Adult Onset Still’s Disease Presenting as Fever of Unknown Origin: A Case Report

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ABSTRACT

26 years’ female patient attended triage with complaints of fever of almost 1-month duration. She was diagnosed as a case of Brucellosis outside. However, her fever persisted and she was finally diagnosed to have new onset adult-onset still’s disease (AOSD) with active macrophage activation syndrome (MAS) and multi organ failure. She met the diagnostic criteria for AOSD. She had high spike fevers, hepatosplenomegaly, Lymphadenopathy, coagulopathy, anaemia with thrombocytopenia, hemophagocytosis, markedly elevated serum ferritin, low to absent natural killer (NK) cells, and remained unresponsive to steroids, intravenous immunoglobulin (IVIG) and hemophagocytic lymphohistiocytosis (HLH) protocol treatment. Interleukin-1 (IL1) inhibitors were not available. Interleukin-6 (IL6) blockers were not considered due to greater concerns about exacerbating bacterial infections with IL-6 blockade than with IL-1 blockade and much longer half-lives of the IL-6 inhibitors. We were also reluctant in using tocilizumab or sarilumab in new-onset disease where diagnostic uncertainty remains, as is often the case. She succumbed to her disease which had rapid fulminating course with multi organ failure. Her diagnostic and therapeutic challenges are discussed.

Keywords: Adult onset Still’s disease (AOSD), hemophagocytic lymphohistiocytosis (HLH), macrophage activation syndrome (MAS), reactive hemophagocytic syndrome (RHS), secondary hemophagocytic lymphohistiocytosis (sHLH).

I. INTRODUCTION

Adult-onset Still's disease is a systemic inflammatory disorder of an unknown aetiology and pathogenesis and is one of the often missed cause of FUO (fever of unknown origin). It is characterized by quotidian (daily) fevers, arthritis, and salmon coloured skin rash. It is very uncommon with an estimated annual incidence to be 0.16 cases per 100,000 people and an equal distribution between the sexes [1]. The diagnosis of AOSD is, in part, a diagnosis of exclusion. There is no single test that can diagnose AOSD. Many sets of diagnostic criteria have been published to assist in the diagnosis including [2]-[4]. Yamaguchi criteria is the most sensitive of all and Cush clinical criteria requires an observation period of 3-6 months. The clinical course of AOSD is characterized by three main patterns: Monophasic, intermittent and chronic disease [4]. Systemic features predominate in monophasic pattern whereas articular symptoms predominate in chronic pattern. The course and treatment of the disease are determined based on whether the patient has a predominant systemic pattern or a joint pattern.

AOSD can be associated with the MAS, which is also referred to as sHLH or RHS, but is usually termed MAS (or RHS) when it occurs in AOSD. MAS is a rare, acute, systemic life-threatening hyper inflammatory syndrome with high mortality resulting from multi-organ failure [5]. It is attributed mainly to two factors: one, to excessive activation of the immune system from increased production of cytokines and second, to enhanced phagocytosis by macrophages in the setting of infection, malignancy or autoimmune disease. MAS can be primary (Genetic/familial) or secondary. Among rheumatic autoimmune diseases, secondary MAS is most commonly associated with systemic juvenile idiopathic arthritis and systemic lupus erythematosus [6]. Adult-onset Still’s disease (AOSD) is less commonly associated with MAS and there are no classification criteria of AOSD-associated MAS. The prevalence of MAS in AOSD is 7.7%–16% [7], [8] with possible triggers being the primary disease activity (75%), infection (18.8%), and drugs such as antibiotics (6.3%) [9].

There are no established guidelines for the treatment of AOSD associated MAS, and several therapies have been tried, for example, biologics targeting tumour necrosis factor-α (TNF-α), [etanercept (ETN), infliximab (IFX), and adalimumab], IL-1[anakinra (ANK) and canakinumab], and IL-6 [tocilizumab (TCZ)] [10]–[12]. Reference [13] reported improved clinical outcomes by early addition of triple regimen including ANK, systemic glucocorticoids, and
cyclosporine. On the contrary there are reports describing aggravation of MAS during biologic treatments for refractory AOSD [14]-[18]. This suggests that the efficacy, safety and outcomes of these therapies used for MAS in AOSD still remain controversial.

We report the case of a patient with new onset AOSD-associated MAS with multiple organ failure who had undergone nonselective immunosuppressive therapy with intravenous methylprednisolone (mPSL) pulse therapy, intravenous immunoglobulin and later etoposide and dexamethasone as per sHLH protocol but succumbed to her disease. AOSD associated MAS management guidelines, especially for new onset AOSD needs to be worked upon.

II. CASE REPORT

A 26-year-old girl attended triage at fortis escorts hospital, Jaipur, on 06/11/21 with complaints of fever since 03/10/21. It was associated with chills, was intermittent and spiky with maximum temperature up to 104°F. She also had sore throat, difficulty in swallowing (odynophagia), diffuse myalgias and multiple joint pains involving bilateral knees, ankles, hands, and wrists since beginning of her illness, vomiting and loose stools for 2 days and altered sensorium with irrelevant talks and wrists since beginning of her illness. She was moved in on stretcher. On systemic examination, she had multiple cervical and axillary lymphadenopathy, tender proximal interphalangeal, wrists, elbows and knee joints bilaterally, and mild non-tender hepatosplenomegaly. The rest of the systemic examination clinically was essentially normal. In addition, the attendants reported that she initially developed a transient erythematous rash on her body with high fever.

Her outside reports were negative for Brucella PCR; Mycobacterium Tuberculosis PCR on lymph node tissue; Leptospirosis, Dengue, Chikungunya and Scrub Typhus IgM and IgG antibodies. Her blood cultures were also sterile on multiple occasions. She was started on Vasopressors (Noradrenaline infusion) and other supportive treatment and further evaluated. Her liver and kidney function were deranged along with leukocytosis, neutrophilia, anaemia and thrombocytopenia. Her Inflammatory markers were raised (Table I).

### TABLE I: HEMATOLOGY AND BIOCHEMICAL PROFILE

| Parameter                              | Normal Values | 6/11 | 7/11 | 8/11 | 9/11 | 10/11 | 11/11 |
|----------------------------------------|---------------|------|------|------|------|-------|-------|
| ESR                                    | <20 mm at 1st hour | 75   | 25   |      |      |       |       |
| CRP                                    | 0-5 mg/L      | 155.7| 42.8 |      |      |       |       |
| D Dimer                                 | < 255 mg/ml DDU | 8500 | 5090 |      |      |       |       |
| IL6                                    | >7 pg/ml      | 24.53|      |      |      |       |       |
| Ferritin                               | 13-150 mg/ml  | >40,000| >64000|      |      |       |       |
| BUN                                    | 6-20 mg/dl    | 31   |      |      |      |       |       |
| Creatinine                             | 0.5-6.9 mg/dl | 2.36 | 1.33 | 0.99 | 0.81 | 1.36  |       |
| Hemoglobin                             | 12-15 g/dl    | 9.0  | 8.1  | 6.2  | 11.6 |       |       |
| Hematocrit                             | 36-46%        | 27.4 | 24.0 | 18.6 | 35.7 |       |       |
| Total Leucocyte Count                  | 4-10 x 10⁹/μL | 13.1 | 19.3 |      |      |       |       |
| DLC                                    | P83L15B0      | 8.0  | 14.1 | 14.2 | 11.5 | 13.1  |       |
| Platelet count                         | 150-410 x 10⁹/μL | 150 | 90  | 80  | 32  | 20  | 100  |
| Creatine Kinase                        | 26-192 U/L    | 10820| 15216| 13561| 5471 |       |       |
| Aspartate Amino Transferase            | < 32 U/L      | 615  | 688  | 279  |      |       |       |
| Alanine Transaminase                   | < 32 U/L      | 210  | 288  | 211  |      |       |       |
| Serum Bilirubin (Total)                | Upto 1.2 mg/dl| 1.38/1.31|      |      |      |       |       |
| Serum Alkaline Phosphatase             | 40-129 U/L    | 203  |      |      |      |       |       |
| Serum Total Proteins                   | 6.4-8.3 g/dl  | 5.3  |      |      |      |       |       |
| Albumin                                | 3.97-4.94 g/dl| 2.6  |      |      |      |       |       |
| Lactate Dehydrogenase                  | 135-214 U/L   | 2198 |      |      |      |       |       |
| Serum Triglyceride                     | < 150 mg/dl   | 686  |      |      |      |       |       |
| aPTT                                    | Seconds       | 42/28.9|      |      |      |       |       |
| control                                | Seconds       | 31.5/28.9|      |      |      |       |       |
| International normalized Ratio (INR)   | Ratio         | 15.2 | 24.2 | 27.3 | 18.0 |       |       |
| Procalcitonin                          | < 0.046 ng/ml | 30.32|      |      |      |       |       |
| NT-ProBNP                              | < 125 mg/ml   | 17346|      |      |      |       |       |
| CK MB                                  | 0.3-4.88 mg/ml| 6   |      |      |      |       |       |
| Creatine Kinase                        | 26-192 U/L    | 10820| 15216| 13561| 5471 |       |       |
| Troponin T                             | < 14 mg/ml    | 63  |      |      |      |       |       |
| NK cell evaluation                     | % CD 16,56    | 5.47 | 60%  | 2.0  |      |       |       |
| Absolute CD16+56                       | 116-612/μL    | 34  |      |      |      |       |       |

ESR: Erythrocyte sedimentation rate; CRP: C Reactive Protein; DDU: D Dimer unit; IL6: Interleukin-6; BUN: Blood Urea Nitrogen; DLC: Differential Leucocyte count; P: Polymorphs; L: Lymphocyte; S: Stab cells; aPTT: activated partial Thromboplastin time; NT-ProBNP: N terminal pro-brain natriuretic peptide; CK-MB: creatine kinase-myoglobin binding; NK: Natural Killer; CD: Neural cell adhesion molecule.
Her X-ray chest show bilateral pleural effusion (Fig. 1). Her other laboratory tests such as Mantoux test, Widal test, serology tests human immunodeficiency virus 1 and 2, hepatitis B and hepatitis C, interferon-gamma release assay for Mycobacterium tuberculosis, malaria parasite, antinuclear antibody (ANA), antineutrophil cytoplasmic antibody (ANCA), ds DNA antibody, rheumatoid factor, anti-cyclic citrullinated peptide, respectively were negative. Her blood, urine, and endotracheal secretions for culture were also negative. CSF (cerebro spinal fluid) examination was not done in view of coagulopathy and low platelet counts.

With above history and investigations, a possibility of autoimmune disease - AOSD (Adult onset still’s disease) was made. Bone marrow aspiration and biopsy, serum ferritin, Natural killer cell panel, Serum triglycerides were done. Upper Gastro Intestinal Endoscopy was done which showed severe erosive esophagitis, Antral gastritis and Duodenitis. However, in view of new onset AOSD and possibility of active MAS (Macrophage activation syndrome), she was given 500 mg of methyl prednisolone on 08/11/21. She was shifted under Department of Internal Medicine on 09/11/21. Bone marrow biopsy reported on 10/11/21 show suppressed erythropoiesis, normal myeloid and lymphoid series, megakaryocytes normal with few hypo lobulated forms, increase in macrophages with few showing hemophagocytosis (Fig. 2).

Her 2D echocardiography show global left ventricular (LV) hypokinesia with severe systolic dysfunction and LV ejection fraction of 30%. Minimal pericardial effusion was also seen.

Considering the patient’s history of having received repeated courses of antibiotics for almost a month, intermittent and persistent fever, myalgias and arthralgia, raised inflammatory markers with leukocytosis, evidence of hemophagocytosis and high serum ferritin, we suspected AOSD with active MAS. She was reviewed on December 9th 2021, and in view of persistent intermittent fever, arthralgia’s, mild hepatosplenomegaly, raised inflammatory markers, leukocytosis with neutrophilia and no evidence of infection, malignancy, rheumatic disease or vasculitis, AOSD was diagnosed. She fulfilled Yamaguchi and Fautrel criteria for AOSD. Further, with presence of fever, duopenia (thrombocytopenia and anemia), hepatosplenomegaly, hyperferritenemia with increasing trend, evidence of hemophagocytosis in bone marrow and absent to low NK cells she was diagnosed to have associated active MAS (RHS). Her H-SCORE (with serum fibrinogen not done) for RHS was 231 points with 98-99% probability.

She was managed with Pantoprazole infusion, antacids, Intravenous antibiotics, Injection Fluconazole, vasopressors, Oxygen inhalation 3-5 l with mask and supportive management. She was given Injection Methyl Prednisolone pulse treatment (500 mg for 3 days) and IVIG (intravenous immunoglobulin 1 gm/kg for 2 days) from 08/11/21. IL1 inhibitor Anakinra and Canakinumab were considered but were not available. However, she showed rapid deterioration clinically and in platelet counts, developed coagulopathy and rhabdomyolysis with marked increase in creatinine kinase levels. On 10/1/21 her haemoglobin dropped to 6.2 gm/dl and platelets decreased to 20x10³/cmm. She received 3 Units of packed red blood cells, 2 units of single donor platelets, 5 units of random donor platelets and 7 units of fresh frozen plasma during her hospital stay.

On 11.11.21 early morning, she developed type 1 respiratory failure and was taken on NIV (non-invasive ventilation) and later intubated and taken on mechanical ventilation. Myocarditis panel examination was done to rule out any infective etiology and it was reported negative. Injection Etoposide and Dexamethasone were started as per HLH protocol on 11/11/21. Despite all efforts she succumbed to her illness on 12/11/21.

III. DISCUSSION

We have presented a case of young patient who had fever for almost a month and was being managed as a case of Brucellosis on the basis of equivocal Brucella IgM antibody report. When she presented to us, she had persistent high spiky fever, arthralgia’s, myalgias, sore throat with odynophagia, neurological symptoms, shock, and hepatosplenomegaly. Her laboratory parameters show raised inflammatory markers, leucocytosis with neutrophilia, duopenia, markedly raised serum ferritin, left ventricular systolic dysfunction, serositis, rhabdomyolysis, and altered...
liver and kidney functions. She fulfilled 3 major, 5 minor and all exclusion criteria of Yamaguchi [2] and 4 major, 1 minor criteria of Fautrel [4] for the diagnosis of AOSD. We have not taken into account the history of rash as it could not be appreciated by us and glycosylated ferritin was not done. She had rapid deterioration in her clinical status and was also diagnosed to have sHLH as per HLH-2004 diagnostic criteria’s [19]. She fulfilled 7 of the 8 criteria’s (Fever, splenomegaly, duopenia, hypertriglyceridemia, Hemophagocytosis in bone marrow, Low NK cell activity and elevated ferritin levels). Soluble CD25 and serum Fibrinogen could not be done. Macrophage activation syndrome (MAS) refers to hemophagocytic syndromes complicating connective tissue diseases and as per the classification criteria for MAS [20] she fulfilled all the criteria (fever, AOSD, ferritin > 684 ng/ml, platelets < 181x109/L, AST > 48 U/L, and Triglyceride > 156 mg/dl) except Serum fibrinogen which was not done due to technical issues. She was thus confirmed as a case of AOSD with active MAS.

AOSD is not an uncommon cause of FUO and is often missed or not thought of in the differential diagnosis of FUO. The authors have earlier published few case reports on such rare cases and advocated early and timely diagnosis to prevent morbidity and mortality [21]-[24]. Similarly, HLH (MAS) is also a rare and under-diagnosed clinical syndrome and can prove rapidly fatal if not diagnosed and managed timely [25].

There is no established standard therapy or validated treatment protocols for AOSD associated MAS. Treatment regimens are based on retrospective case series, case reports and extrapolated from treatment guidelines and protocols in other disease contexts including familial HLH (fHLH) and systemic juvenile idiopathic arthritis (sJIA) associated MAS. The rarity of the condition, heterogenous triggering factors, underlying variable conditions, lack of consensus in nomenclature and classification, all adds to form obstacle to prospective research [26]. Therapeutic decisions in newly diagnosed adult-onset Still’s disease (AOSD) are influenced by three things: first, whether MAS, a “cytokine storm” that can be life threatening, is present or suspected; second, by the severity of disease; and third whether systemic or arthritic features are predominant. The patient discussed had moderate to severe disease, MAS and systemic symptoms i.e., inflammatory stage of the disease. In MAS/sHLH, remission is achieved by immunosuppression-based protocols of which corticosteroids is the cornerstone of treatment. Early use of high-dose steroids may be successful alone, but over half of reported adult cases are steroid resistant [27]. TNF inhibitors appears to be beneficial in AOSD, but this is in the management of the chronic inflammatory arthritis that develops in up to one-third of patients. During the inflammatory phase of the disease with features like fever, rash, serositis, deranged LFTs, hepatomegaly and others will be controlled by either high dose corticosteroid (1-2 mg/kg/day) or anakinra or tocilizumab. However, there are no head-to-head trials to suggest which is the better agent in new onset, active inflammatory Still’s. In the present case high dose methyl prednisolone was initiated on day 3 of admission along with IVIG.

The efficacy and safety of biologics used in this condition still remain controversial. Further, early and aggressive immunosuppressive treatment is advocated in MAS/sHLH to treat Hypercytokinemia in addition to treatment of any trigger (e.g. infection or inflammation) to prevent multiorgan failure and death. IL1 inhibitor Anakinra and Canakinumab were considered but were not available. She succumbed to severe inflammatory form of still’s disease with active MAS.

IV. CONCLUSION

To conclude, in AOSD, early diagnosis is must to prevent morbidity and mortality and it should be considered in all cases of FUO at earliest. Serum Ferritin could be a good screening test to rule in or rule out AOSD. Rarely, AOSD can present with active MAS as in this case.

CONFLICT OF INTEREST

Authors declare that they do not have any conflict of interest.

REFERENCES

[1] Magadur-Joly G, Billaud E, Barrier JH, Pemec YL, Mason C, Renou P, et al. Epidemiology of adult Still's disease: estimate of the incidence by a retrospective study in west France. Am Rheum Dis. 1995; 54(7): 587.
[2] Yamaguchi M, Ohta A, Tsunematsu T, Kasukawa R, Mizushima Y, Kashiwagi H, et al. Preliminary criteria for classification of adult Still's disease. J Rheumatol. 1992; 19(3): 424-30.
[3] Cush JJ, Medsger TA, Jr, Christy WC, Herbert DC, Cooperstein LA. Adult-onset Still's disease. Clinical course and outcome. Arthritis Rheum. 1987; 30(2): 186–194.
[4] Fautrel B, Zing E, Golmard JL, Le Moel G, Bisseray A, Rioux C, et al. Proposal for a new set of classification criteria for adult-onset still disease. Medicine (Baltimore). 2002; 9(1): 194–200.
[5] Janka GE, Lehmburg K. Hemophagocytic lymphohistiocytosis: pathogenesis and treatment. Hematologia 2013; 2013: 605-11.
[6] Crayne CB, Albietumi S, Nichols KE, Cron RQ. The Immunology of Macrophage Activation Syndrome: Front Immunal. 2019; 10: 119.
[7] Gerfaud-Valentin M, Maucort-Boulch D, Hot A, Iwaz J, Ninet J, Durieu I, et al. Adult-onset Still's disease: manifestations, treatment, outcome, and prognostic factors in 57 patients. Medicine (Baltimore). 2014; 93(2): 91-99.
[8] Fukaya S, Yasuda S, Hashimoto T, Oku K, Kataoka H, Horita T, et al. Clinical features of haemophagocytic syndrome in patients with systemic autoimmune diseases: analysis of 30 cases. Rheumatology. 2008; 47(11): 1686-1691.
[9] Chang-Bum B, Ju-Yang J, Hyoun-Ah K, Chang-Hee S. Reactive Hemophagocytic Syndrome in Adult-Onset Still Disease, Medicine. 2015; 94(4): e451.
[10] Maria AT, Le Quellec A, Jorgensen C, Toutou I, Riviere S, Guiplain P. Adult onset Still's disease (AOSD) in the era of biologic therapies: dichotomous view for cytokine and clinical expressions. Autoimmun Rev. 2014; 13(11): 1149-59.
[11] Al-Homood IA. Biologic treatments for adult-onset Still’s disease, Rheumatology. 2014; 53(1): 32-38.
[12] Jamilloux Y, Gerfaud-Valentin M, Henry T, Sève P. Treatment of adult-onset Still's disease: a review. Ther Clin Risk Manag. 2014; 11: 33-43.
[13] Lenert A, Yao Q. Macrophage activation syndrome complicating adult onset Still's disease: A single center case series and comparison with literature. Semin Arthritis Rheum. 2016; 45(6): 711-6.
[14] Schulte GS, Grom AA. Pathogenesis of macrophage activation syndrome and potential for cytokine- directed therapies. Annu Rev Med. 2015; 66: 145-59.
[15] Gianella S, Schaer DJ, Schwarz U, Kurrer M, Heppner FL, Fehr J, et al. Retinal microangiopathy and rapidly fatal cerebral edema in a patient with adult-onset Still's disease and concurrent macrophage activation syndrome. Am J Hematol. 2008; 83(5): 424-7.
[16] Kaneko K, Kaburaki M, Muraoka S, Tanaka N, Yamamoto T, Kusunoki Y, et al. Exacerbation of adult-onset Still's disease, possibly related to elevation of serum tumor necrosis factor-alpha after etanercept administration. *Int J Rheum Dis*. 2010; 13(4): e67-9.

[17] Kobayashi M, Takahashi Y, Yamashita H, Kaneko H, Mimori A. Benefit and a possible risk of tocilizumab therapy for adult-onset Still's disease accompanied by macropage-activation syndrome. *Mod Rheumatol*. 2011; 21(1): 92-6.

[18] Banse C, Vittecoq O, Benhamou Y, Gauthier-Prieur M, Lequerré T, Lévesque H. Reactive macrophage activation syndrome possibly triggered by canakinumab in a patient with adult-onset Still's disease. *Joint Bone Spine*. 2013; 80(6): 653-5.

[19] Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*. 2007; 48(2): 124-31

[20] Opoka-Winiarska V, Grywalska E, Roliński J. Could hemophagocytic lymphohistiocytosis be the core issue of severe COVID-19 cases? *BMC Med*. 2020; 18(1): 214.

[21] Agarwal A, Agarwal M, Khandelwal V, Mathur P. Adult-onset Still's disease masquerading as multiple organ failure: Neither benign nor so rare. *Journal of clinical rheumatology*. 2018; 24(6): 342-346.

[22] Agarwal A, Agarwal A. Adult onset stills disease: Advocating for new markers to overcome the diagnostic challenge. *Asian Journal of Medicine and Health*. 2018; 10(4): 1-8.

[23] Agarwal A, Agarwal A, Khan A. A case of Adult Onset Stills Disease: Not so Uncommon Cause of Fever of Unknown Origin. *Asian Journal of Medicine and Health*. 2018; 11(3): 1-7

[24] Agarwal A, Gondaliya D N. Adult-onset Still's disease: A case report *J Acute Dis*. 2020; 9(4): 179-182.

[25] Agarwal A, Agarwal A. Infection Associated Secondary Hemophagocytic Lymphohistiocytosis in Sepsis Syndromes - A Tip of an Iceberg. *J Assoc Physicians India*. 2016; 64(10): 44-50.

[26] Carter SJ, Tattersall RS, Ramanan AV. Macrophage activation syndrome in adults: recent advances in pathophysiology, diagnosis and treatment. *Rheumatology* (Oxford). 2019; 59(1): 5-17.

[27] Fukaya S, Yasuda S, Hashimoto T, Oku K, Kataoka H, Horita T, et al. Clinical features of haemophagocytic syndrome in patients with systemic autoimmune diseases: analysis of 30 cases. *Rheumatology* (Oxford). 2008; 47(11): 1686-91.

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