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Case Report

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Hemophagocitic Lymphocitosis, First Presentation of Hodgin Lympoma-Case Report and Literature Review

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Hemophagocytic lymphohistiocytosis (HLH) is described as a hyperferritinemic hyperin-inflammatory syndrome, in the pathogenesis of which ,an important role is played by the uncontrolled activation of cells with an important role in the body's immune mechanisms, such as macrophages, lymphocytes, histiocytes, TNF-α, interleukin 6 (IL-6), interferon γ (IFN-γ), and MIP-1α [1].

Clinically, this pathology is characterized by fever, cytopenia, splenomegaly, neurological symptoms, invasion of the bone marrow, liver, or lymph nodes.[2].

Case Presentation

A 23-year-old male, with a negative medical history, presented to the hospital with complaints of continuous febrile episodes for about 3 weeks (Tmax 38.8C), profuse sweating, weight loss of about 9.6kg during this time. The patient was an occasional smoker (declares 1-2 cigarettes per week), negative anamnesis for regular use of alcohol or drugs. Negative family history for hematological malignancies. He refers that he had not traveled during the last 3 months. After 1 short hospitalization 10 days ago, which did not result in an exact diagnosis, the patient presents with persistent symptoms for several days now. Laboratory tests showed pancytopenia with leukocytes 1,300/μL, an absolute neutrophil count of 820/ μL, hemoglobin 7.2 g/dL and platelets 15,000/μL, ferritin levels 1954 ng/mL, fibrinogen- 634 mg/dL, normal level of triglycerides at 124 mg/dL.

Biochemical panel and liver function in the norm. Viral tests were negative for the flu A/B, RSV, CMV, HIV, parvovirus B19 and hepatitis B virus. Serology for SARS-2 COV is also negative. Blood culture and urine culture did not show growth of microorganisms. CT showed diffuse adenopathy, mainly axillary inguinal and retroperitoneal. Biopsy of the lymph node showed the presence of Reed-Sternberg cells, the presence of fibrosis and mixed inflammatory infiltrate.

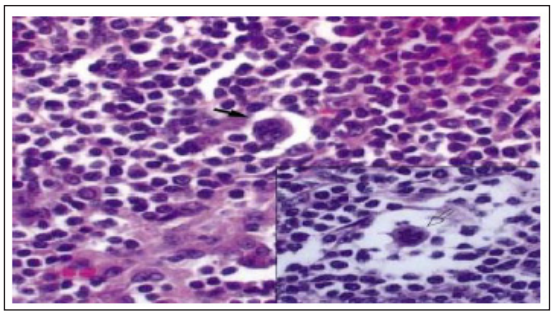

Figure 1: Lymph node biopsy

Immunohistochemistry of the cells showed weak expression of PAX-5, CD30 and CD15, lack of expression of CD20 and CD45. The above findings were classic as it belongs to classic Hodgin.

Bone marrow biopsy revealed fibrotic areas with rare positive CD-30. (Figure 2). Constant presence of hemophagocytosis phenomena was observed in the marrow.

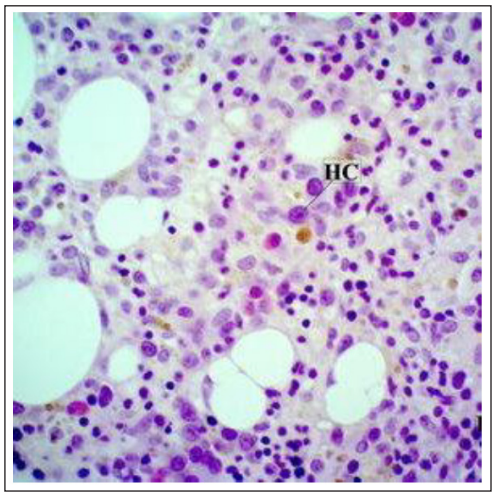

Figure 2: Bone marrow biopsy

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PET CT showed the presence of extensive lymph nodes, splenomegaly, all of which are compatible with the diagnosis of Hodgins's Lymphoma.

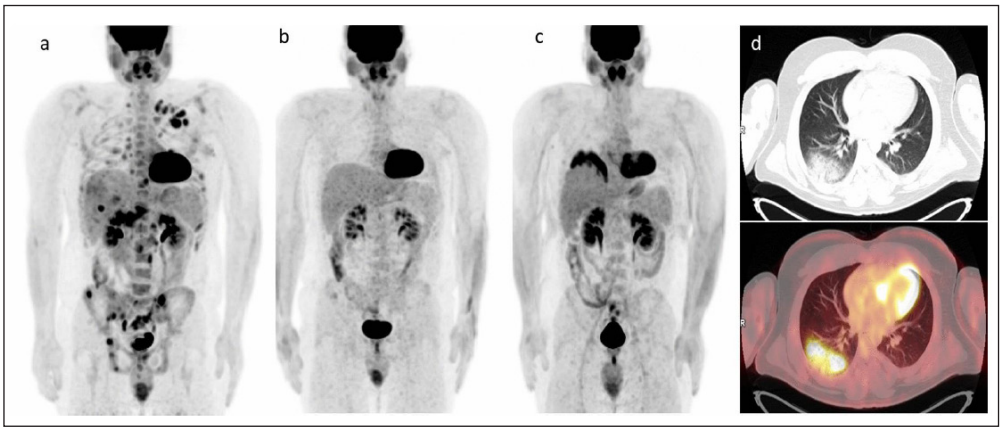


Figure 3: Pre and post chemotherapy

The patient started chemotherapy according to the ABVD scheme and the symptoms such as temperature and profuse sweats were withdrawn after the 20th day of the first treatment cycle.PET scan on day 1 of the 3rd cycle showed a reduction or even elimination of lymphadenopathy in the cervical, thoracic and abdominal regions. (Figure 3). After six cycles of ABVD, PET showed complete response to treatment with elimination of all lymphadenopathy. Figure 3.

Bone marrow biopsy resulted in hypo cellular areas with the presence of areas with erythroid hyperplasia and dyspoesis. There was no increase in eruptions and no evidence of it lymphoma,

Reed-Sternberg cells, or hemophagocytosis. The flow cytometry was negative. The patient continued to improve clinically with improved counts, increased appetite, and weight gain.

Discussion

It is now known that HLH is a not very frequent phenomenon which is generally encountered as companion to other pathologies. But it seems that the HLH is not any more that rare. In a recent study in USA there were found 16136 non elective HLH adult admissions. The pyramid population showed a bimodal population distribution with peaks in interval 16-30 years of age, and 56-70 years of age. The most common associated conditions were malignancy (4953 admissions [30.7%]), infections (3913 admissions [24.3%]), autoimmune conditions (3362 admissions [20.8%]), organ transplant status (639 admissions [4%]), and congenital immunodeficiency syndromes (399 admissions [2.5%]). Congenital immunodeficiency syndromes had the worst in-hospital mortality rate (mortality rate 31.1%, adjusted OR 2.36 [1.56-3.59]), followed by malignancies (mortality rate 28.4%, adjusted OR 1.80 [1.46-2.22]), infections (mortality rate 21.4%, adjusted OR 1.33 [1.10-1.62]), other/no trigger (mortality rate 13.6%, adjusted OR 0.73 [0.58-0.92]), autoimmune (mortality rate 13%, adjusted OR 0.72 [0.57-0.92]), and post-organ transplant status (mortality rate 14.1%, adjusted OR 0.64 [0.43-0.97]) [1].

In another study in Sweden the results on the pediatric age showed the minimal annual incidence rate of primary HLH remained 0.12 per 100,000 children, equating to 1.8 per 100,000 live births. Notably, an increased overall survival was observed in 1997-2006, relative to the period 1987-1996. During the subsequent 5-year period, 2007-2011, the incidence of genetically and/or functionally verified primary HLH was 0.15 per 100,000 children per year, suggesting that new assays may aid the identification of patients with primary HLH [2].

The incidence of diagnosed HLH in England increased 11% year on year between 2003 and 2018 resulting in a 4-fold increase over the 16-year study period. Substantial variation in the incidence occurred by age groups, with no increase over time in those under 5-year olds contrasting with a 9% annual increase in 5–14 year olds, a 14% annual increase in 15–54 year olds and a 16% annual increase in those aged 55 and over. Furthermore, we observed increases in diagnoses of HLH associated with inflammatory rheumatological disease/IBD and hematological malignancy-associated HLH over time, which also varied by age. Among the young and middle age groups, there were increases in both rheumatological disease/IBD and hematological malignancy-associated HLH, whereas in older age groups, the increase was seen mainly with hematological malignancy-associated HLH. These findings imply that the temporal increase in HLH we have observed is being driven more in younger people by changes in autoimmune disease and its treatment, for example, biologics and immunosuppressant, and more in older people by the known increase in the incidence of hematological cancer, particularly non-Hodgkin lymphoma, during the study period [3].

A retrospective study was performed in a teaching hospital in Belgium. All cases of adult HLH, from December 2010 to April 2022, were 52. Mean age (SD) of patients was 48 (18) years old, and 29 patients were of male gender (56%). The underlying diseases associated with HLH were malignancy (M-HLH) in 22 patients, infection related HLH in 20 patients, rheumatologic disease related HLH in 7 patients, idiopathic in 2 patients and secondary to pregnancy in 1 patient. Overall mortality, mortality at 30 days and 90 days were 24/52 (46%), 13/52 (25%) and 4/52 (10%), respectively [4].

In a study edited by American Journal of Medicine part of which were 312 patients, 162 were classified with positive hemophagocytic syndrome (male, 67%; median age, 48 [35-62] years). Patients with hemophagocytic syndrome more frequently had an underlying immunodepression (45% vs 33%,P= .03) and exhibited higher temperature, ferritin, triglycerides, aspartate transaminase, bilirubin, lactate dehydrogenase, and C-reactive

protein. Hematologic malignancies, especially non-Hodgkin lymphomas, were the main trigger of hemophagocytic syndrome, accounting for 56% of cases [5].

In a study edited by Nature,in 2024 ,there was a classification of possible underlying hematological causes of HLL, among which Lymphoma has an important position. B- and T-NHL were equally represented (45.6% and 45.2%), Hodgkin's lymphoma was reported in 8.9% of the cases. Most of patients (91.6%) presented in Ann-Arbor-Stages III and IV, and there was bone marrow in a significant proportion of patients (61.5%). Soluble CD25 levels were significally elevated (median 10,000 U/ml), with levels beyond 10,000 U/ml compromising prognosis for 30-day and overall survival. 66.8% of the patients died after median 5.1 months. Lymphoma associated -HLH remains an important clinical challenge [6].

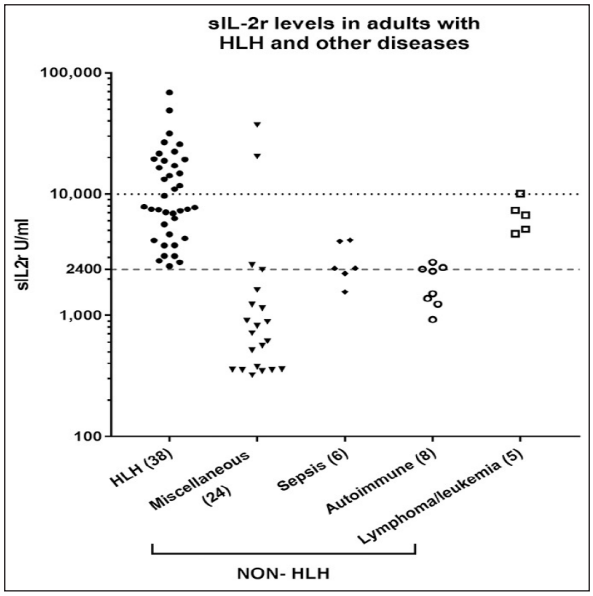
HLH is a diagnostic entity that should be taken into consideration regarding a possible differential diagnosis in adults with malignant pathology who constantly exhibit fever, pancytopenia or organomegaly(splenomegaly). Our patient was diagnosed according to HLH-2004 guidelines with Stage Classic IVB HL with simultaneous HLH. International Program -Notic grade (IPS) was 5, which corresponds to a 5-year progression free survival (PFS) of 42% and overall survival (OS) of 56%. He achieved a complete response after six cycles of ABVD chemotherapy. He also had a quick and full resolution of clinical and cytopenic symptoms which were apparently due to HLH. Given the rarity associated with HL with HLH,

Currently, the diagnosis is considered positive for HLH if the patient fulfills 5 of the following 8 criteria, according to HLH-2004 [7].

The diagnosis of HLH can be established if criterion 1 or 2 is fulfilled
1. A molecular diagnosis consistent with HLH
2. Diagnostic criteria for HLH fulfilled (5 out of 8 below) - Fever - Splenomegaly - Cytopenias affecting at least 2 of 3 lineages in the peripheral blood, hemoglobin <90g/L, platelets<100x10⁹, neutrophils<1.0x10⁹/L, - Hypertriglyceridemia and/or hyperfibrinogenemia. Fasting triglyceridemia >3.0mmol/L, fibrinogen<1.5g/L - Hemophagocytosis in bone marrow, spleen or lymp nodes in no evidence of malignancy - Low or no NK cell activity - Ferritin>500μ/L - sCD25 (ie, soluble IL-2 receptor) ≥2400U/mL

Soluble interleukin-2 receptor has recently been reported as a trustable, low cost marker of HLH (95% confidence interval ,0.83-0.97). In a study published by Blood Advances in 2017 retrospective study of 78 consecutive adults who had sIL-2r measured for suspected HLH.

Serum sIL-2r levels were measured by enzyme-linked immunosorbent assay (adult reference range, 241-846 U/mL). There were 38 patients with HLH and 40 with a non-HLH diagnosis (such as sepsis, liver disease, histiocyte disorders, autoimmune disease, leukemia, or lymphoma). The receiver operating characteristic curve demonstrated that sIL-2r is a good to excellent diagnostic test for adult HLH, with an area under the curve (AUC) of 0.90 (95% confidence interval, 0.83-0.97) compared with AUC 0.78 (95% confidence interval, 0.67-0.88) for ferritin. The optimal threshold for sIL-2r was 2515U/mL (sensitivity, 100%; specificity, 72.5%). Although there was a large indeterminate range for sIL-2r, a level of 2400 U/mL or less was helpful for ruling out HLH (sensitivity, 100%), and more than 10 000 U/mL was helpful for ruling in HLH (specificity, 93%). Higher mean sIL-2r levels were seen in malignancy-associated HLH (20 241 U/mL) compared with infection-associated HLH and macrophage activation syndrome (9720 and 5008 U/mL, respectively; $P < .05$). Levels above 10 000 U/mL were not associated with worse prognosis in patients with HLH. Serum sIL-2r is a sensitive test for diagnosis of adult HLH, but is not as specific as previously reported in children. Additional studies enriched with patients without HLH who have conditions associated with T-cell activation, such as lymphoma and autoimmune lymphoproliferative syndrome, are needed [7].



Other diagnostic tools include hyperbilirubinemia hepatomegaly, hyperbilirubinemia, transaminitis (reported in the vast majority of patients with HLH). This elements might be useful in differentiating HLH from other diagnostic entities such septic shock, autoimmune hemolytic anemia and they are alsoquite helpful assessing therapy response.But again HLH remains a colorful diagnostic panorama. There have been reported cases with bleeding diathesis, purpura, dyspnea, edema diarrhea, ect.

Impressive remains the fact that all this specific and not, symptomatology, may progress so abruptly to create an acute onset of multiorganory insufficiency.

Regarding functional and genetic testing,they are not generally recommended in adults, because in this case we have an underlying cause. On the other hand,in the familial form of HLH there is an impairment of lymphocyte toxicity and the most important gene impairment are presented in the table below [9].

Defective immune function	Gene(locus)	Syndrome	Clinical features	Laboratory
Cytotoxic granule content	PRF1(10q21-2 2)	FHL2		Decreased/absent perforin expression (FC)
	UNC13D(17q2)	FHL3		Low CD107αexpression (degranulation assay, FC)
	STX11(6q24)	FHL4		Low CD107αexpression (degranulation assay, FC)
	STXBP2(19p1 3)	FHL5	Colitis, neurosensory hearing loss	Low CD107αexpression (degranulation assay, FC)
	RAB27A(15q2 1)	Griscelli type2	Hypopigmentation	Abnormal granule pattern in CBC abd hair shafts, low CD 107αexpression
	LYST(1q42-43)	Chediak-Hig ashi	Hypopigmentation	Abnormal granule pattern in CBC abd hair shafts, low CD 107αexpression
Cytotoxic T-cell signaling	SH2D1A(X-q2 4-25)	XLP1 Duncan disease	EBV lymphoproliferation	Decreaseed/absent SAP expression, reduced NKT cells (FC) hypogammaglob ulinemia
Inflammasome regulation, excess apoptosis, NOD signal	BIRC4(Xq25)		Refractory colitis, EBV lymphoprolifer ation	Decreased/absent BIRC4 protein expression, reduced NK Tcells
Inflammsome constitutive activation	NLRC4(2p22.3)	XLP2	Recurrent autoinflammati on enterocolitis	High circulating IL-18 levels

Even though in the adult the genetic screening is not highly recommended, mutations in HLH associated genes can be detected.

The HLH propability score is a web based calculator ((http://saintantoine.aphp.fr/score/) in order to help as a diagnostic tool [10].

Parameter	No of points (criteria for scoring)
Known underlying immunosuppression	0(no) or 18(yes)
Temperature(°C)	0(<38.4),33(38.4-39.4), or 49(>39.4)
Organomegaly	0(no) 23(hepatomegaly or splenomegaly) 38(splenomegaly and hepatomegaly)
Number of cytopenias	0(1 lineage) 24 (2lineages) or 34 (3lineages)
Ferritine(µg/L)	0(<2000), 35 (2000-6000), 50(>6000)
Triglyceride (mmol/L)	0(<1.5), 44(1.5-4), 64(>4)
Fibrinogen(g/L)	0(>2.5), 30 (≤ 2.5)
AST(U/L)	0(<30) 19 (>30)
Hemophagocytosis on bone marrow aspirate	0(no), 35(yes)

The treatment of HLH syndrome remains another important field of battle. Actually the basis of treatment remains the HLH94 protocol, even though it improves time to time. The basis of this protocol are Dexamethasone,Cyclosporine Intrathecal therapy in cases with neurological involvment,and Etoposide in order to make possible deletion of activated T cells and supression of inflamtory cytokine production [11].

Another possible way of treatment should be considered the allogenic transplant, a therapy which has dramatically improved the outcome of HLH syndrome in children [12].

In the patient with resistant or relapsed HLH there is a strong consent upon using chemotherapy and the consolidation is done through allotrasplant. In a prospective study, liposomal doxorubicin, etoposide, and high-dose methylprednisolone resulted in complete remission in 27% of patients and partial remission in 49% of patients within 4 weeks [13].

Novel immunotherapies may induce a cytokine storm resembling HLH that requires specific treatment (strong consensus). With the advent of novel T-cell–engaging immunotherapies, reports of treatment-associated cytokine release syndrome have repeatedly emerged [14].

These T-cell immunotherapies include engineered T cells, such as chimeric antigen receptor modified T (CART) cells targeting CD19, and blinatumomab, a bispecific T-cell engager antibody that connects CD31 T cells to CD191 target B cells [15,16]. Both of these agents are approved for treatment of B-acute lymphoblastic leukemia. CART cells are also approved in relapsed/refractory B-cell NHL. CART cells and blinatumomab

induce a cytokine response that strongly resembles other forms of HLH. The anti–IL-6 antibody tocilizumab has been used with notable rapid resolution of cytokine release syndrome in patients after CART cell or blinatumomab treatment

In recent years HLH is more frequently diagnosed in adults. The results in pediatric HLH treatment has also affected the survival of adults with HLH. HLH-associated mortality remains high, especially in patients with underlying malignancies. Although the drugs used in pediatric HLH are effective even in adult HLH, there is a need for novel agents.

Actually there are on their way studies testin medications like ruxolitinib (JAK1/2 inhibitor; ClinicalTrials.gov identifiers NCT02400463, NCT03795909, NCT03533790), Anakinra (IL-1 blockade; NCT02780583), Alemtuzumab (NCT02472054), and Emapalumab (anti–IFN-g monoclonal antibody; NCT01818492).

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