P041 ALEMTUZUMAB-RELATED HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: NEGOTIATING THE CYTOKINE STORM

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Background/Aims
Alemtuzumab is an efficacious therapy for relapsing remitting multiple sclerosis (RRMS) preventing neural damage and reducing relapse rate by up to 74%. Administered in 2 treatment cycles 12 months apart and authorised for use in >40 countries, it is a humanized monoclonal antibody selectively directed against the CD52 antigen of T- and B-Lymphocytes. Significant autoimmune effects of Alemtuzumab are reported 6-60 months post-treatment including secondary autoimmunity (42%), thyroid disease (18-26%), idiopathic thrombocytopenic purpura (1-3%) and anti-glomerular basement membrane disease (1%). There are 2 case reports of haemophagocytic lymphohistiocytosis (HLH) in people with MS triggered by Alemtuzumab. HLH is a clinical syndrome of dysregulated, pathological overactivation of innate immunity leading to cytokine storm, multi-organ failure and a very high mortality rate. Clinical features are difficult to distinguish from, and may coexist with, other syndromes such as sepsis. Recognition requires a high index of clinical suspicion and management through multidisciplinary teams (MDT) using immune suppression. Early recognition and treatment improve outcome.

Methods
We report a case of HLH in a 30-year-old female 1 year after her first cycle of alemtuzumab (second cycle delayed due to COVID-19 pandemic) for treatment of RRMS. She was well until presentation 2 days post gadolinium-contrasted routine MRI head scan with headache, fever, bacterial pneumonia/empyema and acute kidney injury. Febrile episodes persisted despite antibiotics.

Results
Investigations revealed hepatosplenomegaly, pancytopenia (Haemoglobin: 80g/L, WBC: 0.9x10⁹/L neutrophils: 0.67x10⁹/L, lymphocytes: 0.14 X10⁹/L, platelets: 82x10⁹/L), hypertriglyceridaemia (5.5mmol/L) and hyperferritinemia (9403ng/ml). She fulfilled the Histiocyte Society HLH-2004 diagnostic criteria for HLH (H-score: 238). Initial treatment was IV methylprednisolone (1g) and intravenous immunoglobulin (IVIG) 2g/kg. Ferritin levels initially decreased (69933ng/ml) but re-escalated (8912ng/ml) with clinical deterioration, necessitating additional treatment with subcutaneous Anakinra (4mg/kg recombinant interleukin-1 receptor antagonist) alongside oral prednisolone 1mg/kg. There was rapid, sustained improvement with resolution of fever but ferritin levels remained highly elevated (45000ng/ml) and cytopenia was slow to resolve. Marker T cell subsets showed significant T cell depression presumably post-alemtuzumab. MDT discussion locally and nationally through the HLH Across Specialty Collaboration (HASC) led to discharge with careful outpatient monitoring. Further IVIG 2g/kg was administered which led to complete resolution of HLH and treatment wean.
Conclusion
HLH is an under-recognised complication of alemtuzumab therapy. Severe HLH requires both cytokine storm-directed treatment and identification/treatment of the trigger. Here, HLH was refractory to first line therapy (steroids and IVIG) and required immune modulation. The combination of alemtuzumab-induced immune dysregulation and sepsis were likely triggers, rather than Gadolinium. Supportive regional and national MDT input were required to guide therapy, especially as the patient wished to avoid etoposide (a standard refractory-HLH therapy) to preserve fertility. MDT working enabled early discharge with close monitoring in ambulatory care - a preferred outcome in the coronavirus pandemic.

Disclosure
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