Haemophagocytic Lymphohistiocytosis Syndromein a Patient with Adult Onset Still's Disease; A Diagnostic Challenge

Author's Details:
Madagedara RMD[1], BandaraHGWAPL[1], Wijethilake BHWMGT[1], Athauda SD[2]
Respiratory Diseases Treatment Unit II[1], Hematology unit[2] Teaching Hospital, Kandy Sri Lanka
Corresponding author : Dr Dushantha Madegedara-MBBS,MD,FRCP,FCCP,FCCP(USA) Consultant Respiratory Physician

Abstract:
Heamophagocytic lymphohistiocytosis (HLH) is a syndrome of pathologic immune activation characterized by clinical signs and symptoms of extreme inflammation[1]. It was described as both a familial disorder and as a sporadic one, in association with infections, malignancies, or rheumatologic disorders. HLH results from impaired functions of natural killer (NK) and cytotoxic T cells, whereas activities of lymphocytes and histiocytes are augmented, leading to phagocytosis of hematopoietic cells[2]. Though the primary pathogenic mechanism is linked to genetic and immunologic basis, HLH remains a multisystem disorder having a unique pattern of clinical manifestations. Secondary HLH is triggered by a variety of causative agents including infections, malignancies and rheumatological illnesses. Since the individual clinical features are non-specific, HLH and Adult Onset Stills Disease (AOSD) share overlapping clinical and a number of laboratory features making the accurate diagnosis of both syndromes difficult. HLH that arises in the course of AOSD disease has been reported only rarely. Tuberculosis is yet another infective cause of secondary HLH where reported cases are scanty. Here, we report two cases of secondary HLH; a young male with Still's disease and a young female with tuberculosis both cases complicated with HLH.
Keywords: *Haemophagocytic Lymphohistiocytosis Syndromein*

Case 01

A 16 year old patient was admitted with intermittent spiking fever up to 39.8°C for three weeks duration. He also had arthralgia affecting multiple large and small joints in an asymmetrical pattern without morning stiffness. He developed mild productive cough with pleuratic type of chest pain for same duration. There was a transient erythematous non pruratic rash involving the trunk and extremities which was more prominent with fever spikes. Clinical examination revealed a morbiliform rash over the abdomen, trunk, and both arms. He also had pallor and had moderate hepato-splenomegaly with supra-clavicular and axillary lymphadenopathy.

Initial laboratory investigations showed haemoglobin of 5.9 g/dL, platelet count of 31 x 10^9/L, and white blood cell (WBC) count of 4.5 x 10^9/L with absolute neutrophil count of 2.7x10^9/L. His Erythrocyte Sedimentation Rate (ESR)was 27 mm in 1st hour with C- Reactive Protein (CRP)was 129 mg/L. The biochemistry profile revealed aspartate aminotransferase of 42 U/L, alanine aminotransferase of 62 U/L, total bilirubin of 4.2 mg/dL, serum ionized calcium 4.6 mg/ dL (4-5.4 mg/dL), sodium of 138mEq/L, potassium of 4.5 mEq/L, creatinine of 0.8 mg/dL, glucose of 109 mg/dL, albumin of 3.9 g/dL, and total protein of 5.7g/dL. A chest radiograph revealed hilar lymph adenopathy, bibasal ground glass appearance with patchy consolidation *(Figure-1).*

A computed tomography(CT) scan of the chest revealed bilateral perihilar patchy consolidation with medistinal lymph adenopathy and bilateral small pleural effusion*(Figure-2).* Abdominal cuts of the chest CT showed multiple hypodence infiltrative lesions over the spleen*(Figure-3).* Lymph node biopsy showed only nonspecific reactive changes with no definitive evidence of tuberculosis (TB), sarcoidosis or infiltration by lymphoma or leukaemic cells. Microbiological investigations included repeatedly negative blood cultures, negative sputum cultures and negative smear for Acid Fast Bacilli and Pneumocystis. Mantoux test, gamma interferone assay, serology for Human Immuno deficiency Virus (HIV), Ebstein-Barr virus (EBV), Cytomegalovirus (CMV), Mycoplasma and Brucella also became negative. He had his serum Angiotensin Converting Enzyme (ACE) level normal and negative test for Antinuclear Antibody (ANA), Antibodies for Double strand DNA (dsDNA), Rheumatoid factor(RF), C and PAnti-Neutrophil Cytoplasmic Antibodies (ANCA).

Intravenous broad spectrum antibiotics was commencedand anti-tuberculosis therapy was added to the antibiotic regimen with high clinical suspicion of TB. He was continued to have fever and repeat laboratory data showed worsening pancytopenia.

Given the combination of fever, arthralgia, transient non pruratic rash, hepato-splenomegaly and lymph

adenopathy in a background of negative ANA and RF fulfilled the *Yamaguchi criteria* for AOSD disease. Subsequent investigations showed serum ferritin of > 30 000 ng/ml further strengthen the diagnosis.

However the worsening pancytopenia was not compatible with the diagnostic picture of straightforward AOSD disease. Subsequently he was subjected to bone marrow trephine biopsy which revealed the phenomenon of increased haemophagocytosis (Figure-4). This new hematology picture brought the diagnosis of HLH by fulfilling 6 out of 8 criteria introduced by *Henter et al*. Our patient fulfilled the criteria of fever, splenomegaly, cytopenia, haemophagocytosis in bone marrow and high serum ferritin. Furthermore he was found to have high Triglyceride(TAG) level of 558.3 mg/dL(10-200 mg/dL) and high Lactate dehydrogenase (LDH)which further reinforce the diagnosis of HLH.

The ongoing treatment was modified by adding high dose of oral steroids (dexamethasone), oral etoposide in addition to antibiotics. Patient had a remarkable recovery with both clinical improvement and advance of hematology parameters *(Graph-1 to 3).*

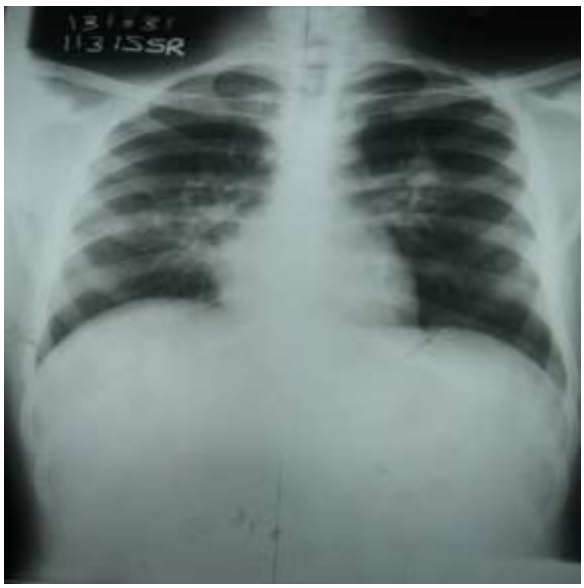


Figure-1, Chest X-ray of the patient demonstrated pulmonary infiltrates

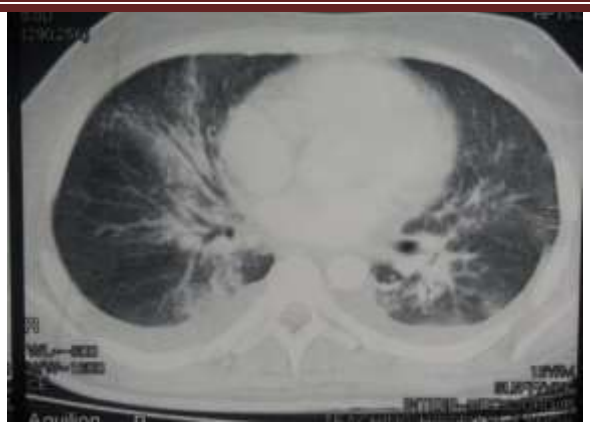


Figure-2, CT scan of the chest showed pulmonary infiltrates, hilar lymphadenopathy and pleural effusion.

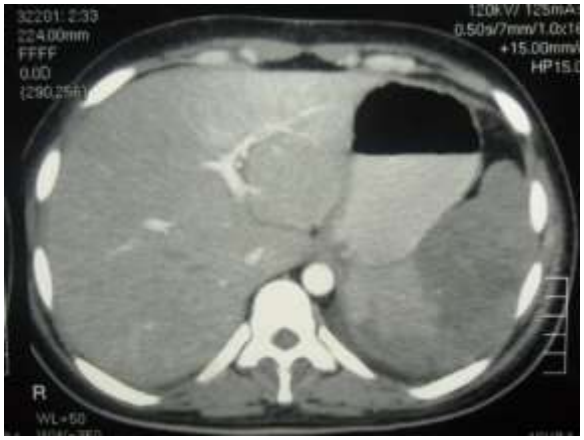


Figure-3, CT scan of the abdomen demonstrated multiple splinic infiltrates.

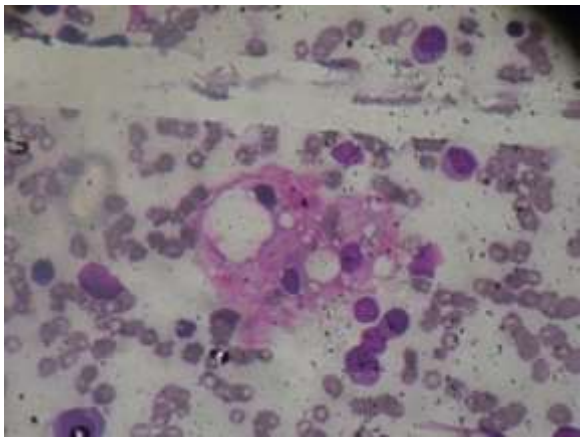
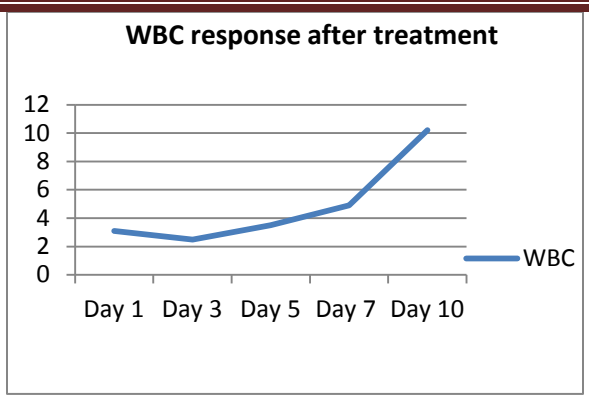
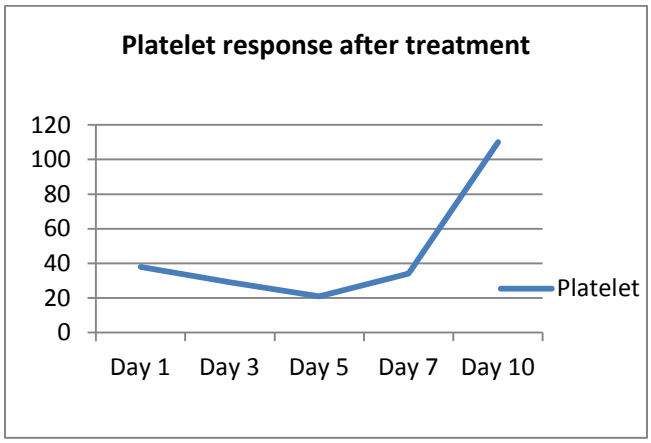


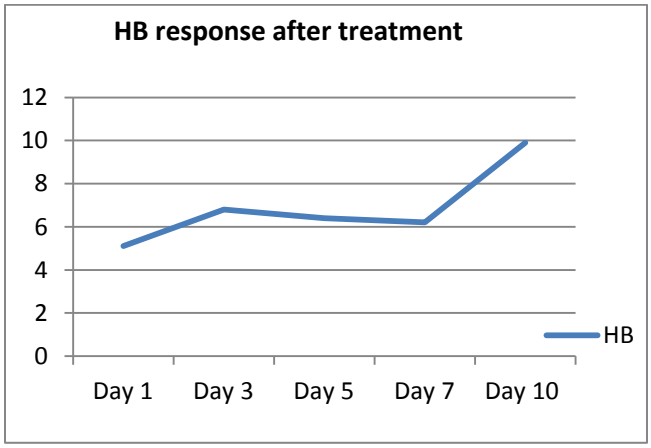
Figure-4, Bone marrow biopsy demonstrated increased haemophagocytosis



Graph-1. WBC response after treatment commenced on Day 7



Graph-2. Platelet response after treatment commenced on Day 7



Graph-3. HB response after treatment commenced on Day 7

Case 02

A 17 year old Sri Lankan Tamil female patient was admitted with fever > 38.5°C for more than 7 days. This illness was followed by a systemic illness requiring hospital admission one month ago. She also had abdominal pain, irritability, malaise and anorexia. She did not have rashes, joint involvement, bleeding diatheses. Physical examination revealed pallor but she did not have lymph adenopathy or hepatosplenomegaly.

Initial laboratory investigations revealed Haemoglobin of 6.7g/dl, White blood cell (WBC) count of 4.5 X 10^9/L with 72% neutrophils; absolute neutrophil count 3.2X 10^9/L and Platelet count of 63X 10^9/L. Erothrocyte Sedimentation Rate (ESR) was 131 in the 1st hour and C-Reactive Protein (CRP) was 103 mg/L. Biochemical profile revealed serum sodium of 138 mmol/l, potassium 3.3mmol/m, blood urea 2.02mmol/l, Serum Creatinine 0.5 mg/ dl, Aspartate Aminotransferase (AST) 54.3 U/L, Alanine aminotransferase (ALT) 36.8 U/L, Fasting Blood Sugar (FBS) 3.2 mmol/l, Serum Albumin 3.8 g/dl with total protein of 6.66g/dl. Alkaline phosphatase level was 229 U/L. Serum Triglyceride level was 588.3 mg/dl whereas Serum Ferritin llevel was 4479.12.

Chest radiograph and USS Abdomen were normal.

Microbiological investigations showed both Blood and urine cultures to be negative. Mycoplasma serology was 1:80 positive. Retro-viral screen was negative. Mantoux test reading was 11mm and sputum smear for Acid Fast Bacilli (AFB) was negative. Sputum culture AFB was positive.

Urine full report revealed trace protein with 1-2 pus cells per high power field. Urine dipstick for hCG was negative.

Rheumatoid factor and Antinuclear Antigen (ANA) were negative.

Initial Blood picture was consistent with features of Iron Deficiency Anaemia and infection with first bone Marrow Biopsy consistent with bacterial infection/ inflammation. The Second Bone Marrow Biopsy showed typical Haemophagocytosis (Figure 5).

Initial treatment with broad spectrum antibiotics was unsuccessful.

This patient fulfilled five criteria out of eight introduced by Henter et al. in diagnosing Haemophagocytic Lymphohistocytosis. Patient had fever, cytopenia, haemophagocytosis in bone marrow, hypertriglyceridaemia and hyperferritinaemia.

Sri Lanka being an intermediate risk burden country for tuberculosis and the presentation with pyrexia of unknown origin and positive mantoux test the patient was started on anti-tuberculosis chemotherapy as for smear negative pulmonary tuberculosis. She was also started on high dose intravenous steroids tailing off over

8 weeks, etoposide for 8 weeks, *Pneumocyctis cariini* prophylaxis with Co-trimoxazole 960mg bd and anti-fungal prophylaxis with fluconazole 100mg bd.

Patient showed a remarkable clinical,biochemical and haematological improvement.

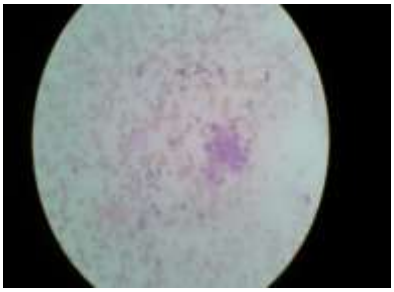
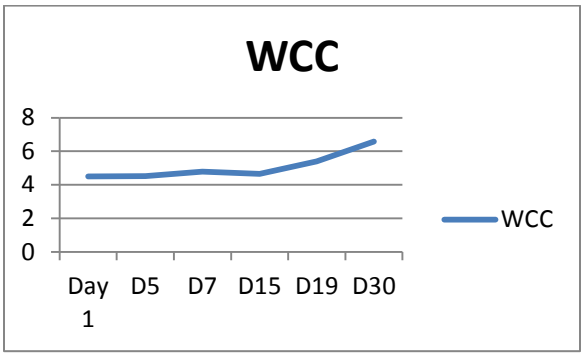
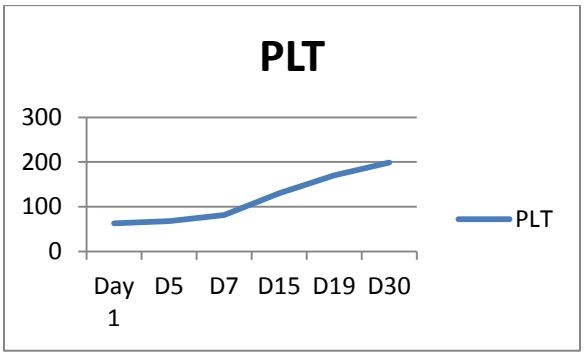


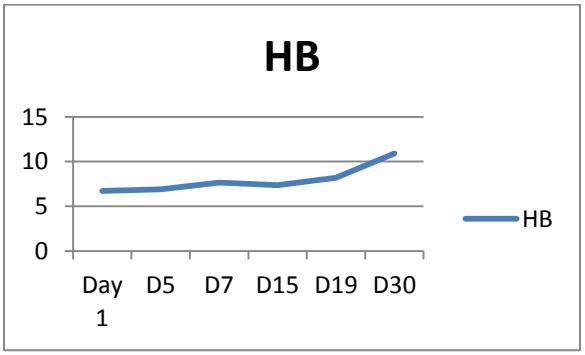
Figure-5, Bone marrow biopsy demonstrated typical haemophagocytosis



Graph-4. White Cell Count response after treatment commenced



Graph-5. Platelet response after treatment commenced



Graph-6. haemoglobin response after treatment commenced

Discussion

HLH syndrome is an activation of mononuclear phagocyte system cells, with hemophagocytosis in bone marrow and the rest of reticulo-endothelial system. This syndrome can be either primary or reactive (secondary)[3]. Genetic HLH has an autosomal recessive inheritance pattern, and usually arises in infants (80%cases); however in rare cases it can also occur in adults[4] and it also associated with impaired NK cell function[5].

Secondary HLH has a better outcome than primary HLH. Itcan be triggered mainly by viral infections (especially EBV)[6] and also by bacterial, parasitic or fungalinfections. It can also develop during malignancies andrheumatoid disorders, as happened in our patients[7].

Secondary HLH and AOSD share several clinical and laboratory features,including high fever, hepatosplenomegaly, lymphadenopathy,liver injury, hyper-ferritinaemia and coagulopathy, whichmay explain the difficulty in recognizing HLH complicatingthe flare of AOSD.The main difference between the twodiseases is cutaneous and articular involvement, which is
a common presentation in AOSD and is uncommon insecondary HLH.In our patient the evidence of relatively low ESR compared to high CRP, leucopenia and hypertriglyceridemia also supports the diagnosis of HLH over straightforward AOSD. Raised serum triglyceride level isconsidered to be a good marker of haemophagocyticsyndrome[8]. In our patient, serum triglycerides were markedlyraised during the acute phase of the illness and it could be used as a differentiating feature for HLH diagnosis.

The diagnostic challenge arises when the features of both of the disorders overlap with one or more features of sepsis, which could be a deadly coexistence of a complex scenario. Here we were able to exclude possible septic foci by demonstratingrepeatedly negative blood cultures for bacteria and fungi, negative serology for HIV, Hepatitis B/C, EBV, CMV and Brucella and negative smears and cultures for TB. Next diagnostic challenge arises, in case of how to determine the secondary HLH is resultant to which triggering factor. In this scenario we were able to exclude as much as possible the possibility of sepsis, tuberculosis, autoimmune disease, vasculitis and hematological malignancies by microbiological, serological and histopathological investigations.

Since our patient is fulfilling criteria for AOST and the bone marrow finding strengthen the necessary criteria for HLH, the reactive HLH secondary to AOSD was made. Extensive studies could not identify any evidence of viral infection or other known underlying disorders associated with reactive HLH.

Although the features of secondary HLH and AOSD are well characterized, the underlying physiopathology is not well understood. The most consistent immunological abnormality described in patients with primary or secondary haemophagocytic syndrome is impairment of cytotoxic function[9]. The deficient cytotoxic function may bring about failure to provide complete pathogen destruction and persistent lymphocyte and macrophage activation[10].Sustained macrophage activation may result in tissue infiltration, production of ferritin and high levels of tumour necrosis factor a (TNFa) and interleukin (IL), IL-6, IL-18, IL-8, observed in flares of AOSD and HLH[11].Highly activated macrophages are thought to have a key rolein the pathogenesis ofAOSD[12].Hence, sustained macrophage activation in AOSD may lead to reactive HLH after a sudden intensification of disease activity.

Pulmonary involvement is well-known though rare in AOSD and is seen in up to 53% of cases, with the most common pulmonary diseases being pleural effusion and transient pulmonary infiltrates[13] as seen in our patient. Though our patient had such a pulmonary infiltrate in a back ground of pancytopenia, the exclusion of the opportunistic infection was the next diagnostic challenge. It has been able to establish by demonstrating negative cultures, cytology and serology for such opportunistic infections.

Tuberculosis remains a health burden in the South East Asia with Sri Lanka is recognized as an intermediate risk country. *Mycobacterium tuberculosis* (MTB) has a diverse variety of clinical manifestations.

HLH is an uncommon yet a potentially fatal complication of tuberculosis with unpredictable clinical course. In patients with tuberculosis cytopenia, organomegaly and coagulopathy should alert the clinician to consider secondary HLH[14]; it remains a diagnostic challenge.

MTB, being an obligate intracellular pathogen, is able to aggravate Th_1 cell-mediated cytotoxicity and macrophage overactivity that can lead to HLH in susceptible patients. This is supported by increased serum levels of IFN-γ, M-CSF, and TNF-α in patient with tuberculosis[14].

Often, the next principle challenge for treating patients with HLH is making a timely diagnosis, search for and treat underlying triggers and institute specific immunomodulatory therapy. Since there is no consensual treatment for HLH in AOSD, we planned out our management according to the *HLH 2004* treatment protocol. He was started on oral dexamethesone to suppress the sever inflammation, Etoposide to restrain the over-stimulated antigen-presenting cells, which are the macrophages with close monitoring the clinical and hematological parameters. He achieved a good clinical and hematological recovery with the above therapy as most reported cases of HLH complicating AOSD have responded well to high-dose corticosteroid therapy.

In the treatment of tuberculosis complicated with HLH immunomodulatory therapy is a debated field but it is advocated to use anti-tuberculous therapy (ATT) early. HLH complicating tuberculosis is known to have high morbidity and mortality with or without ATT[14].

Reference

i. Michael B. Jordan, Carl E. Allen, Sheila Weitzman, Alexandra H. Filipovich, Kenneth L,McClain.How we treat hemophagocytic lymphohistiocytosis. *Blood* 2013: 1-26.

ii. Rouphael NG, Talati NJ, Vaughan C, Cunningham K, Moreira R, Gould C. Infections associated with haemophagocytic syndrome. *Lancet Infectious Disease* 2007; 7:814-22.

iii. Juan Mayordomo-Colunga, Corsino Rey, Soledad González and Andrés Concha. Multiorgan failure due to hemophagocytic syndrome: A case report. *Cases Journal* 2008, 1:209

iv. Maciej Machaczka, Wojciech Sydor, Małgorzata Rucińska, Marta Szostek and Jacek Musiał.Autoimmune-Associated Hemophagocytic Syndrome /Macrophage Activation Syndrome. *Autoimmune Disorders – Current Concepts and Advances from Bedside to Mechanistic Insights* 2011, 80 -98.
    a. Availablefrom: http://www.intechopen.com

v. Gritta Janka and Udo zur Stadt.Familial and Acquired HemophagocyticLymphohistiocytosis. *American Society of Hematology* 2005:82-88.

vi. Janka GE: Hemophagocytic syndromes. *Blood Rev* 2007,21:245-53.

vii. Stabile A, Bertoni B, Ansuini V, La Torraca I, Salli A, Rigante D: The clinical spectrum and treatment options of macrophage activationsyndrome in the pediatric age. *European Review for Medical and PharmacologicalSciences*2006, 10:53-59.

viii. Karras A, Hermine O. Syndrome d'activationmacrophagique [Macrophage activation syndrome]. *Rev Med Interne* 2002;23:768–78.

ix. Grom AA. Macrophage activation syndrome and reactive hemophagocytic
a. lymphohistiocytosis. *Current Opinionin Rheumatology*2003; 1:587–90.

x. Wulffraat NM, Rijkers GT, Elst E, Brooimans R, Kuis W. Reduced perforin
a. expression in systemic juvenile idiopathic arthritis is restored by autologousstem-cell transplantation. *Rheumatology* 2003; 42:375–9.

xi. Villanueva J, Lee S, Giannini EH, Graham TB, Passo MH, Filipovich A, et al.Natural killer cell dysfunction is a distinguishing feature of systemic onset
a. juvenile rheumatoid arthritis and macrophage activation syndrome. *Arthritis Research and Therapy* 2005;7:R30–7.

xii. Amenomori M, Migita K, Miyashita T, Yoshida S, Ito M, Eguchi K, et al. Cytomegalovirus-associated hemophagocytic syndrome in a patient with adult onset Still's disease. *Clinical and Experimental Rheumatology* 2005;23:100–2.

xiii. Cheema GS, Quismorio FP Jr. Pulmonary involvement in adult-onsetStill's disease. *Current Opinionin Pulmonary Medicine* 1999; 5: 305-9.

xiv. Padhi S, Ravichandran K, Sahoo J, Vargese R, Basheer A. Haemophagocytic lymphohistiocytosis: an unusual complication in disseminated *Mycobacterium Tuberculosis. Lung India* 2015 Nov-Dec; 32(6): 593-601