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LETTER TO EDITOR

Enterovirus-Associated HLH: Addition of Anakinra to IVIG and Corticosteroids

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Dear Editor,

Haemophagocytic lymphohistiocytosis (HLH) is a life-threatening syndrome of inappropriate, uncontrolled immune activation. HLH may occur as a primary familial genetic condition or in association with a primary or secondary immunodeficiency, malignancy, infection, metabolic disorder, or autoimmune disease. Both primary and secondary HLH can be triggered by infections. The term macrophage activation syndrome (MAS) is used for autoimmune-related secondary HLH. The 2004 Histiocyte Society diagnostic and therapeutic guidelines provide a protocol for the management of familial HLH (FHLH). Initial therapy is based on dexamethasone, etoposide, and cyclosporine. There is, however, limited guidance for treating secondary infection related HLH with regard to immunomodulation.

Anakinra, an interleukin-1-receptor antagonist, is increasingly used for the treatment of systemic juvenile idiopathic arthritis (SJIA). Its use is not well reported in the treatment of infection triggered HLH. We present a child with an enterovirus-associated, non-familial episode of HLH. He was successfully treated with intravenous immunoglobulins (IVIG), corticosteroids and the addition of anakinra.

A 13-month-old boy presented to a district hospital with diarrhea, vomiting, and fever. He was admitted with a provisional diagnosis of gastroenteritis. By day 6 of his illness, there was no clinical improvement (Fig. 1). His investigations showed thrombocytopaenia, a raised CRP and raised transaminases. He was started on ceftriaxone. Further tests revealed deranged clotting and a raised ferritin of 9038 μg/L. He was transferred to a tertiary hospital for exclusion of leukemia, extensive infection screen, and management of probable HLH.

At the tertiary hospital, he developed melaena. Abdominal ultrasound reported ascites with hepatosplenomegaly. His echocardiogram was normal. He required an octreotide infusion, multiple blood products, and emergency gastroscopy. Ceftriaxone was switched to meropenem for broader cover and fluids restricted due to probable syndrome of inappropriate diuretic hormone secretion.

Enterovirus RNA (Coxsackie B) was detected in his throat, feces, blood, and CSF. There was no evidence of herpes viruses. A bone marrow aspirate showed reactive features with occasional haemophagocytes. CSF cytology for hemophagoctytosis was non-diagnostic. He fulfilled seven of the eight criteria for HLH as per the 2004 diagnostic criteria: fever, splenomegaly, cytopenias (two lineages), hypertriglyceridemia and hypofibrinogenemia, haemophagocytosis (bone marrow), hyperferritinemia, and raised soluble CD25.

Initial immunological screening tests were not suggestive of FHLH. He had normal perforin, signal lymphocyte activation molecule-associated protein, X-linked inhibition of apoptosis protein expression and granule release assay. The following clinical features were carefully considered:

- Significant rash, fever, and young age—possible MAS
- High risk of gastrointestinal bleeding with corticosteroids
- Ascites with hyponatremia—cautious fluid balance, including IVIG
- Enterovirus driven process

Treatment options were discussed with hematology, rheumatology, and a bone marrow transplant immunologist. The HLH 2004 chemotherapy treatment protocol was thought not appropriate. Following the review of limited case reports and due to the risks of high-dose corticosteroids in the context of

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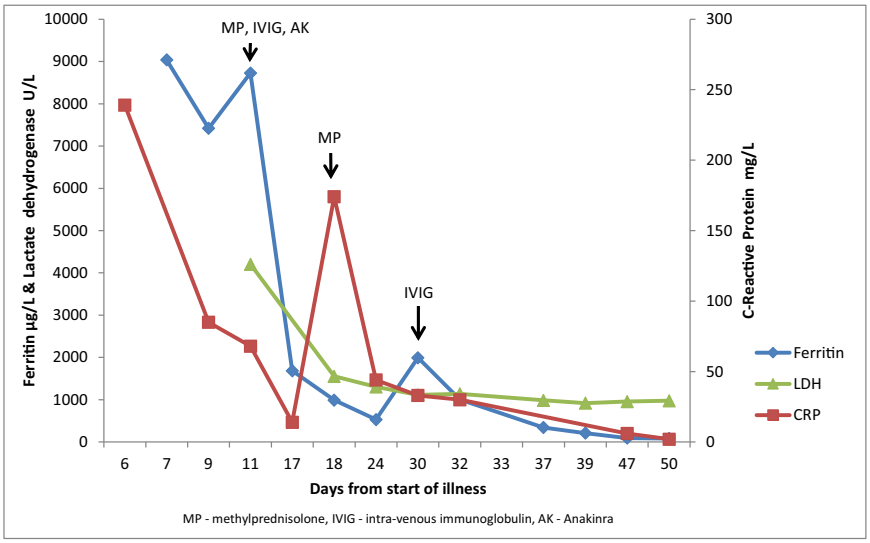

Day	Clinical progression	Investigations	Treatment
1-9	Diarrhoea, vomiting, lethargy and fevers Exudate on tonsils and extensive maculopapular erythematous rash **Day 9 transferred to tertiary hospital**	CRP 239 mg/L Ferritin 9038 µg/L (day 7) Platelets 56x10^9/L ALT 693 u/l , AST 2733 u/l Enterovirus in blood	Ceftriaxone
10-11	Developed melaena, ongoing fevers and florid rash. Increasing ascites	**Ferritin** 7419 µg/L **Platelets** 30x10^9/L**, Haemoglobin** 69 g/L **↓Fibrinogen** 0.4g/L **↑Triglycerides** 4.5 mmol/L **Soluble CD25, GRA, SAP, perforin** requested **U/S – hepatosplenomegaly** with ascites, ↓albumin 19 g/l Peripheral Lymphocyte numbers normal IgG 2.32, IgA 0.74, IgM 0.81 g/l Sodium ↓123 mmol/L	Octreotide 3mg/kg/hr Packed Red cells Platelets Fluid restriction IV Esomeprazole IVIG 0.5g/kg/day x 4days started on day 11
12-14	Ongoing rash and melena – Theatre day 12, then transferred to the intensive care unit **Fulfilled criteria for HLH** 1) Fever 2) Splenomegaly 3) Cytopenias – 2 lineages 4) Hypertriglyceridaemia and hypofibrinogenaemia 5) Haemophagocytosis: bone marrow 6) Hyperferritinaemia Raised Soluble CD25	**Gastroscopy** – gastric erosion and bleeding duodenal vessel **Bone Marrow aspirate**: Occasional haemophagocytes **Lumbar puncture** WBC 6x10^6/L – **enterovirus RNA detected** CSF Cytology – not diagnostic Verbal report – GRA/ Perforin not suggestive of familial HLH Infection screen cultures – no growth	Haemospray Meropenem Parentral nutrition Platelet infusion Cryoprecipitate IVIG 0.5g/kg/day **Day 12 started:** Methylprednisolone pulse 15mg/kg/day x3 doses Anakinra 2mg/kg/day
15-18	Started oral feeds, transferred back to the ward **Working diagnosis: Enterovirus triggered secondary HLH**	CRP 14 mg/L Ferritin 1685 µg/L Triglycerides 3.1 mmol/L	Methylprednisolone reduced to 2mg/kg Octreotide stopped Meropenem changed to ceftriaxone
19	Recrudescence of fevers Possibility of infection or inflammation	CRP 174 mg/L Ferritin 990 µg/L, Triglycerides 3.4 mmol/l Blood cultures - no growth (central/ peripheral)	Teicoplanin added Methylprednisolone 15mg/kg for 3 days (second pulse)
24	Steady improvement	ANA – negative, DsDNA – negative C3 0.7g/L low, C4 – normal	Changed to prednisolone 2mg/kg/day
30-32	Recrudescence of fevers Possible infection or inflammation Shocked	CRP 30 mg /L Ferritin 1994 µg/L, Triglycerides 2.8 mmo/l No growth on blood cultures (central or peripheral)	Fluid bolus Meropenem and Teicoplanin IVIG 1g/kg/day x 2
45	Clinical improvement **Summary of immune investigations**	Soluble CD25 – ↑5131 pg/ml (Resent 26 days after start of treatment) Perforin, SAP, XIAP and GRA - normal Extended Lymphocyte subset analysis – normal Lymphocyte proliferation – normal NK cell mediated Cytotoxicity under research basis was normal	Prednisolone weaned weekly over 4 weeks
52	Discharged home Day 52	CRP <7 mg/L Ferritin 83 µg/l – normal	
73		Enterovirus DNA (blood) not detected for the first time.	
97			Anakinra stopped after 12 weeks

CRP = C-reactive protein, AST = Aspartate aminotransferase, ALT = Alanine aminotransferase, U/S = ultrasound, CSF = cerebrospinal fluid, GRA = granule release assay, SAP = signal lymphocyte activation molecule associated protein, XIAP = X-linked inhibition of apoptosis protein, NK = natural killer cell. First soluble CD25 sent was an inadequate sample.

Fig. 1 Graph of laboratory results for ferritin, LDH, and CRP with tabulated description of clinical progression

gastrointestinal hemorrhage, the decision was made to add anakinra to an adjusted dose of methylprednisolone and administer 2 g/kg IVIG over 4 days. In parallel with active management, investigations were undertaken to exclude primary immune deficiencies, rheumatological, metabolic and liver disorders, known to be associated with secondary HLH.

Initially, there was marked clinical improvement and reduction of fever but he developed recrudescence of fever. He received a second pulse of methylprednisolone and IVIG. The fevers and inflammatory markers gradually subsided. Anakinra was continued for 12 weeks and steroids appropriately weaned. There were no adverse effects. Further immunological investigations were normal including extended lymphocyte subset analysis, lymphocyte proliferation ,and natural killer cell-mediated cytotoxicity. He has had no relapses at 20-months follow up.

Enterovirus-associated HLH is rare. A study of HLH etiology in a hematology-oncology pediatric unit in Athens 2000–2006 had 56 cases of infection-associated HLH [1]. Three were associated with enterovirus and treated with low dose IVIG 400 mg/kg. Two were also prescribed Pleconaril. All three died. Their literature review revealed nine reported cases of enterovirus HLH. Of these, two died having had treatment with IVIG, steroids, and etoposide. The others survived following a combination of IVIG, steroids and, in one case of MAS, cytotoxic therapy. Our subsequent literature review of the MEDLINE database found five further cases of enterovirus-associated HLH reported in neonates. Of these, four survived. Treatment involved blood transfusions, IVIG and, in the one case who died, etoposide-based chemotherapy. Anakinra was not used in any of the reported cases.

Interleukin-1 inhibitors have been used to treat pediatric MAS. Miettunen describes five children with SJIA and infection-triggered MAS (streptococcus/EBV) [2]. They demonstrated a marked response to treatment with the addition of anakinra after an inadequate response to IVIG, corticosteroids, and ciclosporin. MAS may however occur in SJIA whilst on daily doses of 1–2 mg/kg of anakinra. In these situations, higher dosing regimens are required to treat the occurrence of MAS [2]. Features of MAS improve with higher doses, and there are increasing case series documenting the successful addition of anakinra in the management of infection-triggered secondary HLH and MAS. In adults with sepsis and features of MAS, anakinra has been associated with a significant improvement in survival [3]. A current clinical trial may provide further information regarding the efficacy of anakinra in MAS and safety concerning infections [4].

Rajasekaran describes eight children with secondary HLH in an intensive care unit [5]. In five cases, a non-enterovirus infectious trigger was identified, and in three, no trigger was found. All eight received anakinra. Immunoglobulins were prescribed in five cases and corticosteroids in six. The child who died with a relapse of HLH was thought to have primary HLH. Although the standard dosing regimen of anakinra is 1–2 mg/kg/day, Rajasekaran rapidly increased doses up to 11 mg/kg based on clinical response. No adverse events were reported. The rationale for higher doses was that anakinra has a short half-life of 4–6 h and has been used in sepsis, providing support for the safety of higher doses in a systemic inflammatory response setting and previous reports using doses up to 11 mg/kg/day in SJIA [5].

We report that the combination of anakinra, IVIG and corticosteroids controlled an episode of enterovirus-triggered secondary HLH. There were no associated adverse events. It was beneficial in allowing for a quicker weaning of corticosteroids. Related case series suggest that doses greater than 2 mg/kg/day of anakinra may be safe and efficacious.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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