Case Report/Narrative Review

A case-based literature synthesis of extreme hyperferritinemia in critically ill patients with COVID-19

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ABSTRACT

A case-based literature synthesis of extreme hyperferritinemia in critically ill patients with COVID-19.

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COVID-19 has brought up the interest about hyperferritinemic syndromes. Though often seen in COVID-19, especially within the frame of COVID-CSS, hyperferritinemia needs a systematic diagnostic approach, as co-infections or other causes may also increase ferritin. In this article ,we present a case report of extreme hyperferrinemia in an male criticall ill patient with COVID-19 and we perform a short synthesis of the available literature.

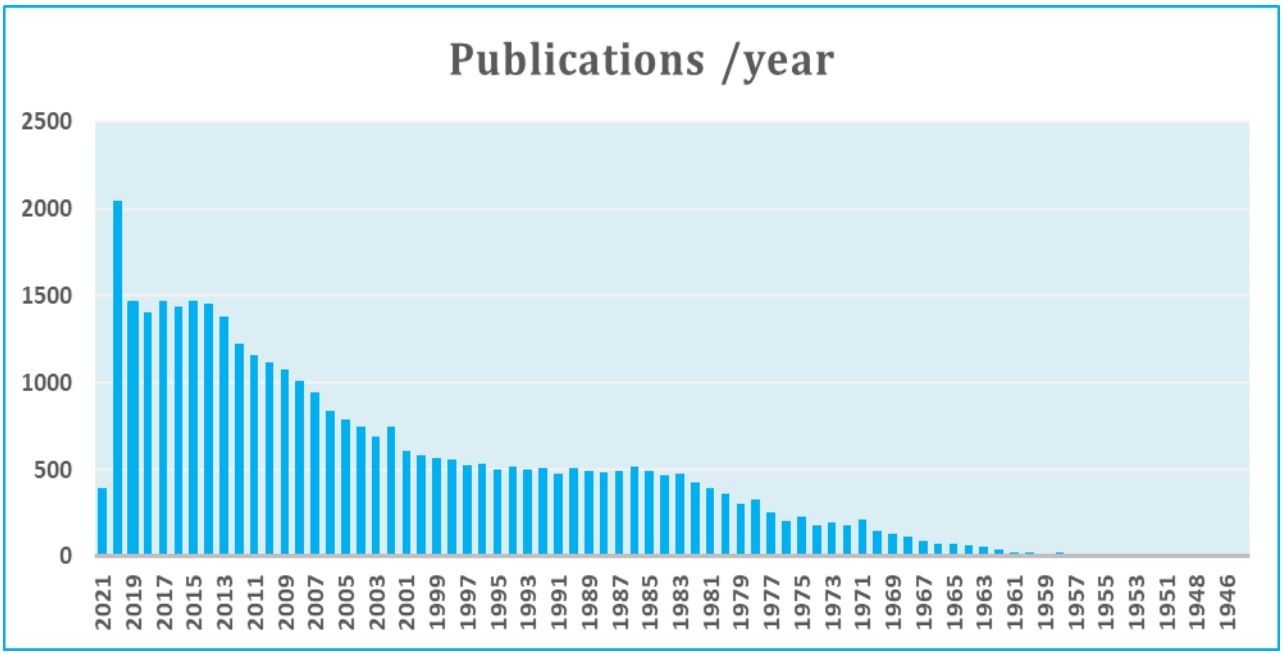
Key words: Hyperferritinemia, COVID-19, ICU, Hemophagocytic Lymphohistiocytosis

INTRODUCTION

Hyperferritinemia or the more general hyperferritinemic syndrome seems to gain again interest due to COVID-19 pandemia[1]. However, research about ferritin physiological and pathophysiological roles has been steadily increasing since the development of laboratory evaluation in 1975 (Graph 1). Today, growing number of roles have been attributed to extracellular ferritin, ranging from iron homeostasis, to angiogenesis, inflammation, immunity, signaling and

cancer[2]. The normal range of serum ferritin is gender and age specific, 7 to 10 ng/ml for infants and 20 to 300 ng/ml for adults. Under hyperferritinemic syndromes lay an extremely complex and variable aetiology and pathogenesis. The clinical significance of hyperferritinemia (>500ng/ml) or extreme hyperferritinemia (term used for levels from >2000 ng/ml to >10.000 ng/ml) is still under research; yet in most reports it is related to worse outcomes[3]. In the present article we present a case report of extreme hyperferritinemia in patient with COVID-19 and perform a literature synthesis upon the subject.

Graph 1. Resluts of MESH term search "ferritin" in National Library Medicine PubMed® Database. (acceced 16/02/2021).



CASE REPORT

A 64-year-old male patient (Height: 176cm, Weight: 77kg, BMI 24.9) was admitted to our ICU due to Type I acute respiratory failure due to COVID-19 infection. The man was initially refereed to another hospital for fever (38.2ºC), fatigue, dyspnea, reduced level of conscientiousness (Glasgow coma scale GCS – E3/V3/M4) with consequent fall and nasal bones fractures and low oxygen saturation (SpO_2 85%), where he was hospitalized for 4 days, and then transferred to our hospital as COVID-19 infection positive patient; where he was also remained for 4 days, before ICU admission. Previous history included epilepsia and hypothyreoidism under valproate sodium 500 mg. q.d. p.os, diazepam 10 mg. q.d. p.os, lacosamide 150 mg b.i.d p.os, topiramate 100 mg b.i.d p.os., risperidone 1 mg b.i.d p.os. and levothyroxine sodium 25 μg q.d. p.os; no allergies, previous surgeries or family history reported.

Clinical severity scores on admission were APACHE (Acute Physiology and Chronic Health Evaluation) II 17, SAPS II (Simplified Acute Physiology Score) 86 and SOFA (Sequential Organ Failure Assessment) score 8. ICU therapeutic strategy included Enoxaparine 60 mg s.c q.d, Omeprazole 40 mg i.v. q.d , Levothyroxine sodium 25 μg q.d. p.os, lacosamide 200 mg b.i.d p.os, Meropenem 2rg q8h i.v, Linezolide 600 mg q12h i.v, Dexamethasone 6mg i.v. q.d , along with sedation, analgesia,muscle relaxant (for 3 days), inotropic support, antiepileptics and diuretics infusion. On 7th day percutaneous tracheostomy and elective central venous catheter change were performed. On 8th and 9th day an abrupt ferritin increase was noted, while the rest of the lab examination and the clinical status remained unchanged. Drug therapy was re-evaluated and samples from microbiological cultures were collected. Bronchial alveolar lavage revealed Candida dubliensis and antimycotic therapy initiated. The patient was transported to ward 3 days later, and ferritin levels returned to previous levels 4 days after. (Table 1 and 2.)

Table 1. Daily drug regimenent course.

Day **Drug regiment**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Enoxaparine													
Omeprazole													
Levothyroxine sodium													
Lacosamide													
Meropenem	1	2	3	4	5	6	7	8	9	10			
Linezolide	1	2	3	4	5	6	7	8	9	10			
Voriconazole											1	2	3
Dexamethasone	9	10											
Noradrenaline													
Midazolam													
Fentanyl													
Rocuronium													
Isoproterenol													
Remifentanyl													
Dexmedetomidine													
Valproate sod.										*	*	*	*
Furosemide													
Bromazepam													

*For antibiotics and corticosteroids therapy day number is given.*half dose (from 1600 mg/day to 800 mg/day).*

Table 2. Selected lab values course

Day	1	3	5	8	9	10	11	14	16	17
Ferittin	1222	1447	1536	24236	33511	17978	10686	2100	1170	763
WBC	4.71	10.58	16.15	9.19	10.67	8.24	10.15	10.87	5.62	5.57
CRP	12.8	13.9	8.1	14.3	15.6	20.7	19.3	8.6	7.6	5.8
PCT	0.1	0.11	0.06	0.05	0.08	0.09	0.08	0.06	0.08	0.04
D-dimers	0.38	0.23	0.18	0.32	0.66	0.54	0.42	0.31	0.4	0.4
LDH	209	262	482	305	365	378	463	228	197	162

The patient was discharged from hospital 22 days after ICU admission to a rehabilitation center.

DISCUSSION

Hyperferritinemia is often encountered in clinical practice, with its frequency reported as much as 7% of hospitalized patients[4]. However, the frequency decrseases with the increase of ferriting levels. Thus, extreme hyperferritinemia with ferritin levels>10.000 ng/ml is ranging from 0.4% - 0.08% of the total cases[5,6]. Most extreme values in the literature (>190.000 ng/ml) are related to hematological malignancies, while other conditions related to hyperferretinemia are liver diseases, massive or chronic transfusions, infections (bacterial, viral or fungal), hemoglinopathies and primary or secondary hemophagocytic Lymphohistiocytosis[6]. The combination of high fever with extremely elevated ferritin level is considered a medical emergency being associated with the following four life threating conditions: Adult-onset Still's disease, catastrophic antiphospholipid syndrome, septic shock and macrophage activating syndrome[7].

A simplistic vision can distinct three major mechanism for hyperfferetinemia: total body iron storage overload, presence of inflammation (which causes hypersecretion of ferritin into the serum from storage cells without total body iron overload) and spillover of intracellular ferritin into the serum from cellular injury. However, the pathways engaged can be extremely complex. That is why there is need for a systematic stepwice diagnostic approach for managing such cases[8].

In SARS-Cov2 infection ferritin is an early, non-specific indicator of inflammation and is related to “cytokine storm syndrome” (CSS) or secondary secondary haemophagocytic lymphohistiocytosis (sHLH) (or “hemophagocytic syndrome” (HPS) or “Macrophage activation syndrome (MAS)). It resulted to be the first severely elevated biomarker together with lymphopenia[9]: thus, its levels in at-home symptomatic patients might be extremely useful in individuating those who can benefit of early hospitalisation. After its initial rise, ferritin can take longer than a month to normalise after an infection. Along with levels of d-dimer, high-sensitivity cardiac troponin I, lactate dehydro-

genase, and IL-6, serum ferritin was clearly elevated in non-survivors; in the latter category, it exceeded 2000 ng/ml after 16th day[9]; and even more in patients with comorbidities[10]. Yet, despite the relation of hyperferritenemia in COVID-19 patients with increased mortality it is still under investigation weather it is a marker of disease progression, or a modulator in disease pathogenesis[11].

Viral hemoglobinopathy due to SARS-Cov2 interaction with hemoglobin molecule, through CD147, CD26 and other receptors located on erythrocyte and/or blood cell precursors (such as GRP78) on one hand and hepcidin-mimetic action of a viral spike protein, inducing ferroportin blockage on the other has been widely recognised as the main pathophysiological mechanisms (especially the second one) which could explain progressive anemia and hyperferritinemia[12].

In their turn viral hemoglobinopathy and iron dysregulation results/intereferes with i) decrease of functioning hemoglobin quote; ii) iron overload in cell/tissue (hyperferritinemia); iii) release of free toxic circulating heme; iv) hypoxemia and systemic hypoxia; v) reduction of nitric oxide; vi) coagulation activation; vii) ferroptosis with oxidative stress and lipoperoxidation; viii) mitochondrial degeneration and apoptosis[12] that are found in COVID-19 patients.

Increased serum ferritin may provoke even more inflammatory activity (via increased Interleukin-1β, inducible Nitric Oxid Synthetase, Intercellular Adhesion Molecules e.t.c) and immunosuppression (via inhibiting T-cell proliferation, B-cell maturation or IgG production) induce a series of direct and indirect (via autoimmunity) injuries to most organs during COVID-19, such as coagulopathies, sHLH, hemochromatosis-like liver injury, and other ferroptosis-driven syndromes[13-14].

Specifically, for the sHLH diagnosis, several tools are available (HLH-2004 score, HScore, MH score); yet HScore seem to be the more popular in COVID patients[9]. Another score, the FAD-85 score, defined as age+0.01 * ferritin+D-dimer, was used to predict risk of mortality with good results[15].

Since the research about COVID 19 is increasing, more information both about the role of hyperferritinemia and the COVID -CSS is expecting[16]. Yet, two facts seem to be certain: high ferritin levels are related to decreased survivor and that ferritin itself aggravates disease progress1[17]. Till now (Feb 2021) there are several suggestions that handling with hyperferritinemia may be beneficial for the outcome of those patients. Thus, for example therapies that have demonstrated benefit in other cytokine storm syndromes (like MCD–Multicentric Castleman Disease, CAR-T–Chimeric antigen receptor T cell, CRS–Cytokine Release Syndrome) are under active investigation for COVID -19 CSS[15]. Iron chelating agents, (deferoxamine, deferiprone, deferasirox) are under investigation ((NCT04333550,

NCT04361032) since small in vitro and in vitro studies have shown that they may endothelial inflammation in viral infection[18]. Case reports also suggest iron redistribution effect of recombinant human erythropoietin (rhEPO) may have also a role[19].

CONCLUSION

COVID-19 has brought up the interest about hyperferritinemic syndromes. Though often seen in COVID-19, especially within the frame of COVID-CSS, hyperferritinemia needs a systematic diagnostic approach, as co-infections or other causes may also increase ferritin. In COVID-19 ferritin seem to be both a result and a modulator of the disease progress. The research boost around the subject is expecting to provide more information both about pathogenesis and, specially, about the management of such cases.

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Authors' contributions

AT: conception of idea+data analysis+manuscript draft+literature review+fnal review.

MA: literature review +fnal review.

PD, FEN, TG, DF: data collection+literature research+fnal review.

All authors read and approved the fnal manuscript.

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The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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No IRB approval required.

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Patient consent obtained

Competing interests

The authors declare that they have no competing interests.

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