یازدهمین همایش سراسری
انجمن خون و سرطان کودکان ایران
و کنگره بین المللی تازه های هیستوسیتوز

زمان برگزاری: ۲ و ۳ آذرماه ۱۳۹۷

11 National Congress of Iranian Pediatric Hematology & Oncology Society
& the International Congress of Histiocytosis Updates

Holding time: 23-24 November 2018

Topics:

- Langerhanc Cell Histiocytosis Disorders (LCH)
- Non Langerhanc Cell Histiocytosis Disorders (Non- LCH)
- Updates of Histiocytosis Treatment
- Complications in Histiocytosis Disorders
- Hemophagocytic Lymphoghistiocytosis Syndromes (Heriditary & Aqcuired), Protocols and new treatment
- Hematopoietic Stem Cell Transplanttaion in
- Hemophagocytic Lymphoghistiocytosis Syndromes

محورهای برنامه

- اختلالات هیستوسیتوز سلول های لانگرهانس
- اختلالات هیستوسیتوز سلول های غیر لانگرهانس
- تازه های درمان اختلالات هیستوسیتوز
- عوارض اختلالات هیستوسیتوز
- سندرم های هموفاگوسیتیک ارثی و اکتسابی
- پروتکل ها و تازه های درمان سندرم های هموفاگوسیتیک
- پیوند سلول های بنیادی در سندرم های هموفاگوسیتیک

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یازدهمین همایش سراسری انجمن خون و سرطان کودکان ایران

و

کنگره بین المللی تازه های هیستوسیتوز

۲ و ۳ آذرماه ماه ۱۳۹۷

جزیره کیش

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سپاس به درگاه احدیت که بار دیگر توفیق پیدا کردیم برگزار کننده یکی دیگر از همایش های منطقه‌ای انجمن باشیم. هیئت مدیره انجمن تصمیم گرفت عناوین اختصاصی برای همایش های خود داشته باشد تا موجب تعمیق بحث های تخصصی و در نتیجه بهره برداری بیشتر همکاران فراهم آید. یازدهمین همایش سراسری انجمن با موضوع تازه های هیستوسیتوز را که از عناوین مهم و در عین حال مغفول مانده در سالهای اخیر بود برای همایش انتخاب کند. امیدوارم این همایش دو روزه که توسط انجمن خون و سرطان کودکان ایران تدارک دیده شده طلیعه ای برای تلاش های بیشتر و موثرتر در این زمینه باشد و تمام بیماران عزیز بتوانند از نتایج آن بهره مند شوند.

لازم است از دبیر محترم همایش جناب آقای دکتر باهوش و سرکار خانم دکتر شمسیان عضو محترم هیئت مدیره انجمن که زحمات ارزنده ای برای برگزاری بهتر این همایش متحمل شدند تشکر و از کلیه اعضای انجمن و همکاران هیئت علمی که فعالانه و با اشتیاق در این همایش شرکت می کنند سپاسگزاری کرده و امیدوارم بتوانیم بحث های مفید و با ارزشی را از طرف سخنرانان و مدعوین شاهد باشیم.

در پایان باید اشاره کنم برگزاری این همایش در جزیره زیبای کیش بزرگترین جزیره خلیج همیشه فارس فرصت خوبی برای همکاران گرامی است تا بتوانند از مواهب الهی و چشم اندازهای زیبای منطقه بهره مند شوند.

توفیق همکاران را از خداوند متعال خواستارم.

دکتر حسن ابوالقاسمی

رئیس انجمن خون و سرطان کودکان ایران

و

رئیس همایش

اختلالات هیستوسیتوزگروهی نادر و متنوع از اختلالات پرولیفراتیو با درگیری سلولهای دندریتیک و ماکروفاژ می‌باشند. این گروه اختلالات، طیفی از بیماریها در نتیجه ارتشاح واکنشی سلولهای التهابی، افزایش پاتولوژیک فعالیت سیستم ایمنی و یا پرولیفراسیون نیو پلاستیک کلونال را شامل می‌شوند.

تقسیم بندی جدید اختلالات هیستوسیتوز بر اساس یافته های هیستولوژی، فنوتیپ، تغییرات مولکولی، بالینی و تصویر برداری صورت می‌گیرد. بر اساس بازبینی در این تقسیم بندی اختلالات در ۵ گروه عمده شامل: اختلالات لانگرهانس (Langerhans-related) اختلالات پوستی و پوستی مخاطی (Cutaneous and Mucocutaneous)بیماری روزای دورفمن (Rosai Dorfman disease -RDD) , اختلالات هیستوسیتوز بدخیم (Malignant histiocytoses)و اختلالات هموفاگوسیتیک لنفو هیستوسیتوز و سندرم فعالیت ماکروفاژ (Hemophagocytic Lymphohistiocytosis and Macrophage activation syndrome)قرار میگیرند.

طیف وسیع تظاهرات بالینی, از طرفی وقوع نادر اختلالات هیستوسیتوز موجب اختلالات تشخیصی میشوند . ماهیت نامشخص و سیر متنوع این گروه اختلالات شامل بیماران فاقد علایم بالینی تا بیماران با تظاهرات بالینی بسیار متغیر، پش آگهی متفاوت و وقوع عوارض طولانی مدت در بسیاری موارد از مشکلات تشخیصی درمانی محسوب می شوند.

طی سالهای اخیر ارایه و استفاده از تکنیکهای مولکولی جدید و پیشرفته موجب درک و شناخت بهتر پاتوفیزیولوژی اختلالات هیستوسیتوز شده است. از مهمترین موارد، شناسایی موتاسیون ژن BRAF.V600Eدر بیماران هیستوسیتوز سلولهای لانگرهانس(LCH) در مسیر فعالیت MAPK inase RAS-RAF-MEK-ERK cell signaling pathway است که در ۵۵٪ بیماران شناسایی و نقش ان در موارد عود بیماری و گروه بیماران پر خطر مشخص شده است. در این زمینه استفاده از ترکیبات درمانی مهار کننده

شامل (BRAF/MAPK inhibitor Vemarufinib) در بیماران(LCH) دارای موتاسیون BRAF.V600E مورد بررسی و تایید قرار گرفته است.

با توجه به اهمیت موضوع اختلالات هیستوسیتوز در گروه سنی کودکان و نوجوانان ,طیف وسیع بیماری و از طرفی ارایه راهکارهای جدید تشخیصی –درمانی طی سالهای اخیر, بر آن شدیم در "یازدهمین همایش سراسری انجمن خون و سرطان کودکان ایران" **با** همکاری و حضور اساتید برجسته و صاحب نظر انجمن بین المللی هیستوسیتوز، همچنین مشارکت اساتید و همکاران ارجمند داخل کشور سمینار دو روزه‌ای با عنوان "تازه های هیستو سیتوز" **در** تاریخ ۲و۳ آذرماه ۱۳۹۷ **در** جزیره کیش برگزار شود.

امید است اساتید و همکاران ارجمند با حضور و مشارکت فعال و صمیمانه در این سمینار ما را یاری و سرافراز نمایند و برگزاری سمینار با ره اوردهای مطلوب علمی همراه شود.

دکتر غلامرضا باهوش- دکتر بی بی شهین شمسیان

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Contents

No. 01

New Classification of Histiocytosis Diosrders

Professor Hassan Abolghasemi
Professor of Pediatric Hematology and Oncology
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Dentritic cells, monocytes, and macrophages are members of the mononuclear phagocyte system, whereas a histiocyte is a morphological term referring to tissue-resident macrophages.

Histiocytosis syndromes are a group of disorders that have in common the proliferation of cells of the mononuclear phagocyte system and or the dendritic cell system. More than 100 different subtypes have been described, with a wide range of clinical presentation and histologies. The first classification of histiocytosis, published in 1987 by the Working Group of the Histiocyte Society (HS), consisted of 3 categories: Langerhans cell (LC) or non-LC-related, and malignant histiocytoses (MH). The second revision was performed by working party together with WHO members and took the classification one step further in 1997.

These classifications were based on biologic behavior and histopathology, including "dendritic cell"

related (e.g. LCH, JXG family), "macrophage" related (e.g. "hemophagocytic syndromes", RDD),

and malignant disorders (typically grouped by their most common

Since the classification of histiocytosis disorders in 1997 by the Histiocyte Society, this organization has made a number of revisions this categorization. It should be noted that several other classifications by other groups or sources are also available. The Histiocyte Society's 2016 revision of the classification of histiocytosis and neoplasms of the macrophage and dendritic cell lineages is as follows.

L (Langerhans) group diseases

Members of the L group include the following:

- Langerhans cell histiocytosis
- Indeterminate cell histiocytosis (ICH) - Including polyostotic sclerosing histiocytosis (Erdheim-Chester disease [ECD]) and mixed Langerhans cell histiocytosis/ECD

Langerhans cell histiocytosis

Subtypes of Langerhans cell histiocytosis include the following:

- Single system
- Lung
- Multiple system - No risk organs involved
- Multiple system - Risk organs involved
- Associated or not associated with another myeloproliferative or myelodysplastic disorder

ECD

Subtypes of ECD include the following:

- Classical type
- Without bone involvement
- Associated with another myeloproliferative/myelodysplastic disorder
- Extracutaneous or disseminated juvenile xanthogranuloma with mutation in mitogen-activated protein kinase (MAPK) pathway or anaplastic lymphoma kinase (ALK) translocation

C group (non–Langerhans cell histiocytosis of skin and mucosa)

Members of the C group include the following:

- Cutaneous non–Langerhans cell histiocytosis
- Cutaneous non–Langerhans cell histiocytosis with a major systemic component

Cutaneous non–Langerhans cell histiocytosis

Types of cutaneous non–Langerhans cell histiocytosis belong to the following families:

- Xanthogranuloma family - Juvenile xanthogranuloma, adult xanthogranuloma, solitary reticulohistiocytoma, benign cephalic histiocytosis, progressive nodular histiocytosis
- Non-xanthogranuloma family - Cutaneous Rosai-Dorfman disease, necrobiotic xanthogranuloma, cutaneous histiocytoses not otherwise specified

Cutaneous non–Langerhans cell histiocytosis with a major systemic component

The following types of cutaneous non–Langerhans cell histiocytosis with a major systemic component also belong to the xanthogranuloma and non-xanthogranuloma families:

- Xanthogranuloma family - Xanthoma disseminatum
- Non-xanthogranuloma family - Multicentric reticulohistiocytosis

M Group (malignant histiocytosis)

The M group includes primary and secondary malignant histiocytosis.

Primary malignant histiocytosis

This is characterized by negative phenotypic analysis for keratins, epithelial membrane antigen (EMA), Melan-A, HMB45, follicular dendritic cell markers, and B- and T-lymphocyte markers, as well as positivity for at least two of the following markers: CD68, CD163, CD4, and lysozyme. Primary malignant histiocytosis is localized to the skin, lymph nodes, digestive system, central nervous system (CNS), or others or is disseminated.

Secondary malignant histiocytosis

This occurs following or in association with conditions such as the following:

- Follicular lymphoma
- Lymphocytic leukemia/lymphoma
- Hairy cell leukemia
- Acute lymphoblastic leukemia
- Histiocytosis (Langerhans cell histiocytosis, Rosai-Dorfman disease, others)
- Other hematologic neoplasias

R Group (Rosai-Dorfman disease and miscellaneous noncutaneous, non–Langerhans cell histiocytoses)

R group histiocytosis includes the following:

- Familial Rosai-Dorfman disease
- Classical (nodal) Rosai-Dorfman disease
- Extranodal Rosai-Dorfman disease
- Neoplasia-associated Rosai-Dorfman disease
- Immune disease–associated Rosai-Dorfman disease
- Other non-C, non-L, non-M, non-H histiocytoses

Familial Rosai-Dorfman disease

Familial Rosai-Dorfman disease includes the following:

- Faisalabad (or H) syndrome (OMIM #602782)
- Fas protein deficiency or autoimmune lymphoproliferative syndrome (ALPS)–related Rosai-Dorfman disease (OMIM #601859)
- Familial Rosai-Dorfman disease not otherwise specified

Classical (nodal) Rosai-Dorfman disease

Classical (nodal) Rosai-Dorfman disease includes the following:

- Without immunoglobulin G4 (IgG4) syndrome

- IgG4 associated

Extranodal Rosai-Dorfman disease

Extranodal Rosai-Dorfman disease includes the following:

- Bone Rosai-Dorfman disease
- CNS with and without IgG4 syndrome association
- Single-organ Rosai-Dorfman disease (other than lymph node, skin, and CNS) without IgG4 syndrome
- Single-organ Rosai-Dorfman disease (other than lymph node, skin, and CNS) with IgG4 association
- Disseminated Rosai-Dorfman disease

Neoplasia-associated Rosai-Dorfman disease

Neoplasia-associated Rosai-Dorfman disease includes the following:

- Rosai-Dorfman disease postleukemia
- Rosai-Dorfman disease postlymphoma
- Rosai-Dorfman disease associated with malignant histiocytosis
- Rosai-Dorfman disease associated with Langerhans cell histiocytosis or ECD

Immune disease–associated Rosai-Dorfman disease

Immune disease–associated Rosai-Dorfman disease includes the following:

- Systemic lupus erythematosus related
- Idiopathic juvenile arthritis related
- Autoimmune hemolytic anemia associated
- Human immunodeficiency virus associated

H Group (hemophagocytic lymphohistiocytosis)

The H group includes the following:

- Primary hemophagocytic lymphohistiocytosis (HLH) - Mendelian-inherited condition
- Secondary HLH - HLH that is apparently non-Mendelian

Primary HLH

This includes the following:

- HLH associated with lymphocyte cytotoxic defects - Familial hemophagocytic lymphohistiocytosis type 2 (FHL2 PRF1]), FHL3 (UNC13D), FHL4 (STX11), FHL5 (STXBP2), X-linked lymphoproliferative disease type 1 (XLP1 [SH2D1A]), Griscelli syndrome type 2 (RAB27A), Chediak-Higashi syndrome (LYST)

- HLH associated with abnormalities of inflammasome activation - XLP2 (BIRC4), NLRC4
- HLH associated with defined Mendelian disorders affecting inflammation - Lysinuric protein intolerance (SLC7A7), HMOX1, other defined Mendelian disorders affecting inflammation
- Familial (apparently Mendelian) hemophagocytic lymphohistiocytosis of unknown origin

Secondary HLH - infection associated

Infection-associated secondary HLH includes the following:

- Viral - Epstein-Barr virus, cytomegalovirus, herpes, human immunodeficiency virus, influenza
- Bacterial
- Fungal
- Parasitic agents

Secondary HLH - malignancy associated

Malignancy-triggered HLH occurring at the onset of malignancy is associated with the following:

- Hematologic malignancies - T-cell lymphoblastic leukemia/lymphoma, T-cell non-lymphoblastic lymphomas, B-cell leukemias, B-cell lymphomas (non-Hodgkin), Hodgkin lymphomas, NK-cell lymphomas/leukemias, myeloid neoplasia, other hematologic malignancies
- Solid tumors
- Unclassified malignancies

Other malignancy-associated forms of HLH include the following:

- HLH occurring during chemotherapy - Unassociated with the initial malignancy diagnosis
- HLH associated with a malignancy but not further defined

Secondary HLH associated with rheumatologic conditions

This includes HLH associated with the following:

- Systemic onset juvenile idiopathic arthritis
- Adult-onset Still disease
- Systemic lupus erythematosus
- Vasculitis
- Additional defined or undefined autoimmune conditions

Secondary HLH - other types

- Transplant-related HLH
- HLH associated with iatrogenic immune activation
- HLH associated with iatrogenic immune suppression
- HLH associated with other apparently non-Mendelian conditions
- HLH of unknown/uncertain origin

No. 02

Overview of Langerhancs Cell Histiocytosis (LCH) Langerhans cell histiocytosis in children: from the bench to bedside for an updated therapy

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Abstract

Summary Langerhans cell histiocytosis (LCH) is a rare disease, affecting subjects of any age, with extremely variable clinical manifestations. Although most patients with LCH have localized disease, requiring local or even no therapy, those patients with disseminated, 'multi-system' disease require specific therapy because they may be at risk for morbidity or even mortality. The current standard of care has developed empirically, based mainly on the experience of treating children with leukaemia and other haemo-proliferative disorders. combined use of vinblastine and prednisone remains the standard of care for children with multi-system LCH. The combination of cytarabine and cladribine is the current standard for second-line therapy of refractory cases with vital organ dysfunction.

Recent advances in the knowledge of the pathogenesis of LCH may support a change in treatment strategy. Evidence of mutations that aberrantly activate RAF/MEK/ERK signalling in over two thirds of patients with LCH may direct a target therapy strategy. Vemurafenib, a small molecule widely used in the treatment of melanoma, is the main candidate for testing in prospective trials for patients with evidence of BRAFV600E mutation on lesional tissue. Additional molecules, including the recently approved trametinib, could follow.

Identification of mutations in other genes in the remaining multisystem LCH cases could contribute to define a scenario in which target therapy becomes the main therapeutic choice in this intriguing disorder. However, because the long-term risks and benefits of these agents in children are unknown, and other effective treatments

exist for many LCH patients, the optimal indications for administering a tyrosine kinase inhibitor to children is an open question.

No. 03

Treatment of Langerhancs Cell Histiocytosis (LCH)

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No. 04

New treatments (BRAF/MAPK inhibition & JAK Inhibitors) in Langerhancs Cell Histiocytosis (LCH)

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No. 05

DNA viruses and Langerhans Cell Histiocytosis in Iranian Children

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Abstract:

Purpose: Viruses are suggested as possible etiologic factor of Langerhans cell histiocytosis (LCH) by some investigators. Nonetheless, no report was found on this subject in Iranian children. We looked for the presence of Epstein-Barr virus (EBV), human herpesvirus-6 (HHV-6), herpes simplex virus (HSV) types 1 and 2, and Cytomegalovirus (CMV) in children with LCH.

Methods: The investigation in this retrospective study, was for the presence of HHV-6 DNA in 48 patients and CMV, HSV types 1 and 2 and EBV DNA in 30 patients with LCH, using paraffin-embedded tissue samples and 48 and 30 (respectively) age and tissue-matched controls from the department of pediatric pathology, using nested polymerase chain reaction (nested-PCR for HHV-6 and HSV types 1 and 2), qualitative PCR method (for CMV) and qualitative TaqMan Real-time PCR (for EBV).

Results: HHV-6 was found in one (2.1%) patient and six (12.5%) control specimen (P= 0.11, OR: 0.15; 95%CI: 0.02-1.29). Two (6.66%) patients and one (3.3%) control sample had CMV, with a P value of 1.0, and OR: 2.07; 95% CI of OR: 0.18-24.15. We did not find HSV types 1 and 2 DNA in any of the patients or controls. EBV was detected in 19 (63.33%) patients and 8 (26.7%) control group. P value was 0.004 with Odds Ratio: 4.75; 95% CI of OR: 1.58-14.25.

Conclusions: CMV, HSV types 1 and 2, and HHV6 do not appear to have any role in the pathogenesis of LCH. However, considering the statistically significant P value of

0.004, our findings suggest a possible position for EBV in the pathogenesis of LCH in Iran.

Keywords: Cytomegalovirus, Epstein-Barr virus, Histiocytosis, Langerhans-Cell, Herpes Simplex Virus, Human Herpes Virus-6, Polymerase Chain reaction.

No. 06

Complications of Langerhans Cell Histiocytosis

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Background:
Langerhans cell histiocytosis (LCH) is an inflammatory myeloid neoplasia characterized by the accumulation of clonal CD207+ myeloid dendritic cells amidst an inflammatory background of macrophages, T lymphocytes, and eosinophils, with a wide range of clinical presentations. [1] LCH occurs in 2-10 per million children and 1-2 per million adults per year, with extreme clinical heterogeneity. It can affect any organ system, but most commonly involves the skeletal system (80%). Other commonly affected sites include the skin (33%), pituitary gland (25%), liver, spleen, lungs, and brain. Localized or "single-system" disease (especially solitary skin involvement) has an excellent survival rate. Multisystem disease (MS-LCH), ie, involving two or more organs or systems, however, has an unpredictable course, especially when there is involvement of risk organs like liver, spleen and bone marrow, frequently associated with a poor prognosis. Because of this wide disease spectrum, different complications of LCH may be related to the disease itself, or treatment related. The somatic BRAF-V600E mutation has been identified in pathological dendritic cells of LCH lesions in approximately 60% of patients. Although BRAF status of the lesion does not predict risk-organ involvement, detection of BRAF-V600E in circulating blood cells has been associated with an increased risk of disease recurrence independent of risk-organ involvement. [2] Here these two spectrums of complications will be discussed.

Disease-related complications in LCH:
Single system involvement is frequent, especially in older children, teenagers, and adults. Skin lesions are a classical feature of LCH. Because the appearance of LCH skin lesions is variable and easily confused with more common childhood rashes, such as eczema or seborrheic dermatitis, consideration of LCH and diagnostic biopsy are often delayed. Eosinophilic granuloma is an older term for unifocal LCH. It is a slowly progressing disease characterized by an expanding proliferation of Langerhans cells most commonly involving the skeletal system. It may involve skull bone but few

cases of dura involvement have been reported. Involvement of Sella Tursica may cause endocrinologic complications like central diabetes insipidus. LCH of the spine is rare. Immobilization and observation are recommended in cases without spinal instability or neurological deficit. However, in the case of spinal instability, surgical excision, followed by segmental fusion and internal fixation, is indicated. Due to its endocrine, cardiac and growth complications, radiotherapy is not recommended for spine LCH, except in emergent cases of spinal cord compression. [3]

Multi system involvement:

All patients with LCH, especially those with a prolonged uncontrolled disease, may develop long-term morbidity, including chronic pain, problems with growth, endocrinopathies, and neurocognitive deficits. Therefore, timely recognition, staging, and therapy of LCH are essential for optimal outcomes. Given the high frequency of multisystem involvement in patients with skin LCH, early biopsy of suspicious lesions and comprehensive organ evaluation has long been indicated for all patients diagnosed with skin LCH. In cases of the multifocal bone disease, or disease that involves "CNS-risk" sites (odontoid, vertebrae with intra-spinal soft-tissue extension, facial bones, skull base, orbit, oral cavity). In these types of LCH, the risk of recurrence is high (30–50%), as is the risk of invasion into neurological tissue or development of neurologic sequelae (40%) such as endocrinopathies, diabetes insipidus, and parenchymal brain disease.

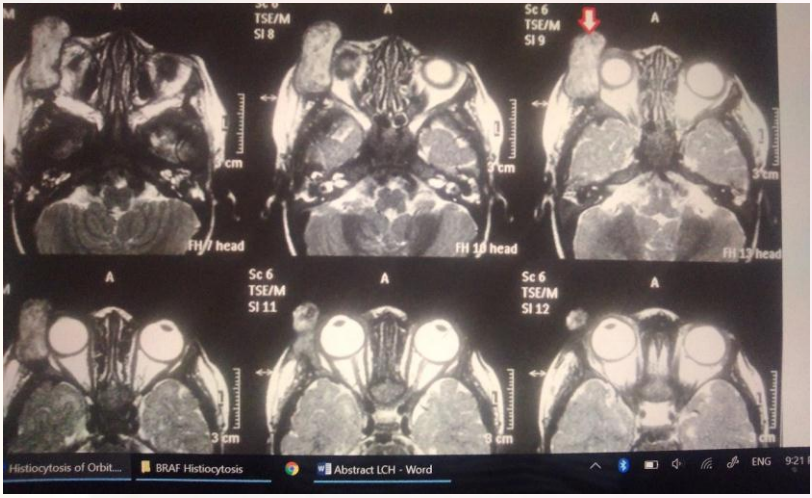

Figure 1: Orbital involvement as a solitary lesion of LCH with proptosis and visual problems.

In figure 1, CT scan shows 25 × 27mm round well-defined smooth-outlined homogenously enhancing space-occupying mass arising from the zygomatic bone at the inferotemporal periorbital area of right orbit with bone erosion. The MR imaging showed an exophytic infiltrative mass with irregular margins arising from the anterolateral wall of right orbit, localized to the extraconal space sparing the intraconal compartment. The lateral rectus muscle was not involved and was distinctly visible and separate from the mass.

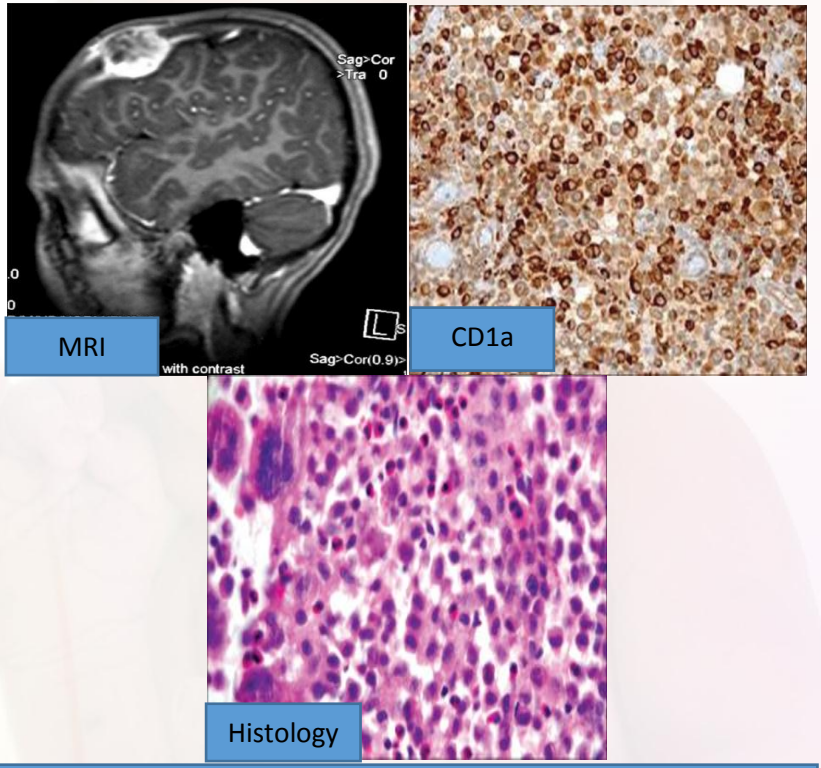

Figure 2: MRI of a case of frontal bone mass, its histology and IHC for CD1a.

Therapy related complications: Toxicity with prednisolone vinblastine is generally transient. Overall, the World Health Organization (WHO) grade 3/4 toxicity occurs in 30% of patients receiving protocols which included MTX; prominent toxicities (WHO grade 3/4) are infections (48%), bone marrow dysfunction (28%), hepatotoxicity

(25%), gastrointestinal symptoms (less often), and transient neurotoxicity (rarely). However, distinguishing between therapy-related and disease-induced findings in MS-LCH is not always possible. For example, pancytopenia may be either primary disease involvement and/or an effect of therapy**.**

Conclusion: All patients with LCH, especially those with a prolonged uncontrolled disease, may develop long-term morbidity, including chronic pain, problems with growth, endocrinopathies, and neurocognitive deficits. Therefore, timely recognition, staging, and therapy of LCH are essential for optimal outcomes.

Therapy-related complications are mild and tolerable in most cases. Mortality is not so high; however, disease-related complications might be lifelong and sever causing significant organ related morbidity.

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No. 07

Report of a rare case of Hand-Schuller-Christian disease

Prof M. Pedram

No. 08

The "Rare" or "Non-LCH" Histiocytic Disorders in Childhood: A Brief Overview

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Abstract

Diseases of the monocyte, macrophage and dendritic cell system are referred to as histiocytoses. Based on improved understanding of their pathobiology and molecular background histiocytoses have been recently re-classified into five groups. Nevertheless, for practical reasons the histiocytoses are grouped into: Langerhans cell histiocytosis (the most common entity), hemophagocytic lymphohistiocytosis (encompassing primary and secondary hyperinflammatory syndromes), non-Langerhans cell histiocytoses (encompassing entities and syndromes not belonging to one of the first two categories), and true histiocytic malignancies. Proliferation of bone marrow-derived mature histiocytes with CD68+/CD163+/CD1a-/CD207- phenotype is the common denominator of the non-Langerhans cell histiocytoses (non-LCH). The clinical manifestations are extremely heterogeneous, though partially overlapping. There are some distinct disease forms (particularly those belonging to the juvenile xanthogranuloma family) confined to the skin. Some other entities may present as systemic diseases requiring differential diagnosis with hematopoietic malignancies and solid tumors. This paper provides a brief overview on key clinical features, diagnostic criteria, and management of the most common systemic non-LCH entities: Juvenile Xanthogranuloma (JXG), Rosai-Dorfman disease (RDD), and Erdheim-Chester disease (EDD).

The non-LCH with systemic manifestation are uncommon diseases in the pediatric hematology/oncologypraxis. Due to their broad spectrum of manifestations, keeping in mind their key features and an adequate index of suspicion are important for timely and correct diagnosis. Non-LCH have to be considered in the differential diagnosis of papulonodular cutaneous lesions with xanthomatous appearance, osteolytic and osteosclerotic lesions with benign morphology and histiocytic infiltration, orbital lesions with proptosis, suprasellar masses presenting with central diabetes insipidus, as well as leptomeningeal mass lesions.

Introduction

Diseases, in which monocytes, tissue macrophages (histiocytes) and dendritic cells, as well as their bone marrow precursors play a dominant role, are referred to as histiocytoses. The histiocytoses are currently divided into 5 large groups. Relevant from a pediatric hematological point of view are the groups L (Langerhans cell histiocytosis - LCH, Erdheim-Chester disease – ECD, and systemic juvenile xanthogranuloma - JXG), R (Rosai-Dorfman disease - RDD and other systemic non-LCH syndromes), and group H (hemophagocytic lymphohistiocytoses HLH)(1).

Rare histiocytoses, also called Non-Langerhans cell histiocytoses (non-LCH), include all proliferative disorders of histiocytes, macrophages and dendritic cells that are not classified as Langerhans cell histiocytosis (LCH) and do not belong to the hemophagocytic lymphohistiocytosis (HLH) group of diseases(2). The non-LCH are very rare in childhood. Their classification is challenging due to extreme diversity of clinical manifestations, extent and prognosis. Furthermore, aside of overlapping clinical manifestations, the non-LCH share common histology, cellular immunophenotype, molecular mechanisms and causative mutations (1, 3).

In 2005 Weitzman & Jaffe proposed a pragmatic classification of the rare histiocytoses into three groups: primarily cutaneous histiocytoses (i.e. cutaneous juvenile xanthogranuloma family, reticulohistiocytoma, and cutaneous Rosai-Dorfman disease); cutaneous histiocytoses with major systemic component (xanthoma disseminatum and multicentric reticulohistiocytosis); and mainly systemic histiocytoses with or without cutaneous involvement (ECD, systemic JXG, and systemic RDD) (4). This overview will focus on systemic non-LCH.

Juvenile xanthogranuloma (JXG) Epidemiology

JXG is a disease of early childhood (median age at presentation 2 years), but it can be present at birth or manifest in school age. With an estimated incidence of one case per million children it is the most common non-LCH disorder. However, the disease may be underreported, particularly those cases presenting with solitary cutaneous lesions, which account for 80-90% of all cases (5, 6). Males are more frequently affected, particularly among patients with multiple cutaneous lesions and those with systemic disease. There is an association between JXG, neurofibromatosis type 1 (NF1), and juvenile myelomonocytic leukemia (JMML). Patients with JXG and NF1 have a 20-32-fold risk of JMML compared to those with NF1 only (7).

Pathology

The pathogenesis of JXG is still not fully understood. Based on the immune phenotype of the lesional cells (CD14+, CD68+, CD163+, FXIIIa+, CD1a- and CD207-) JXG should be categorized as a macrophage-related histiocytosis, but the evidence of ERK activation and the rare cases of co-existing LCH and JXG lesions suggest relation to dendritic cell progenitors. Typical JXG lesions have benign appearance and reveal accumulations of histiocytic cells that are morphologically very similar to Langerhans cells. Frequently, so-called Touton giant cells are found in

variable numbers. The histiocytic cells may have a partially very foamy, vacuolated cytoplasm. In some of the lesions also a spindle cell cytology is found. The lesions are mostly localized in the dermal connective tissue. Immunohistochemistry is essential for a reliable differentiation from other histiocytic proliferation, particularly from LCH.

Clinical manifestations

Cutaneous JXG can present as a single or multiple brown to yellow papules or nodules, predominantly localized on the face, head, and neck, followed by upper trunk and the extremities. It can present at any site, including the nails, eyelid, lips, palms and soles, penis and clitoris. During infancy, JXG more commonly presents as multiple, ranging from few to hundred lesions. Cutaneous JXG usually has a benign course, but the spontaneous involution of the lesions can take months to years.

Systemic JXG accounts for 4% of all cases and is typically seen in very young children (median age 3 months). Its diagnosis could be quite challenging, as about half of the cases do not have cutaneous manifestations. The most common presentation is a solitary mass in the deeper soft tissues, followed by liver, spleen, lung, ocular and brain involvement (6, 8). Several organs and sites can be affected in different combinations and, therefore, careful laboratory and imaging work-up has to be performed in all patients, including those with apparently localized cutaneous disease. Marrow involvement can manifest with unexplained cytopenia (9). Pulmonary lesions are solid nodules of varying size on imaging, and in the experience of the author may be clinically silent (9). Liver disease can manifest with hepatomegaly and signs of organ dysfunction (10).

There are some extracutaneous manifestation, which can present either as an isolated finding or in the setting of systemic disease, but their timely recognition is important to prevent irreversible complications (e.g. intraocular and cerebral JXG). Intraocular JXG occurs in 1% of the children with cutaneous JXG, mostly in infants (6). It can present as a visible scleral nodule or red eye, glaucoma, hyphema, retina or optic nerve involvement and may result on complete loss of vision, despite treatment (11). JXG affecting the central nervous system is estimated to account for 1.2% of all cases (6). Depending on location it can manifest clinically with increased intracranial pressure, seizures, polyuria and polydipsia, blindness, or developmental delay. On MRI single or multiple leptomeningeal lesions can be identified, which are not characteristic for JXG, and thus in the absence of cutaneous manifestation the diagnosis can be confirmed only after a biopsy. The intracranial JXG lesions are typically homogenous lesions with iso-intense appearance on T1- and T2-weighted images and enhancement after gadolinium administration.

Diagnosis

Typical cutaneous lesions can be reliably diagnosed without biopsy by an experienced physician. However, in some cases differential diagnosis with dermatofibroma, mastocytosis and other histiocytic disorders can be difficult. Biopsy is mandatory for extracutaneous JXG due to uncharacteristic appearance of the lesions. Systemic and

extracutaneous lesions of JXG are in many cases indistinguishable from ECD. Therefore, besides histopathological and immunohistochemical findings, the final diagnosis has to consider the clinical pattern of organ involvement and the imaging findings. Extracutaneous JXG and ECD are considered to be a continuum of the same disease by some experts (1, 8). In case of positive testing for BRAF, NRAS, KRAS, or MAP2K1 gain-of-function mutations, the disease is classified as ECD (1).

Management

The majority of the patients have cutaneous JXG with a favorable course and prognosis and do not need treatment. However, extensive diagnostic work-up is needed to exclude systemic disease, particularly in patients below the age of 2 years. For children < 4 years with concurrent JXG and NF1 frequent follow-up visits including CBC are mandated by the increased risk for JMML (8).

Likewise, structured ophthalmological follow-up (every 3-6 monthsuntil age of two years) is recommended for younger children due to the increased risk for ocular involvement (8). Ocular involvement requires treatment in experienced ophthalmology center.

Surgery can be sufficient as a treatment option for solitary, symptomatic extracutaneous lesions (including intracerebral ones). For unresectable lesions and systemic disease treatment with the standard regimen used in LCH (prednisolone + vinblastine) is effective in most cases (12). Clofarabine seems to be another effective drug for non-LCH, including JXG (13).

Rosai-Dorfman Disease (RDD)

Synonyms: sinus histiocytosis with massive lymphadenopathy; Rosai-Dorfman-Destombes disease; Faisalabad syndrome, H syndrome

RDD is a non-LCH characterized by a benign proliferation of S100-positive histiocytes within the sinus of the lymph nodes and the lymphatic vessels of internal organs (14).

Epidemiology

Due to lack of population-based studies the exact incidence of RDD is unknown. The most reliable source of information about this disease is the RDD registry founded by J. Rosai (14). The estimated incidence of RDD is probably less than 10% of the incidence of LCH (14). RDD can manifest at any age from birth till elderly, but with a median age at presentation of 20 years, it is most frequently diagnosed in children and young adults. The male: female ratio is 1.4: 1. A familial from of RDD has been later recognized to occur in patients with underlying Faisalaband, H, or autoimmune lymphoproliferative (ALPS) syndromes (8).

Pathogenesis and histopathology

The etiology and the pathogenesis of RDD remain still uncovered. The fact, that characteristic RDD histopathology has been documented in patients with familial

syndromes or other malignancies, suggests that it is a heterogeneous syndrome with common morphology, rather than a single entity. Indeed, J. Haroche and O. Abla proposed a classification encompassing all clinical forms of RDD (8). Based on the clinical observations, it is believed that RDD is the result of an aberrant immune regulation with cytokine-mediated monocyte migration and activation. In contrast to LCH and ECD BRAF mutations have not been found in RDD to date (3, 15). Other mutations (KRAS, MAP2K1, NRAS, and ARAF) have been identified in less than 50% of the studied cases.

The hallmark of RDD is the proliferation of a characteristic subpopulation of macrophages with signs of emperipolesis (red blood cells, lymphocytes and plasma cell are engulfed by activated histiocytes) in the lymph node sinusoid.The sinusoids are expanded due to accumulation of pale stained histiocytes in combination with a variety of polyclonal plasma cells. The histiocytes are positive for CD14, CD68, CD163, and S100, but negative for CD1a and CD207 on immunostaining. Another characteristic feature of RDD is the thickened and fibrotic lymph node capsule.

The microscopic picture of extranodal foci of CMLD is similar to that observed in the lymph nodes. It is amazing to see structures similar to pathologically altered lymph nodes in organs such as the kidneys and the brain. However, there are some differences in the morphology of nodal and extranodal foci. In general, the extranodal foci are characterized by more pronounced fibrosis, less pronounced accumulation of histiocytes and less pronounced emperipolesis compared with affected lymph nodes. The fibrotic stroma contains more expressed vessels and plasma cells located along these vessels. As with Hodgkin's lymphoma, diagnostic criteria for extranodal lesions are less strict if the patient has documented lymph node involvement (14).

Clinical manifestations

RDD most frequently presents with a massive bilateral, painless cervical lymphadenopathy with constitutional symptoms (e.g. fever, night sweats, and weight loss), a typical picture which has given the name SHML of the classical nodal disease. Only lymph nodes were affected in 239 of 423 patients in the international registry (14). In 97% of all patients with RDD the presence of bilateral (symmetrical or asymmetric) cervical lymphadenopathy was noted at various stages of the disease, which in typical cases is the leading disease manifestation. All groups of cervical lymph nodes can be affected, each group separately or in different combinations. At the onset of the disease, the lymph nodes are mobile and single, but often merge into large multinodular conglomerates during the course of the disease. In some patients, these conglomerates reach enormous sizes, causing neck deformation. The remaining groups of lymph nodes, including axillary, inguinal and intrathoracic, are affected in 80% of cases.

Analysis of the RDD registry showed that in 43% of cases the disease occurs in extranodal sites, which are sometimes the only disease manifestation. The most frequent localizations of extranodal lesions according to the international register are skin, soft tissue, upper respiratory tract, bone, eye and retroorbital tissue, and the

brain. The clinical manifestations of extranodal lesions are unspecific. The diagnosis is established almost always after a biopsy.

Skin lesions in RDDare the most frequent extranodal localization, but they are rarely isolated. They present in the form of multiple papules and nodules. Half of the patients recover independently of treatment, but the skin lesions can also persist or recur for a long time.

Skeletal lesions are osteolytic in nature, which in children requires a differential diagnosis with multifocal osteomyelitis, LCH and bone metastases of neuroblastoma, especially in patients without severe lymphadenopathy (16). Lesions of different size, with uneven contours, usually without periosteal reaction, are localized more often in tubular bones.

One of the most frequent extranodal localizations is the involvement of the cavity and paranasal sinuses in the form of polyps or tumor-like masses. RDD can affect the orbit, eyelids and the eyeball (17). Orbital damage is often accompanied by exophthalmos, which requires differential diagnosis with LCH, neuroblastoma and rhabdomyosarcoma. RDD can also affect suprasellar structures and cause diabetes insipidus and loss of function of the anterior pituitary, which are indistinguishable from LCH.

Although rare, RDD can present with isolated CNS lesions. Intracranial disease presents as meningioma and usually occurs without extracranial lymphadenopathy (8, 18).

Frequent, but unspecific laboratory findings are light normochromic normocytic or hypochromic microcytic anemia, elevated ESR and elevated serum immune globulins (14).

Diagnosis

RDD diagnosis requires histopathological examination with immunohistochemistry(8). Once the diagnosis has been confirmed a structured work-up is need to rule out associated autoimmune disease and to document all involved sites (8).

Differential diagnosis depends on disease presentation. The classical nodal SHML requires work-up for infection-related lymphadenopathy, as well as exclusion of Hodgkin and non-Hodgkin lymphoma. The extranodal RDD is usually diagnosed by histopathological findings of biopsy performed for other suspected diseases (e.g. meningioma in case of cerebral RDD).

Clinical course and prognosis

The disease course is hardly predictable. Observation of spontaneous regression in some cases and the fact that many patients have lost contact after diagnosis, indicate a non-aggressive course in most cases (14). The lack of a staging system and of a uniform patient assessment does not allow to identify prognostic factors. Nevertheless, in patients with an unfavorable prognosis, immunological disorders as well as multiple extranodal lesions were more often detected. Particularly adverse effects on the prognosis have lesions of the kidneys, lower respiratory tract and liver.

Treatment

There are no systematic data on the effectiveness of treatment of RDD. Patients presenting with nodal disease only and without associated autoimmune disease tend to have higher chances for spontaneous regression. For such patients wait and watch approach is justified. Therapy is needed in patients with associated diseases and those with extranodal RDD, particularly for those with involvement of vital organs. Surgical debulking may be helpful in patient with intracranial disease or with obstruction of the upper airways. Radiation therapy has been successfully used for orbital disease and impeding visual compromise (19). Systemic steroids stop the fever, but their effect on the dynamics of the size of the lymph nodes is not very well proven. Various combinations of steroids, vinblastine, methotrexate, mercaptopurine and alkylating agents have been used without consistent effect (20-23). According to the scarce data available, it seems that the most effective combinations in the past were steroids, vinca alkaloids and alkylating agents. In more recent publications treatment success in cases with refractory or recurrent RDD have been reported for imatinib, cladribin and clofarabine (13, 24). In patients with associated autoimmune disease, particularly ALPS, rituximab and sirolimus may be effective.

Erdheim-Chester Disease (ECD)

Synonyms: lipoid granulomatosis

ECD is a non-LCH, characterized by the infiltration of involved tissues by foamy CD68+CD1a- histiocytes(25).

Epidemiology

The incidence of ECD is unknown. Less than 1000 cases have been reported since the first description in 1930(25).The disease usually presents in adults aged 40-60 with a male predominance. It is very uncommon in childhood with less than 15 pediatric cases reported to date (8). Interestingly among the reported pediatric cases girls were more frequently affected (26).

Pathology

Due to its inflammatory clinical features ECD has been considered for decades to be a reactive disorder due to aberrant immunity. The recent discovery, that it is a clonal disease resulting of constitutive activation of the MAPK pathway, completely changed the view on its pathobiology. It is now classified as an inflammatory myeloid neoplasm (25). BRAF mutations have been documented in 57-75% of the cases in larger cohorts, which is similar to the mutation frequency observed in LCH (3, 25).

The histological appearance can vary considerable depending on location and evolution phase of the lesions (27). An overarching feature is the proliferation of mature histiocytes in a background of inflammatory stroma. However, the histiocyte content can vary considerably in reverse proportion to the tissue fibrosis. Characteristic foamy histiocytes are also not always present. Moreover, the histiocytes

in ECD share common immune phenotype with the other non-LCH disease, revealing positive staining for CD68, CD163, FXIIIa, and fascin. Therefore, compatible histopathology is obligatory for the diagnosis of ECD, however, the final diagnosis has to be corroborated by molecular studies and by the pattern of clinical manifestations and imaging findings (28).

Clinical manifestations

ECD is a systemic disease and can affect virtually all organs. Constitutional symptoms include fever, weakness and weight loss. Patients may present with skeletal, pulmonary, retroperitoneal, endocrine, neurologic, skin, renal, and cardiovascular involvement (28). The extent and distribution of the disease determine the clinical course and prognosis (8, 28). The disease spectrum varies from asymptomatic skeletal lesions to multisystemic involvement with life-threatening complications.

Involvement of the long bones is seen in almost all (> 90%) patients. It characteristically presents as a symmetric bilateral osteosclerotic lesions of the distal lower limbs with metadiaphysal location. The bone lesions can present with mild to moderate pain, but may be asymptomatic. Orbital infiltration occurs in about 25% of the patients. On it is more often bilateral, with orbital masses causing more or less prominent proptosis, and less frequently oculomotor nerve palsy or optic nerve compression. Xanthelasma of the eyelids are encountered also in about 25% of the ECD patients. Skin lesions located elsewhere can present as scaly plaques or papulonodular lesions with xanthomatous appearance. Pituitary gland infiltration leads to diabetes insipidus in about 25% of the patients, and in some cases is accompanied by hyperprolactinemia and gonadotropin insufficiency. Orbital and pituitary involvement are also seen in LCH and JXG, and their differential diagnosis based on clinical findings only is difficult.

Distinct feature of ECD compared to other histiocytic disorders is its predilection to the cardiovascular system. It is encountered in 70% of the patients, and requires rigorous imaging work-up as the lesions can be clinically silent. The most frequent finding on CT or MRI (40-50%) is a circumferential sheathing of the aorta, described as “coated aorta”. The periaortic infiltration may extend to other main arteries (e.g. renal arteries) and cause complications, such as renovascular hypertension. Pericarditis is another serious cardiovascular manifestation, documented in about 30% of the patients.Pseudo-tumoral infiltration of the right atrium has also beenreported.

The lung can be also involved and the radiologically presents with interstitial opacification. Advanced pulmonary lesions are associated with extensive fibrosis that may lead to cardiorespiratory failure (29).

Retroperitoneal infiltrates mimicking retroperitoneal fibrosis are another characteristic feature of ECD observer in about 50-70% of the patients. The radiologic findings on CT or MRI are described as “hairy kidney”. The retroperitoneal ECD can result in unilateral or bilateral hydronephrosis.

Central nervous system involvement can cause cerebellar and pyramidal synptoms, headaches, seizures, cognitive impairment, cranial nerve palsies and sensory disturbances.

Prognosis

ECD has a variable prognosis but is overall poorer in those with CNS involvement. Before IFN-alpha, the mean survival after diagnosis was 19.2 months. Nowadays, with IFN-alpha treatments, the mortality rate is only 26%, and 5-year survival is 68%. The introduction of the very effective targeted BRAF inhibitor vemurafenib promises further improvement of the patient fate.

Diagnosis

The diagnosis of ECD is based on histopathologic findings within the appropriate clinical and radiological context (8, 28). The hallmark histological finding is the xanthogranulomatous or xanthomatous infiltration of tissues with foamy histiocytes, which stainpositive for CD68, CD163, FXIIIa and negative for CD1a and CD207. Bone x-rays usually display bilateral and symmetric cortical osteosclerosis of the long bones, while technetium 99m bone scintigraphy shows almost constantly evidence of symmetric and abnormally strong labeling of the distal ends of the long bones of the lower limbs. Abdominal CT scan may reveal a "hairy kidney" appearance (in 50-70%) and/or “coated aorta”(40-50%), findings highly suggestive for ECD. Recommendations for the baseline clinical evaluation of patients with ECD are available in the consensus guidelines elaborated by an international panel of experts (28).

Differential diagnosis

Due to the multisystemic character of the disease and the innumerable manifestation related to ECD, the list of differential diagnoses is very long, depending of involved system and location. The most common differentials to be considered include LCH, RDD, Takayasu arteritis, Wegener's granulomatosis, primary hypophysitis, chronic recurrent multifocal osteomyelitis, malignancies, neurosarcoidosis, mycobacterial infections and metabolic disorders.

Management and treatment

Therapy is recommended at diagnosis in all patients, except for those patients with minimally symptomatic disease (28). Standard or pegylated IFN-alpha is considered a first line treatment for all forms of ECD. Higher doses (9 million units, 3 times per week) are required on a long-term basis for those with CNS and cardiac localizations. Bisphosphonates may be given to alleviate bone pain. Cladribine can be effective in those with orbital involvement that have been resistant to other forms of treatment.

Discovery of recurrent mutations of the MAPK pathway (particularly BRAFV600E) in the majority of the ECD patients opened an opportunity for a targeted therapy. The first report on vemurafenib used to treat adult patients with concomitant ECD and

LCH showed dramatic response (30). This observation has been subsequently validated by a larger patient cohorts and in addition it has been shown that sustained remissions are possible with continuous treatment (31). Recently published results of a basket trial corroborate the previous reports and suggest considering vemurafenib as the new standard treatment for ECD patients positive for BRAFV600E (32). Indeed vemurafenib has been recently approved for this indication by the FDA (33).

Summary:

The non-LCH, particularly those with systemic manifestation are uncommon diseases in the praxis of pediatric hematology/oncology. Due to their broad spectrum of manifestations, keeping in mind their key features and an adequate index of suspicion are important for timely and correct diagnosis. Non-LCH have to be considered in the differential diagnosis of papulonodular cutaneous lesions with xanthomatous appearance, osteolytic and osteosclerotic lesions with benign morphology and histiocytic infiltration, orbital lesions with proptosis, suprasellar masses presenting with central diabetes insipidus, as well as leptomeningeal mass lesions.

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No. 09

A Rare Presentation of L.C.Histiocyosis in Chiasma Optic Region

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Introduction:

L.C.Histiocytosis has different clinical presentation but presentation of a mass at chiasma optic region is rare that we present.

Case Presentation:

A 4 year boy referred to Amirkola Children Hospital with visual problem and strabismus and unilateral petosis. Visual problem has started since 3 years ago and the first MRI showed small mass on his chiasma optic region. MRI repeated every 6 month up to age of 4 when tumor size was increased.

Biopsy operated by neurosurgeon and pathologic review and I.H.C study reported L.C.H at chiasma optic region. Strabismus and unilateral petosis happened after neurosurgery operation.

He referred for chemotherapy and received systemic chemotherapy with 6-MP and MTX and vinblastine for 4 courses and then MRI repeated. There was no any response to treatment and tumor size was increased. So, he went on intensive chemotherapy by cladarabin every 3-4 week and after to courses we evaluate response to therapy by MRI.

Keywords: L.C.H, chiasma optic, cladarabin.

No. 10

Langerhance Cell Histiocytosis 5 Years After B-cell Acute Lymphoblastic Leukemia in a 11 year-old boy

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Background and Objective:
Langerhance Cell Histiocytosis (LCH) is associated with a variety of malignancies. But the onset of LCH during or after the treatment of acute leukemia is rare. To the best of our knowledge, there is only a single case of B-ALL followed by localized LCH with 2 lesions in the bones 2 years after the completion of the chemotherapy. We report a case of LCH with one lesion in skull bone in a patient 5 years after completion of chemotherapy of ALL.

Patient Report:
A 11-year-old boy admitted in oncology ward of Ali-Asghar children hospital with a local pitting region on the right side of the head. Skull X-ray showed a small lytic lesion. The patient past medical history was notable for diagnosis of pre B-cell ALL at age 3 years old and has been received chemotherapy for 3 years and he has not any problem in 5 years until that time.
The patient underwent excision of the lesion and diagnosis of the LCH was confirmed according the report of pathology.
The published case reports on the association of LCH and acute lymphoblastic lymphoma (ALL) revealed that LCH has preceded the diagnosis of leukemia or occurred within 6-12 months after diagnosis of leukemia.
To the best of our knowledge, there is only a single case of B-ALL followed by localized LCH with 2 lesions in the bones 2 years after the completion of the chemotherapy.

Conclusion:
Finally, according to this case, it would be highly valuable to identify clinical or pathological risk factors or typical symptoms in the follow up that can predict the development of a histiocytic disorder.

Key Words: Langerhance Cell Histiocytosis (LCH), acute leukemia

No. 11

Cerebral infiltrative lesion and chronic nature of the Rosai-Dorfman disease: case report

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Abstract

Introduction: Rosai-Dorfman disease (RDD) is a rare of unknown etiology characterized by histiocytic benign proliferation in lymph nodes as well as extranodal sites. The classic finding of this disease is painless cervical lymphadenopathy in most patients. In exteranodal disease involves skin, soft tissue, bone, genitourinary system, lower respiratory tract, and central nervous system.

Case report: A seven-year-old boy referred to the hospital with left parietal swelling, headache, fever, imbalance, weight loss, speech and walking impairment. Which had a hyposignal infiltrative lesion in lateral ventricle and choroid plexus by expanding to subcortical white matter of bilateral temporo occipital in the early studies. After surgery and sampling, he was diagnosed with cerebral Rosai-Dorfman disease.

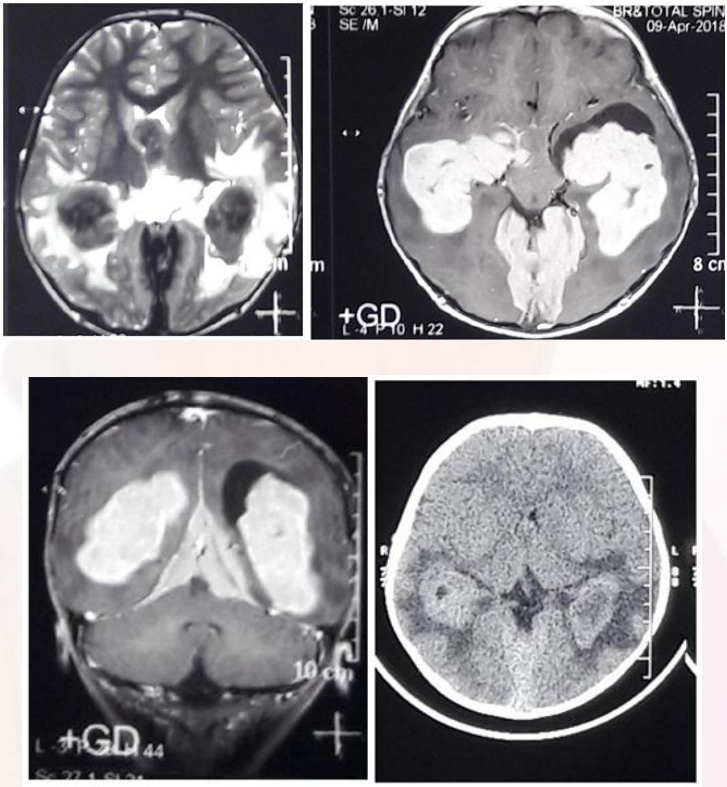
In past history, the patient had bilateral cervical lymphadenopathy at the age of 2 years, and at the age of 3, femoral soft tissue involvements, and at the age of 5, a skin disorder that improved with local treatments. However, at the time of refer to hospital, there were no other symptoms in other parts except brain symptoms.

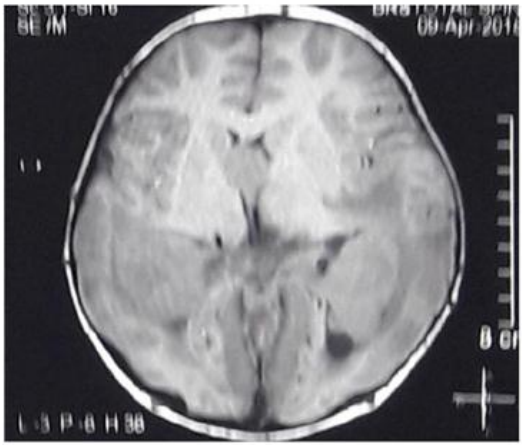
Conclusion: In differential diagnosis of brain lesions with specific borders and radiologic high contrast view similar to meningioma, the probability of Rosai-Dorfman disease is highlighted. The presence of painless and extensive bilateral cervical lymphadenopathy helps to diagnose the disease. Isolated brain involvement in Rosai-Dorfman disease is very rare, and it can be seen in less than 5% of cases, but the chance of complications decreases and prognosis will improve by early diagnosis and interventions.

Keyword: cerebral lesion, histiocytic proliferation, Rosai-Dorfman disease

There are mutilobulated intraventricular masses in lateral ventricles cause hydrocephalus and significant edema in adjucent parenchyma, another extra axial dural base mass located on tentorium is also noted encasing posterior aspect of

superior sagital sinus. Mentioned masses appear hyperdense in CT, low signal at T1 and T2 weighted images and show avid contrast enhancement after contrast administration





No. 12

A 6-years-old boy presented with neck and mediastinal mass

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Case Report

A 6-years-old boy presented with history of low-grade fever and suprasternal notch mass for 2 months. On examination, child had mass in suprasternal notch and wheezing on auscultation of chest. There was no hepatosplenomegaly or skin rash. Laboratory studies including CBC, ESR, LDH, Uric acid, AST, and ALT were normal. A chest X-ray showed massive mediastinal widening. Computerized tomography (CT) scan of the chest showed a large soft tissue mass in the anterior mediastinum. A sonography-guided biopsy of the mass was done. Histopathology was suggestive for LCH and immunohistochemical stains were positive for S-100 and CD1a. BMA, BMB, abdominal sonograghy and skeletal survey were normal. He received induction chemotherapy with prednisolone, vinblastine and MTX followed consolidation with vinblastine, prednisolone and 6-mercaptopurine according to LCH III protocol. A chest CT scan after 2 months of treatment showed complete resolution of mediastinal mass. Patient is doing well after 10 months of treatment with LCH protocolPatient is well now and is asymptomatic 6 months of continuation therapy. In conclusion, langerhans cell histiocytosis should be considered in differential diagnosis of mediastinal mass in children.

Keywords: histiocytosis, mediastinal mass, children

No. 13

Salvage chemotherapy in the treatment of pediatric refactory multifocal langerhans cell histiocytosis with the Japan langerhans cell histiocytosis study Group-96 Protocol: Results from Tabriz Children Hospital

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Background and objectives:
The outcome and poor therapeutic responses in pediatric refractory multifocal langerhans cell histiocytosis (LCH) are associated with high motality and morbidity in literature. The purpose of this study is to investigate effectiveness of salvage therapy with practical Japan langerhans cell histiocytosis study Group-96 (JLSG-96) Protocol due to lack of access to 2-chlorodeoxyadenosine (2-CdA) from 2010 to 2015 in Tabriz children hospital.

Materials and methods:
This was a cross sectional study of 10 (4 male and 5 female) refractory multifocal LCH children. Mean age of the participating was 22±33 months. Induction therapy initially was consisted of 6 weeks treatment with prednisolone, vinblastine, and methotrexate after documenting the diagnosis. Patients who had a poor therapeutic response to this standard induction therapy were switched to alternative salvage chemotherapy with combination of vincristine, cyclophosphamide, doxorubicin, and prednisolone according to JLSG-96 Protocol. Between 2010 and 2015, we had very limited access to 2-CdA drug.

Findings:
At the median 5-years follow-up, 8 patients have been survived with favorable response status. 2 patients were died with late sequelae (one patient with chronic CNS involvement and the other patient from chronic diffuse lung disease). Diabetes insipidus developed in 2 patients.

Conclusion:
The JLSG-96 Protocol has been associated with low mortality and improved outcome in refractory childhood multifocal LCH in this study.

Key words: langerhans cell histiocytosis, Japan langerhans cell histiocytosis study Group-96, diabetes insipidus, 2-chlorodeoxyadenosine.

No. 14

Biology and treatment of HLH

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Introduction:

Hemophagocytic lymphohistiocytosis (HLH) is an inflammatory syndrome where a deregulated immune response results in uncontrolled activation of lymphocytes and histiocytes (macrophages), resulting in hypercytokinemia, that, untreated, may lead to organ failure and death (Janka and Lehmberg 2014). Characteristic, although unspecific symptoms and laboratory findings are prolonged fever, hepatosplenomegaly, pancytopenia, elevated ferritin and triglycerides as well as low fibrinogen. Neurological symptoms are frequent. Hemophagocytosis, which has given the disease its name, may be absent initially and is not necessary for diagnosis.

HLH may occur at any age. It was first described in children as a familial disease (Farquhar and Claireaux 1952); with increasing frequency it is being reported in adults as well (La Rosée 2015).

Classification of HLH:

HLH can be inherited (primary, familial) or acquired (secondary). So far, mutations in four genes have been identified in familial HLH (fHLH). Mutations in *PFR1* were the first to be linked to fHLH, followed by mutations in UNC13D, STX11 and STXBP2. In addition, the immune deficiencies Griscelli syndrome 2 (GS2) and Chédiak-Higashi Syndrome (CHS), which both are characterized by hypopigmentation, and the 2 x-linked lymphoproliferative diseases XLP-1 and XLP-2 are alsocounted among primary HLH. In babies and young children a genetic basis for HLH predominates. However, considering all pediatric age groups, non-genetic cases prevail (Chinn 2018). These children have either infectious triggers (that can also be found in fHLH), or, less frequently, autoimmune/autoinflammatory diseases, metabolic diseases, malignancies, or other rare immune deficiencies.Infectious triggers have also been reported in genetic HLH (Henter 1993). Recently, the need for an infectious trigger for primary HLH has been questioned (Heeg 2018).

In adults, malignancies or infectious triggers predominate (Ramos-Casals 2014); a minority of patients harbors mutations in HLH-relevant genes. In a large series in 178 adults, biallelic or monoallelic mutations in HLH genes were found in 6.8%, respectively 7.4% of the patients (Zhang 2011). The preponderance of hypomorphic mutations in adults correlates with the later-onset of disease. HLH in the context of autoinflammatory/autoimmune diseases is commonly called macrophage activation syndrome (MAS) or MAS-HLH.

Biology of HLH:

Biology of HLH can be divided into the biological mechanisms that lead to the disease (pathogenesis) and the physiological processes, which explain clinical symptoms and laboratory finding (pathophysiology).

Pathogenesis of HLH(Figure 1)

The genes mutated in fHLH play an important role in recruitment, trafficking and contents of cytotoxic vesicles in natural killer (NK) cells and cytotoxic T lymphocytes (CTLs), leading to failure of apoptosis of the target cell (Pachlopnik Schmid 2010). UNC13D is important for priming of docked cytotoxic granules for membrane fusion. STX11 regulates granule membrane fusion and interacts with STXPB2. PRF1 codes perforin which together with serine proteases, secreted into the immunologic synapse by cytotoxicvesicles, leads to apoptosis of the target cell. Perforin is also vital in downregulating the immune response by eliminating activated dendritic cells.Mutations in LYST (CHS) cause defective formation and maturation of cytotoxic granules. In GS2 the mutated protein prevents docking at the membrane. The inabilityof NK cells and CTLs to kill the target cell leads to failed disengagement of killer cell and target cell, prolonging mean synapse time fivefold and greatly amplifying the amount of inflammatory cytokines (Jenkins 2015). In XLP-1, where SH2D1A codes SAP, impairment of cytotoxicity does not involve the secretory pathway of cytotoxic granules. The specific susceptibility to Epstein-Barr virus is explained by a selective cytotoxic impairment of SAP-deficient CTLs towards infected B cells(Sepulveda 2017). XLP-2 is linked to mutations in XIAP (BIRC4) that are not associated with loss of cytotoxic function (Sepulveda 2017). XIAP restricts inflammasome activation in mice (Yabal 2014). Like patients with NLRC4-related disorders, also a rare cause for HLH (Cannae 2014), XLP-2 patients may develop inflammatory bowel disease and have high levels of IL-18.

Besides defects in cytotoxicity, there can be other mechanisms that lead to the clinical picture of HLH, as proven by patients with a severe combined immune deficiency and lack of T-cells, developing HLH nevertheless (Bode 2015). There is evidence from several studies in mice that the innate immune system plays an important role in the development of HLH. Repeated activation of toll-like receptor (TLR) 9 induces HLH

in mice (Behrens 2011), and abrogating the function of the TLR adaptor myd88 prevents HLH in UNC13D mice (Krebs 2011). A recent paper showed that blockade of ST2, the myd88-dependent receptor for interleukin-33, markedly improved survival of LCMV-infected perforin-deficient mice (Rood 2016). IL-33, an alarmin, is likely released from damaged tissues and adds to increased interferon-γ production, and thus hyperinflammation.

Pathogenesis of HLH may also involve inhibition of cytotoxic function by viruses and cytokines (Hsieh 2006, Cifaldi 2015), interference with apoptosis by viruses and tumor cells (Alcami 2000, Hassan 2014), secretion of cytokines from tumor cells (Nishiwaki 2016), acquired immune defects by drugs or HIV infection, and possibly also an imbalance between viral load and immune effector cells. Genetic factors include mutations or single nucleotide polymorphisms in genes important for the immune response (Lee 2017); heterozygous mutations in HLH-genes may also contribute (Cheng 2018). Finally, environmental factors cannot be excluded.

Pathophysiology of HLH

The clinical symptoms and laboratory findings of HLH can all be explained by hypercytokinemia and organ infiltration by activated lymphocytes and histiocytes. Fever is caused by interleukin (IL)-1 and IL-6. Several factors are involved in pancytopenia besides phagocytosis of mature blood cells: interferon-γ (INF- γ) and tumor necrosis factor- α (TNF-α) both inhibit hematopoiesis and increase apoptosis (Selleri 1995, Papadaki 2002). A recent paper presented evidence that hematopoietic stem cells (HSCs) themselves are phagocytosed in HLH patients (Kuriyama 2012).Self-recognition to prevent phagocytosis is regulated by interaction of CD47 (expressed in hematopoietic cells) and SIRPA (expressed in macrophages).Inflammatory cytokines downregulate CD47 specifically in HSCs. CD47 was shown to be downregulated in stem cells of HLH patients with active disease. Consequently, the number of HSCs in HLH patientswas reduced to 23% of those in healthy adults (Kuriyama 2012). Infection of HSCs or supportive stromal cells by several viruses may also play a role in pancytopenia. Increased triglycerides can be explained by decreased lipoprotein lipase (Henter 1991) and increased synthesis (Feingold 1989). Several mechanisms exist for the elevated ferritin levels which are found in nearly every patient with HLH: TNF-α and oxidative stress lead to increased synthesis of hemoxygease-1 (Otterbein 2003) which cleaves hemoglobin, thus stimulating ferritin synthesis. Passive release of ferritin from damaged liver cells may be another cause (Kirino 2005). Finally, increased iron absorption could play a role (Wu 2013). Various cytokines induce plasminogen activator (Loscalzo 1996), leading to cleavage of plasminogen into plasmin, which induces hyperfibrinolysis.

The large number of activated lymphocytes can explain the high levels of the α-chain of the soluble interleukin-2 receptor (sCD25).

Treatment of HLH

HLH treatment aims at suppressing hyperinflammation with its dangerous side effects for the host. Another aim is to eliminate the target cells by cytotoxic treatment since apoptosis of the (infected) cell is deficient. It is of vital importance also to treat the underlying trigger to prevent persistent stimulation of the immune cells. If there is an underlying genetic defect, the immune system has to be replaced by hematopoietic stem cell transplantation.

Agents directed at hyperinflammation are immunosuppressive/ immunomodulatory or cytotoxic agents.Corticosteroids are included in all HLH treatment protocols.Immunomodulatory agents compriseintravenous immunoglobulins, cyclosporine A, antagonists of single cytokines (IL-1, IL-6, INFγ), the janus kinase 1/2 inhibitor ruxolitinib, and antibodies against the IL-2 receptor (basiliximab). Cytokines can also be removed by plasmapheresis (Bosnak 2016) or a cytokine-adsorption column (Greil 2017). Corticosteroids and T-cell antibodies are cytotoxic for lymphocytes; cytotoxicity of rituximab is restricted to CD19 positive cells. In 1980, a seminal paper appeared, showing that etoposide had marked efficacy in patients with HLH (Ambruso 1980). In perforin-deficient mice, etoposide selectively ablated activated T-cells (Johnson 2014).

In 1989 the HLH Study Group of the Histiocyte Society was founded; in 1994 the first international HLH protocol started. Therapy consisted of dexamethasone, etoposide, and cyclosporine A. In the subsequent protocol HLH-2004, cyclosporine A was moved upfront to increase the initial response rate and to prevent the reactivations that were frequent when dexamethasone was tapered and etoposide doses decreased. Both protocols targeted children with familial disease or infection-triggered disease without known underlying condition such as malignancies or autoimmune diseases. The results of both studies have been published (Trottestam 2011, Bergsten 2018). Most patients entered into the studies had genetic/familial HLH. In both protocols, 14% patients died within 2 months, nearly all because of nonresponse to treatment. Another 10% (HLH-1994), respectively 6% of patients (HLH-2004) died within 12 months. Mortality after stem cell transplantation was over 30% in both studies. Altogether, probability of 5-year survival was 61% in the 369 patients of study HLH-2004 (Bergsten 2018). CNS reactivations with a high potential of late sequelae continue to pose a severe problem (Horne 2017).

Since results of HLH-2004 were not significantly different, and there was some concern about neurotoxicity with combined high-dose dexamethasone and

cyclosporine A, the recommendation of the HLH Study Group is to use protocol HLH-1994. Just recently, the HLH Steering Committee of the Histiocyte Society has worked out recommendations on the use of protocol HLH-1994 (Ehl 2018).

Therapy of HLH is a two-sided sword: On one hand, it has to suppress hypercytokinemia to prevent its dangerous effects on organ function, but on the other hand, treatment should not destroy all defense mechanisms and may be counterproductive for control of infectious triggers and recovery of the bone marrow.

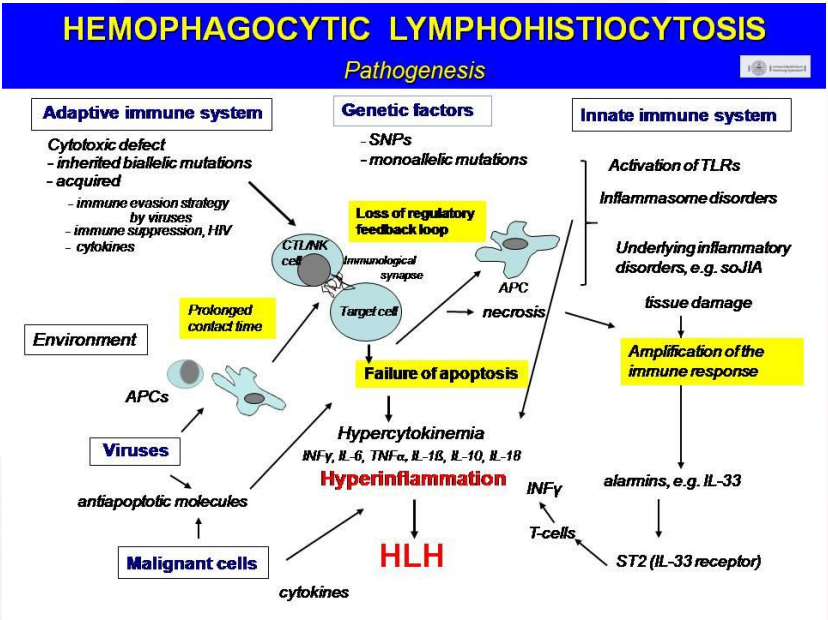
Not all patients need the full HLH-1994 protocol. Less severe cases often respond to corticosteroids +/- immunoglobulins or fewer doses of etoposide. However, the dynamics of the disease have to bewatched carefully. Patients with MAS-HLH usually respond to high-dose methylprednisolone +/- cyclosporine A; anakinra is also a very useful agent for this condition (Ravelli 2012).

Patients who do not respond within 2 weeks, are candidates for salvage treatment. Data on salvage treatment are scarce; the most frequent data are on alemtuzumab (Marsh 2017) which is very effective in front-line treatment (Moshous 2015). Emapalumab, an interferon-γ antibody has been tested in in children, most of whom had relapsed or refractory disease. (Jordan 2015). Comprehensive data have not been published yet. A study, using liposomal doxorubicin, etoposide and methylprednisolone in 34 adults refractory to HLH-1994 treatment after 2 weeks (lymphoma patients excluded) showed 12 complete and 14 partial remissions; 8 patients failed to respond (Wang 2015). There are anecdotal reports on other agents, including ruxolitinib, which seems to be a promising agent. Ruxolitinib has shown good efficacy in several mouse models (Maschaldi 2016, Das 2016).

Patients with genetic HLH can only be cured by hematopoietic stem cell transplantation (HSCT). Myeloablative conditioning was associated with a high transplant mortality in both study HLH-1994 and HLH-2004. Reduced intensity conditioning leads to a better survival rate (Cooper 2008, Lehmberg 2013), but mixed chimerism often necessitates donor lymphocyte infusions or a second stem cell boost (Allen 2018). In a recent international survey on patients transplanted with HLH, donor chimerism of 20-30% was found to be protective against late reactivation. Interestingly, several patients did not reactive in spite of a persistently low overall and lineage-specific donor chimerism of ≤10% (Hartz 2016). Children with acquired HLH are usually no candidates for HSCT. However, the experience with EBV-associated HLH that is very frequent in Asia, shows that these patients often have a refractory course, possibly associated with evolution into a proliferation of malignant cells, which necessitates HSCT (Ohga 2010).

In conclusion, HLH is a hyperinflammatory syndrome arising on the basis of many underlying conditions. Treatment has to be adjusted to the severity of the disease and

the underlying condition. Etoposide-based treatment protocols have improved survival considerably; however, mortality in the first 2 months is still high. Some newer drugsare in clinical testing and could prove to be valuable alternatives or additions.



Legend to figure 1

Adaptive immune system: Normally, natural killer cells and cytotoxic T-lymphocytes engage with the antigen-presenting target cell,leading to apoptosis. Failure of apoptosis as consequence of inherited or acquired cytotoxic defects or defective activation or signaling of T-cells, results in a prolonged synapse time with augmentation of cytokine secretion, leading to the clinical picture of HLH. Perforin deficiency as consequence of genetic disorders of the cytotoxic granule pathway,results in the loss of the regulatory feedback loop that eliminates antigen-presenting cells. Failed apoptosis is associated with alternate cell death, which, as does tissue damage, elicits the production of alarmins that can amplify the immune response by signaling through ST2. Genetic factors: Besides biallelic mutations leading to cytotoxic defects,or mutations affecting T cell signaling or activation, single nucleotide polymorphisms in genes important for the immune response, or monoallelic mutations in HLH-relevant genes, can be contributing factors. Innate immune system: activation of toll-like receptors and inflammasome disorders, can

also lead to the clinical picture of HLH. Autoinflammatorydiseases, such as systemic-onset juvenile idiopathic arthritis, already have a high inflammation levels that can be further augmented by infections. Viruses: Virusesare able to interfere with cytotoxicity, as well as apoptosis. Malignant cells: Malignant cellsinhibit the extrinsic and intrinsic pathway of apoptosis and produce cytokines. The role of environmental factors is debated.

Abbreviations: CTL=cytotoxic T-lymphocyte; NK cell=natural killer cell; HIV=human deficiency virus; SNPs=single nucleotide polymorphisms; APC= antigen-presenting cell; TLRs=toll-like receptors; soJIA=systemic-onset juvenile idiopathic arthritis.

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No. 15

Acquired Hemophagocytic lymphohistiocytosis - Report of 2 Cases

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Hemophagocytic lymphohistiocytosis (HLH) is an aggressive and life-threatening syndrome of excessive immune activation. It most frequently affects infants from birth to 18 months of age, but the disease is also observed in children and adults of all ages. HLH can occur as a familial or sporadic disorder, and it can be triggered by a variety of events that disrupt immune homeostasis. Infection is a common trigger both in those with a genetic predisposition and in sporadic cases.

Use of the term "primary HLH" to denote the presence of an underlying genetic disorder and "secondary HLH" to denote presence of the HLH phenomenon occurring secondary to another condition.

Both primary and secondary HLH can be triggered by infections or other immune activating events, and gene mutations can be found in individuals of any age and with any family history.

In practice, a distinction between primary and secondary HLH is not essential for the initial diagnosis and management. However, identification of a gene mutation may be useful for subsequent management.

- Primary HLH, also called familial hemophagocytic lymphohistiocytosis (FHL), refers to HLH caused by a gene mutation, either at one of the FHL loci or in a gene responsible for one of several immunodeficiency syndromes. FHL loci include:

  FHL1, FHL 2 , FHL 3, FHL 4, FHL 5

Griscelli syndrome 2 (RAB27A), Hermansky–Pudlak, XLP1, XLP2, BLOC1S6, CD27, ITK, LYST, MAGT1 (XMEN), SLC7A7 and XIAP (BIRC4) genes

- Secondary (sporadic, acquired) HLH is generally used to describe patients without a known familial mutation and who typically have a clear trigger for developing acute HLH (eg, viral illness, autoimmune disease, lymphoma).

However, this term can create confusion because many patients with "secondary HLH" have an underlying genetic defect associated with the syndrome (eg, heterozygous defect, mutation resulting in partial protein expression); conversely, many patients with primary HLH can develop an acute HLH flare in response to one of these triggers.

The persistent activation of macrophages, NK cells, and CTLs in patients with HLH leads to excessive cytokine production (cytokine storm) by all of these cell types, and is thought to be responsible for multiorgan failure and the high mortality of this syndrome. It is estimated that approximately 1 child in 3000 admitted to a tertiary care pediatric hospital will have HLH, which corresponds to several cases per center per year.

CLINICAL FEATURES

Initial presentation: HLH presents as a febrile illness associated with multiple organ involvement. Thus, initial signs and symptoms of HLH can mimic common infections, fever of unknown origin, hepatitis, or encephalitis. With few exceptions, the clinical features are similar regardless of whether an underlying genetic defect has been identified.

The HLH-2004 study reported the following clinical findings :

- Fever – 95 percent
- Splenomegaly – 89 percent
- Bicytopenia – 92 percent
- Hypertriglyceridemia or hypofibrinogenemia – 90 percent
- Hemophagocytosis – 82 percent
- Ferritin >500 mcg/L – 94 percent
- Low/absent NK cell activity – 71 percent
- Soluble CD25 elevation – 97 percent

Laboratory and radiographic abnormalities

Cytopenias: Cytopenias, especially anemia and thrombocytopenia, are seen in >80 percent of patients on presentation. Platelet counts range from 3000 to 292,000 (median 69,000)/microL, and hemoglobin levels of 3.0 to 13.6 (median 7.2) g/dL are typical.

Serum ferritin levels: A very high serum ferritin level is common in HLH and, especially in children, has high sensitivity and specificity. Elevated soluble IL-2 receptor alpha (sIL-2R) and sCD163 in patients with HLH may help to exclude these

other possible diagnoses. Disease activity in some patients may correlate more closely with elevated sIL-2R or sCD25 than with ferritin.

Growth differentiation factor 15, which is a protein responsible for modulation of iron homeostasis, is dramatically upregulated in patients with HLH and is responsible for increased serum ferritin by enhancing the ferroportin-mediated iron efflux.

Liver function and coagulation abnormalities : Nearly all patients with HLH will have hepatitis, manifested by elevated liver function tests (LFTs), including liver enzymes (AST, ALT, GGT), lactate dehydrogenase (LDH), and bilirubin.

Hypertriglyceridemia: can be due to severe liver involvement, but may not be elevated until the liver has been affected for some time.

Coagulation abnormalities due to impaired hepatic synthetic function and/or disseminated intravascular coagulation are common.

Neurologic findings : Neurologic abnormalities have been observed in one-third of patients with HLH, are highly variable, and may include seizures, mental status changes (including severe changes consistent with encephalitis), and ataxia.

Infections: HLH is often associated with viral infections, including EBV, CMV, parvovirus, herpes simplex virus, varicella-zoster virus, measles virus, human herpes virus 8, H1N1 influenza virus and HIV alone or in combination.

Patients with rheumatologic diseases who are treated with anti-TNF agents and develop HLH may be infected with mycobacterium tuberculosis, CMV, EBV and other bacteria.

Although less common, HLH may also occur in the setting of infections due to bacteria (eg, *Brucella*, gram negative bacteria, tuberculosis), parasites (eg, Leishmaniasis, malaria), and fungi.

Malignancy : HLH has been reported in association with malignancies, most commonly lymphoid cancers and leukemias, but also solid tumors. Rarely, the diagnosis of HLH may precede the identification of the malignancy. Overall prognosis is quite poor for any malignancy-associated HLH, regardless of the patient's age at presentation.

Rheumatologic disorders/MAS: HLH can occur in the setting of rheumatologic disorders. The most common association is in children with systemic juvenile idiopathic arthritis (sJIA, formerly called Still's disease, systemic onset JIA, or systemic onset juvenile rheumatoid arthritis). The term macrophage activation

syndrome (MAS) is used when a hemophagocytic syndrome develops in children with JIA and other rheumatologic conditions.

Diagnostic criteria for HLH:

We recommend that the diagnosis of HLH be based on the following criteria, which were used in the HLH-2004 trial.

In children, homozygosity or compound heterozygosity for genetically verified HLH mutations including: (PRF1, UNC13D, STX1, STXBP2, Rab27A, SH2D1A, BIRC4, LYST, ITK, SLC7A7, XMEN, HPS) or gene defects of other immune regulatory genes.

OR

Five of the following eight findings:

- Fever ≥38.5°C
- Splenomegaly
- Cytopenia, with at least two of the following:

  hemoglobin <9 g/dL (for infants <4 weeks, hemoglobin <10 g/dL); platelets <100,000 microL; absolute neutrophil count <1000/microL
- Hypertriglyceridemia (fasting triglycerides >265 mg/dL) and/ or hypofibrinogenemia (fibrinogen <150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent NK cell activity
- Ferritin > 500 ng/mL; however, ferritin >3000 ng/mL is reported as more indicative of HLH.
- Elevated soluble CD25 (soluble IL-2 receptor alpha [sIL-2R]) with two standard deviations above age-adjusted laboratory-specific norms.

It should be noted that these diagnostic criteria were devised for use in clinical trials and are therefore unlikely to capture every case of HLH. Because of the high mortality of HLH in the absence of appropriate treatment, we do not always require these diagnostic criteria to be met in order to initiate treatment. Specifically, we do not delay treatment while awaiting the results of genetic or specialized immunologic testing.

We consider flow cytometry for reduced/absent NK cell, perforin and/or CD107 alpha as a satisfactory alternative to the NK cytotoxicity assay.

We consider the following modified criteria sufficient to diagnose HLH:

3 out of 4 clinical findings (fever, splenomegaly, cytopenias, hepatitis) plus abnormality of one of four immune markers (hemophagocytosis, increased ferritin, hypofibrinogenemia, absent or very decreased NK cell function) .

These criteria are useful because it is common for a patient with HLH to exhibit only three or four of the eight diagnostic criteria, but also have central nervous system (CNS) symptoms, hypotension, and renal or respiratory failure.

Case reports:

Case 1:

A 9-year-old girl with prolonged fever, facial edema, generalized lymphadenopathy and huge splenomegaly was admitted for further follow up. Laboratory tests revealed pancytopenia, increased liver function tests and hyperferritinemia (Ferritin: 3000 ng/ml). Initial infectious workups were negative. Bone marrow aspiration was inconclusive. Ct scan imagings showed cervical, mediastinal (paratracheal, hilar) and para-aortic lymphadenopathy. Bone marrow biopsy reported abundant hemophagocytic cells. Biopsy of abdominal lymph nodes was compatible with diagnosis of "Anaplastic large cell lymphoma" (ALCL).

She underwent chemotherapy for ALCL with APO-1 protocol. In a few days fever and facial puffiness subsided and laboratory abnormalities returned to normal very soon after induction chemotherapy. Cytopenia reversed during the first week following treatment. The patient is in good general condition receiving maintenance treatment for ALCL.

She was diagnosed with HLH complicating ALCL presenting simultaneously.

Case 2:

A 4-month-old girl infant was admitted to hematology deprtment due to pancytopenia and generalized maculopapular rash whole over the body. The parents complained of similar skin lesions in previous baby at the same age who was a boy.

She was febrile. Physical examination was remarkable for generalized skin rash and splenomegaly. Laboratory tests showed pancytopenia. Infectious workup reported a positive PCR for CMV-DNA. Bone marrow aspiration was normal. A presumptive diagnosis of HLH was suggested for the patient.

A specific array of tests including Ro/SSA and La/SSB antibodies was performed in order to rule out "neonatal systemic lupus erythematosus", which were positive with

very high titers in two occasions. Mother serum was also highly positive for the anti-nuclear antibodies.

A course of corticosteroid was started for the baby, Skin lesions went away and she was discharged in good general condition. The mother was referred to rheumatology clinic for further follow-up.

No. 17

HLH Protocols and New Treatments in HLH

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No. 18

The Role of Hematopoietic Stem Cell Transplant in Hemophagocytic Lymphohistiocytosis Syndrome

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Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory clinical syndrome of uncontrolled immune response that results in hypercytokinemia due to underlying primary or secondary immune defect. (HLH) is a life-threatening condition that clinically characterized by fever, hepatosplenomegaly, and cytopenia. The strategies for proper treatment of HLH should include countermeasures for suppression of the hyperinflammation, elimination of triggering causes, killing of infected cells, and replacing defective immune system for patients with genetic disorders. HLH used to be a fatal disease with 1-year overall survival of only 5%, but the survival of HLH patients has improved to more than 60% with the use of chemo-immunotherapy combined with Hematopoietic stem cell transplantation (HSCT) over the past 2 decades. However, HSCT is still the only curative option of treatment for primary (familial) HLH and refractory/relapsed HLH after chemo-immunotherapy. HCT is generally recommended in patients with documented FHL, recurrent or progressive HLH despite recommended chemo-immunotherapy, and CNS involvement. The outcome of HSCT for HLH patients has improved steadily during past decades, but HSCT for HLH still carries significant mortality and morbidity and there remains controversies in various aspects of HSCT.

Moreover, there remain ongoing controversies in various aspects of HCT including indication of HCT, donor selection, timing of HCT, conditioning regimen, and mixed chimerism after HCT.

As pre-transplant infections in these patients lead to high mortality rates, selecting a conditioning regimen which improves the probability of successful engraftment without increasing the risk of mortality and morbidity is very important. Currently, conditioning regimens used for HSCT in HLH (RIC vs. MAC) are still controversial issues among authors. For this reason, we believe that reduced conditioning regimen may be better in this regard.

Key words: HLH, HSCT, FHL, conditioning

No. 19

Post hematopoietic stem cell transplantation Hemophagocytic lymphohistiocytosis

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Hemophagocytic lymphohistiocytosis (HLH) is a very severe and rare syndrome of pathologic immune activation characterized by cytopenia and clinical signs and symptoms of extreme inflammation. HLH occurs as a familial disorder or as an acquired condition usually secondary to a variety of pathologic states: infections, rheumatologic, malignant or metabolic diseases. HLH is reported In natural killer cell malignancies as well as B-cell neoplasms and other types of cancer. HLH has also been reported as a complication of stem cell transplantation especially cord blood ao haploidentical stem cell transplantations.HLH occurring after stem cell transplantation (SCT-HLH) is a very rare complication and particularly difficult to diagnose. It is characterized by severe clinical manifestations and high mortality. Delayed engraftement or unengraftement are the most important manifestation of post transplant HLh.CMV might have a role in pathp physiology of post transplant HLH.A specific, separate set of criteria for HLH after SCT has been developed recently. The diagnosis of SCT-HLH requires both major criteria, or one major and all four minor criteria. The major criteria are (1) engraftment failure, delayed engraftment or secondary engraftment failure after SCT, and (2) histopathological evidence of hemophagocytosis. The four minor criteria are high-grade fever, hepatosplenomegaly, elevated ferritin and elevated serum LDH. Despite current therapeutic approaches, outcomes remain poor. In this lecture we present the case of a young male patient who underwent autologous stem cell transplantation for relapsed Hodgkine lymphoma, complicated with graft failure due to severe HLH .

No. 20

CNS involvement in Hemophagocytic Lymphohistiocytosis (HLH) syndrome

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CNS involvement is one of the most important causes of morbidity and mortality in HLH syndrome. There is no consensus regarding its definition, but most HLH experts agree that an abnormal CSF and/or MRI of the brain, with or without distinct neurological signs or symptoms, is compatible with CNS involvement in HLH syndrome.CNS disease in HLH syndrome may be resulted to long-term sequelae, ,motor and cognitive deficits.So , Early recognition and prompt treatment of CNS disease may prevent irreversible CNS injury.

The incidence of CNS -HLH is about 30–73% and the presentation may be seen At /or during the course of the disease. The neurologic sign and symptoms are highly variable .They are including Seizures ,Impaired consciousness ,Meningismus and ….

Diagnosis is based on 3 part of investigation: presence of neurological signs/symptoms ,Evaluation of CSF and Neuroimaging abnormalities. CSF abnormality may be with or without neurologic symptoms. MRI is the choice modality in CNS disease of HLH syndrome but Neuroimaginfg findings are in differential diagnosis with other Centeral nervous system disorders such as Vasculitis ,Acute disseminated encephalomyelitis (ADEM) and Infection. So to narrowing differential diagnosis and diagnosis of HLH ,Correlation of neuroimaging, Clinical findings ,Laboratory data and pathology findings should be considered.

Hemophagocytosis is seen in 91% of Brain Biopsies which mostly located in the Meninges –and 39% of CSF samples of pediatric cases.

Treatment in CNs-HLH syndrome include using of systemic immune suppressive theray based of HLH 2004 protocol and intrathecal(IT) therapy with dexametasone and Metotheraxate.

Patinets with CNS involvement in HLH syndrome may be cured with HSCT. It may prevent both reactivations and CNS disease progression and may prevent the

emergence of neurological late effects ,But reactivation of CNS disease may occur after HSCT.

Also ther are some new treatment in HLH syndrome including CNS involvement on study,such as Anti-IFNγ monoclonal antibody NI-0501 (NCT01818492) and JAK1/2 inhibitor Ruxolitinib .

Conclusion : First step towards optimal treatment of CNS-HLH is prompt and accurate Diagnosis. All patients should receive a brain MRI and lumbar puncture, Therapy should be started in all HLH cases with neurological symptoms even if a LP or MRI have not been obtained or results are still pending.

No. 21

Spectrum of genetic and clinical presentation of Iranian children with hemophagocytic lymphohistiocytosis

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BACKGROUND:
We analyzed pediatric patients with hemophagocytic lymphohistiocytosis (HLH) in Iran to assess the clinical and genetic features and treatment outcomes in pediatric HLH.
METHODS:
Pediatric patients with HLH who had molecular diagnosis and followed or referred to Department of Pediatrics, Tehran University of Medical Sciences during a ten year period (2008-2018) were selected.
RESULTS:
In this study, 35 cases were categorized with familial HLH. Genetic tests revealed RAB27A mutations in 18, UNC13D in 8 and PRF1 mutations in 3 patients. Isolated molecular defects in other major predisposing genes were also documented. Some RAB27A mutations were frequently detected probably due to a founder effect. Most of the patients died despite institution of HLH-2004 protocol. Hematopoietic stem cell transplantation (HSCT) was done for some of them with variable results.
CONCLUSION:

Our study showed the unique predominance of mutations in RAB27A followed by UNC13D. The overall prognosis was poor considering HLH-2004 protocol alone. More effort should be done to do early HSCT in this fatal group of primary immunodeficiencies

No. 22

Severe Refractory Langerhans cell histiocytosis in an infant with association of haemophagocytic syndrome

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Background
The concomitant accordance of hemophagocytic lymphohistiocytosis and Langerhans cell histiocytosis is very rare.
Striking improvements in recognition and treatment of both diseases have been detected.
Basically the two mentioned diagnoses behave in varied ways, which could lead to delay in diagnosis and treatment.LCH is the commonest histiocytic disorder with an incidence of 8–9 cases per million/year.
The pathogenesis of LCH is unascertained and suggested mechanisms include immune dysregulation versus malignant transformation. The hypothesis is that LCH is a reactive disease leading to an aberrant reaction between Langerhans cells and T-lymphocytes, provoked by different stimuli, such as viruses and malignancy.
The clinical course may differ from benign to a rapidly progressive disease. LCH could be restricted to one organ or it can include two or more organs or systems (multisystem LCH). Multisystem LCH is more severe, chiefly when it involves risk organs (liver, spleen and bone marrow).
Secondary haemophagocytic lymphohistiocytosis (HLH) is an additional type of histiocytic disorder which is rarely outlined in association with LCH.
Here by we report a rare case of a 14-month-old infant with multisystem LCH, which the clinical course expresses a severe form of the disease with an association with secondary HLH. We emphasize this association, as it may obscure the diagnosis and delay in the initiating of treatment.
Case presentation

A 14 month-old boy presented with recurrent fever and skin rash on his head and upper extremities and trunk 43, since 6 months ago were admitted in our ward for further evaluation.

He was the first child of non-consanguineous and healthy parents.

He had a high fever with refractory skin rash. Physical examination revealed Hepatosplenomegaly. and CT scan evaluation revealed hepatosplenomey and mild pleural effusion and also considerable amount of ascites. Laboratory examinations showed anemia, thrombocytopenia and hypoalbuminemia. Hypertriglyceridemia and hypofibrinogenemia were detected respectively. Table 1

TG	296	WBC	1300/µl
Ferritin	800mg/dl	Neut	32%
Fibrinogen	80mg/dl	Hb	6.4g/dl
Total protein	2.7 g/dl	Hct	22
Albumin	1.8 g/dl	Plt	45000×10^{4} /µl

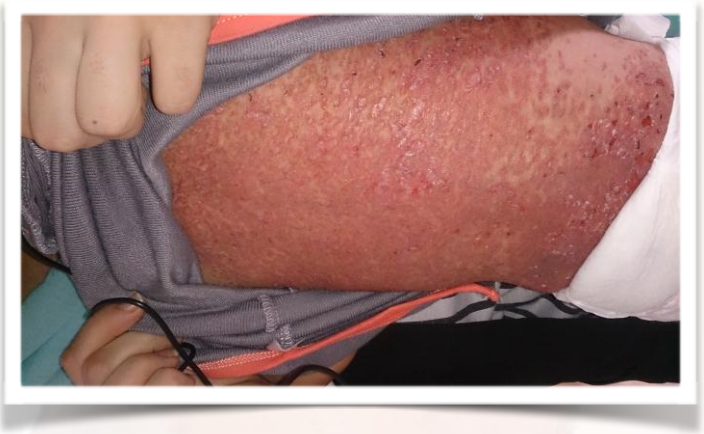
Blood test of the patient on admission (Table 1)

Hemophagocytosis was observed in his bone marrow, and bone survey was normal without any lytic lesions.Skin biopsy of rashes was in favor of LCH, immuohisto chemistry staining revealed S 100 + CD 68 + CD 1a + in favor of LCH Virology panel was without any specific finding.

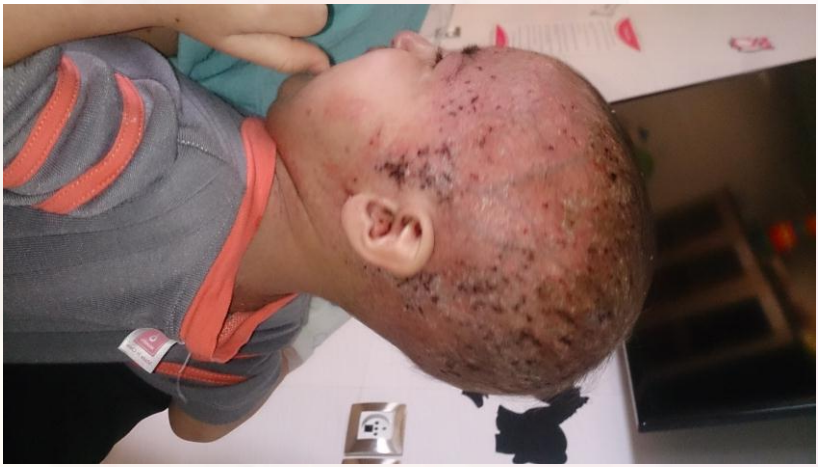
We diagnosed him with secondary HLH following LCH, and initiate the protocol of HLH2004 (dexamethasone, cyclosporine A and VP16). After one month of HLH 2004 therapy, he could not achieve remission of LCH or HLH and were suffering from refractory thrombocytopenia which caused to administer weekly vinblastines and Methotrexate due to LCH protocol.

Of note, according to refractoriness of skin rashes and persistent bicytopenia and hypoalbuminemia therefore, we considered performing whole exon sequencing in oder to rule out familial hemophagocytosis (picture 1 ,2)

Picture 1



Picture 2



Discussion

LCH is a rare clonal disorder described by the production and accumulation of clonal CD1a-positive immature dendritic cells, along with the in infiltration of different type of inflammation cells The clinical manifestation of LCH is varying, ranging from benign to aggressive disease, which may be fatal.

The certainty that the infant was diagnosed with LCH may lead physicians to fail to notice the developing secondary HLH or regard its symptoms and signs to the underlying disease. More to add some crucial symptoms and signs of HLH, such as cytopenias and heptosplenomegaly, are also attributable to LCH too. We are highlighting this case in order to emphasize that secondary HLH may arise out of a wide variation of neoplastic, autoimmune or infectious disorders which one of them could be LCH.

Conclusion

Despite its rare incidence, the probability of HLH presence should be bear in mind in a child with hepatosplenomegaly and cytopenias, with or without a known primary disorder.

No. 23

3 cases of Hemophagocytic Lymphohistiocytosis Syndrome (HLH) and hematopoietic stem cell transplantation

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HLH is a life-threatening hyperinflammatory clinical syndrome of uncontrolled immune response which results in hypercytokinemia due to underlying primary or secondary immune defect.

HLH can be classified into genetic (primary) and acquired (secondary) forms according to the underlying defect. The primary HLH can be categorized into 2 subgroups, one including 5 subtypes of familial HLH (FHL), and the other expanding subgroup of separate primary immune deficiencies including Chediak-Higashi syndrome (CHS), Griscelli syndrome type 2 (GS2), Hermansky-Pudlak syndrome and X-linked lymphoproliferative (XLP) syndrome 1 and 2 (XLP1, XLP2).

Important advances have been made during the last 20 years in the diagnosis and treatment of HLH. The Histiocyte Society has proposed diagnostic guideline using both clinical and laboratory findings in HLH-2004 protocol. The strategies for proper treatment of HLH should include countermeasures for suppression of the hyperinflammation, elimination of triggering causes, and replacing defective immune system for patients with genetic disorders.

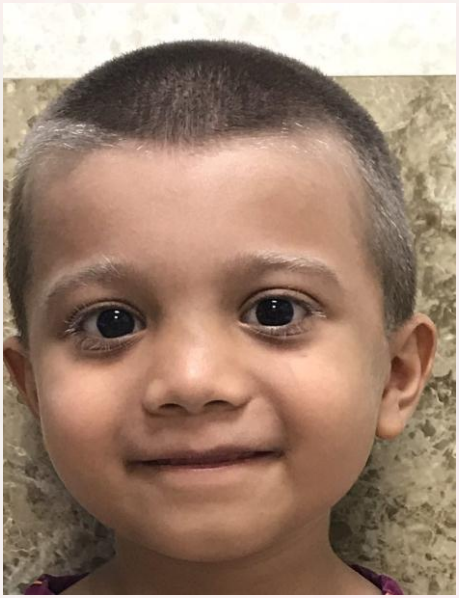
HSCT is the only curative option of treatment for Familial (primary) HLH and refractory/relapsed HLH after chemoimmunotherapy.

Here we report three cases of Familia HLH and the results of HSCT in these three patients:

1-Chediak Higashi Syndrome & HLH (LYST1 - Lysosomal trafficking regulator , Ch 1q42.3. HSCT: MRD – BM

2- Heriditary HLH -type 5 (Gene STXBP2,defect Munc 18- 2,syntaxin binding protein 2 ,Ch 9p). HSCT : MSD –PB

3--Griscelli Syndrome & HLH (RAB27A, -15 q21). HSCT: Unrelated Cord Blood (5/6- Female)



No. 24

Case series of Hemophagocytic lymphohistiocytosis in Buali Hospital, Ardabil, Iran in July 2018

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Background and Objective

we present an one year-old boy and a 4-month old girl from Iran with hemophagocytic lymphohistiocytosis (HLH) associated with Leishmania. HLH is not an independent disease but rather a life-threatening clinical syndrome that occurs in many underlying conditions and in all age groups[1].It is commonly appears in infancy[2]. In our cases, treatment with was dexamethasone and Etoposide started and second case responded and first case unfortunately died.

Case1

a one-year-old boy was admitted to the Buali Hospital, Ardabil, Iran on July 2018, with a 3-week history of fever, Hepatosplenomegaly and pancytopenia. Serum testing showed elevated transaminase levels (ALT:750,AST:820), hypertriglyceridemia (TG:420), hyperferritinemia (Ferritin:9780) and fibrinogen level was less than 50 unit. Hemophagocytic lymphohistiocytosis was diagnosed on bone marrow examination that showed HLH with Leishmania body (fig-1). The patient was tested for various infectious agent that all of them were negative expect Leishmania, (HBS Ag: negative HCV Ab: negative HIV Ab: negative), DAT for Leishmania was positive. After one week she doesn't have response to antibiotic.Glucantime was added. But unfortunately he didn't response to treatments and died.

Case2

4 month old girl was admitted to the hospital because of fever, pallor and Hepatosplenomegaly for 2 week. Intermittent high grade fever persisted with anorexia and weight loss. Examination revealed fever, pallor and petechiae. Abdominal examination revealed Hepatosplenomegaly. Respiratory, cardiac and neurological were normal. Lab data showed pancytopenia, liver function tests were abnormal (ALT: 672 AST: 1449 ALP: 386 Bill Total: 8 Bill Direct: 3.6). Ferritin was very high (16493). Coagulogram revealed coagulopathy and hyperfibrinogenemia. Renal

function and electrolytes were normal. Abdominal sonography showed Hepatosplenomegaly. DAT WAS 1/1600. Fever persisted and Glucantime was started. Bone marrow examination (BMA) revealed hem phagocytosis with leishman bodies. (Fig-1) Treatment with dexamethasone and Etoposide result in a dramatic resolution of all signs and symptoms within 10 day.

Conclusion

In conclusion, HLH secondary to Leishmania is extremely rare and potentially fatal. The diagnosis is often missed due to overlapping clinical features and negative bone marrow. A high index of clinical suspicion, repeated marrow evaluation with culture and or serology is often required to establish leishmaniasis [6]. Leishmania must be considered and excluded in patients with HLH before immunosuppression is considered.as a result we understand Treatment with dexamethasone and Etoposide provides a dramatic response in these cases.

Keywords: Visceral leishmaniasis, Hemophagocytic lymphohistiocytosis, Hepatosplenomegaly

No. 25

Hemophagocytic lymphohistiocytosis in non-transplant setting: Report of two cases and their treatment challenges

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Background and Objective:
Hemophagocytic lymphohistiocytosis (HLH) is an uncommon hyper-inflammatory syndrome with high mortality associated with different conditions, including neoplastic, infectious, autoimmune, or hereditary diseases [1]. The incidence of HLH has been estimated to be 1-225 per 300 000 live births in different ethnic groups, and is reported in all ages, races and both genders [1-3]. HLH is grouped into two forms, which include familial type due to genetic mutations affecting the cytotoxic function of T lymphocytes and natural killer (NK) cells or acquired form presenting in different conditions such as infectious, malignant, rheumatologic, or metabolic diseases [1, 4]. The diagnostic criteria for acquired HLH include fever; cytopenias affecting at least 2 of 3 lineages in the peripheral blood; splenomegaly; hyperferritinemia; hemophagocytosis in the bone marrow, spleen, or lymph nodes; hypertriglyceridemia and/or hypofibrinogenemia; low or absent NK-cell activity determined by the 51-Cr release assay; and high levels of sCD25. Five of these eight criteria are essential for diagnosis of acquired HLH. In familial cases with a known genetic abnormality (FHL with mutations), the diagnosis can be made even if the criteria are not completely fulfilled [5].
Hematopoietic stem cell transplantation (HSCT) is the recommended treatment for patients with familial HLH or those with CNS involvement or recurrent/refractory disease [6].
We present two cases of recurrent HLH with no available HLA-matched donor, and discuss the treatment challenge.

Patient report
Case 1:
An 8-year-old boy was admitted to the hematology department in Amir Hospital (Shiraz, Iran) due to clinical findings such as fever, jaundice, hepatosplenomegaly,

and pancytopenia. Laboratory studies showed an increased level of aspartate amino transferase (AST), alanine aminotransferase (ALT), lactic dehydrogenase (LDH), total and direct bilirubin, prolonged prothrombin time (PT), and activated partial thromboplastin time (aPTT), high serum ferritin (nearly 1000 ng/ml), and low level of fibrinogen, total protein, and albumin. A high titer of Ebstein-Barr virus (EBV) viral capsid antigen IgM antibody proved an acute EBV infection. Hepatitis A, B, and C infections, HIV infection, auto immune hepatitis and Wilson disease were ruled out by appropriate tests. Liver biopsy and bone marrow aspiration and biopsy was inconclusive with non-specific findings. Laboratory tests such as NK cells function and sCD25 was not checked as they were not available in our center. The proband was a product of consanguineous marriage (first-degree cousins) and there were no documented HLH disease phenotype, immune disorders, hepatic diseases and blood malignancies in the immediate and extended family. The patient was suspected as a case of HLH according to HLH-2004 protocol[5] given the fact that he fulfilled the necessary criteria mentioned above. The diagnosis was confirmed with an unbiased next generation DNA sequencing (NGS) which covered the entire coding exons which revealed a homozygous missense mutation in PRF1 gene. He was treated with dexamethasone, cyclosporine and etoposide with dramatic response including resolution of fever and correction of hepatitis, pancytopenia and bleeding tendency. Gradually, the patient developed clinical signs of central nervous system (CNS) involvement such as convulsion, ataxia, spasticity and slurred speech. Cerebral spinal fluid (CSF) analysis for cell count, protein and cytology were normal. Brain MRI with and without contrast injection revealed spots of white matter hyper signal intensities on T2 and FLAIR images which were in favor of CNS involvement in HLH (7). Thus, we added intrathecal (IT) methotrexate and hydrocortisone to his treatment regimen, and searched for an HLA-matched donor for HSCT. Despite a global search in BMT registries, no HLA-matched donor was found. Though we continued his maintenance treatment with cyclosporine, intermittent monthly dexamethasone and IT methotrexate and hydrocortisone, his CNS symptoms were progressive. Currently, he has no systemic or laboratory evidence of HLH reactivation, and is still waiting for a suitable stem cell donor.

Case 2:

An 8-month-old boy was admitted to the hematology department in Amir Hospital (Shiraz, Iran) due to prolonged fever and hepatosplenomegaly for a 2-month duration. Laboratory studies showed an increased level of AST, ALT, LDH, serum ferritin (>800 ng/ml), pancytopenia and high level of triglyceride. Serological markers for hepatitis A, B, and C and EBV were negative, and antibody titers for autoimmune hepatitis were within normal range. Bone marrow aspiration and biopsy was inconclusive with non-specific findings. Laboratory tests such as defective killing activity of either CD8 or NK cells and soluble CD25 were not available in our center. The proband was a product of consanguineous marriage (first-degree cousins) with no significant past or family history. The patient was screened for immunodeficiency

disorders with non-specific findings except persistently low IgG titers several times. Moreover, no known genetic mutation involving FHL genes was founded by NGS method. Given that he fulfilled at least five out of eight HLH-2004 criteria [5], treatment with dexamethasone, cyclosporine and etoposide was started and continued for 40 weeks with complete resolution of clinical and laboratory findings of HLH. There was no clinical, laboratory or radiologic evidence of CNS involvement both initially and during treatment monitoring. He was off treatment for about one year, but he returned with reactivation of his disease. As he had good response to conventional treatment for HLH in the primary disease, we restarted the same treatment while searching for an HLA-matched stem cell donor. He was also treated with monthly IVIG. As we found no suitable stem cell donor in the global search, his treatment continued for 40 weeks. Since then, he is on daily cyclosporine and intermittent doses of monthly dexamethasone for 5 consecutive days. We are still waiting for an HLA-matched stem cell donor.

Discussion:

HLH is a rapidly progressive, life-threatening syndrome of excessive immune activation. Prompt initiation of treatment for HLH is essential for the survival of affected patients. If left untreated, patients with HLH survive for only a few months, due to progressive multi-organ failure.

Often, the greatest barrier to treatment and a successful outcome for individuals with HLH is a delay in diagnosis. Several aspects of the clinical presentation of HLH contribute to this delay, including the rarity of the syndrome, the variable clinical presentation, and the lack of specificity of the clinical and laboratory findings (6).

The goal of therapy for patients with HLH is to suppress life-threatening inflammation by destroying immune cells. Intrathecal methotrexate and hydrocortisone are given to those with central nervous system disease.

After induction, patients who are recovering are weaned off therapy, while those who are not improving are continued on therapy as a bridge to allogeneic HSCT. HSCT will be required in those with an HLH gene mutation, central nervous system disease, or disease relapse (8).

Herein, we presented two typical cases of HLH who were strict candidates of HSCT with no appropriate HLA-matched donor worldwide. The big challenge is how long they should be treated with maintenance chemotherapy and what will be the best treatment option.

With regards to the 1st case with familial HLH and CNS involvement, it would be too risky to discontinue maintenance therapy given he is at high risk of disease flare up. However, IT injection of cytotoxic agents will be accompanied by long-term sequels and will impact the quality of life. On the other hand, repeated exposure with chemotherapy agents especially etoposide will increase the risk of second malignant neoplasm.

The second case experienced a relapse event which made it necessary to take HSCT into account very seriously. As there was no donor source available, we had to

continue immunosuppressive therapy with steroid and cyclosporine. This will remarkably diminish T- cell function and increase the risk of opportunistic infections. Given that the patient was hypogammaglobulinemic as well, the resultant combined immunodeficiency will worsen the issue of recurrent infection.

Conclusion:

In conclusion, HSCT is the treatment of choice in familial HLH as well as recurrent disease and CNS involvement. Finding an HLA-matched donor is the most important obstacle. Alternative treatments in non-transplant setting face major limitations and raise many unresolved questions yet to be answered.

Key Words : hemophagocytic lymphohistiocytosis , stem cell transplantation , relapse

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No. 26

Hereditary Spherocytosis and Hemophagocytic Syndrome(HPS). Case Report and Literature Review

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Introduction: Hemophagocytic syndrome (HPS) is clinically defined as a combination of fever, liver dysfunction, coagulation abnormalities, pancytopenia, progressive macrophage proliferation throughout the reticuloendothelial system and cytokine overproduction, which may be primary or secondary to other disease including infectious. The association between HPS and infections has been widely documented and both familial or sporadic cases are often precipitated by acute infections. A better understanding of the pathophysiology of HPS may clarify the interactions between the immune system and the variously implicated potential infectious agents. A number of viral infections associated with HPS are including: EBV, CMV, adenovirus, paramyxovirus (leading to measles and mumps), rubella, virus, human parainfluenza viruses, Inf (rare), Hepatitis, Enterovirus infection and parvovirus B19. Epstein- Barr virus (EBV) infection has been prominently associated with HPS, with clonal proliferation and the hyperactivation of EBV-infected T cells. Although associated with
substantial morbidity and mortality, early recognition and prompt therapy may result in successful treatment of EBV-induced HPS. Also bacterial, fungal and parasitic infections have been reported in association with HPS.

Case report: An 8-month-old-girl, 4th child after normal vaginal delivery, term, body weight 3400 gr, from non cansanguinous parents was reffered in our hospital due to

persistant fever since 2 months ago, pancytopenia and hempatosplenomegaly. She had history of jaundice, severe hemolytic anemia (Hb; 5Gr/dl), high reticulocyte count; (12%), blood transfusion and 1 time IVIG treatment in age of 40 days of life. Blood group of child was O negative. The specific diagnosis for hemolytic anemia was unegative and other children were healthy. Before starting of fever she had history of 2–3 times of blood transfusion duo to hemolytic anemia. During the follow up for anemia at age of 6 months she progressed to fever, hepatosplenomegaly and pancytopenia. She was referred in our hospital for more evaluation. Laboratory tests revealed: WBC:1300/mm3, RBC:2.300.000/mm3, Hb:7Gr/dl, MCV:84 Fl Platelet:45000/mm3, Reticulocyte: 0.2%. Repetition of reticulocyte count in next laboratory test also showed low reticulocytes (0.4%). Direct and indirect coombs tests: Negative, SGOT:110IU/l, SGPT:30IU/l, LDH:951 IU/mL, Bilirubin Total: 2.1 Mg/dl, Bilirubin indirect 0.9 Mg/dl, Albumin: 2.2 g/l, ESR:40, Uric acid:3.5mg/dl, PT:19.5 second (control; 13), INR: 1.2, PTT:50 second (control 43),TG:534Mg/dl(<180 Mg/dl), Cholestrol:129Mg/dl(< 200Mg/dl),D-Dimer:0.5Mg/l; (Nl; 0.45) Fibrinogen:120Mg/dl (Normal 200–400), Ferritin: > 2000 Ng/ ml, BUN:2Mg/dl, Cr:0.4 Mg/dl, IgA:124 Mg/dl(19–220), IgE:5Mg/dl (up to 10), IgG:2732Mg/dl(800–1000), IgM:854Mg/dl(20–100).TORCH study: negative, CMV-PCR: neg, EBV IgG: positive, EBV IgM: positive but EBV-DNA peripheral whole blood (PCR): negative, Parvovirus B19 PCR:negative, HbsAg: negative: HbsAb: positive, HCV AB: negative and HIVAb: negative. Wright, Coombs wright and Widal tests: negative. Blood culture: negative. CXR: Normal, Abdominal Sonography and color Doppler sonography showed: Large spleen, Liver; upper limit Normal and mild increase echogenicity, No collateral vein, portal vein normal. CSF analysis: normal, **Bone survey:** normal. Eye examination: normal, First bone marrow aspiration (BMA) and bone marrow biopsy (BMB) showed normocellular marrow with erythroid hyperplasia and maturation arrest in myeloid series. Report of CD-Flow cytometry: normal. However, in second BMA some hemophagocytic cells were seen. So due to clinical findings and laboratory tests sampling for evaluation of hereditary HLH were sent and treatment with IVIG 1gr/ kg/day 2days and prednisone 2mg/kg/ day oral were stated. Her response to treatment was very good. After 2 weeks of treatment she improved clinically and the result of CBC revealed: WBC:13400/ mm3, Neut 38%, lymph:62% RBC: 2,730.000/mm3, Hb: 8.2Gr/dl, MCV:86Fl, pltate- let:464000/mm3, BilirubinTotal:4.3Mg/dl, Bilirubin direct: 0.6Mg/dl, Reticulocyte:18%. She followed and in next CBC; Hb: 9gr/dl and Reticulocyte; 25%. In peripheral blood smear; 2þ spherocytic cells was reported. The results of other laboratory tests 2 months after the last blood transfusion revealed increased osmotic fragility tests (OFT) before and after incubation. Autohemolysis tests without **incubation:** 25% and after adding glucose

10%.G6PD, pyruvate kinase tests were normal. The result of gene mutation for hereditary HLH including perforin- and syntaxin11 were negative. Other types of gene mutation were not possible to do. Now our patient has just splenomegaly 3 cm below costal margin and she is on follow up for anemia dueto underlying disease, hereditary spherocytosis.

Conclusion: In patients with persistentfever, pancytopenia and hepatosplenomegaly, it is necessary to think about HPS, but we should be careful about underlying disease. So it might not be necessaryto start aggressive treatment and based on etiology, patients with HPS may have good response to mild treatments such as prednisone and IV IG.

No. 27

Langerhans Cell Histiocytosis following B cell- ALL

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Langerhans Cell Histiocytosis (LCH)is a rare histiocytic disorder characterized by abnormal proliferation of Langerhans cells,the frequency of involving ribs in LCH is about 12% .

Our patient was a 6 year old girl looked up for recent back pain. Retrospectively she completed chemotherapy for B-cell Acute Lymphoblastic Leukemia twelve months ago.

Despite high cure rates, approximately 20% of patients with ALL have disease relapse so Symptoms made us to be concern about leukemia extramedulary relapse.

Investigations include radiograph shows a lytic lesions surrounded by cortical tickening,bone marrow aspiration and CD flowcytometry was normal without blast gate and whole body ^{99m} Tc bone scan revealed increase uptake in an active lesion localized on rib 11,her rib resecred and bone biopsy revealed Langerhanns cell histiocytosis ,Immunohistochemistry staining was positive for CD1a and S-100.The patient had no organ involvement.

Because of partially response to our less intensive chemotherapy with steroids,vinblastin and methotrexate after 6 months ,started Cladarabine 5mg/m^2/day every 4 weeks,after 4 courses obvious remission was seen.

Keywords:Langerhans cell histiocytosis(LCH),B Cell ALL,back pain,cladarabine.

No. 28

Visceral leishmaniasis associated hemophagocytic lymphohistiocytosis in an Iranian child: a case report

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Background and objectives:
Visceral Leishmaniasis (VL) or kala-azar is a life threatening parasitic infection rarely occurring in association with Hemophagocytic Lymphohistiocytosis (HLH). Management of the patients will be complicated in individuals suffering concomitant VL and HLH.

Patient report: In this report we will discuss a 14-month-old girl who experienced malaise, anorexia and intermittent fever for a month. Hepatosplenomegaly and pancytopenia was detected in her physical examination and lab data respectively.
According to clinical and paraclinical findings she was diagnosed to have HLH. CSF analysis, blood and urine cultures and also viral markers were negative. The patient went on treatment by HLH-2004 protocol. A month later hematologic investigations revealed presence of pancytopenia again. This time bone marrow aspiration showed evidences of kala azar infection in addition to hemophagocytosis. Thus, the patient received liposomal amphotericin B followed by resistance to glucantime therapy. Hemophagocytosis treatment was also administered. Eventually after 40 weeks of therapy, the child recovered and evidences of disease disappeared.

Conclusion: HLH is one of the differential diagnoses of pancytopenia plus splenomegaly. Secondary causes of the disease should be considered particularly in endemic areas and also should be distinguished from primary ones.

Keywords: Hemophagocytic Lymphohistiocytosis, Visceral Leishmaniasis, Childhood,

Histiocytosis Updates Meeting
Date: 23-24 Nov. 2018
(2 days)

2018 (23. Nov .2018)

Welcome		
8.00-8.15	Quran & National Anthem	
8.15-8.30	Welcome	Professor Hassan Abolghasemi

Session 1		
Title: Histiocytosis Disorders **Chairman:** Professor H. Abolghasemi **People:** Prof MT. Arzanian; Prof M. Minkov; Prof M. Arico; Prof H. Abolghasemi		
8.30- 8.50	New Classification of Histiocytosis Diosrders	Professor H. Abolghasemi
8.50-9.25	Overview of Langerhancs Cell Histiocytosis (LCH)	Professor M. Arico
9.25-10.00	Treatment of Langerhancs Cell Histiocytosis (LCH)	Professor M. Minkov
10.00-10.30	New treatments (BRAF/MAPK inhibition & JAK Inhibitors) in Langerhancs Cell Histiocytosis (LCH)	Professor M. Arico
10.30-10.40	Question & Answer	----------
10.40-11.00	**Break**	

Session 2		
Chairman: Prof P. Eshghi **People:** Prof M. Pedram; Prof P. Eshghi; Dr A. A. Hasanpour Feizi; Dr A. Mehrvar		
11.00-11.20	DNA viruses and Langerhans Cell Histiocytosis in Iranian Children	Dr M. Khodami
11.20- 11.40	Complications in Langerhancs Cell Histiocytosis (LCH)	Dr M. Shahriari
11.40-12.00	Report of a rare case of Hand–Schuller–Christian disease	Prof M. Pedram
12.00-12.45	Non Langerhans Cell Histiocytosis Disorders (Non - LCH)	Professor M. Minkov
12.45-13.00	Question & Answer	----------
13.00-14.00	**Lunch and Rest**	
Session 3		

Case Presentation **Chairman:** Professor M.Faranoush **People:** Professor M. Minkov; Professor M. Arico; Dr Y. Abtahi; Professor M.Faranoush;			
14.00-16.00	**Case presentation**		----------
	14.00-14.20	Langerhancs Cell Histiocytosis and CNS involvement	Dr A. Tamadoni
	14.20-14.40	Langerhancs Cell Histiocytosis 5 years after acute lymphoblastic leukemia in an 11 years old boy	Dr Sh .Ansari
	14.40- 15.00	Case presentation of Rosai Dorfman syndrome and CNS involvement	Dr Sh. Nazari
	15.00-15.20	Langerhancs Cell Histiocytosis with mediastinal and supra sternal mass presentation	Dr Gh. Miri
	15.20- 15.40	Salvage therapy in refractory Langerhancs Cell Histiocytosis and multifocal involvement	Dr AA. Hiradfar
	15.40-16.00	Question & Answer	----------

Events

Session 7		
Title: Lecture and Dinner event **Sponsor:** Roche Company		
19.30	Rituximab in Pediatric Non Hodghkin Lymphoma	
19.30-19.50	Rituximab in Pediatric NHL	Professor M. Faranoosh
19.50-20.10	Advantages of SC Formulation of Rituximab and It's Clinical Data	Dr. Hassan Ahmadian
20.30	**Dinner Event**	

2018 (24. Nov .2018)

Session 4		
Title: Hemophagocytic lymphohistiocytosis syndrome **Chairman:** Dr Gh. Bahoush **People:** Professor M. Mardawig Alebouyeh. Professor G. Janka, Dr Gh. Bahoush , Dr S. Alavi		
8.00-8.40	Biology of Hemophagocytic Lymphohistiocytosis Syndrome	Prof. G.Janka-Schaub
8.40-9.00	Secondry Hemophagocytic Lymphohistiocytosis Syndrome (HLH)	Dr S.Alavi
9.00-9.40	HLH Protocols and New Treatments in HLH	Prof. G. Janka-Schaub
9.40-10.00	HSCT in Hemophagocytic Lymphohistiocytosis Syndrome (HLH)	Dr. Gh. Bahoush
10.00-10.15	Question & Answer	----------
10.15- 10.45	**Break**	

Session 5		
Chairman: Dr M. Mehdizadeh **People:** Dr M. Mehdizadeh; Dr B.S. Shamsian; Dr Z.Badiei; Dr M. Shahriari		
10.45-11.05	Hemophagocytic lymphohistiocytosis syndrome after HSCT	Dr M Mehdizadeh
11.05- 11.25	CNS Involvement in Hemophagocytic Lymphohistiocytosis Syndrome	Dr B.S.Shamsian
11.25-11.55	Report of Mutations in Heriditary Hemophagocytic Lymphohistiocytosis Syndrome from Iran	Dr N.Parvaneh
11.55-12.15	Rare Case presentation Of Langerhancs Cell Histiocytosis and Hemophagocytic Lymphohistiocytosis Syndrome (HLH)	Professor P. Eshghi
12.15-12.30	Question & Answer	----------
12.30-13.30	**Lunch and Rest**	

Session 6			
Case presentation **Chairman:** Dr S. Hejazi **People:** Professor G. Janka; Dr M. Hashemieh; Dr. N. Beigom Mirbehbahani; Dr S. Hejazi			
13.30-16.00	**Case presentation**		----------
	13.30-14.00	3 cases of Hemophagocytic Lymphohistiocytosis Syndrome (HLH) and hematopoietic stem cell transplantation	Dr B.S. Shamsian
	14.00-14.30	Case presentation of Hemophagocytic Lymphohistiocytosis Syndrome(HLH) and Leishmaniasis infection	Dr. A. Fathi
	14.30- 15.00	Challenges in treatment of Hemophagocytic Lymphohistiocytosis Syndrome(HLH)in the absence of hematopoietic stem cell transplantation (HSCT)	Dr H. Mothaghi Pisheh
	15.00-15.30	Seminar Closing	

سمینار تازه های هیستوسیتوز زمان:۳-۲ آذرماه ۱۳۹۷

روز اول: ۲ آذرماه ۱۳۹۷

خوش آمد گویی		
۸/۰۰-۸/۱۵	قرآن و سرود جمهوری اسلامی	----
۸/۱۵-۸/۳۰	خوش آمد گویی	پروفسور حسن ابوالقاسمی

(صبح)

موضوع: اختلالات هیستوسیتوز

اداره کننده جلسه: پروفسور حسن ابوالقاسمی

اعضای هیئت رئیسه: پروفسور محمدتقی ارزانیان- پروفسور M. Minkov- پروفسور M.Arico- پروفسور حسن ابوالقاسمی

۸/۳۰-۸/۵۰	تقسیم بندی جدید اختلالات هیستوسیتوز	پروفسور حسن ابوالقاسمی
۸/۵۰-۹/۲۵	مرور ی بر بیماری هیستوسیتوز سلولهای لانگرهانس	پروفسور M.Arico
۹/۲۵-۱۰/۰۰	پروتکل های درمان بیماری هیستوسیتوز سلولهای لانگرهانس	پروفسور M. Minkov
۱۰/۰۰-۱۰/۳۰	درمانهای جدید بیماری هیستوسیتوز سلولهای لانگرهانس (BRAF/MAPK inhibition &JAK Inhibitor)	پروفسور M.Arico
۱۰/۳۰-۱۰/۴۰	پرسش و پاسخ	----------
۱۰/۴۰-۱۱/۰۰	استراحت	----------

اداره کننده جلسه: پروفسور پیمان عشقی

اعضای هیئت رئیسه: پروفسور محمد پدرام- پروفسور پیمان عشقی- دکتر عباسعلی حسین پورفیضی- دکتر عظیم مهرور

۱۱/۰۰-۱۱/۲۰	ویروس هرپس سیمپلکس و بیماری هیستوسیتوز سلولهای لانگرهانس	دکتر ملیحه خدامی
۱۱/۲۰-۱۱/۴۰	عوارض بیماری هیستوسیتوز سلولهای لانگرهانس	دکتر مهدی شهریاری
۱۱/۴۰-۱۲/۰۰	گزارش یک مورد بیمار نادر مبتلا به بیماری hand schuller christian	پروفسور محمد پدرام
۱۲/۰۰-۱۲/۴۵	اختلالات هیستوسیتوز غیر لانگرهانس	پروفسور M. Minkov
۱۲/۴۵-۱۳/۰۰	پرسش و پاسخ	----------
۱۳/۰۰-۱۴/۰۰	ناهار و نماز	----------

(بعد از ظهر)

معرفی بیمار		
اداره کننده جلسه: پروفسور محمد فرانوش		
اعضای هیئت رئیسه: پروفسور محمد فرانوش- پروفسور M. Minkov- پروفسور M.Arico- دکتر یاسمین ابطحی		
معرفی بیماران جالب		
۱۴/۰۰-۱۴/۲۰	معرفی یک مورد بیمار هیستوسیتوز سلولهای لانگرهانس با درگیری CNS	دکتر احمد تمدنی
۱۴/۲۰-۱۴/۴۰	معرفی یک مورد بیمار هیستوسیتوزسلولهای لانگرهانس۵ سال پس ازابتلای لوسمی لنفوبلاستیک حاد	دکتر شهلا انصاری
۱۴/۴۰-۱۵،۰۰	معرفی یک مورد بیمار سندرم Rosai Dorfman با درگیریCNS	دکتر شیوا نظری
۱۵/۰۰-۱۵/۲۰	معرفی یک مورد بیمار هیستو سیتوز سلولهای لانگرهانس با تظاهر توده ناحیه گردن -Suprasternal و مدیاستین	دکتر قاسم میری
۱۵/۲۰-۱۵/۴۰	Salvage Chemotherapy-در درمان کودکان مبتلا به هیستو سیتوز سلولهای لانگرهانس با درگیری کانونهای متعدد مقاوم به درمان	دکتر امیر عطاالله هیرادفر
۱۵/۴۰-۱۶/۰۰	پرسش و پاسخ	----------

(شام)

بخش چهارم برنامه: برگزار کننده: شرکت ROCHE		
۱۹/۳۰	کاربرد درمانی ریتوکسیماب در کودکان مبتلا به لنفوم غیر هوچکین	
۱۹/۳۰-۱۹/۵۰	کاربرد ریتوکسیماب در لنفوم کودکان	دکتر محمد فرانوش
۱۹/۵۰-۲۰/۱۰	مزایای فرم زیر جلدی ریتوکسیماب و مطالعات بالینی	دکتر حسن احمدیان
۲۰/۳۰	برنامه شام	----------

روز دوم: ۳ آذرماه ۱۳۹۷ (صبح)

موضوع برنامه: سندرم هموفاگوسیتیک لنفوهیستوسیتوز

اداره کننده جلسه: دکتر غلامرضا باهوش

اعضای هیئت رئیسه: پروفسور مرداویژ آل بویه- پروفسور G.Janka- دکتر غلامرضا باهوش- دکتر ثمین علوی

۸/۰۰-۸/۴۰	بیولوژی سندرمهای هموفاگوسیتیک لنفوهیستوسیتوز	پروفسور G.Janka
۸/۴۰-۹/۰۰	سندرمهای هموفاگوسیتیک لنفوهیستوسیتوز اکتسابی	دکتر ثمین علوی
۹/۰۰-۹/۴۰	پروتکلها و تازه های درمان سندرمهای هموفاگوسیتیک لنفوهیستوسیتوز	پروفسور G.Janka
۹/۴۰-۱۰/۰۰	پیوند سلولها بنیادی خون ساز در سندرمهای هموفاگوسیتیک لنفوهیستوسیتوز	دکتر غلامرضا باهوش
۱۰/۰۰-۱۰/۱۵	پرسش و پاسخ	----------
۱۰/۱۵-۱۰/۴۵	استراحت	----------

اداره کننده جلسه: دکتر مهشید مهدیزاده

اعضای هیئت رئیسه: دکتر مهشید مهدیزاده - دکتر بی بی شهین شمسیان- دکتر زهرا بدیعی- دکتر مهدی شهریاری

۱۰/۴۵-۱۱/۰۵	سندرم های هموفاگوسیتیک لنفوهیستوسیتوزیس پس از پیوند سلول های بنیادی	دکتر مهشید مهدیزاده
۱۱/۰۵-۱۱/۲۵	درگیری سیستم عصبی مرکزی CNS در سندرمهای هموفاگوسیتیک لنفوهیستوسیتوز	دکتر بی بی شهین شمسیان
۱۱/۲۵-۱۱/۵۵	گزارش موتاسیونهای ژنی در سندرمهای هموفاگوسیتیک لنفوهیستوسیتوز ارثی از ایران	دکتر نیما پروانه
۱۱/۵۵-۱۲/۱۵	گزارش یک مورد بیمار نادر مبتلا به هیستوسیتوز سلولهای لانگرهانس و سندرم هموفاگوسیتیک لنفوهیستوسیتوز همزمان	پروفسور پیمان عشقی
۱۲/۱۵-۱۲/۳۰	پرسش و پاسخ	----------
۱۲/۳۰-۱۳/۳۰	ناهار و نماز	----------

(بعد از ظهر)

معرفی بیمار **اداره کننده جلسه:** دکتر ساسان حجازی **اعضای هیئت رئیسه:** پروفسور G.Janka - دکتر مژگان هاشمیه- دکتر نرگس بیگم میربهبهانی- دکتر ساسان حجازی		
معرفی بیماران جالب		
۱۳/۳۰-۱۴/۰۰	گزارش سه بیمار مبتلا به سندرم هموفاگوسیتیک ارثی تحت پیوند سلولهای بنیادی خون ساز	دکتر بی بی شهین شمسیان
۱۴/۰۰ -۱۴/۳۰	معرفی دو بیمار مبتلا به سندرم هموفاگوسیتیک لنفوهیستوسیتوز و عفونت لیشمانیا	دکتر افشین فتحی
۱۴/۳۰-۱۵/۰۰	معرفی مشکلات درمانی دو بیمار سندرم هموفاگوسیتیک لنفوهیستوسیتوز در غیاب پیوند سلولهای بنیادی خون ساز	دکتر هادی متقی پیشه
۱۵/۰۰-۱۵/۳۰	اختتامیه	

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