Hemophagocytic Lymphohistiocytosis Prior to the Diagnosis of Kawasaki Disease

We read the recent case report regarding macrophage activation syndrome secondary to Kawasaki disease [1]. We report a unique case with hemophagocytosis preceding the diagnosis of Kawasaki disease.

A 9-year-old girl was hospitalized on 7th day of illness because of prolonged fever and cervical lymphadenopathy. On admission, leukopenia (total leukocyte count $1.1 \times 10^9/L$) and thrombocytopenia (platelet count $60 \times 10^9/L$) were present. Serum aspartate aminotransferase (518 U/L), alanine aminotransferase (99 U/L), ferritin (823 mg/dL), soluble interleukin-2 receptor (1,636 U/mL), interleukin-8 (371 pg/mL) and interferon (IFN)-γ (541 pg/mL) levels were elevated. Triglyceride and C-reactive protein levels were normal. Coagulation studies revealed increased d-dimer levels. A bone marrow aspiration revealed appreciable numbers of hemophagocytosing macrophages. Serology for cytomegalovirus, Epstein-Barr virus and human parvovirus B19 was negative. On 2nd day of hospitalization, conjunctival injection, lip erythema and erythematous papules appeared. There was no hepatosplenomegaly. Echocardiogram showed dilation of right coronary artery. The patient was diagnosed as having Kawasaki disease complicated by hemophagocytic lymphohistiocytosis (HLH) like illness. Clinical symptoms and laboratory findings improved after the initiations of intravenous immunoglobulin (2 g/kg/dose) and flurbiprofen (4.5 mg/kg/day). Coronary artery lesion regressed at the 13th day of illness.

HLH generally complicates Kawasaki disease with prolonged or relapsing course [2]; it developing before the diagnosis of Kawasaki disease is unusual. The pattern of serum cytokines in the present patient was similar to those in virus-associated HLH [3]. Increased IFN-γ level suggests the exaggerated systemic inflammatory response to viral pathogens [3]. Although no pathogen was identified in this case, an unknown virus might have induced the symptoms.

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Albendazole-induced Autoimmune Hepatitis

There are no published data on drug-induced autoimmune hepatitis caused by albendazole. We present here a patient with autoimmune hepatitis (AIH) induced by albendazole prescribed for hydatid cyst. A six-year-old girl was referred to our outpatient clinic with the diagnosis of liver hydatid cyst. Her physical examination and routine laboratory analyses were unremarkable. Albendazole treatment (15 mg/kg/day) was given for two weeks to perform puncture, aspiration, injection and re-aspiration (PAIR). But she was lost to follow up and she was admitted with abdominal pain after 2 months. AST, ALT, and GGT were 663, 800, and 92 IU/L, respectively. Laboratory investigations to exclude infectious, autoimmune, and metabolic liver disease were normal. The elevated transaminase levels returned to the normal range after cessation of albendazole. At 9th month, abdominal ultrasound revealed a progressive increase in the size of the cyst. Treatment with PAIR technique was considered. Albendazole treatment (15 mg/kg/day) was initiated again...
2 weeks before the PAIR procedure. She had mild elevation of transaminase levels at time of the procedure, but albendazole was continued for a week. Three weeks later, AST and ALT were 496 and 468 IU/L. ANA titers became positive (1:100; granular pattern). The pattern of liver enzyme derangement in the child is depicted in Fig. 1. Liver biopsy showed widespread portal lymphoplasmacytic inflammation with extensive interface (piecemeal) necrosis. Prednisolone and azathioprine were started. Transaminase levels rapidly decreased to normal ranges in two weeks. One month later, she had no complaints; physical examination and laboratory parameters were all normal. The steroid dose was tapered. Four months later, laboratory findings and clinical features were also normal. Afterwards, the dose of azathioprine was also tapered.

AIH can be triggered in susceptible persons by an external factor. Previous data suggest [2] that drug-induced AIH makes up a significant proportion, approximately 9%, of AIH cases [1]. Björnsson, et al. [2] suggested that a substantial number of patients who were found to develop drug-induced liver injury were diagnosed with AIH during follow-up.

Our patient had transaminitis recurring every time after treatment of albendazole. In the first episode, elevated transaminase levels rapidly returned to the normal ranges following the cessation of albendazole. Also, ANA was negative and IgG level was in normal range. Hence, she was diagnosed as drug-induced hepatotoxicity due to albendazole. AIH was considered during second episode as ANA became positive, IgG level raised, and liver biopsy showed histologic features of AIH. Rapid response to immunosuppressive drugs supported our diagnosis, as well.

To our knowledge, this is the first report of AIH induced by albendazole. We speculate that drug-induced AIH may be prevented by avoiding use of drugs which have previously caused hepatotoxicity in a given patient.

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MMR at 9 Months!!

A cursory glance at the major changes in the recommendations for immunization by IAP 2014 [1] startled me and made me sit up and take notice. The committee recommends two doses of MMR at 9 and 15 months; no standalone measles dose at 9 months; and no MMR dose at 4-6 years of age. While there is no doubt about the need for two doses of MMR, it is their timing in the recommendation that is questionable.

There is indeed undeniable evidence that both mumps and rubella are also significant problems and this matter has been addressed beautifully in recent articles [1,2] and in the IAP Guidebook on Immunization 2013-14 [3]. Till the new recommendations became available, we were giving measles vaccine at 9 months and 2 doses of MMR at 15 months and 5 years. This schedule clearly combined the benefit of early protection against measles, coverage of all three diseases as recommended by WHO, and the very important issue of long term protection against mumps and rubella.

In the pre-vaccine era, mumps usually occurred primarily in young children between the age of 5 and 9 years [4]. It is most unusual to see mumps in children younger than below 5 years; so why the haste in completing both doses of mumps by 15 months?