Case Report

Iranian Journal of Immunology

https://iji.sums.ac.ir

Variations in Macrophage Activation Syndrome-associated Cardiac Diseases: A Report on Two Cases

Na Lin[1]*, Li Ping Xu[1], Qiao Ding Dai[1]

[1]Rheumatology and Immunology department, The First Affiliated Hospital of Zhejiang Chinese Medical University (Zhejiang Provincial Hospital of Traditional Chinese Medicine), Hangzhou, Zhejiang, China

ABSTRACT

Macrophage activation syndrome (MAS), a secondary hemophagocytic lymphohistiocytosis characterized by an excessive systemic inflammatory response, is a life-threatening and rare disease. Cardiovascular damage is a common and severe complication of the disease, however, it is easily ignored and not well studied. Herein, we report two cases of patients with MAS-associated heart damage and review the clinical characteristics, mechanism, and treatment. Case 1 along with systemic lupus erythematosus and Kikuchi necrotizing lymphadenitis occurred in fatal acute heart failure, and case 2 complicated adult-onset Still's Disease began with atrial fibrillation and had some improvement with the treatment of high dose corticosteroids. MAS-associated heart damage is a critical issue in clinical settings, and the etiology and mechanisms of MAS-associated cardiovascular diseases are likely multifactorial. The manifestations were various and high levels of the cytokines and cardiac damage may contribute to poor prognosis. Therefore, early intensive immunosuppressive therapy probably improves the treatment outcome.

Keywords: Cardiovascular diseases, Case report, Hemophagocytic lymphohistiocytosis, Macrophage activation syndrome

*Corresponding author:
Na Lin,
Rheumatology and Immunology department, The First Affiliated Hospital of Zhejiang Chinese Medical University (Zhejiang Provincial Hospital of Traditional Chinese Medicine), No.54 in Youdian Road, Hangzhou, Zhejiang, 310000, China
Email: linna_0314@163.com

Cite this article as:
Lin N, Xu LP, Dai QD. Variations in Macrophage Activation Syndrome-associated Cardiac Diseases: A Report on Two Cases. *Iran J Immunol.* 2023; 20(1): 135-143,
doi: 10.22034/iji.2023.93355.2218.

Received: 2021-10-21
Accepted: 2022-02-02

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a syndrome of severe excessive inflammation induced by aberrantly activated cytotoxic T cells and macrophages with a variety of etiologies. It is normally triggered by malignancies or infections and induced by an autoimmune disorder called macrophage activation syndrome (MAS). MAS is a well-recognized complication of adult-onset Still's Disease (AOSD), systemic juvenile idiopathic arthritis (sJIA), and systemic lupus erythematosus (SLE) and occurs in 4-10% of patients. Patients often suffer from sustained fever, hyperferritinemia, pancytopenia, liver dysfunction, fibrinolytic coagulopathy, and a sepsis-like syndrome that may rapidly progress to terminal multiple failures [1-4]. Macrophage activation syndrome associated with heart damage is critical in clinical environments, which can present many

symptoms, and its severity can change rapidly and unpredictably. Here, we compare and contrast two cases of patients with MAS-associated heart damage, one patient had a rapid fatal acute heart failure, and the other suffered from a combined atrial fibrillation at the onset of MAS.

CASE 1

A 38-year-old woman was admitted for fever and tender cervical lymph nodes for 3 weeks, accompanied by headache, fatigue, alopecia, finger joints pain, and poor appetite. 3 days after the onset of symptoms she was diagnosed with leukopenia (leukocyte: 2.5×10^9/L) and empirical Chinese herbs extraction "berbamine" (a G-CSF stimulant) was prescribed in the local hospital. There was no history of genitourinary, cardiopulmonary, musculoskeletal, or dermatologic complaints. The examination was notable for bilateral firm matted tender cervical, groin, and armpit lymphadenopathy. Initial laboratory findings showed leukocyte of 1.6×10^9/L, platelets of 74×10^9/L, elevated ferritin 6336 ng/ml, and normal transaminase, triglycerides, and fibrinogen. Serum ANA 1:320 was positive. Complement C3 was lower than 0.5g/L. Serum interleukin (IL)-10, IL-6, and interferon (IFN)-γ increased to 40.25pg/mL, 62.82pg/mL, and 211.82pg/mL respectively. The correlation tests of infectious diseases were negative. Several days later laboratory findings showed transaminase elevated, ferritin increased steadily, fibrinogen decreased to 1.30g/L, and triglyceride increased to 4.20mmol/L (Table 1). Bone marrow morphology test found hemophagocytosis (Figure 1H) and hemophagocytic lymphohistiocytosis was diagnosed according to 2004-HLH diagnostic criteria.

Left cervical lymph node biopsy performed for imaging examination (ultrasonography, contrast enhanced CT, and PET/CT) showed systemic lymph enlargement (bilateral isthmic, submental, submaxillary, inguinal, parapharyngeal space, deep parotid, posterior triangular, occipital deltoid, clavicular region, para-aortic, mesenteric) (Figures 1A-G).

Table 1. Comparison of the biochemical and haematological parameters of both cases

	Case 1	Case 2	Normal
Leukocyte count(10^9/L)	2.7	2.9	3.5-9.5
Hemoglobin(g/L)	86	84	115-150
Platelet count(10^9/L)	34	53	125-350
CRP(mg/L)	42	28	1-8
AST(U/L)	328	898	10-42
ALT(U/L)	680	724	5-35
LDH(U/L)	2990	1859	109-245
Ferritin(ng/ml)	25461	30233	14-233.1
TG(mmol/L)	4.2	2.42	0.5-1.8
Fibrinogen(g/L)	1.3	0.83	2.0-4.0
CK-MB(U/L)	73	64.2	0-25
TNI(ug/L)	0.005	0.103	0-0.026
ANA	1:320	(-)	<1:80
IL-2(pg/ml)	0.83	0.20	0-4.10
IL-6(pg/ml)	62.82	2.36	0-2.90
IL-10(pg/ml)	40.25	13.41	0-5.00
IFN-γ(pg/ml)	211.82	8.83	0-18.00
TNF-α(pg/ml)	1.08	0.73	0-23.00

CRP: C-reactive protein; AST: aspartate aminotransferase; ALT: Alanine aminotransferase; LDH: Lactate dehydrogenase; TG: Triglyceride; CK: TNI; ANA: Anti-nuclear antibody; IL-2: Interleukin 2; IL-6: Interleukin 6; IL-10: Interleukin 10; IFN-γ: Interferon γ; TNF-α: Tumor necrosis factor-α

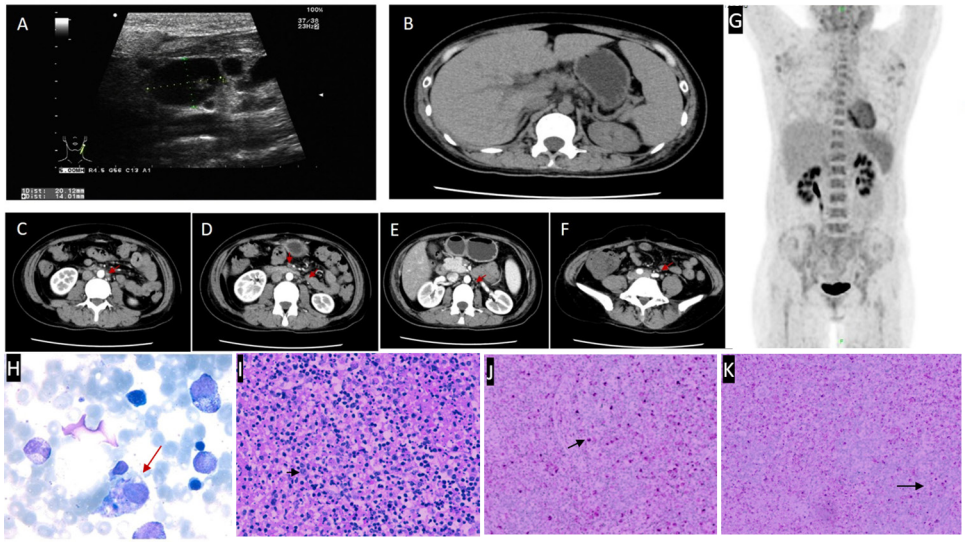


Figure 1. Imageological and pathological examinations of case 1. Picture A showed that ultrasonography found a lymph node measuring ultrasonography after the left ear, which demonstrated clear border, cortical layer thicker and some medulla disappeared. Picture B showed splenomegaly. Pictures C to F showed enlarged para-aortic, bilateral iliac artery, mesenteric and inguinal lymph nodes. Picture G showed systemic lymph enlargement of PET/CT. Picture H showed bone marrow morphology test found evidence of hemophagocytosis. Picture I showed Histopathological left cervical LN examinations exhibited structural destruction, geostrophic, multifocal, or lamellar necrosis, nuclear debris, epithelioid histiocytes. Pictures J to K showed the LN immunohistochemical lymphohistiocytic cells expressing CD68 and MPO.

HLH-94 treatment dexamethasone 15 mg/d was combined with etoposide 200 mg for once and immunoglobulin 0.4 g/kg/d was first used for malignant lymphoma for suspicion of a possible primary disease. But the histopathological and immunohistochemical LN examinations exhibited structural destruction, geostrophic, multifocal, lamellar necrosis, nuclear debris, epithelioid histiocytes, and lymphohistiocytic cells expressing CD68 and MPO (Figure 1I-K). There was no evidence of leukemia or lymphoma according to cytogenetic analysis and flow cytometry of the lymph node. For these histopathological findings, a diagnosis was done of Kikuchi Necrotizing Lymphadenitis. She suffered from sudden chest distress, a drop in blood pressure, increased heart rate, and orthopnea, laboratory data found BNP 925.4ng/L, and ultrasonography showed left ventricular ejection fraction was only 35%(Teich) on the 18th hospital day. Although we rescued her on time, yet, she deteriorated and died after 2 days.

CASE 2

A 70-year-old woman had a 2 years history of adult-onset Still's Disease and was without medication for one year. When she was admitted to our hospital, she suffered from fever, arthralgia, rash, and sore throat for half a month, and the laboratory data showed elevated leukocyte and ferritin, so the diagnosis was a relapse of AOSD. She denied any cardiopulmonary diseases. These symptoms improved when methylprednisolone 0.5 mg/kg/d was prescribed, and then she was discharged.

14 days later, she was readmitted to our hospital with obvious fatigue and anorexia. On admission, she had a fever of 38-40 °C and irregular heart rhythm and sounds, lung, and abdomen examinations were unremarkable, and musculoskeletal examination showed no swelling or point tenderness of any joint. Laboratory findings showed elevated transaminase (ALT 724U/L, AST 898U/L), hyperferritinemia (30233ng/ml),

hypersensitive C-reactive protein 28mg/L normal blood counts, triglycerides, and fibrinogen. Serum IL-10, IL-6, and IFN-γ were 13.41 pg/mL, 2.36 pg/mL, and 8.83 pg/mL respectively. The level of serum troponin I (TNI) and brain natriuretic peptide (BNP) slightly elevated, 0.103ug/L and 191.4ng/L respectively (Table 1). Electrocardiogram (ECG) suggested atrial fibrillation (Figure 2A). The abdominal CT showed low-density foci in the spleen and calculus of the kidney, except that, everything was normal. The correlation tests of infectious diseases were negative. Several days later laboratory findings showed three-line cytopenia (WBC 2.9×10^9/L, HGB 84g/L, PLT 53×10^9/L), ferritin increased steadily, fibrinogen decreased to 0.83g/L, triglyceride increased to 2.42mM (Table 1), the HLH-probability calculator(Hscore) was 204, and then MAS was diagnosed.

Dexamethasone 15mg/d was used initially combined with immunoglobulin 0.4g/kg/d×5d, meanwhile, low molecular weight heparin calcium was prescribed for the treatment of atrial fibrillation. However, atrial fibrillation developed into slow ventricular rate(30-46bpm/min) (ECG shown in Figure 2B) in the treatment, maximum R-R interval was 2.8s, then methylprednisolone 160mg tapered daily over 1 week by 20mg every 3 days and isoprenaline was prescribed for one week . Her condition steadily improved following the treatment, and she was discharged after 27 days in the hospital.

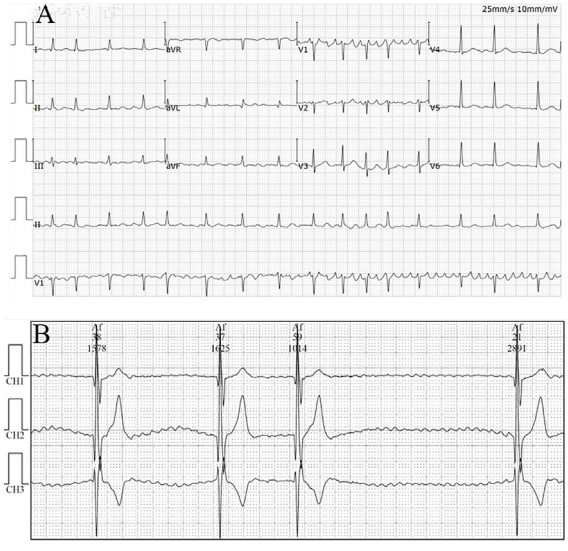


Figure 2. Electrocardiogram of case 2. Picture A showed atrial fibrillation; Picture 2 showed slow ventricular rate AF, R-R interval was 2.8s.

DISCUSSION

Macrophage activation syndrome (MAS), a secondary hemophagocytic lymphohistiocytosis characterized by an excessive systemic inflammatory reaction, is a life-threatening and rare disease. The feature of MAS is an uncontrolled and disordered immune response involving the continued activation and multiplication of T lymphocytes and macrophages, resulting in marked hypercytokinemia. It is characterized by prolonged fever, hyperferritinemia, pancytopenia, fibrinolytic coagulopathy, elevated liver enzyme levels, and hepatosplenomegaly and may involve many other organs like lymph nodes, the nervous system, and the heart. The MAS-associated cardiac complication is not rare, in fact, the incidence is estimated at 24.8%-44.7% by previous articles [4, 5]. The mortality in autoimmune disease-associated MAS ranges from 5 to 39%, however, cardiac involvement is an important prognostic factor [6-9].

The etiology of macrophage activation syndrome with cardiac complications is various, usually associated with conditions that cause immune dysregulations, including but not limited to SLE, sJIA, AOSD, rheumatoid arthritis, polymyositis/dermatomyositis, and Sjogren's syndrome [1-3]. Infections agents, including viruses (EBV, CMV, HSV, HIV, enteroviruses, influenza, etc.), bacteria, fungi, and parasites may be the trigger [10]. Finally, drugs (chemotherapy, immune therapy, antiretroviral drugs, etc.) might also be associated with the disease [11].

The mechanisms of cardiovascular injury have not yet been fully understood and may be multifactorial. Excessive cytokine release may cause vascular inflammation, plaque

Table 2. Comparison of the main clinical features and treatment of the two cases

	Case 1	Case 2
Age and Gender	38 year old female	70 year old female
Combined diseases	SLE and KNL	AOSD
Clinical presentation	High fever, systemic lymphadenopathy, 3 lines-cytopenia, hypocomplementemia, hyperferritinemia, positive ANA	Fever, 3 lines-cytopenia hyperferritinemia and atrial fibrillation
Cardiovascular manifestation	Sudden acute heart failure	Chronic ventricular rate atrial fibrillation
Treatment	HLH-94 treatment protocols(DXM 15mg and etoposide 200mg) with IVIG	Methylprednisolone 160mg with IVIG

IVIG: Intravenous immunoglobulin; HLH-94 treatment protocols: Hemophagocytic lymphohistiocytosis treatment components, including corticosteroids typically dexamethasone, cyclosporin A (CsA), and etoposide, plus intrathecal MTX for progressive CNS involvement; DXM: Dexamethasone

instability, hypercoagulability, myocardial inflammation, and direct myocardial inhibition [12]. Continuously activated T lymphocytes and macrophages may destroy cardiac homeostasis and cause irreversible damage, contributing to heart failure, myocarditis, and arrhythmia [13, 14]. Furthermore, hypertriglyceridemia (especially component of triglyceride-rich lipoproteins) could induce endothelial cell apoptosis by increasing the secretion of the pro-apoptotic cytokines IL-1β and tumor necrosis factor-α (TNF-α), giving rise to vascular injury and atherosclerosis [15]. Finally, other systemic damages, including liver function failure and dysfunction of thromboembolism, may also mediate cardiac injury.

Heart involvement in connective tissue disease associated with MAS was reported with extensive clinical manifestations, ranging from pericarditis to arrhythmia, heart failure, cardiomegaly, myocarditis, coronary enlargement, and hypotension, in which pericarditis is most commonly seen. A previous report summarized 362 cases of MAS, and 90 cases of complicated heart involvement, including 57 pericarditis, 4 arrhythmias, 4 heart failures, 5 cardiomegaly, and 20 others [9]. A study that summarized 103 episodes in 89 adult patients with SLE-associated MAS by Pierre-Edouard Gavand et al., found 46 complicated cardiac damage, including 22 myocarditis and 24 pericarditis [16]. For the diagnosis, there is no consensus on diagnostic criteria so far, thus the HLH-2004 diagnostic criteria are often used. The criteria include cytopenias, fever, splenomegaly, hyperferritinemia, hypertriglyceridemia, hemophagocytosis, soluble IL-2 receptor alpha levels (sCD25), and NK-cell activity, in addition, individuals need to meet ≥5 of 8 diagnostic criteria [1-3], however, a physical malaise, feverish patient should be taken into account in some high-risk populations.

For most autoimmune disease-associated MAS patients, the prognosis is poor, and the overall mortality ranges from 5 to 39% [17]. In the two cases presented here, the presence of MAS in the context of connective tissue disease occurred with cardiovascular complications, one was heart failure, another was arrhythmia, and had differential prognoses. Tables 1 and 2 compare the clinical, biochemical, and hematological features and treatment of the two cases. Both cases demonstrated higher C-reactive protein (CRP), serum ferritin levels, and lactate dehydrogenase at diagnosis, which were reported and associated with multiple disorders and detected as mortality predictors of Hemophagocytic syndrome [18-20]. Furthermore, case 1 had a worse prognosis, which might be connected to the following reasons. The specific clinical and laboratory findings associated with systemic lymphadenopathy were mistakenly diagnosed as malignant lymphoma, and high-dose corticosteroids were not prescribed first. Furthermore, the patient manifested multi-organ involvement, which had been reported

as a predictive biomarker of mortality [18, 19]. Finally, an increased level of IL-18, INF-γ, IL-6, and a decreased ratio of IL-10/TNF-α in MAS were also reported and associated with hyperinflammation phenomena, resulting in multiple disorders [21]. Of these cytokines, pro-inflammatory cytokines TNF-α, IFN-γ, and IL-6 have been extensively implicated in the pathogenesis of heart failure and autoimmune myocarditis [22].

MAS-associated cardiac disease prognosis is bleak, and early treatment is required. Although the study of MAS-associated cardiac diseases is rare, a tight control of primary disease treatment with combination treatment of co-triggers and cardiac diseases helps to improve the symptoms, so the patients need multidisciplinary cooperation with relevant medical disciplines. For the treatment of autoimmune disease-associated MAS, an early use of high-dose corticosteroids may be very effective, and immediate treatment of intravenous methylprednisolone 1g daily is recommended [1]. Carter SJ et al. also recommend the treatment of intravenous immunoglobulin (IVIG) as the first-line therapy [13]. If there are any features of clinical deterioration despite immediate treatment, anakinra, etoposide, and cyclosporin A could be alternative regimens [1-8, 16]. Considerations for concurrent therapy include the identification and eradication of EBV with rituximab treatment and aggressive, targeted antibiotic treatment to address infectious triggers. AN69ST continuous hemodiafiltration (CHDF) with cytokine absorbing and plasma exchange therapy were also reported to rescue deteriorated SLE-associated MAS complicated three-grade atrioventricular block [23]. For the treatment of cardiac diseases, symptomatic therapy was the principle, and multidisciplinary cooperation with cardiovascular disciplines was required. Furthermore, IL-6, TNF-α, and IFN-γ were reported in the pathogenesis of heart failure and autoimmune myocarditis. More research on biological treatments targeting TNF-α, interleukin-6 and IFN-γ is needed.

CONCLUSION

An Estimated 24.8%-44.7% of MAS cases complicated the heart damage, yet the clinical manifestation was various and the prognosis was poor. Our cases demonstrated differential prognoses and served to remind physicians to be alert to macrophage activation syndrome-associated cardiac complications. Recognizing and treating affected patients with early enhanced immunosuppressive therapy and integrated treatment are recommended for successful outcomes.

ACKNOWLEDGMENTS

This article was funded by a general research project of the Zhejiang Provincial Department of Education(Y202045121).

STATEMENT OF ETHICS AND CONSENT OF PARTICIPATION

The research was conducted ethically following the World Medical Association Declaration of Helsinki. In the manuscript, we obtained signed, informed patient consent. (attached below)

Conflict of Interest: None declared.

REFERENCES

1. Paul LaRose´e, AnnaCarin Horne, Melissa Hines, Tatiana von Bahr Greenwood, Machowicz R, Berliner N, Birndt S et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. Blood. 2019 Jun;133(23):2465-2477. Available from: URL: https://doi.org/10.1182/blood.2018894618
2. Crayne CB, Albeituni S, Nichols KE, Cron RQ. The Immunology of Macrophage Activation Syndrome. Front Immunol. 2019 Feb ;10:119. Available from: URL: https://doi.org/10.3389/fimmu.2019.00119
3. Schulert GS, Grom AA. Pathogenesis of

macrophage activation syndrome and potential for cytokine- directed therapies. Annu Rev Med. 2015; 66 :145-159. Available from: URL: https://doi.org/10.1146/annurev-med-061813-012806
4. Minoia F, Davì S, Horne A, Demirkaya E, Bovis F, Li C, et al; Pediatric Rheumatology International Trials Organization; Childhood Arthritis and Rheumatology Research Alliance; Pediatric Rheumatology Collaborative Study Group; Histiocyte Society. Clinical features, treatment, and outcome of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a multinational, multicenter study of 362 patients. Arthritis Rheumatol. 2014 Nov;66(11):3160-3169.
5. Zou LX, Zhu Y, Sun L, Ma HH, Yang SR, Zeng HS, et al. Clinical and laboratory features, treatment, and outcomes of macrophage activation syndrome in 80 children: a multi-center study in China. World J Pediatr. 2020 Feb;16(1):89-98.
6. Moradinejad MH, Ziaee V. The incidence of macrophage activation syndrome in children with rheumatic disorders. Minerva Pediatr. 2011 Dec;63(6):459-466.
7. Gavand PE, Serio I, Arnaud L, Costedoat-Chalumeau N, Carvelli J, Dossier A, et al. Clinical spectrum and therapeutic management of systemic lupus erythematosus-associated macrophage activation syndrome: A study of 103 episodes in 89 adult patients. Autoimmun Rev. 2017 Jul;16(7):743-749. Available from: URL:https://doi.org/10.1016/j.autrev.2017.05.010
8. Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. Lancet. 2014 Apr 26;383(9927):1503-1516. Available from: URL: https://doi.org/10.1016/S0140-6736(13)61048-X
9. Bae CB, Jung JY, Kim HA, Suh CH. Reactive hemophagocytic syndrome in adult-onset Still disease: clinical features, predictive factors, and prognosis in 21 patients. Medicine (Baltimore). 2015 Jan;94(4) : e451. Available from: URL: https://doi.org/10.1097/MD.0000000000000451.
10. Mostaza-Fernández JL, Guerra Laso J, Carriedo Ule D, Ruiz de Morales JM. Hemophagocytic lymphohistiocytosis associated with viral infections: Diagnostic challenges and therapeutic dilemmas. Linfohistiocitosis hemofagocítica asociada a infecciones virales: reto diagnóstico y dilema terapéutico. Rev Clin Esp (Barc). 2014;214(6):320-327. Available from: URL:https://doi.org/10.1016/j.rce.2014.03.009
11. Tocchetti CG, Cadeddu C, Di Lisi D, et al. From Molecular Mechanisms to Clinical Management of Antineoplastic Drug-Induced Cardiovascular Toxicity: A Translational Overview. Antioxid Redox Signal. 2019;30(18):2110-2153. Available from: URL:https://doi.org/10.1089/ars.2016.6930
12. Prabhu SD. Cytokine-induced modulation of cardiac function. Circ Res. 2004 Dec 10;95(12):1140-53. Available from: URL: https://doi.org/10.1161/01.RES.0000150734.79804.92.
13. Bozkurt D, Bozgul SMK, Emgin O, Butun O, Kose T, Simsek E, Hekimgil M, Kilic S. Mortal Interaction Between Hemophagocytic Syndrome and Newly Developed Heart Failure. Arq Bras Cardiol. 2021 Mar;116(3):395-401. Available from: URL: https://doi.org/10.36660/abc.20190642.
14. Swirski FK, Nahrendorf M. Cardioimmunology: the immune system in cardiac homeostasis and disease. Nat Rev Immunol. 2018 Dec;18(12):733-744. Available from: URL:https://doi.org/ 10.1038/s41577-018-0065-8.
15. Peng J, Luo F, Ruan G, Peng R, Li X. Hypertriglyceridemia and atherosclerosis. Lipids Health Dis. 2017 Dec 6;16(1):233. Available from: URL:https://doi.org/10.1186/s12944-017-0625-0.
16. Gavand PE, Serio I, Arnaud L, Costedoat-Chalumeau N, Carvelli J, Dossier A, et al. Clinical spectrum and therapeutic management of systemic lupus erythematosus-associated macrophage activation syndrome: A study of 103 episodes in 89 adult patients. Autoimmun Rev. 2017 Jul;16(7):743-749. Available from: URL:https://doi.org/10.1016/j.autrev.2017.05.010.
17. Carter SJ, Tattersall RS, Ramanan AV. Macrophage activation syndrome in adults: recent advances in pathophysiology, diagnosis and treatment. Rheumatology (Oxford). 2019 Jan ;58(1):5-17. Available from: URL: https://doi.org/10.1093/rheumatology/key006.
18. Di Benedetto P, Cipriani P, Iacono D, Pantano I, Caso F, Emmi G, et al. Ferritin and C-reactive protein are predictive biomarkers of mortality and macrophage activation syndrome in adult onset Still's disease. Analysis of the multicentre Gruppo Italiano di Ricerca in Reumatologia Clinica e Sperimentale (GIRRCS) cohort. PLoS One. 2020 Jul 9;15(7):e0235326. Available from: URL: https://doi.org/10.1371/journal.pone.0235326.
19. Ruscitti P, Cipriani P, Ciccia F, Masedu F, Liakouli V, Carubbi F, et al. Prognostic factors of macrophage activation syndrome, at the time of diagnosis, in adult patients affected by autoimmune disease: Analysis of 41 cases collected in 2 rheumatologic centers. Autoimmun Rev. 2017;16:16–21.
20. Bozkurt D, Bozgul SMK, Emgin O, Butun O, Kose T, Simsek E, et al. Mortal Interaction Between Hemophagocytic Syndrome and Newly Developed Heart Failure. Arq Bras Cardiol. 2021 Mar;116(3):395-401. Available from: URL: https://doi.org/ 10.36660/abc.20190642.
21. Kyriazopoulou E, Leventogiannis K,

Norrby-Teglund A, Dimopoulos G, Pantazi A, Orfanos SE, et al. Macrophage activation-like syndrome: an immunological entity associated with rapid progression to death in sepsis. BMC Med. 2017 Sep;15(1):172. Available from: URL: https://doi.org/10.1186/s12916-017-0930-5.

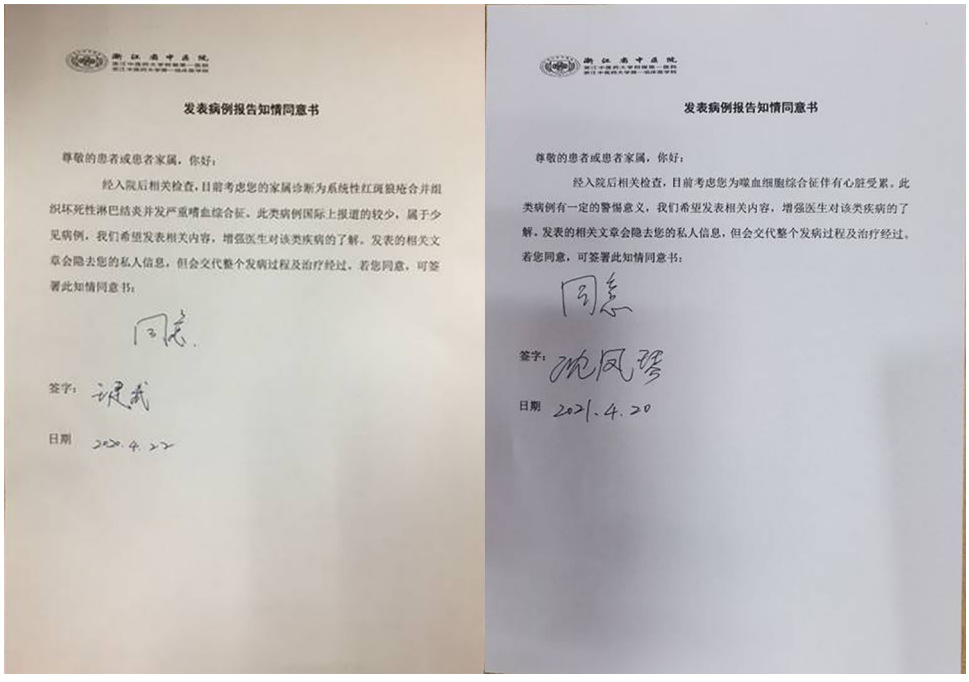
22. Hanna A, Frangogiannis NG. Inflammatory Cytokines and Chemokines as Therapeutic Targets in Heart Failure. Cardiovasc Drugs Ther. 2020;34(6):849-863. Available from: URL: https://doi.org/10.1007/s10557-020-07071-0

23. Harano Y, Ishikawa Y, Hattori K, Ichinose M, Tomofuji Y, Okano H, et al. A case of complete atrioventricular block in secondary hemophagocytic syndrome/hemophagocytic lymphohistiocytosis recovered by plasma exchange and cytokine absorbing therapy with AN69ST continuous hemodiafiltration. Immunol Med. 2020 Dec;43(4):171-178. Available from: URL: https://doi.org/10.1080/25785826.2020.1761145.

Consent

Case 1

Case 2



发表病例报告知情同意书

尊敬的患者或患者家属，你好：

经入院后相关检查，目前考虑您的家属诊断为系统性红斑狼疮合并组织坏死性淋巴结炎并发严重嗜血综合征。此类病例国际上报道的较少，属于少见病例，我们希望发表相关内容，增强医生对该类疾病的了解。发表的相关文章会隐去您的私人信息，但会交代整个发病过程及治疗经过。若您同意，可签署此知情同意书：

同意

签字：[illegible]

日期 2021.4.22

发表病例报告知情同意书

尊敬的患者或患者家属，你好：

经入院后相关检查，目前考虑您为噬血细胞综合征伴有心脏受累。此类病例有一定的警惕意义，我们希望发表相关内容，增强医生对该类疾病的了解。发表的相关文章会隐去您的私人信息，但会交代整个发病过程及治疗经过。若您同意，可签署此知情同意书：

同意

签字：[illegible]

日期 2021.4.20