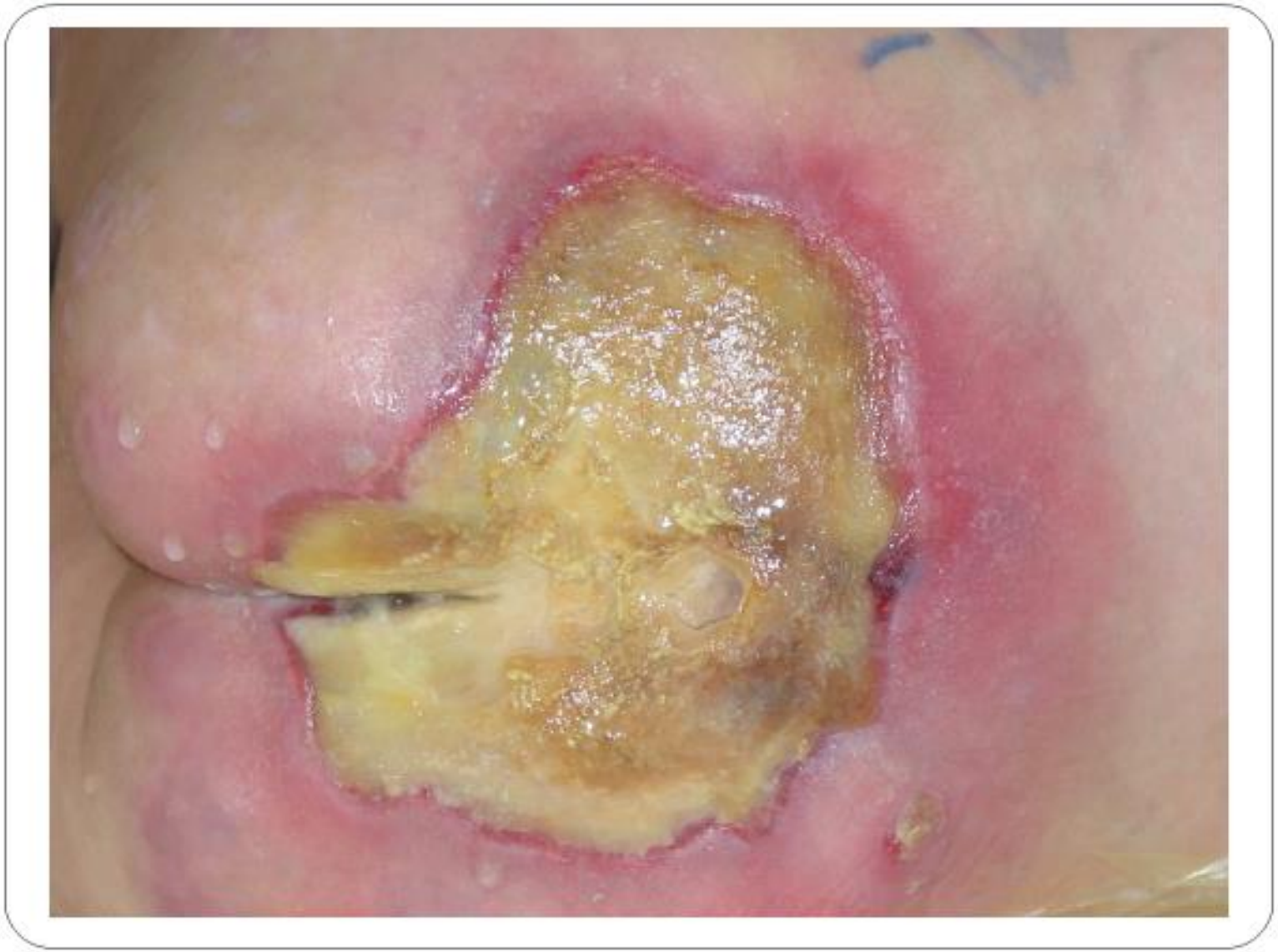


Case Presentation

- allogeneic PBSCT from her six-yr old HLA-identical sister
- RIC
- $8.82x10^8$/kg and $12.8x10^6$/kg of total nucleated cells and CD34-positive cells, respectively
- Prompt hematopoietic engraftment
  - ANC of $0.5x10^9$/L by day +14 and
- platelet count >50x 10^9/L by day +17.
- Mixed-chimerism



Cutaneous ulcerative lesion present at the time of transplant, was gradually resolving during conditioning!!!



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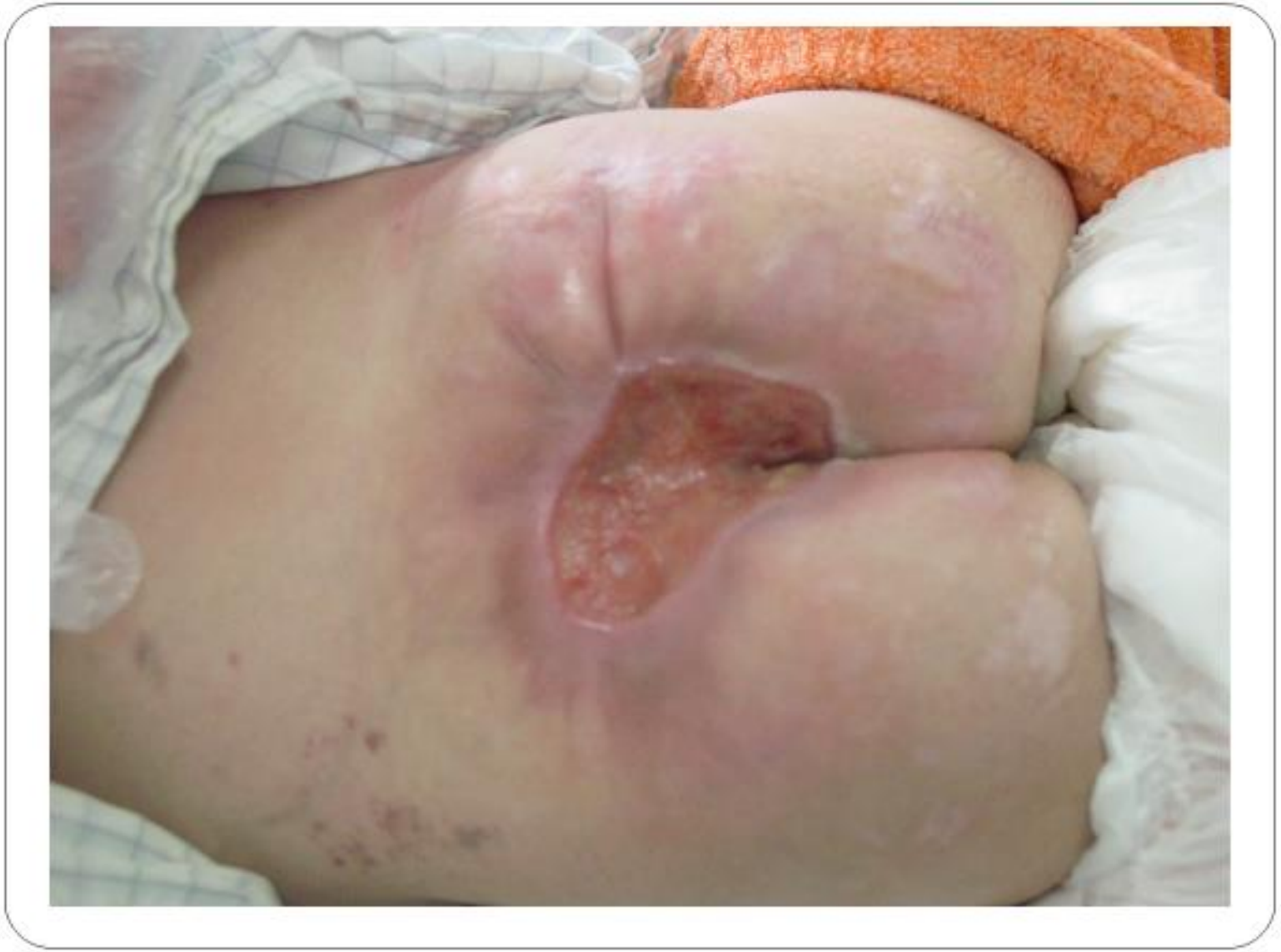
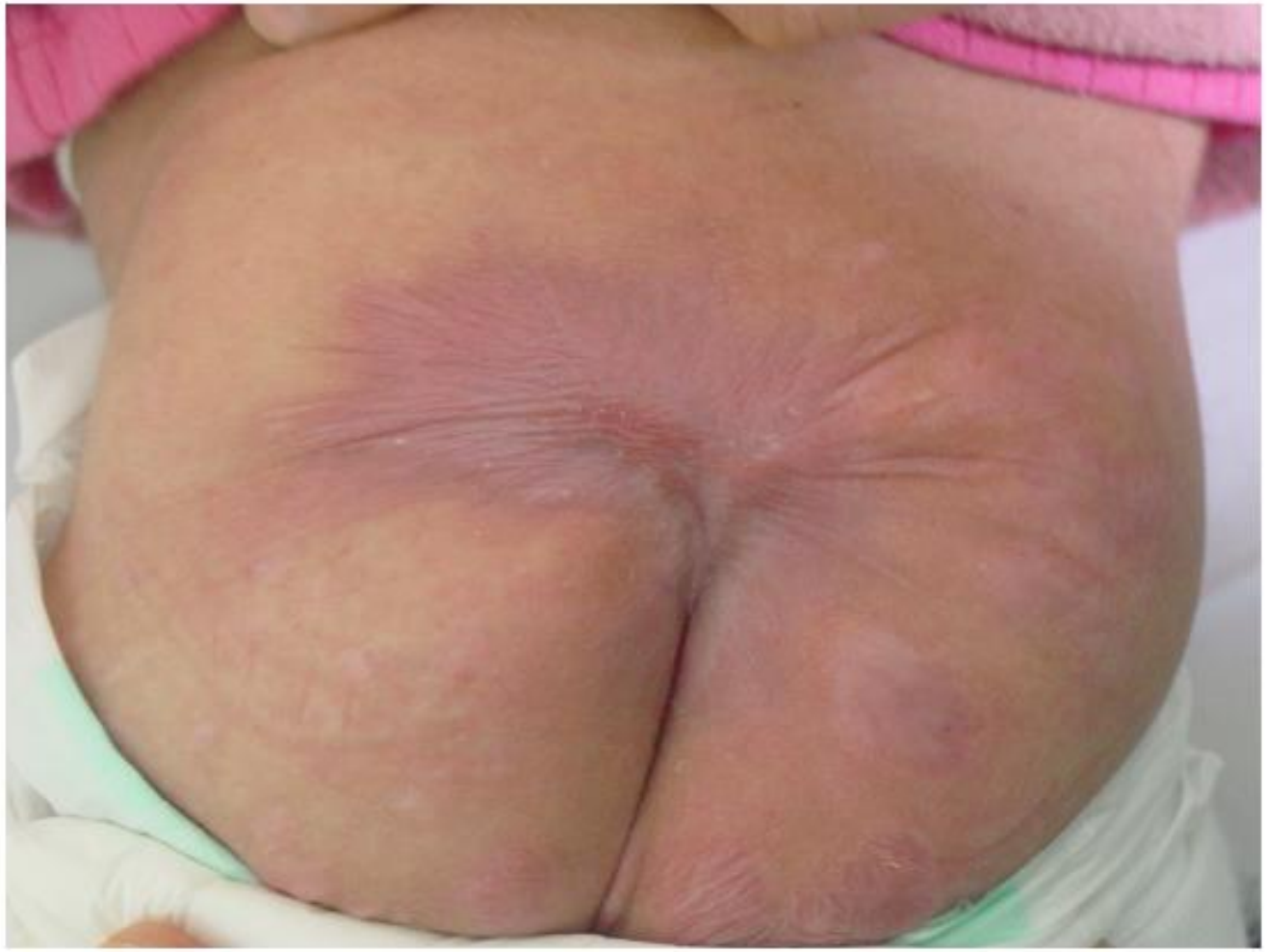


Finally gradually and completely resolved after engraftment



Treatment dilemmas in asymptomatic children with primary HLH

Treatment dilemmas in asymptomatic children with primary HLH

- Asymptomatic carriers (ACs) of pathogenic biallelic mutations in causative genes for primary hemophagocytic lymphohistiocytosis (HLH) are at high risk of developing life-threatening HLH, which requires allogeneic hematopoietic stem cell transplantation (HSCT) to be cured.
- There are no guidelines on the management of these asymptomatic patients.

Introduction

- Primary hemophagocytic lymphohistiocytosis (HLH) is
- a rare disease with an estimated incidence of 1.8 per 100 000 live births per year.
- caused by genetic mutations ➔ exocytosis of cytotoxic granules in T and NK cells, thus hampering their killing function.
- To date, 4 different genes have been identified as causative for primary HLH and an additional 5 genes are responsible for immunodeficiencies in which HLH is a prominent clinical feature

Introduction

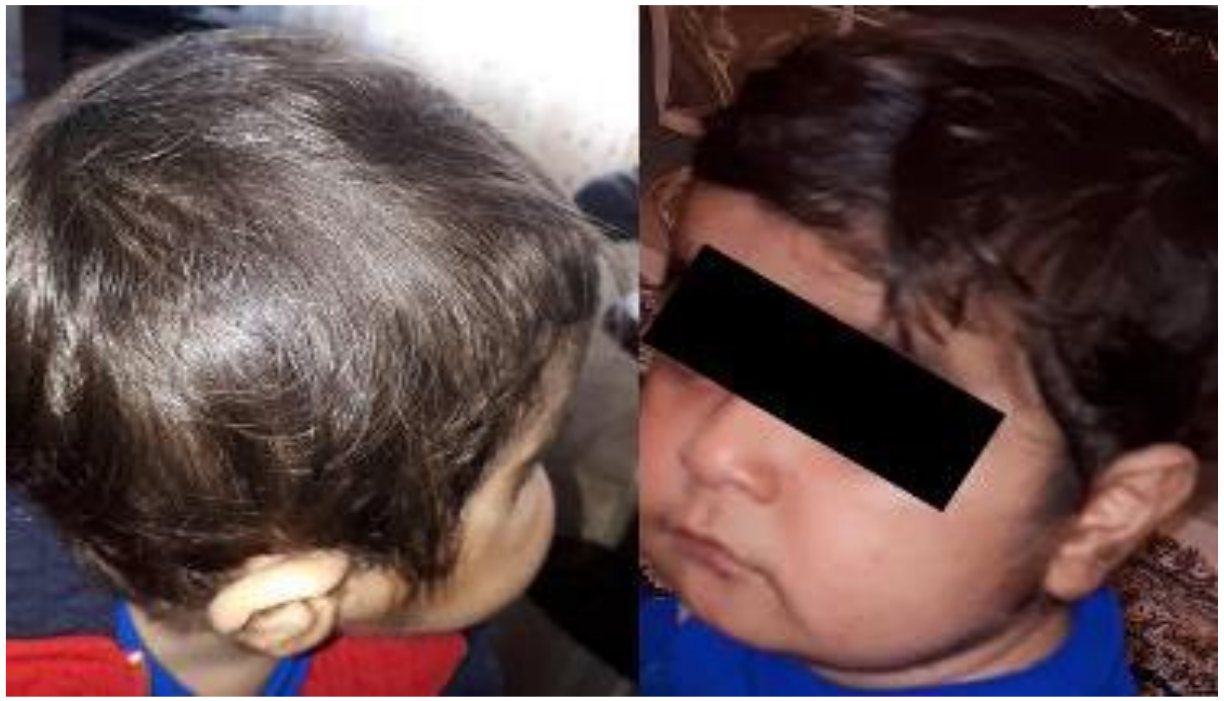
- The curative treatment in primary HLH is HSCT.
- overall survival (OS) remains at only about 59%, with virtually no survivors reported among patients who did not receive a transplant once the disease was fully active.
- Data from the largest cooperative prospective international studies (HLH-94 and HLH-2004 protocols) show that
  - up to 20% of patients do not achieve a durable complete remission (CR) with first-line chemotherapy, and disease progression represents the overriding cause of death for patients not receiving HSCT within 12 months from disease onset

Introduction

- the question of whether to offer HSCT to asymptomatic siblings who have been diagnosed genetically before the onset of symptoms remains unanswered.
- To date there are no data on the natural history of asymptomatic siblings to guide clinicians or families in making this decision.
- The risks of HSCT, often performed at a very young age, need to be balanced with the risk of waiting for the first HLH episode to manifest, which can be fatal in up to 20% of the patients.

Case presentation

- An 8.5-month-old boy
- fever, petechial purpura, and several times of vomiting
- phenotypically normal without skin and hair pigmentation
- huge splenomegaly and hepatomegaly
- without any detected source of infection
- third child of the family
- result of in vitro fertilization (IVF)
- complete vaccination history
- typical developmental milestones
- neutropenia (ANC=640) despite leukocytosis,
- anemia, and thrombocytopenia

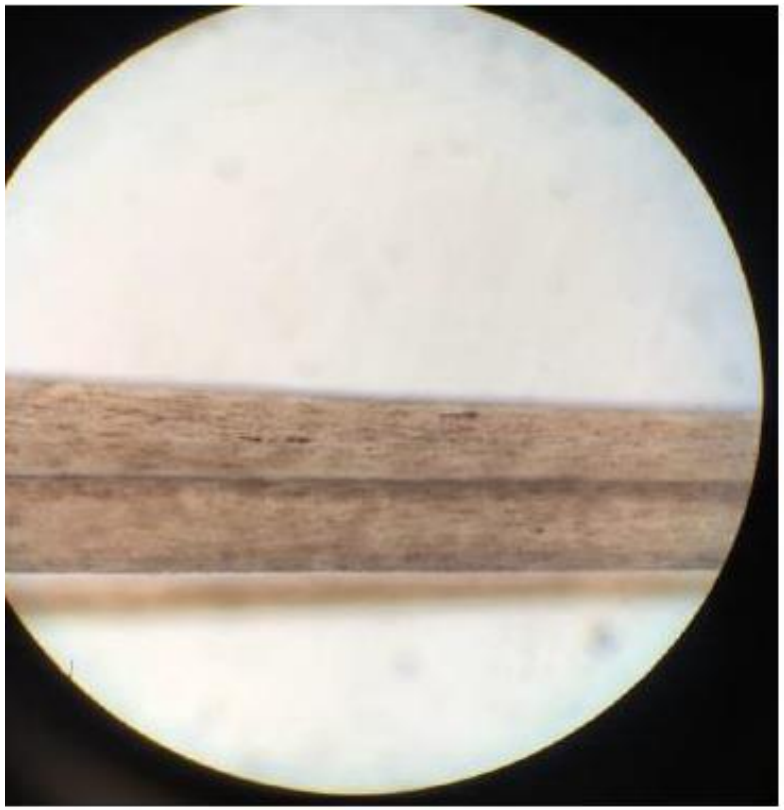


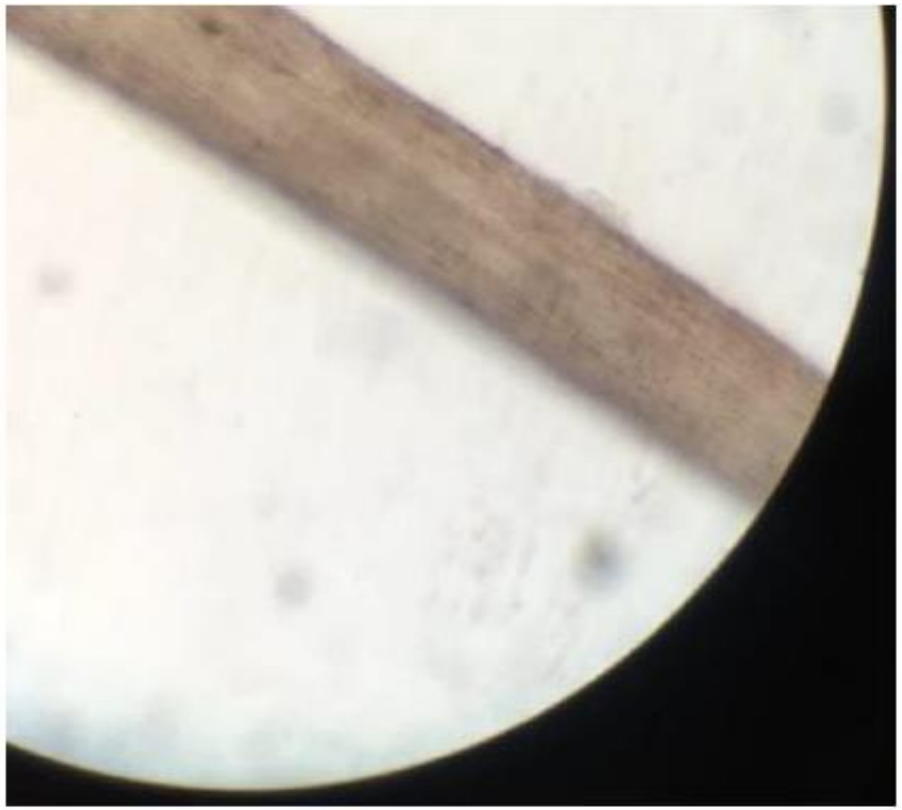
Case Presentation

- Recurrent infection (3 times hospitalization during 2 months)
- negative for
- Epstein-Barr virus (EBV),
- Cytomegalovirus (CMV),
- hepatitis B virus (HBV), hepatitis C virus (HCV) and
- human immunodeficiency virus (HIV)
- Kala Azar serology test was normal.
- PCR and ELISA tests results were negative for adenovirus.
- PCR and BK test results were negative for Mycobacterium tuberculosis
- BMA was normal in two times.
- the genetic test result showed a mutation in the RAB27A gene indicating GS-II

Case Presentation

- On microscopic examination, his hair strand was normal in color.
- However, the accumulation of melanosomes was observed in hair shafts, which indicated GS





Case presentation

- IVIg therapy was started along with cyclosporine and dexamethasone prescriptions without any chemotherapeutic drugs.
- He became a candidate for the bone marrow transplant (BMT).
- Unfortunately, HSCT was not done due to failure to find a suitable donor.
- Medical therapy was discontinued after 40 weeks.
- Up to now and after 6 years, he is not completely in accelerated phase and hepatosplenomegaly is only physical findings.
- During this period, he has not experienced any recurrent infection yet.
- Also, he has normal milestone.

Griscelli Syndrome

- rare autosomal recessive disease
- mutations in MYO5A, RAB27A, and MLPH genes
- GS-I,
  - mutation in the MYO5A gene,
  - involves severe dysfunction of the central nervous system (CNS)
- GS-II,
  - RAB27A mutation
  - light skin and silvery-gray hair initiating in infancy
  - associated with primary immunodeficiency
  - HLH
- GS-III
- mutations in the MLPH gene,
- is characterized by only pigment dilution of skin and hair

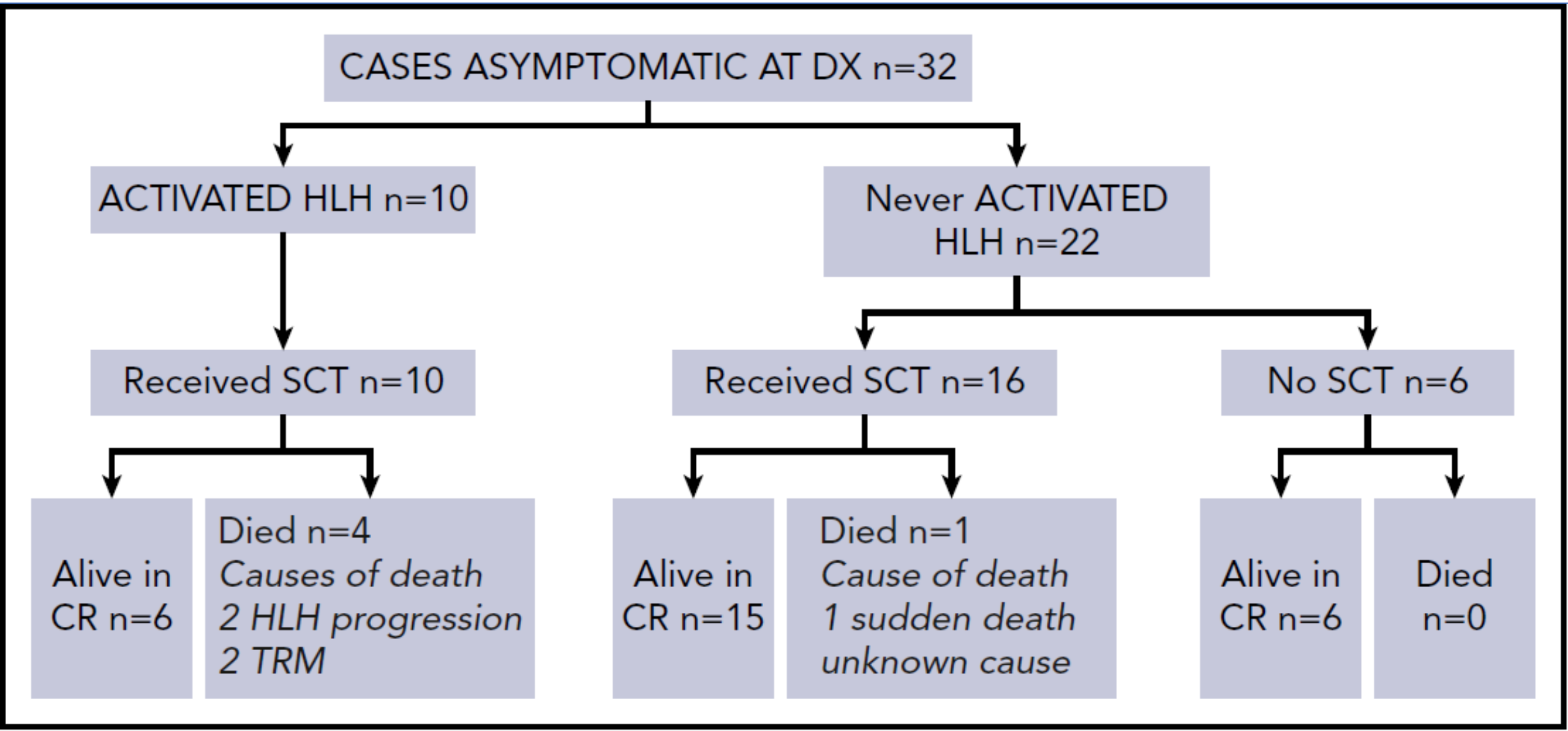
Literature Review

Patient	Protein deficit	Genetics	Age at diagnosis (mo)	Treatment	Disease status if AC at diagnosis	Outcome	Follow-up from diagnosis (mo)
IC 27	*RAB27A*	281G>A	18	HLH04 + HSCT		Alive CR	25
AC 27	*RAB27A*	281G>	144	None	Never activated	Alive CR	2
IC 28	*RAB27A*	467+1G>A	12	HLH94		Lost to follow-up	NA
AC 28	*RAB27A*	467+1G>A	Birth	Cyclosporine + HSCT	Never activated; receiving prophylactic treatment	Alive CR	12
IC 29	*RAB27A*	220G>C;335delA	9	Dexamethasone + etoposide		Died HLH progression	36

Literature Review

Patient	Protein deficit	Genetics	Age at diagnosis (mo)	Treatment	Disease status if AC at diagnosis	Outcome	Follow-up from diagnosis (mo)
AC 29	*RAB27A*	220G>C;335delA	1	HSCT	Never activated	Alive CR	91
IC 30	*RAB27A*	Not available	9	Corticosteroids, cyclosporine, intrathecal methotrexate, HSCT × 3		Alive CR	84
AC 30	*RAB27A*	Not available	Prenatal	Corticosteroids, cyclosporine, HSCT	Activated while waiting for HSCT	Died HLH progression	18
IC 31	*RAB27A*	Not available	126	Alemtuzumab, corticosteroids, cyclosporine, intrathecal methotrexate, natalizumab, HSCT		Died TRM	30
AC 31	*RAB27A*	Not available	180	HSCT	Never activated; receiving prophylactic treatment while waiting for HSCT	Alive in CR	36
IC 32	*RAB27A*	Not available	84	Cyclosporine + alemtuzumab + steroids		Died HLH progression	12
AC 32	*RAB27A* *RAB27A*	Not available	84	Cyclosporine + HSCT	Never activated; receiving prophylactic treatment while waiting for HSCT	Alive in CR	26

Diagram of treatment and outcome for ACs



OS per Kaplan-Meier estimate comparing ICs and ACs

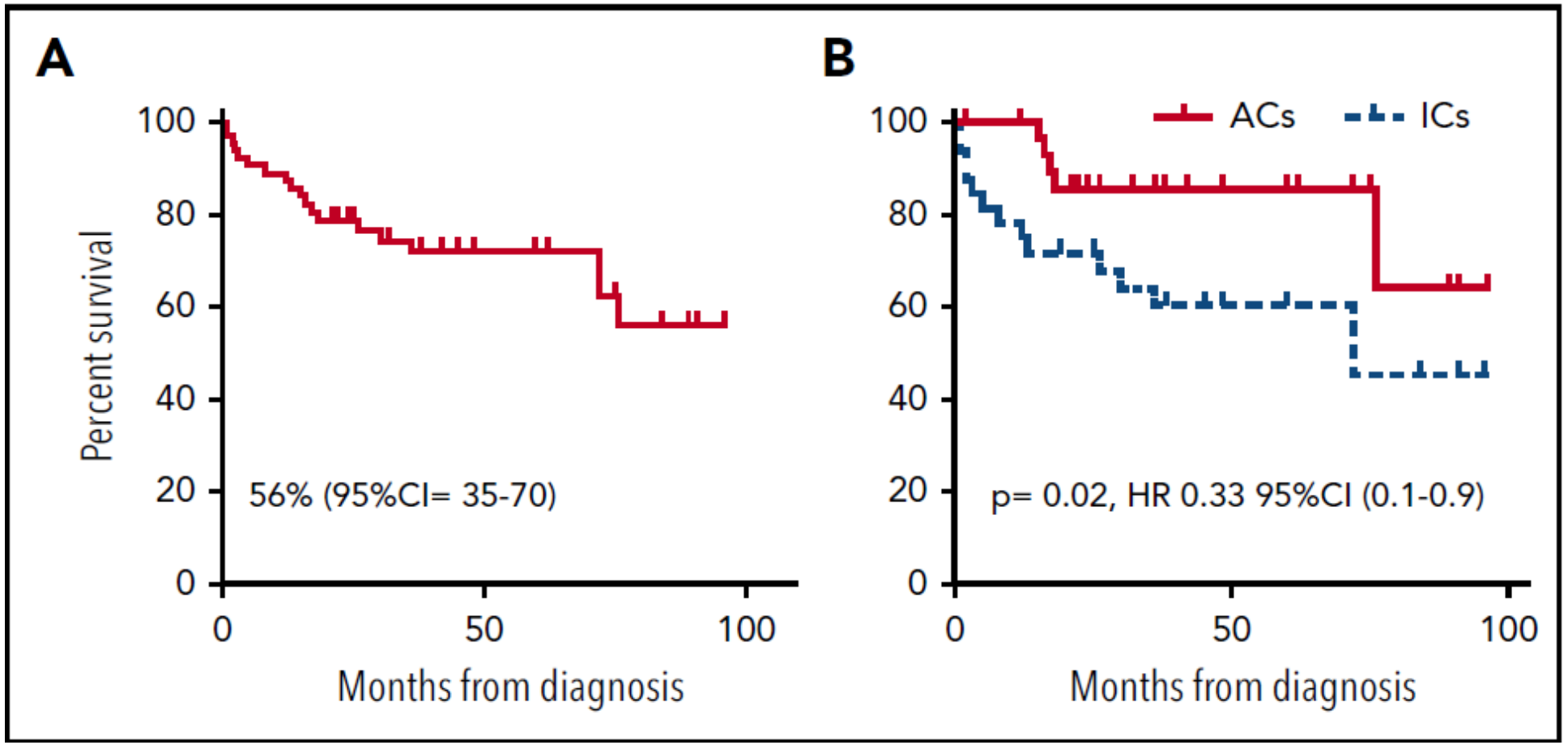
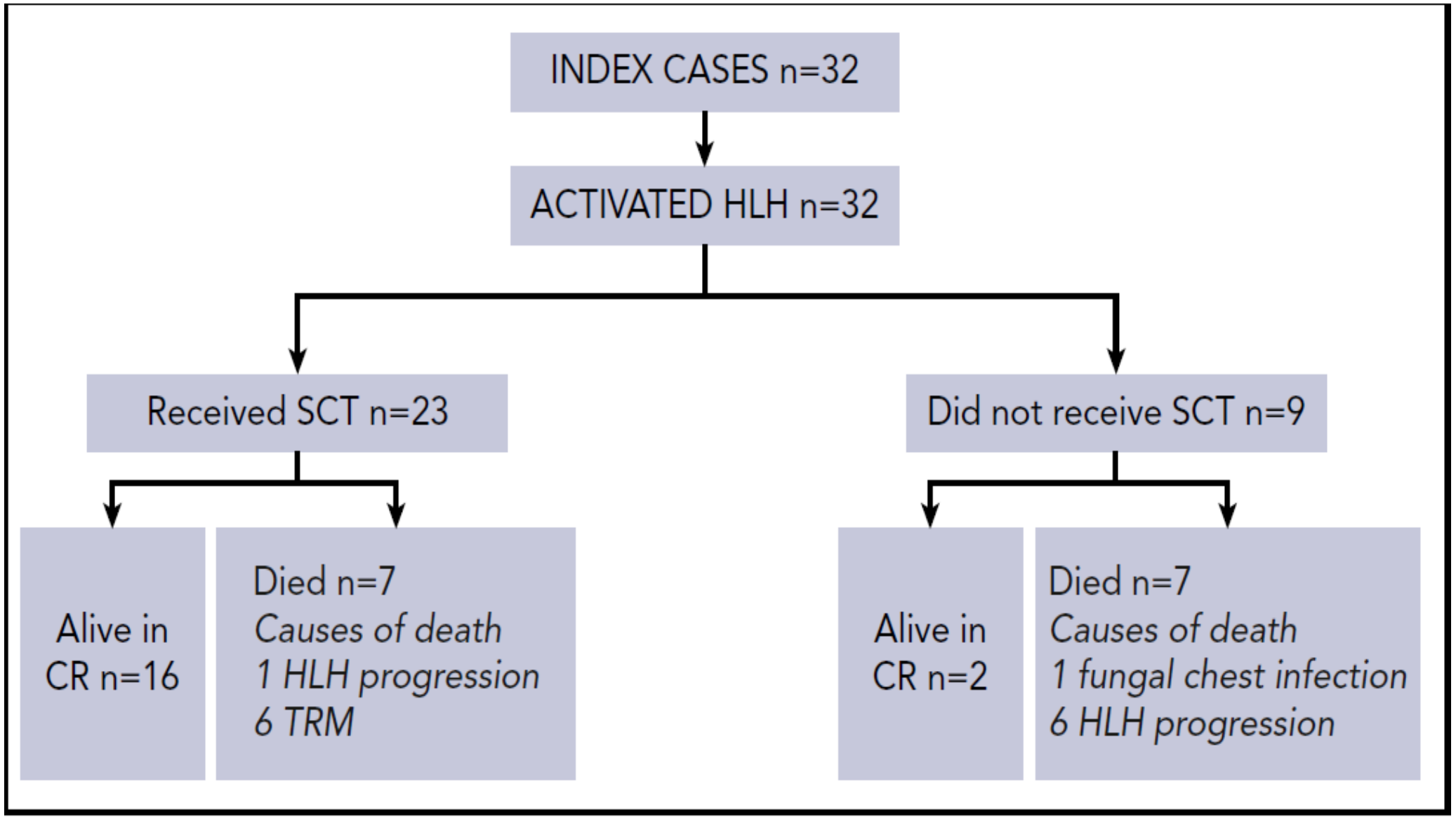
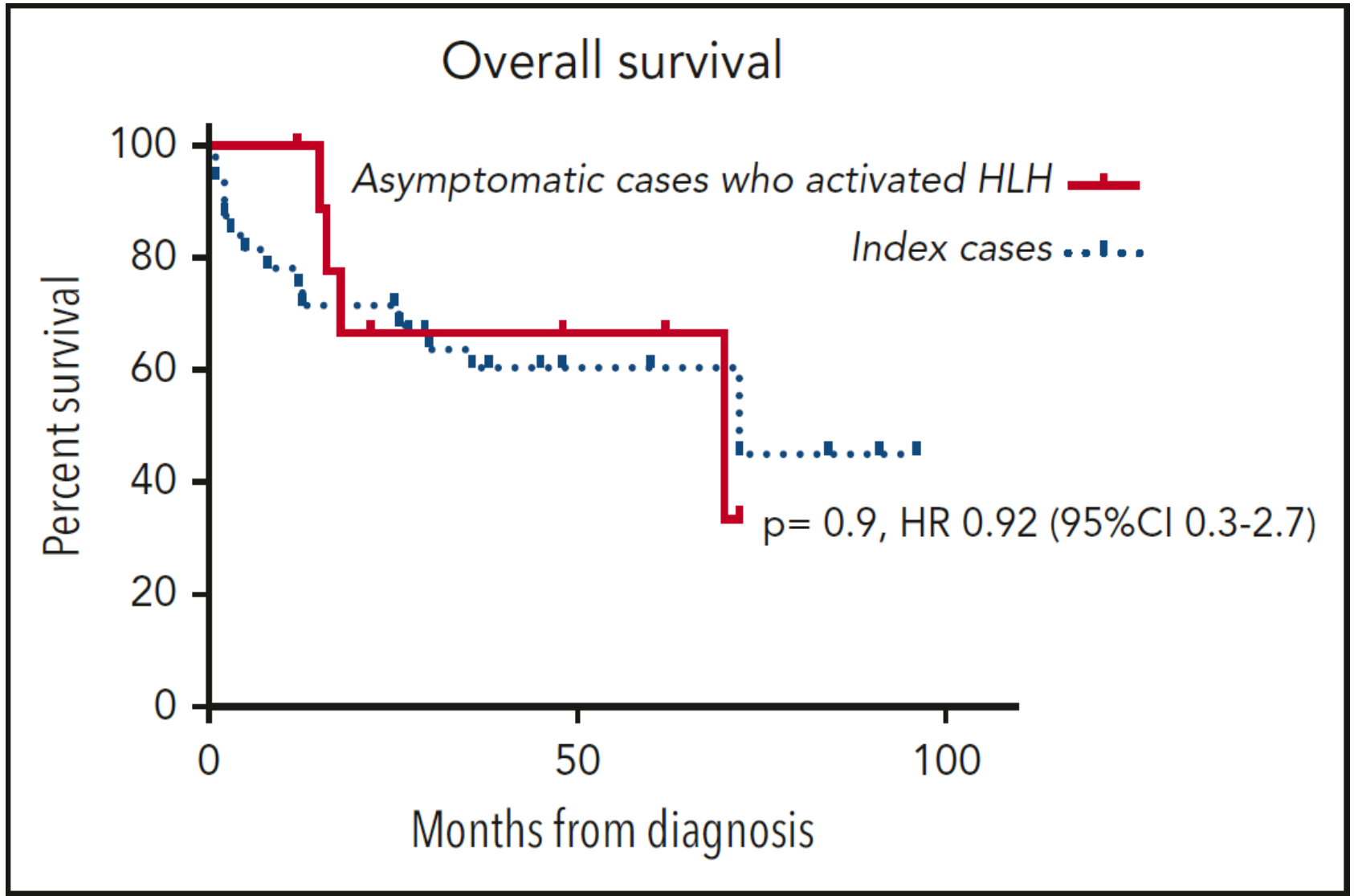


Diagram of treatment and outcome for ICs.



Estimated OS in our population of patients comparing ACs who experienced activated HLH with Index cases while on follow-up



Conclusion

- Preemptive HSCT in ACs with certain subtypes of primary HLH
  - PRF1 mutations with absent perforin expression and
  - RAB27A mutation
- In those ACs who have other genetically confirmed primary HLH mutations with unclear genotype-phenotype correlation,
  - HSCT with a well-matched donor after adequate counseling of families.
- A watch-and-wait policy could be suggested for patients affected with MUNC18-2 deficiency with mutations associated with milder phenotypes

Eurocord team 2008-2009