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Hyperinflammation readily resolved by dexamethasone in pediatric patients with hematological malignancies

Hiperinflamacija uspešno otklonjena deksametazonom kod pedijatrijskih bolesnika obolelih od hematoloških maligniteta

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Abstract

Background/Aim. Hyperinflammatory syndromes are a relatively rare phenomenon, but can be life-threatening for children suffering from malignancy. Hemophagocytic lymphohistiocytosis (HLH) is perhaps the best recognized of several such hyperinflammatory syndromes that share a key aspect of pathogenesis – the "cytokine storm". However, conditions that resemble HLH but do not fully meet its diagnostic criteria are not uncommon and often present a diagnostic challenge. The aim of this study was to examine clinical features, disease course, and response to dexamethasone treatment in children with hematological malignancy and hyperinflammation. **Methods**. This retrospective observational study analyzed medical records of 11 children (four females and seven males; median age 10.8 years, range 3.1–16.3 years) investigated for potential hyperinflammation during treatment for a hematological malignancy at the University Children's Hospital in Belgrade, Serbia, from January 2023 to July 2024. Relevant clinical and laboratory parameters were retrieved (serum triglyceride concentration was measured in ten children), as well as data on potential triggers, dexamethasone treatment, and treatment outcome. **Results.** All children were febrile. Bicytopenia/pancytopenia was noted in six (54.5%), and splenomegaly in two (18.2%) children. Bone marrow aspiration was performed in nine children, and no hemophagocytosis was observed. Serum triglyceride concentration was elevated in one (10.0%) child. Fibrinogen levels were above 1.5 g/L in all cases, and ferritin levels exceeded 500 μg/L in ten (90.1%) children. Two (18.2%) children had soluble interleukin-2 receptor (sIL-2R) above 2,400 IU/mL (the median sIL-2R level was 1,041 IU/mL, range 396–9,069 IU/mL, and the interquartile range was 1,012 IU/mL). Only one child met five of the eight HLH-2004 criteria. A potential viral, bacterial, or fungal trigger was identified in eight children. Eight children were treated with dexamethasone, resulting in the rapid resolution of the hyperinflammatory episode. **Conclusion**. In the diagnostic work-up of a febrile child with a hematological malignancy, one should always consider an inflammatory condition that may respond favorably to glucocorticoid treatment.

Key words:
adolescent; child; diagnosis, differential; drug therapy; febrile neutropenia; inflammation; lymphohistiocytosis, hemophagocytic; treatment outcome.

Apstrakt

Uvod/Cilj. Hiperinflamatorni sindromi su relativno retka pojava, ali mogu ugroziti život dece obolele od maligniteta. Hemofagocitna limfohistiocitoza (HLH) je najpoznatija od nekoliko takvih hiperinflamatornih sindroma koji dele ključni aspekt patogeneze – „citokinsku oluju". Međutim, stanja koja podsećaju na HLH, ali ne ispunjavaju u potpunosti njene dijagnostičke kriterijume, nisu retka i često predstavljaju dijagnostički izazov. Cilj rada bio je da se ispitaju kliničke karakteristike, tok bolesti i odgovor na lečenje deksametazonom kod dece koja imaju hematološke malignitete i hiperinflamaciju. **Metode.** Retrospektivnom opservacionom studijom analizirane su istorije bolesti jedanaestoro dece (četiri devojčice i sedam dečaka; medijana uzrasta 10,8 godina, raspon 3,1–16,3 godine) ispitivane zbog potencijalne hiperinflamacije tokom lečenja od hematološke maligne bolesti na Univerzitetskoj dečjoj klinici u Beogradu, Srbija, od januara 2023. do jula 2024. godine. Prikupljeni su relevantni klinički i laboratorijski parametri (koncentracija triglicerida u serumu izmerena je kod desetoro dece), kao i podaci o potencijalnim okidačima, lečenju deksametazonom i ishodu lečenja. **Rezultati.** Sva deca bila su febrilna. Bicitopenija/pancitopenija je zabeležena kod šestoro (54,5%), a splenomegalija kod dvoje (18,2%) dece. Aspiracija koštane srži obavljena je kod devetoro dece, a hemofagocitoza nije uočena. Koncentracija triglicerida u serumu bila je povišena kod jednog (10,0%) deteta. Nivoi

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fibrinogena bili su iznad 1,5 g/L kod sve dece, a nivoi feritina nadmašili su 500 μg/L kod desetoro (90,1%) dece. Kod dvoje (18,2%) dece nivo solubilnog receptora za interleukin-2 (sIL-2R) bio je iznad 2 400 IU/mL (njegova medijana iznosila je 1 041 IU/mL, raspon 396–9 069 IU/mL, a interkvartilni opseg 1 012 IU/mL). Samo jedno dete ispunilo je pet od osam HLH-2004 kriterijuma. Potencijalni virusni, bakterijski ili gljivični okidač identifikovan je kod osmoro dece. Osmoro dece lečeno je deksametazonom, uz brzo okončanje naleta hiperinflamacije. **Zaključak.** U dijagnostičkoj obradi febrilnog deteta koje ima hematološki malignitet uvek bi trebalo razmotriti zapaljensko stanje koje povoljno reaguje na lečenje glukokortikoidima.

Ključne reči:
adolescenti; deca; dijagnoza, diferencijalna; lečenje lekovima; neutropenija, febrilna; zapaljenje; limfohistiocitoza, hemofagocitna; lečenje, ishod.

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a severe hyperinflammatory condition that may occur as a primary disorder or secondary to a range of diseases of diverse etiology (infectious, autoimmune, malignant, or metabolic) [1]. A common pathogenetic feature of all forms of HLH is a disturbance (either transient or permanent) in the function of cytotoxic lymphocytes, believed to compromise the timely termination of immune responses to a wide variety of noxae and stimuli, thereby fostering an uncontrollable amplification of inflammatory cascades at the level of mononuclear phagocytes [2]. While primary HLH most often presents in early childhood and features a clearly defined genetic etiology, secondary HLH may be diagnosed at any age, and its relationship to a potential genetic predisposition is much more complex [3].

Secondary HLH is relatively infrequent in children with malignancy, as compared to adults [4]. However, HLH is just one of several nosological entities comprising the wider group of hyperinflammatory syndromes that share important aspects of pathogenesis, such as an excessive and uncontrollable release of proinflammatory cytokines (i.e., cytokine storm) [5]. While HLH is a well-defined condition, mostly diagnosed using the HLH-2004 criteria issued by the Histiocyte Society [6], demarcation from other hyperinflammatory states may often be difficult in clinical practice, particularly since hallmarks of HLH (or its diagnostic criteria) may not all be present initially or concurrently. Thus, clinicians are often confronted with patients suffering from poorly defined hyperinflammation with a wide spectrum of clinical features that may only remotely resemble HLH, but still dictate a thorough investigation [7]. This spectrum of clinical presentation is reflected in a spectrum of response to anti-inflammatory treatment – many children with hyperinflammation may respond to glucocorticoids alone.

The aim of this study was to examine clinical features, disease course, and response to dexamethasone treatment in children with hematological malignancy and hyperinflammation.

Methods

This retrospective observational study reviewed the medical records of 11 children (four females and seven males, median age 10.8 years, range 3.1–16.3 years), who were investigated upon the request of the treating physician while being treated at the University Children's Hospital in Belgrade, Serbia, between January 2023 and July 2024. The patients were treated for a hematological malignant disorder, including: acute lymphoblastic leukemia (3 children), acute myeloid leukemia (excluding acute promyelocytic leukemia) (3 children), acute promyelocytic leukemia (1 child), mixed-phenotype acute leukemia (1 child), myelodysplastic syndrome (2 children), and anaplastic large cell lymphoma (1 child). The study was approved by the Ethics Committee of the University Children's Hospital in Belgrade, Serbia (No. 16/264, dated November 21, 2024).

All children were in full remission at the time of the inflammatory episodes under investigation. We retrieved relevant clinical data (presence of fever and splenomegaly) and laboratory findings [complete blood count with leukocyte differential, C-reactive protein (CRP), fibrinogen, triglycerides, ferritin, and soluble interleukin-2 receptor (sIL-2R)], as well as information on potential triggers of the hyperinflammatory reaction, dexamethasone treatment, and the obtained response/outcome. The patients were evaluated according to the HLH-2004 diagnostic criteria [6]. The diagnosis of HLH was established by the presence of either a molecular diagnosis consistent with HLH or five out of eight of the following criteria: fever > 38.5 °C; splenomegaly; cytopenia (bicytopenia or pancytopenia) (at least two of the following three: hemoglobin < 9 g/dL, platelets < 100×10^9/L, or neutrophils < 1.0×10^9/L); hypertriglyceridemia and/or hypofibrinogenemia (fasting triglycerides > 3.0 mmol/L or fibrinogen ≤ 1.5 g/L); hemophagocytosis in bone marrow, spleen, liver, lymph nodes, or other tissues; low or absent natural killer cell activity; serum ferritin concentration ≥ 500 μg/L and sIL-2R ≥ 2,400 U/mL.

Due to the small sample size, no statistical inferences were possible, and only descriptive statistics were used, except in determining the correlation between the number of HLH-2004 criteria fulfilled and sIL-2R serum concentration, where Spearman's rank correlation coefficient (r_s) was applied.

The response to glucocorticoid treatment was assessed based on clinical improvement (cessation of fever) and laboratory parameters.

Results

Individual patient data are displayed in Table 1. All children were febrile at the time of investigation, while six (54.5%) had bicytopenia or pancytopenia as *per* HLH-2004 criteria. Splenomegaly was present in two (18.2%) children. Bone marrow aspiration was performed in nine patients, and no signs of hemophagocytosis were found. CRP was elevat-

ed in all children [range 18.4–307.0 mg/L; interquartile range (IQR): 150.8 mg/L; reference range (RR): 0–5 mg/L]. Serum triglyceride concentration was measured in ten children and was elevated in one (10.0%; upper limit of RR: 3.5 mmol/L). None of the children had a fibrinogen level below the HLH-2004 cut-off of 1.5 g/L; in fact, in nine (81.8%) children, it was elevated (upper bound of RR: 4.6 g/L). The median fibrinogen level was 9.5 g/L (IQR: 8.5 g/L). Serum ferritin concentration was above 500 μg/L in ten (90.1%) children, with a median ferritin level of 1,483.5 μg/L (range 182.5–6,260.5 μg/L; IQR: 3,545.0 μg/L). Only two (18.2%) children had sIL-2R levels above 2,400 IU/mL. The median sIL-2R level was 1,041.0 ± 2,617.9 IU/mL (range 396–9,069 IU/mL).

Only one child met five of the eight HLH-2004 criteria. Another two children met four criteria, while most children in our series (six) fulfilled three. One child met two criteria, and another one fulfilled only one (Table 2).

Table 1

Basic characteristics, hematological malignant disorders, and laboratory findings of patients

Patient No.	Age (years)	Gender	sIL-2R (IU/mL)	Dg.	Fev	Spl	Hem	Cyt	Fer (μg/L)	Trig (mmol/L)	Fib (g/L)	CRP (mg/L)
1	16.2	f	9,069	MDS	+	+	n.p.	no	1,390.9	1.05	9.0	140.4
2	16.3	m	4,198	AML	+	–	–	yes	5,320.0	2.06	10.9	197.9
3	10.6	m	1,288	MPAL	+	–	–	no	1,485.3	1.58	3.9	18.4
4	6.2	m	519	ALL	+	–	n.p.	yes	3,157.9	1.29	9.6	128.2
5	13.4	f	440	APL	+	–	–	yes	3,181.3	3.53	9.5	68.9
6	3.8	f	539	AML	+	–	–	yes	1,031.8	0.73	6.6	81.3
7	14.8	m	447	ALCL	+	–	–	yes	6,260.5	1.94	14.5	307.0
8	10.8	f	396	MDS	+	–	–	no	182.5	0.50	10.5	29.1
9	16.0	m	1,386	ALL	+	+	–	no	849.2	2.67	5.9	137.6
10	3.5	m	1,041	ALL	+	–	–	yes	1,253.8	2.58	2.2	28.0
11	3.1	m	1,431	AML	+	–	–	no	4,273.6	N.p.	11.9	230.0

No. – number; f – female; m – male; sIL-2R – soluble interleukin-2 receptor; Dg. – diagnosis; Fev – fever; Spl – splenomegaly; Hem – hemophagocytosis on bone marrow aspiration; Cyt – cytopenia; Fer – ferritin; Trig – triglycerides; Fib – fibrinogen; CRP – C-reactive protein; MDS – myelodysplastic syndrome; AML – acute myeloid leukemia; MPAL – mixed-phenotype acute leukemia; ALL – acute lymphoblastic leukemia; APL – acute promyelocytic leukemia; ALCL – anaplastic large-cell lymphoma; n.p. – not performed.
All values are expressed as numbers.

Table 2

Fulfilment of HLH-2004 criteria, potential triggers, treatment, and outcome of patients

Patient No.	Age (years)	Gender	HLH Cr	Potential Trigger	Treatment	Outcome
1	16.2	f	5	EBV infection/reactivation (PCR-confirmed)	Dexamethasone	Resolution
2	16.3	m	4	None apparent	Dexamethasone	Resolution
3	10.6	m	2	Bacterial infection of CVK	Dexamethasone and antibiotics	Resolution
4	6.2	m	3	Bacterial pneumonia with pleural effusion	Dexamethasone and antibiotics	Resolution
5	13.4	f	3	Pulmonary aspergillosis	Dexamethasone and antimycotics	Resolution
6	3.8	f	3	*Pneumocystis jiroveci* pneumonia	Antibiotics	Resolution
7	14.8	m	3	None apparent	Dexamethasone and antibiotics	Resolution
8	10.8	f	1	None apparent	[1] None	Resolution
9	16.0	m	4	Crural abscess and anal fissure	Antibiotics	Resolution
10	3.5	m	3	Septicemia (*Escherichia coli*)	Dexamethasone and antibiotics	Resolution
11	3.1	m	3	Septicemia (*Streptococcus sanguinis*)	Dexamethasone and antibiotics	Resolution

HLH – hemophagocytic lymphohistocytosis; No. – number; HLH Cr – number of HLH-2004 criteria met; f – female; m – male; EBV – Epstein-Barr virus; PCR – polymerase chain reaction; CVK – central venous catheter.
[1] Note: one child underwent spontaneous resolution.

There was a significant correlation between sIL-2R level and the number of criteria fulfilled ($r_s = 0.7$, $p = 0.016$).

In eight children, a potential trigger was identified, while the remaining three exhibited no conceivable trigger for a hyperinflammatory episode (Table 2). Five of the presumed triggers were bacterial, two were fungal (including *Pneumocystis jirovecii*), and one was viral in nature [Epstein-Barr virus (EBV)]. Eight children were treated with dexamethasone (10 mg/m^2 for 7 to 10 days, initiated within three days from the onset of the febrile episode), with rapid resolution of their hyperinflammation. Of the remaining three, two were successfully treated by antibiotics (the child with *Pneumocystis jirovecii* and another with crural abscess and anal fissure), while one case resolved spontaneously (Table 2). In four of the eight children treated with dexamethasone (50.0%), a recurrent hyperinflammatory episode occurred one to eight months later, which again rapidly resolved upon another course of dexamethasone. All children were alive at the time of manuscript preparation (median follow-up 10 months, range 4–22 months).

Discussion

In a previously published series of 45 pediatric patients from our institution, investigated for hyperinflammation of all etiologies over a ten-year period, 11 (24.4%) patients had a hematological malignancy, of whom only one (9.1%) met the HLH-2004 criteria for HLH [8]. Given that only one patient in the present series (also consisting of eleven patients) met the same criteria (again, 9.1%), the proportion of children with true HLH among those exhibiting signs of potential hyperinflammation that may prompt the clinician to order appropriate investigation appears to be fairly constant. However, such instances have obviously become more frequent, as judged by the respective length of the time periods covered by the two series comprising an equal number of patients (ten years vs. two years). This may well be due to increased awareness of hyperinflammatory complications during the treatment of hematological malignancies, as well as enhanced diagnostic capacities. The rarity of true HLH in children with malignancy is in line with published reports on its incidence, such as the work of Löfstedt et al. [9] in Sweden, who retrospectively found only nine confirmed pediatric cases between 1997 and 2018. The annual incidence in malignancy-affected adults, on the other hand, was found to equal or exceed 0.62 *per* 100,000. It is, however, reasonable to assume that these figures, since they pertain to HLH alone, represent merely the tip of the iceberg of hyperinflammation.

At the time, all children in our series were undergoing aggressive chemotherapy; all were febrile, and most (10/11, 90.1%) had a ferritinemia above the HLH-2004 threshold. Therefore, it can be said that all children had febrile neutropenia, highlighting the principal diagnostic quandary in hyperinflammation arising during treatment of a hematological malignancy: how to differentiate an infectious complication from pure uncontrolled inflammatory response, given that clinical findings may be identical [10]. This dilemma is compounded by the fact that probable or confirmed presence of an infectious agent, in itself, does not preclude the possible diagnosis of a hyperinflammatory state [11]. Furthermore, the diagnostic value of splenomagaly and cytopenias is quite problematic in this setting, as these findings may result from the underlying condition and/or its treatment [12]. It is notable that the only child in our series who met the HLH-2004 criteria (patient number 1) had a polymerase chain reaction-confirmed reactivation of EBV infection and was therefore confronted with a potent HLH-triggering agent, apparently no less relevant in children undergoing treatment for malignancy than in the general population [13].

It is notable that patient number 1, a child with apparent EBV-associated HLH, was successfully treated with dexamethasone alone, as were seven of the ten children who met fewer than five HLH-2004 criteria. Among these seven children, one had pulmonary aspergillosis and was also treated with antimycotics (patient number 5), four had bacterial infections and received antibiotics (patients 3, 4, 10, and 11), while two had no apparent trigger (patients 2 and 7); however, patient number 7 also received antibiotics as part of the pre-emptive approach for febrile neutropenia. Of the three patients not treated with dexamethasone (patients 6, 8, and 9), two were eventually found to suffer from infections curable by antimicrobial treatment alone (*Pneumocystis jirovecii* pneumonia and crural abscess/anal fissure, respectively), while in the remaining child, initial inflammatory symptoms and signs resolved spontaneously. This was also the only patient in the series not exhibiting a ferritin level above 500 μg/L. Nevertheless, the inclusion of this patient in the diagnostic work-up for hyperinflammation (as with the other two children with "pure" infection) could still be justified by reasonable excess of caution, since in pediatric hematology and oncology, hyperinflammatory complications can progress rapidly and may be fatal if treatment is delayed [14]. Although it is impossible, in the absence of large controlled studies, to say how much glucocorticoid treatment actually contributed to the observed favorable outcome, it is conceivable that these time-tested antiinflammatory agents with a complex and multifaceted set of mechanisms of action at the very least accelerated the resolution of the (hyper)inflammation [15]. It is also noteworthy that some children meeting the HLH-2004 criteria have previously been reported to respond well to glucocorticoid therapy alone, or in combination with intravenously administered immunoglobulins [16]. In addition, the fact that four of our patients had a repeated hyperinflammatory episode that cleared upon another course of dexamethasone indirectly attests to a probable existence of a relative genetic predisposition [17]. Our experience supports the notion that in the setting of an inflammatory condition arising in pediatric malignancy, HLH-2004 criteria *per se* would not be a sound basis for treatment decisions. Moreover, differential diagnosis between potential sepsis and some form of systemic inflammatory response syndrome remains a constant issue of concern [18]. This could perhaps be resolved by an in-depth investigation of the inflammatory response at the cytokine level, such as the application of proteomics to look into interferon-γ signatures [19], once such diagnostic modalities become more widely available.

Another notable point is that sIL-2R was elevated above the HLH-2004 threshold of 2,400 IU/mL in only two patients (the first and second patient) – the child with apparent EBV-associated HLH and another one without an identified trigger, but with four criteria met. This is in line with the reported sensitivity and specificity of sIL-2R level measurement [20, 21]. However, most children in our series displayed moderately elevated sIL-2R values, which correlated significantly with the number of criteria fulfilled. This is somewhat expected, since HLH-2004 criteria have generally been devised to detect hyperinflammation. Nevertheless, moderately elevated plasma levels clustering around the midpoint between physiological and HLH-associated range may not be without significance in patient work-up. This raises the question whether a lower threshold for sIL-2R level might be diagnostically useful in detecting more broadly defined hyperinflammation in complex clinical settings. Ideally, the answer should be determined through appropriately designed studies in large patient populations, endowed with sufficient statistical power.

Finally, although the HLH-2004 protocol was not applicable to our patient series as such, it still offered us a useful orientation tool for diagnostic investigation. The possibility of an overlap between HLH and other (hyper)inflammatory states, along with the inherently diachronic nature of its diagnostic criteria, is explicitly acknowledged in the Protocol [22], where it is stated that not all patients meet the criteria, and many may indeed do so only later in the course of the disease. This additionally strengthens the case regarding hyperinflammation that we encountered as a type of pathophysiological process related to, yet distinct from, HLH, which, fortunately, proved to be fully treatable by dexamethasone.

Conclusion

An inflammatory state responding well to glucocorticoid treatment should always be considered a possibility in the work-up of a febrile condition arising during the treatment of pediatric hematological malignancies, whether or not an apparent infectious trigger is present.

Conflict of interest

The authors declare no conflict of interest.

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