Scientific Research Publishing

Open Journal of Rheumatology and Autoimmune Diseases, 2022, 12, 119-127
https://www.scirp.org/journal/ojra
ISSN Online: 2164-005X
ISSN Print: 2163-9914

Extreme Hyperferritinemia in a Filipino Male Patient with Adult Onset Still's Disease: A Case Report

Denise Joy Emmanuelle Lopez*, Karla Sofia Reyes, Aileen U. Agbanlog

Section of Rheumatology, Department of Medicine, St. Luke's Medical Center Quezon City, Metro Manila, Philippines
Email: *djelopez@stlukes.com.ph

How to cite this paper: Lopez, D.J.E., Reyes, K.S. and Agbanlog, A.U. (2022) Extreme Hyperferritinemia in a Filipino Male Patient with Adult Onset Still's Disease: A Case Report. *Open Journal of Rheumatology and Autoimmune Diseases*, **12**, 119-127.
https://doi.org/10.4236/ojra.2022.124013

Received: January 25, 2022
Accepted: November 7, 2022
Published: November 10, 2022

Abstract

Background: Elevated serum ferritin is more commonly due to reactive causes such as infection, hepatic disorders, rheumatologic conditions, and malignancy than true iron overload. Extreme hyperferritinemia (>10,000 ng/mL), on the other hand, should prompt consideration of rare conditions such as adult-onset Still's disease (AOSD) or hemophagocytic lymphohistiocytosis. This paper aims to present the case of the highest reported extreme hyperferritinemia (actual level 256,000 ng/mL) in a patient eventually diagnosed with adult onset Still's Disease (AOSD). **Case Presentation:** A 55-year-old male, Filipino, was admitted due to acute onset fever and shortness of breath. He was initially assessed to have community-acquired pneumonia and a suspect for coronavirus disease 2019 (COVID-19), hence inflammatory markers were requested. Ferritin was notably elevated at 44,255 ng/mL. He eventually tested negative for COVID-19 RT-PCR. He was investigated for other causes of markedly elevated ferritin levels. His complete blood count (CBC) only showed leukocytosis with no peripheral blasts, iron level and liver function tests were normal, HIV immunoassay was negative, ANA was 1:80 speckled with normal complement level, rheumatoid factor negative, and positron emission tomography (PET) scan revealed presence of lymphadenopathies and did not show solid tumors. He was treated for urinary tract infection and pneumonia but still had intermittent fever and increasing ferritin trend, with the highest documented level at 256,000 ng/mL. Fulfilling the Yamaguchi criteria, he was managed as a case of severe AOSD and received tocilizumab. He had lysis of fever and decreasing trend of ferritin levels thereafter, with ferritin level of 34,184 ng/mL three weeks after tocilizumab infusion. He was discharged and improved with prednisone and methotrexate as home medications. **Conclusion:** To our knowledge, the highest level of extreme hyperferritinemia recorded in literature as of 2016 is 143,931 ng/mL, which was

associated with hematologic malignancy. This case documents the highest noted ferritin level of 256,000 ng/mL associated with AOSD. AOSD remains a diagnosis of exclusion due to its nonspecific symptoms and absence of definitive tests. The treatment comprises NSAIDs, steroids, and immunosuppressives; however biological treatments such as tocilizumab can be considered in severe cases.

Keywords

Still's Disease, Hyperferritinemia, Autoimmune, Tocilizumab, Case Report

1. Background

Elevated serum ferritin (>200 ng/mL in women and >300 ng/mL in males) is more commonly due to reactive causes such as infection, hepatic disorders, rheumatologic conditions, and malignancy than true iron overload. Extreme hyperferritinemia (>10,000 ng/mL), on the other hand, should prompt consideration of rare conditions such as adult-onset Still's disease (AOSD) or hemophagocytic lymphohistiocytosis. To our knowledge, the highest level of extreme hyperferritinemia recorded in literature as of 2016 is 143,931 ng/mL, which was associated with hematologic malignancy [1].

This case documents the highest noted ferritin level of 256,000 ng/mL from a 55-year-old male who presented with fever, arthritis, lymphadenopathy, elevated liver enzymes, and elevated inflammatory markers. He was subsequently diagnosed with Adult Onset Still's Disease based on Yamaguchi criteria after exclusion of other diagnoses.

AOSD is a rare inflammatory condition of unknown origin. It is primarily a diagnosis of exclusion and its overall annual incidence is extremely low with only 0.16 cases per 100,000 people. There is a lack of robust epidemiological data on AOSD with studies only coming from a single center or certain geographic region. In the Philippines, there are three case series to date with a total of 7 patients reported to have AOSD. All reports demonstrate variability of disease presentation. Bimodal age distribution (15 - 25 years old and 36 - 46 years old) was observed and there is no predilection between the sexes [2] [3] [4].

2. Case Presentation

This is a case of a 55-year-old Filipino male who was admitted last May 2020 due to fever and shortness of breath few hours prior to consult. Patient had no other symptoms such as cough, chest pain, changes in urinary or bowel habits, rash, or joint pains. He was rushed to the emergency room for further assessment and treatment.

On review of systems, there was a note of bilateral knee pain with pain scale of 2 - 3/10 and low-grade fever 2 months prior to admission, which lasted for 2 weeks. Interventions were done to alleviate the symptoms by taking ibuprofen

and paracetamol which provided relief of symptoms. There was no associated swelling, warmth, redness, weight loss, changes in gait. The rest of the systems were unremarkable.

Patient has unrecalled congenital heart disease and childhood asthma but with no limitations in activity and with no maintenance medications. He has no history of liver disease, bleeding disorder, malignancies or rheumatologic problems. He has no known allergies. He denied intake of iron supplements, medications, antibiotics, or herbal supplements. He is 40-pack-year smoker and heavy drinker of alcoholic beverages, consuming 500 mL of beer per day for more than 10 years (69.3 grams of alcohol per day).

He has a family history of prostate cancer and lung cancer on the paternal side and osteoarthritis on the maternal side; the rest of family history was unremarkable

Upon admission, patient was febrile with temperature of 38˚C and slightly tachypneic with respiratory rate of 22 breaths per minute. Pertinent findings revealed that he was clinically dry with flat neck veins, with bibasal crackles; with normal rate and regular rhythm, with grade 3 holosystolic murmur heard best on 4th ICS left parasternal area. There was no note of active skin lesions, lymphadenopathy, hepatomegaly. The rest of his physical examination was unremarkable.

Patient underwent diagnostics with complete blood count showing leukocytosis with neutrophilic predominance (Table 1) and chest x-ray showing bibasal pneumonia and minimal pleural effusion. He was managed as a case of community-acquired pneumonia and was a suspect for Coronavirus Disease 2019 (COVID-19) hence inflammatory markers were requested (Table 2). Ferritin was notably elevated at 44,255 ng/mL.

Table 1. Complete blood cell count.

Test	Result	Reference Interval
Hemoglobin	12.2	13.0 - 17.0 g/dL
Hematocrit	36.0	40.0% - 52.0%
Red Blood Cell Count	4.53	4.70 - 6.10 mil/mm^3
White Blood Cell Count	18,540	mm^3
Neutrophils	93	40% - 74%
Lymphocytes	3	19% - 48%
Eosinophils	1	0% - 7%
Monocytes	3	309%
Platelet Count	316,000	150,000 - 400,000 mm^3
MCV	80	82% - 98%
MCH	27	28% - 33%
MCHC	34	32% - 38%
RDW	14.6	11.0% - 14.0%

Table 2. Clinical immunology and serology laboratory results.

Test	Result	Reference Interval
Ferritin	44,255	21.81 - 274.60 ng/mL
D-dimer	2224	0 - 246 ng/mL
Lactate Dehydrogenase (LDH)	362	85 - 227 U/L
Erythrocyte Sedimentation Rate (ESR)	103	0 - 20 mm/hr
C-Reactive Protein (CRP)	48	<6.00 mg/L
Procalcitonin	0.5	<0.5 ng/mL

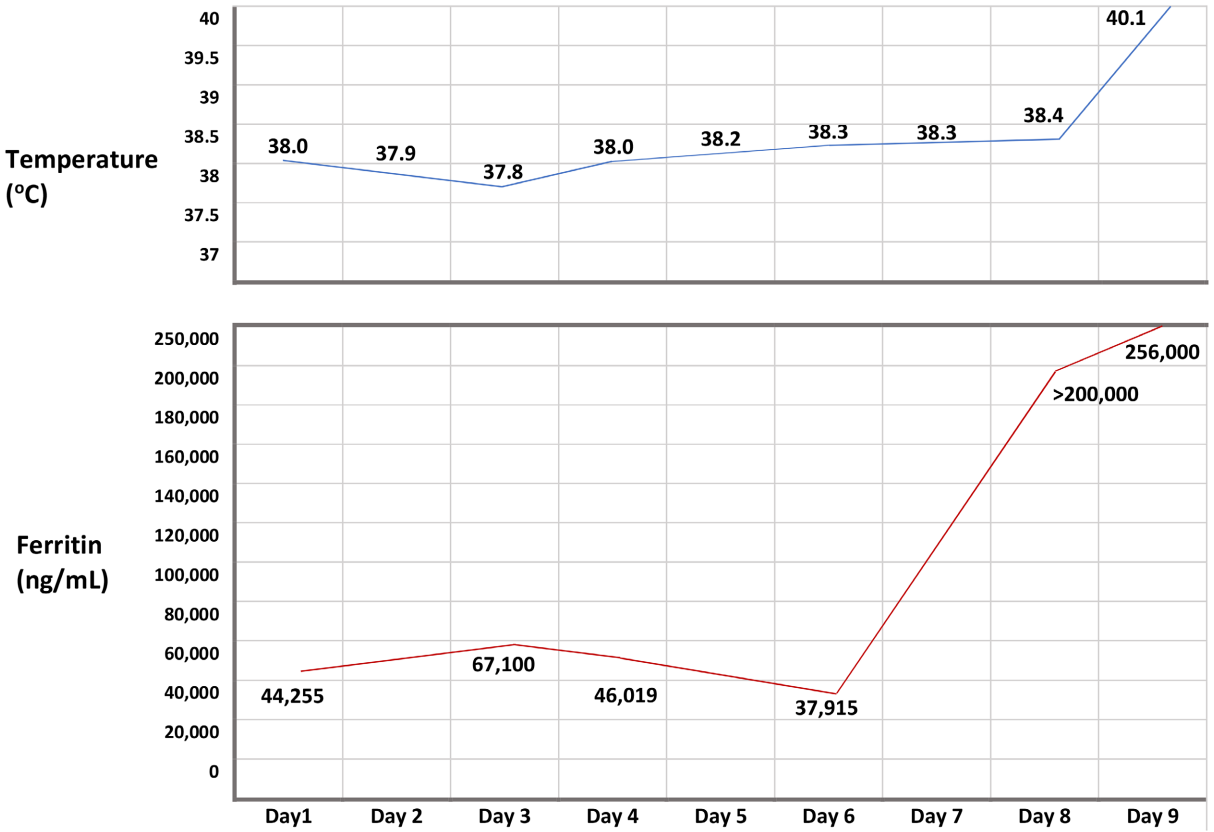

Figure 1. Increasing ferritin trend with associated persistent febrile episodes of the patient.

He was tested negative twice for COVID-19 RT-PCR. He was treated for urinary tract infection and pneumonia but still had intermittent fever and increasing ferritin trend, with highest documented level at 256,000 ng/mL (Figure 1).

He was investigated for other causes of markedly elevated ferritin levels. Transferrin saturation (TSAT) was first determined to eliminate the possibility of iron overload; however, the patient has low TSAT level of 17%. His complete blood count (CBC) only showed leukocytosis with no peripheral blasts. Iron level and liver function tests were normal; HIV immunoassay was negative; ANA was 1:80 speckled with normal complement level; rheumatoid factor was negative. Positron emission tomography (PET) scan revealed presence of lym-

phadenopathies and did not show solid tumors. Metabolic syndrome was also ruled out. After excluding secondary causes of extreme hyperferritinemia, patient was diagnosed as a case of severe AOSD fulfilling Yamaguchi criteria (Table 3).

Elevated ferritin (≥5× upper limits of normal) also supports the presence of the Adult-Onset Still's Disease with an 80% sensitivity and 40.8% specificity. If combined with a decrease in the proportion of glycosylated ferritin < 20%, the specificity will rise to 93% [5]; however, this laboratory examination is not yet locally available.

3. Therapeutic Intervention

Tocilizumab is a recombinant humanized monoclonal antibody directed against interleukin-6 (IL-6) receptors and is indicated for the treatment of rheumatoid arthritis (RA), juvenile idiopathic arthritis, and polyarticular juvenile rheumatoid arthritis. It is an effective drug for the global treatment of AOSD, both for systemic and joint manifestations, as well as for some severe life-threatening manifestations of the disease. The benefit/risk ratio and safety profile of tocilizumab is favorable and similar to that described in RA and other rheumatic diseases [6].

Tocilizumab is administered intravenously at a dose of 8 mg/kg for patients weighing ≥ 30 kg; its total dose should not exceed 800 mg. There is also an option to repeat the dose if clinical improvement does not occur within 24 to 48 hours [7]. The patient was given 2 doses of tocilizumab 12 hours apart due to persistently elevated ferritin levels and no observed improvement in the level of sensorium. He then had lysis of fever and decreasing trend of ferritin levels thereafter, with ferritin level of 34,184 ng/mL three weeks after tocilizumab infusion. He was discharged and improved with no joint pains and fever recurrence. He was given prednisone and methotrexate as home medications.

Table 3. Yamaguchi Criteria (at least 5 features with 2 major).

Major criteria	
Fever ≥ 39˚C for ≥1 week	✔
Arthralgias or arthritis ≥ 2 weeks	✔
Maculopapular nonpruritic skin lesion	☐
Leukocytosis (≥10,000/mL), with N ≥ 80%	✔
Minor criteria	
Sore throat	☐
Lymphadenopathy	✔
Hepatomegaly or splenomegaly	☐
Elevated AST, ALT, or LDH	✔
Negative ANA and RF	☐

4. Follow-Up and Outcomes

The disease pattern of AOSD can be characterized into three different clinical courses: monocyclic or self-limited course, polycyclic or intermittent course, and chronic course. Monocyclic course follows a single episode (2 months to 1 year) followed by sustained remission throughout the whole follow-up period. This is the most common pattern in a study by Zeng showing clinical features and prognosis of 61 patients with AOSD in China [8]. Polycyclic course occurs with recurrent systemic flares between remissions; while chronic course requires at least one episode of persistent symptoms lasting longer than 1 year [9]. The patient has been only newly diagnosed but may be considered to have either monocyclic or polycyclic due to resolution of fever and improvement of symptoms upon discharge.

In a retrospective study by Ruscitti *et al.* on 100 patients with AOSD who fulfilled Yamaguchi criteria, Pouchot systemic score was used to determine risk of Still's related death. The prognostic factors included the following with each manifestation given a score of 1: fever, rash, pleuritis, pneumonia, pericarditis, transaminitis, splenomegaly, lymphadenopathy, leukocytosis > 15,000/mm^3, sore throat, myalgia, and abdominal pain. A score of equal or more than 7 is associated with high risk for still's-related death [10]. The patient, newly diagnosed with Still's disease, with systemic score of 6 has a good survival up to 5 years.

5. Discussion

Hyperferritinemia is sensitive but very nonspecific for iron overload. Reactive causes of raised serum ferritin levels including malignancy, inflammatory disorders, renal failure, liver disease and metabolic syndrome, should always be considered as they are all considerably more common than true iron overload. Markedly elevated ferritin levels, however, suggests possibility of rare conditions such as AOSD.

The primary clinical features of AOSD present in a triad of fever, rash, and arthritis or arthralgia which are seen in 75% - 95% of patients. Fever is usually quotidian, which is daily recurring observed late during the day and generally precedes other symptoms. Rash is classically evanescent, salmon-colored, macular or maculopapular which is usually nonpruritic and occurs with the fever. Arthritis can initially be mild, transient, and oligoarticular and may evolve to severe, symmetric, polyarticular forms. Other common symptoms are myalgia, pharyngitis, lymphadenopathy, and splenomegaly, while less commonly observed symptoms are hepatomegaly, pleurisy, pericarditis, and abdominal pain [11]. Our patient presented with recurring fever and arthritis in both knees which eventually developed during the admission. He was also noted to have lymphadenopathies and pleurisy.

The usual laboratory examination findings of AOSD include elevated inflammatory markers (e.g., ESR, CRP, LDH, d-dimer), white blood cell count of more than 15,000 with neutrophilic predominance greater than 80%, elevated transaminases (in 75% of patients), and ferritin levels higher than five times the upper

limits of normal. Less than 10% of the patients have ANA and RF but generally only in low titer [12]. All of these were also observed in our patient; however, it should be noted that no laboratory examination finding is specific for AOSD.

The pathogenesis of AOSD remains unclear. However, cytokine-mediated inflammation may be responsible for the features of the disease, and a role of interleukin-6 (IL-6) has been suggested. Tocilizumab, a humanized anti IL-6 receptor antibody, has successfully treated patients with AOSD in various observational studies [3] [4] [9].

6. Conclusion

AOSD remains a diagnosis of exclusion due to its nonspecific symptoms and absence of definitive tests, hence this should be considered only after excluding several other differential diagnoses. It is a rare inflammatory disorder but should also still be considered in the presence of fever, arthritis, rash, and extreme hyperferritinemia. NSAIDs, steroids, and immunosuppressives are considered the first line of therapy; however, biological treatments such as tocilizumab are given in severe to refractory cases. The prognosis of AOSD is generally good depending on the presence of unfavorable prognostic favors and timing of initiation of treatment.

Acknowledgements

The authors thank all the medical staff members in St. Luke's Medical Center Quezon City.

Authors' Contributions

DL, KR, and AA were involved in diagnosis and management of the patient. All authors researched and drafted the document. All authors have read and approved the manuscript.

Consent for Publication

Written informed consent for this case report has been obtained from the patient.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Sackett, K., Cunderlik,, M., Sahni, N., *et al.* (2016) Extreme Hyperferritinemia: Causes and Impact on Diagnostic Reasoning. *American Journal of Clinical Pathology*, **145**, 646-650. https://doi.org/10.1093/ajcp/aqw053

[2] Hernandez, A.T.S., Magbitang, A.T.D., Tee, K.D., Uy, P., Amante, E.J., Lorenzo, J.P. and Tee, M.L. (2013) A Rare Cause of Fever, Rashes, and Arthritis: A Report of Three Cases of Adult-Onset Still's Disease in the Philippine General Hospital. Philippine College of Physicians, Article No. 62, 2013-2014.

[3] Durano II, R. and Robles, J. (2021) An Unusual Cause of Fever, Rash, and Joint

Pain: A Case Report of Adult Onset Still's Disease. *Philippine Journal of Internal Medicine*, **58**, 153-157.

[4] Cuenco, F.M.T. and Navarra, S.V. (2021) Tocilizumab for Refractory Adult-Onset Still's Disease: Report of Three Cases. *Philippine Journal of Internal Medicine*, **58**, 4.

[5] Fautrel, B., Le Moël, G., Saint-Marcoux, B., Taupin, P., Vignes, S., Rozenberg, S., Koeger, A.C., Meyer, O., Guillevin, L., Piette, J.C. and Bourgeois, P. (2001) Diagnostic Value of Ferritin and Glycosylated Ferritin in Adult Onset Still's Disease. *The Journal of Rheumatology*, **28**, 322-329.

[6] Lee, D.W., Gardner, R., Porter, D.L., Louis, C.U., Ahmed, N., Jensen, M., Grupp, S. A. and Mackall, C.L. (2014) Current Concepts in the Diagnosis and Management of Cytokine Release Syndrome. *Blood*, **124**, 188-195. https://doi.org/10.1182/blood-2014-05-552729

[7] Castañeda, S., Martínez-Quintanilla, D., Martín-Varillas, J.L., García-Castañeda, N., Atienza-Mateo, B. and González-Gay, M.A. (2019) Tocilizumab for the Treatment of Adult-Onset Still's Disease. *Expert Opinion on Biological Therapy*, **19**, 273-286. https://doi.org/10.1080/14712598.2019.1590334

[8] Zeng, T., Zou, Y.Q., Wu, M.F. and Yang, C.D. (2009) Clinical Features and Prognosis of Adult-Onset Still's Disease: 61 Cases from China. *The Journal of Rheumatology*, **36**, 1026-1031. https://doi.org/10.3899/jrheum.080365

[9] Wang, M.Y., Jia, J.C., Yang, C.D. and Hu, Q.Y. (2019) Pathogenesis, Disease Course, and Prognosis of Adult-Onset Still's Disease: An Update and Review. *Chinese Medical Journal*, **132**, 2856-2864. https://doi.org/10.1097/CM9.0000000000000538

[10] Ruscitti, P., Cipriani, P., Masedu, F., *et al.* (2016) Adult-Onset Still's Disease: Evaluation of Prognostic Tools and Validation of the Systemic Score by Analysis of 100 Cases from Three Centers. *BMC Medicine*, **14**, Article No. 194. https://doi.org/10.1186/s12916-016-0738-8

[11] Bhargava, J. and Panginikkod, S. (2022) Still Disease. [Updated 2020 Jul 10]. In: StatPearls. StatPearls Publishing Treasure Island (FL), 2021 Jan. https://www.ncbi.nlm.nih.gov/books/NBK538345/

[12] Mehta, B.Y., Ibrahim, S., Briggs, W. and Efthimiou, P. (2019) Racial/Ethnic Variations in Morbidity and Mortality in Adult Onset Still's Disease: An Analysis of National Dataset. *Seminars in Arthritis and Rheumatism*, **49**, 469-473. https://doi.org/10.1016/j.semarthrit.2019.04.004

Abbreviations

AOSD	adult-onset Still's disease
COVID-19	Coronavirus disease 2019
RT-PCR	Reverse Transcription Polymerase Chain Reaction
HIV	Human Immunodeficiency Virus
ANA	Antinuclear Antibody
PET	Positron Emission Tomography
LDH	Lactate Dehydrogenase
ESR	Erythrocyte Sedimentation Rate
CRP	C-Reactive Protein
TSAT	Transferrin saturation
IL-6	Interleukin-6
RA	Rheumatoid Arthritis
HLH	Hemophagocytic Lymphohistiocytosis