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Letters to the Editor

Haemophagocytic Lymphohistiocytosis, Kawasaki Disease and Use of Intravenous Immunoglobulin

Dear Editor,

We read with interest the case report by Hui et al[1] titled "Haemophagocytic lymphohistiocytosis (HLH) in an infant: important aspects in management" and would like to congratulate the authors for their successful management of the affected patient. However, we disagree with the proposed management that "for mild cases, intravenous immunoglobulin (IVIG) has been recommended as the initial treatment, while preparing to switch to etoposide-containing regimens at first signs of failure." First, this approach has never been tested in clinical trials. Second, the available evidence suggests that IVIG alone may actually jeopardize the clinical outcomes in children with HLH. In addition, we would also like to draw the attention of a possible association between HLH and Kawasaki disease.

The authors' argument for the use of IVIG in "mild" cases of HLH has been largely based on a retrospective study of virus-associated HLH from Taiwan (doubly cited in references 10 and 20). In this study,[2] 9 children were first treated with IVIG with 2 (22%) complete responders. Among the other 7 children who only responded partially or not at all, they went on to receive etoposide-containing regimens with only 2 (29%) survivors. Both survivors were only 2 months after cessation of treatment at the time of report. For the remaining 8 children who receive etoposide-containing regimens at the outset, presumably because they had more serious illness as all had profound cytopenias, 4 (50%) responded and were surviving 6 to 11 months after treatment was stopped. Thus, given the limit of statistical power for the small number of cases, treatment with IVIG in virus-associated HLH seems to be associated with worse outcomes as compared with etoposide-containing regimens. Indeed, when the same group reported their experience in a subsequent study (cited as reference 19), IVIG alone was no longer a treatment option for children with non-familial HLH.[3]

The other study that the authors have cited to support the use of IVIG treatment in virus-associated HLH is a retrospective observation study from Japan (cited as reference 14). Among the 21 patients who received IVIG or other non-etoposide-containing regimens, only one complete remission occurred. The other 20 patients either died or went on to receive etoposide-containing regimens. For the remaining 26 patients who received etoposide-containing regimen upfront, the survival estimate at 4-year after diagnosis was 85.7%. The results led to the conclusion that "early administration of etoposide, preferably with cyclosporine A, is the treatment of choice for patients with Epstein-Barr virus-associated HLH."[4]

Charged with the duty to review the evidence regarding the use of IVIG for 18 haematological conditions, the National Advisory Committee on Blood and Blood Products of Canada and Canadian Blood Services convened a panel of national experts to develop an evidence-based practice guideline.[5] The virus-associated haemophagocytic syndrome has clearly been excluded as an indication for the use of IVIG treatment. The evidence with regard to the use of IVIG has been described as sparse, poor quality and dated.

Therefore, it cannot be overemphasized that children whose illnesses fulfill the diagnostic criteria of HLH of the Histiocytic Society should be treated according to the internationally adopted protocol with steroid, etoposide and cyclosporine A, which has been tested in a prospective manner with much better outcomes compared with prior or other alternative treatments.[6] In this latest version of the management protocol, the role of IVIG is not even mentioned.

The rapid and dramatic response of the infant's illness to a single infusion of 2 g/kg of IVIG was reminiscent of the clinical course of Kawasaki disease. Indeed, Muise et al has reported a patient and reviewed 3 other cases from the literature of Kawasaki disease complicated by macrophage activation syndrome, a condition that is

clinically indistinguishable from HLH.[7] Avcin et al described a 13-month-old boy with Kawasaki disease complicated by HLH with negative molecular diagnosis for perforin mutations.[8] We have also observed haemophagocytosis in a 9-year-old child with Kawasaki disease (Figure 1). Although all these children presented with an illness that was refractory to IVIG therapy, this may reflect a publication bias as marrow examination is often not needed for the evaluation for Kawasaki disease unless there are serious concerns of marrow failure or infiltration.

The report by Hui et al should be credited for calling for the attention to this uncommon but rapidly fatal disorder in any sick children presenting with fever. The Histiocytic Society has laid down the diagnostic criteria and a highly effective treatment protocol, provided the affected children can be recognised in time. Rheumatic disorders, including Kawasaki disease, are now recognised as differential diagnosis to HLH, but optimal management of rheumatic disease-associated HLH remains uncertain.

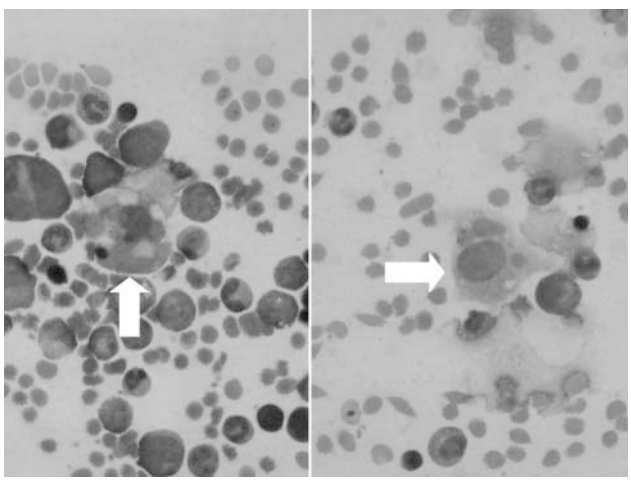

Figure 1 Bone marrow smear in a 9-year-old boy with Kawasaki disease showing erythrophagocytosis in histiocytes.

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Author's Reply

Dear Editor,

With reference to the article "Haemophagocytic lymphohistiocytosis (HLH), Kawasaki disease and use of intravenous immunoglobulin", we would first like to thank the author for the valuable comments on our case report on HLH.

Our case report was prepared prior to the recently published (April 2007) guidelines on the use of intravenous immunoglobulin (IVIG) for haematological condition which concluded that IVIG would not be appropriate in virus-associated haemophagocytic syndrome.[1] The option of using IVIG as an initial treatment in haemophagocytic lymphohistiocytosis (HLH) was mainly suggested as the authors' opinion in a few retrospective reports[2-5] and a literature review on management of HLH by Janka.[6] rather than evidence-based data. There have not been any clinical trials studying this approach. Our case report on the role of IVIG may be somewhat biased by the good outcome in our patient after treatment with IVIG. Although the approach using IVIG in mild diseases had been mentioned by some authors as one of the treatment options, we agreed that the recommendation of treatment of a disease with such a high mortality should be based on a more evidence-based and well-designed protocol – the HLH-protocol,[7] rather than individual authors' opinion.

Atypical Kawasaki disease had been considered as one of the differential diagnoses in our patient initially. However, the echocardiogram finding was normal and our patient's clinical features only fulfilled one criteria (rash) apart from the prolonged fever. The resolution of fever in our patient after IVIG may just represent a spontaneous resolution in a very mild case of HLH. Spontaneous resolution of secondary HLH was previously reported.[8] We agreed that apart from the importance of considering both HLH and Kawasaki disease as differential diagnoses of prolonged fever, HLH should always be carefully watched out as a potential complication of Kawasaki disease.

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