HISTIO UK

No-one should die of Histiocytosis

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Haemophagocytic Lymphohistiocytosis HLH

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HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

IN A SINGLE LARGE CENTRE OBSERVATIONAL COHORT STUDY OF HOSPITALISED COVID-19 PATIENTS, SECONDARY HLH (SHLH) WAS RARE BUT HYPERINFLAMMATION (HI) COMMON AND HI SEVERITY PREDICTED RESPONSE TO EARLY INTERVENTION WITH DEXAMETHASONE ASSESSED BY DAY 28 MORTALITY.

ANDREW DUNCOMBE PRESENTING

Introduction COVID-19 is responsible for at least 4.5 million deaths worldwide. A significant proportion of COVID-19 patients show evidence of hyperinflammation (HI) of which secondary Haemophagocytic Lymphohistiocytosis (sHLH) is the most severe manifestation. The success of early dexamethasone therapy may reflect anti-HI activity.

Aims We set out to determine the prevalence of sHLH and HI in a cohort of COVID-19 inpatients and their response to Dexamethasone.

Methods The prevalence of sHLH was determined by a modified H score in a cohort of 567 COVID-19 positive inpatients receiving conventional treatment. HI was assessed on admission by a novel clinico-pathological algorithm, HI5-NEWS2, in a larger cohort of 1265 inpatients, 653 of whom received Dexamethasone treatment as per NICE guidance. The primary outcome was 28 day mortality.

Results The overall incidence of patients developing sHLH was 1.59% on admission and only rose to 4.05% over the whole admission. This small cohort showed no excess mortality compared with the whole cohort. However, high risk of HI (high HI5-NEWS2 score) (n=367, 29.0%) conferred a strikingly increased mortality (36.0% vs 7.8%; Age adjusted hazard ratio (aHR) 5.9; 95% CI 3.6-9.8, p<0.001) compared to the low risk group (n= 455, 36.0%). Early dexamethasone treatment conferred a 50.0% reduction in mortality in the high risk group (36.0% to 18.0%, aHR 0.56, p=0.007) which was not observed in the low risk group (7.8% to 9.2%, aHR 1.4, p =0.31).

Conclusion sHLH is rare but HI is common in hospitalised COVID-19 patients and HI severity correlates with Dexamethasone mortality reduction.

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HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

A MULTI-CENTRE EVALUATION OF THE USE OF ANAKINRA IN THE MANAGEMENT OF HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS SECONDARY TO COVID-19

LUKE FLOWER PRESENTING

Introduction A sub-group of patients with COVID-19 develop secondary haemophagocytic lymphohistiocytosis (sHLH). Diagnosis of sHLH remains a challenge; no scoring systems are validated in critical illness and limited evidence exists on its management. The IL-1 receptor antagonist anakinra has a good safety record and is used in several hospitals.

Aims The aim of this evaluation was to describe the use of anakinra in patients with COVID-19 associated sHLH (COV-HLH).

Methods We evaluated data from patients with COV-HLH treated with anakinra admitted to three NHS Trusts between 01/02/2020 and 28/06/2020. Ten patients were included. Data were collected over a three-week period from treatment initiation under local service evaluation permissions and with individual case consent. Ethical opinion was not required.

Results All patients required critical care admission and mortality was 40%. Median age was 40 and 9/10 were male. Anakinra treatment regimens varied from 70mg IV BD to 200mg IV TDS. Patients initiated on lower dosing regimens required up-titration due to initial lack of response. For one-person, rapid weaning of anakinra resulted in rebound sHLH with re up-titration required. No adverse effects related to anakinra were observed. In all median temperature (38·8-37·9^{o}C), HScore (164-84) and ferritin (9576-3034µg/L) reduced following treatment.

Conclusion Challenges associated with sHLH diagnosis became more apparent during the COVID-19 pandemic. An improvement in biochemical and clinical parameters was seen following anakinra, with a mortality lower than that previously reported in sHLH. Anakinra dosing regimens in the management of sHLH continue to vary with further research required.

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HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

A CASE OF MACROPHAGE ACTIVATION SYNDROME (MAS)/HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH) REQUIRING EXTRA-CORPOREAL MEMBRANE OXYGENATION IN A PATIENT WITH SEVERE MULTISYSTEM LUPUS ERYTHEMATOSUS

JOSEPH GUPPY PRESENTING

A 29-year-old Nigerian female, diagnosed with systemic lupus erythematosus (SLE) in 2021, was admitted to a district general hospital with fever, ascites, abdominal pain and confusion. She had recently arrived from Nigeria and an extensive infection panel was negative. She was treated for severe multisystem lupus based on constitutional symptoms, lymphadenopathy, pancytopenia, serositis, probable lupus nephritis, positive anti-dsDNA antibodies and hypocomplementaemia. Despite immunosuppression with pulsed intravenous methylprednisolone followed by rituximab, she continued to deteriorate resulting in cardiorespiratory arrest.

An echocardiogram demonstrated severe biventricular impairment with an estimated left ventricular ejection fraction of 15%, a significant deterioration from the scan one day prior. This deterioration was associated with the emergence of features consistent with MAS/HLH including pancytopenia, transaminitis (ALT 1240 iU/L), hyperferritinaemia (ferritin 60,045 ug/L) and hypofibrinogenaemia (fibrinogen 1.2 g/L). At this time, her H-score was 195. She was therefore transferred to our centre for veno-arterio-venous extra-corporeal membrane oxygenation (ECMO) for lupus myocarditis and cardiogenic shock, which facilitated further immunosuppression with intravenous cyclophosphamide.

She made a significant recovery post-decannulation. A repeat echocardiogram after 2 months of immunosuppression was normal (ejection fraction 59%).

This case highlights the life-threatening nature of MAS/HLH. The diagnosis should be considered alongside differentials such as sepsis in acutely unwell patients with autoimmune rheumatic diseases. Secondly, our case illustrates the use of ECMO as a bridging measure to facilitate further immunosuppression addressing the underlying autoimmune trigger in patients with MAS/HLH and allowing for a full cardiac recovery in this case.

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HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

HLH AND TB: LETHAL BUT TREATABLE

NISHA GEORGE — PRESENTING

Haemophagocytic lymphohistiocytosis (HLH) can be associated with a variety of infections, most commonly viral. HLH in association with tuberculosis (TB) is a less common entity.

A 54-year-old Indian man with no history of TB was admitted with a fever and tachycardia. Within a week of admission, he developed severe thrombocytopenia (nadir 2 $x10^9$/L) with purpura and epistaxis. He was treated with intravenous immunoglobulin and prednisolone for presumed immune thrombocytopenia, but failed to respond to this. Multiple blood cultures, and autoimmune screens were negative, and broad spectrum antibiotics did not impact his fever.

As his condition progressed, a bone marrow biopsy was arranged which showed active haemophagocytosis mainly directed against platelets. Elevated ferritin, soluble CD25 and triglycerides along with bicytopaenia and his persistent fever established the diagnosis against the 2004 HLH criteria. Imaging studies initially showed multiple small lung nodules which progressed to miliary shadowing. He was initiated on dexamethasone, anakinra and empirical TB treatment, and improved over several weeks. Bone marrow cultures were later positive for *Mycobacterium tuberculosis*.

TB-associated HLH has been occasionally described in the literature, and carries a significant mortality. Infective triggers for HLH should always be sought, as effective treatment for these may reduce the need for higher-risk therapies. Obtaining the appropriate microbiological samples prior to starting treatment is essential, and in cases where TB is a possibility, empirical therapy can be justified especially where immunosuppressive treatment is being used. Patient consent was obtained for this case report.

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HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

FATAL SECONDARY HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS DUE TO VISCERAL LEISHMANIASIS IN A PATIENT WITH RHEUMATOID ARTHRITIS.

DIANA AYOOLA MABAYOJE PRESENTING

Describe original case

We describe a rare case of Visceral Leishmaniasis with secondary HLH in an immunosuppressed patient.

Reason for report

An underlying diagnosis of VL may easily be missed due to the similarity in clinical presentation with HLH. Leishmania blood PCR and serology should be requested in all HLH patients with a compatible travel history.

Case description

A 79-year-old man presented with 4 weeks' malaise, sore throat and oral ulceration. He took methotrexate for rheumatoid arthritis and travelled to Ibiza annually. Blood tests showed pancytopaenia, ferritin >10,000ug/L and elevated triglycerides; CT imaging showed cervical lymphadenopathy and marked splenomegaly. A bone marrow aspirate showed leishmania amastigotes. Liposomal amphotericin B was initiated for visceral leishmaniasis. He was transferred to UCLH, where a clinical diagnosis of HLH was made (H score 199, 80-88% probability) and methylprednisolone initiated. He developed disseminated intravascular coagulation and multi-organ dysfunction and was transferred to ITU where Anakinra and IVIg were commenced. After an initial treatment response he worsened dramatically, requiring intubation and ventilation. Repeat imaging showed multifocal cerebral and splenic infarcts, pneumatosis coli and portal venous gas; palliative treatment was commenced following discussion with his relatives. Consent for post-mortem examination was obtained, this showed disseminated aspergillosis and leishmania amastigotes in bone marrow with histological confirmation of HLH.

Discussion

Treatment of secondary HLH is complex, requiring identification and treatment of the driver while simultaneously treating the hyperinflammatory state. Opportunistic infection is often the cause of death in HLH and all patients should be screened for invasive fungal infection.

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HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

HEMOPHAGOCYTES IN COVID-19 DISEASE: A NOVEL PILOT STUDY USING CELLSIEVETM LIQUID BIOPSY

JERONIMO MORENO-CUESTA PRESENTING

Introduction Some patients with severe COVID-19 exhibit a pattern of immune dysregulation characterized by hyperinflammation with some features of hemophagocytic lymphohistocytosis. This research develops a new test of hemophagocytosis using microfiltration to improve upon stained blood smears.

Aims Feasibility of a detection of hemophagocytes in a microfilter (CellSieveTM).

Methods The study population were adults admitted in ICU with sepsis (control group, N=17) or confirmed COVID-19 disease (Experimental group, N=13). After getting consent blood was collected in CellSave preservation tubes and processed following the Creatv MicroTech's CellSieve protocol: 1) incubation of 7.5 mls of blood with 7.5 mls of prefixation buffer; 2) microfiltration at a speed of 5 mls/min; 3) fixation and permeabilization with washing after each step; 4) staining of cells on the filter with haematoxylin-eosin, followed by mounting on a glass slide. A duplicate of a blunt smear test of the blood was used for comparison. Data is presented as median (max-min) and counts. Comparisons using Pearson's chi-square test were made using R with $p < 0.05$ considered significant. The study is sponsored by North Middlesex Hospital (IRAS 286674, REC 20/LO/1296).

Results Neither liquid biopsy nor smears identified hemophagocytes. Cellularity and type of cells were similar between both groups under light microscopy.

Conclusions In this small sample, COVID-19 disease does not represent a different entity compared with patients with sepsis in regards the presence of hemophagocytes in blood.

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