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Case Report

Hemophagocytic Lymphohistiocytosis and Kikuchi-Fujimoto Disease Associated with Mumps in a Previously Vaccinated Child - A Case Report and Review of the Literature

Paul K. Pattengale[1*], Rhina D. Castillo[2], Arumina B. Agarwal[2], Anusha Ramanathan[2], Joseph A. Church[3]

[1]Department of Pathology and Laboratory Medicine, Children's Hospital Los Angeles, and Keck School of Medicine at the University of Southern California, USA

[2]Division of Pediatric Rheumatology, Children's Hospital Los Angeles, and Keck School of Medicine at the University of Southern California, USA

[3]Division of Clinical Immunology and Allergy, Children's Hospital Los Angeles, and Keck School of Medicine at the University of Southern California, USA

[*]**Corresponding Author:** Paul K. Pattengale, Department of Pathology and Laboratory Medicine, Children's Hospital Los Angeles, and Keck School of Medicine at the University of Southern California, USA, Tel: +1 3233615608; Fax: +1 3233618039; E-mail: ppattengale@chla.usc.edu

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Abstract

Kikuchi-Fujimoto Disease (KFD), a rare and usually self-limited inflammatory condition, and Hemophagocytic Lymphohistiocytosis (HLH), an unrestrained immune activation syndrome characterized by cytokine storm and accumulations of activated histiocytes/macrophages, are often triggered by viral infections, and are further characterized by the proliferation of activated CD8+ T lymphocytes. Despite these similarities there are only a few reported cases of KFD co-presenting with HLH, and no cases of co-existent KFD and HLH have been reported to be triggered by mumps virus infection. Here we present the case of a 9 year old boy with fever of unknown origin, enanthem, exanthem, and parotitis with serologic confirmation of an acute mumps virus infection who developed co-existent KFD and HLH despite previous immunization. Importantly, Natural Killer (NK) cell dysfunction and genetic variants in MUNC13-4 and MEFV were identified as potential contributing factors in the hyper-inflammatory processes observed in this patient.

Keywords: Hemophagocytic Lymphohistiocytosis; Kikuchi-Fujimoto Disease; Mumps; Natural Killer Cells

Introduction

Kikuchi-Fujimoto Disease (KFD) and Hemophagocytic Lymphohistiocytosis (HLH) are both inflammatory conditions mediated by CD8+ T cells and activated histiocytes/macrophages [1,2] with only a few reports describing their occurrence together [2-7]. KFD is a rare and usually self-limited inflammatory condition, and is more commonly reported in young Asian women and very rarely seen in children. KFD is characterized by diffuse cervical lymphadenopathy, fevers, anemia and leucopenia, and is identified by the histological findings of necrotizing lymphadenitis, karyorrhexis and histiocyte aggregates on lymph node biopsy [8-14]. Hemophagocytic lymphohistiocytosis (HLH) is an unrestrained immune activation process characterized by accumulations of well-differentiated mononuclear cells with a macrophage phenotype [1,15,16]. Familial HLH is caused by loss-of-function mutations in genes that code for factors that are critical for cytotoxic T-lymphocyte elimination of virus-infected cells [17]. Sev-

eral triggers for these conditions have been described and include Juvenile Myelomonocytic Leukemia (JMML), infections with Epstein-Barr virus (EBV), parvovirus B19, Cytomegalovirus (CMV), human immunodeficiency virus (HIV), and Human Herpes Virus 8 (HHV8), and autoimmune conditions particularly systemic juvenile idiopathic arthritis [7,18-21]. Mumps virus as a trigger for either HLH or KFD has been reported in three adults, none of whom presented with both KFD and HLH [22-24]. Mumps virus infection in otherwise healthy previously vaccinated patients has been reported [25-27].

However in many of these patients their immunity may have waned after 10 years from immunization, or they were in such frequent close contact with the source of virus that their degree of exposure may have overcome vaccine-induced protection [25-27]. None of these recent reports described both HLH and KFD as a result of mumps virus infection, and it may be that genetic variability in host immune responses play a significant role in the simultaneous development of these two diseases. We present a case of a previously immunized child with genetic variants in MUNC 13-4 and MEFV who developed KFD and HLH that were likely triggered by mumps virus infection. To our knowledge this is the first report of such an individual.

Case Presentation

A 9 year old previously healthy Armenian-American boy presented with 10 days of fever, night sweats, fatigue, malaise, frontal headaches, periorbital swelling, and a generalized maculopapular rash with ulcerations on both cheeks. His symptoms began shortly after a trip to Berkeley, California during a mumps outbreak, but with no specific exposures or ill contacts. The fevers were continuous ranging between 101-104.5°F with poor response to antipyretics. It was noted by his pediatrician that he had enlarged cervical lymph nodes and parotitis. Laboratory evaluation revealed marked leucopenia at which point he was referred for urgent evaluation. In the Emergency Department, although his temperature was 104°F, he was in no acute distress. A Complete Blood Count (CBC) showed a White Blood Cell Count (WBC) of 1.2k/uL (normal 5-13k/uL), a differential of neutrophils 26%, bands 21%, lymphocytes 38%, and monocytes 15%; a hemoglobin (Hgb) of 11.2g/dl (normal 11.5-15g/dl), a hematocrit (Hct) of 32.8% (normal 34-45%); and platelets of 178k/uL (normal 150-450k/uL). Sedimentation rate (ESR) was 41mm/hr and rose to 108mm/hr within a few days (normal 0-10mm/hr), while C-Reactive Protein (CRP) was slightly elevated at 1.1 mg/dL (normal 0-0.9 mg/dL). D-dimer was elevated at 2,350ng/ml (normal 0-500ng/ml). Urinalysis was unremarkable. Serum Aspartate Aminotransferase Level (AST) 78U/L (normal 15-46U/L) was slightly elevated, alanine aspartate (ALT) 16U/L (normal 3-35U/L) was normal, and Lactate Dehydrogenase (LDH) was 2,142U/L and elevated (normal 370-340 U/L). He was admitted to the hospital for further evaluation and management. His past medical history was unremarkable for allergies and recurrent infections, and all immunizations were documented to be up to date for his age. Upon initial hospital evaluation he was noted to have coryza, parotitis, bilateral non-tender, cervical and left supraclavicular lymphadenopathy, a generalized maculopapular rash with central ulceration and crusted borders of the lesions over his cheeks, and oral ulcers. No hepatosplenomegaly, axillary or inguinal lymphadenopathy was appreciated on physical exam.

Over the course of two days he developed frank arthritis in his hands, knees and feet, and he was empirically treated with meropenem 60mg/kg/day. A multidisciplinary diagnostic evaluation was performed to look for possible infectious, malignant or rheumatologic etiologies. An echocardiogram was done and was normal. Chest radiograph showed no significant pulmonary abnormalities. Neck, chest and abdominal Computed Tomography (CT) showed enlarged lymph nodes in the cervical, axillary, and inguinal areas, and parotid gland enlargement. An abdominal ultrasound showed a small amount of peritoneal fluid and hepatosplenomegaly.

Blood bacterial and fungal cultures on several occasions were negative, as were Antibody (ab) tests suggestive of acute infection for the following: Coccidiomycosis, Bartonella, Parvovirus B19, Adenovirus, measles virus, Epstein-Barr virus (EBV), and Cytomegalovirus (CMV). Additional negative studies included anti-streptolysin O, Herpes Simplex Virus (HSV) culture, enterovirus PCR from oral lesions, HSV and enterovirus PCR from blood, Respiratory Viral Panel (RVP), Human Immunodeficiency Virus (HIV) serology, and interferon-gamma release assay for tuberculosis.

However, mumps IgM and IgG antibody titers, as tested by Immunofluorescent Assay (IgM) and immunoassay (IgG),were strongly positive and indicative of acute infection at 1:1280 (normal <1:20) and >5.00 respectively (<0.9 negative, 0.91-1.09 equivocal, >1.10 positive result). Studies for an autoimmune process were uniformly negative including Antinuclear Ab (ANA), Double Stranded DNA (dsDNA) ab, Anti-Neutrophil Cytoplasmic Ab (ANCA), Angiotensin Converting Enzyme (ACE) level, Smith Ab, and Sjögren's (SSA and SSB) ab. Serum immunoglobulin levels were elevated with IgG of 1580mg/dl (normal 613-1295mg/dl) and IgM of 387mg/dl (normal 53-334mg/dl), respectively. Serum IgA, serum C3, and serum C4 were within normal limits. The possibility of malignancy was evaluated with bone marrow, skin (from ulcerative lesion on cheeks) and lymph node biopsies. In summary, no malignant changes were identified. Both bone marrow and skin biopsies showed non-specific, nonneoplastic findings. In contrast, the cervical lymph node biopsy, although benign, met the morphologic criteria for Kikuchi-Fujimoto necrotizing lymphadenitis (Figures 1A and 1B). Interestingly, immunostaining demonstrated

increased CD 68+ histiocytes/monocytes (Figure 1C), increased CD138+ plasmacytoid lymphocytes and plasma cells (Figure 1D), and a predominance of infiltrating CD8+ T lymphocytes (Figure 1F), as compared to CD4+ T lymphocytes (Figure1E).

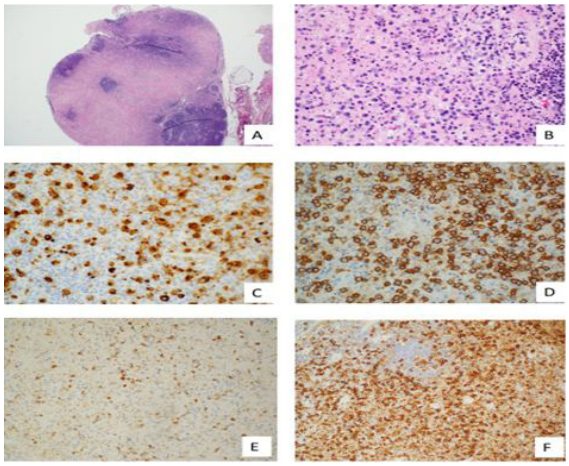

Figure 1: A. Low power view of a cervical lymph node demonstrating extensive necrosis (H and E staining). B. High power view showing karyorrhexis intermingled with a mononuclear infiltrate (H and E staining). C. High power immune stain showing increased numbers of infiltrating CD68 positive histiocytes/macrophages. D. High power immune stain of infiltrating CD138 positive plasmacytoid lymphocytes and plasma cells. E. Medium power immune stain of infiltrating CD4 positive T cells. F. Medium power immune stain of infiltrating CD8 positive T cells.

After 8 days of persistent fever, the patient's WBC remained low at 1.46k/uL, and Hgb dropped to 7.7g/dL. AST and ALT increased to 307U/L and 204U/L respectively. D-Dimer increased to >5000 ng/ml (normal 0-500 ng/ml), and triglycerides and ferritin levels were also noted to be increased at 236mg/dL (normal 40-160 mg/dL) and 3,240ng/ml (normal 10-140ng/ml), respectively. At this time NK cell function studies using standard chromium release assays (Cincinnati Children's Diagnostic Immunology Laboratory) demonstrated profoundly reduced NK cell cytolytic activity (0.0 lytic units; normal >2.6). With NK cell dysfunction, hyperferritinemia, cytopenias in two cells lines, hypofibrinogenemia/hypertriglyceridemia, persistent fevers and splenomegaly, our patient met criteria for HLH (16). Consequently, he was treated with methylprednisolone 2mg/kg/day while awaiting results of pending infectious and oncologic studies. He responded within 24 hours with resolution of fever, down-trends of D-dimers, AST, ALT and triglycerides, and an increase of his WBC to 12.14k/uL. His course significantly improved over several days and he was discharged home on a tapering course of oral prednisone.

After his complete recovery and discontinuation of all medications, additional immunologic studies were performed. Decreased NK cell function was demonstrated on two additional occasions (0.2 and 0.7 lytic units). In contrast, CD107a, perforin, granzyme B, XIAP and SAP expression were normal. Soluble IL-2 receptor levels were also normal. Targeted sequencing of specific genes known to be associated with familial HLH using standard polymerase chain reaction (PCR)-based amplification techniques was performed (Cincinnati Children's Molecular Genetics Lab) and revealed a single missense variant of unknown significance in MUNC13-4 c.1662G>C (p.E554D). Variants were not found in PRF1, STX11, RAB27A, and STXBP2. Similarly, targeted sequencing of MEFV, the gene affected in familial Mediterranean fever (LabCorp, San Diego, CA) revealed a heterozygous mutation in MEFV: c.2282G>A, Arg761His. Neither parent was genetically tested. Additional immunologic studies demonstrated normal T-cell proliferative responses to phytohemagglutinin, concanavalin A, and pokeweed mutagen. Pneumococcal antibody responses to Pneumovax^{tm} immunization were positive (>1.3 mcg/mL) for 20 out of 23 serotypes tested; and Haemophilus influenza type b antibody was protective. He has remained in remission off of medications, and his mumps IgM antibody titer decreased from 1:1280 on admission to 1:40 two months after discharge, and was negative by 1 year (<1:20).

Discussion

KFD, also known as necrotizing lymphohistiocytosis, was described independently in Japan in 1972 by Kikuchi [28] and Fujimoto [29]. KFD is characterized by cervical lymphadenopathy, fever, and leucopenia, elevated ESR and elevated transaminases. ANA positivity was found in 3% of patients in a large study [9]. KFD is more common in young Asian women, under the age of 30 [9,10], with some studies reporting the female to male ratio as high as 4:1. [10,11]. The disease is considered rare in children [12]. The differential diagnosis of KFD at onset includes a variety of infectious, neoplastic, autoimmune and inflammatory diseases that present with lymphadenopathy and fever such as tuberculosis, lymphoma, myeloid tumor, Kawasaki's disease, cat scratch disease and Systemic Lupus Erythematosus (SLE) [9,13,21]. A definitive diagnosis requires lymph node excisional biopsy and demonstration of characteristic histologic features: apoptotic necrosis with karyorrhexis in the cortical and paracortical areas and the presence of histiocyte aggregates [11]. Generally a benign and self-limiting condition, KFD requires no specific treatment, although some authors have suggested the use of steroids for recalcitrant or recurrent episodes [9]. Several viruses have also been associated with KFD, including EBV, HIV, parvovirus B19 and HHV-8 [20].

Primary or familial HLH manifests as a hyper-inflammatory response often to EBV infection that cannot be controlled because mutations in specific genes result in absent or inadequate cytotoxic T-cell or NK cell elimination of EBV-infected B-cells [17]. Additional triggers for HLH include other infections, malignancies, autoimmune disorders and auto-inflammatory disorders, particularly juvenile idiopathic arthritis [7,18-21]. Mumps virus-associated

KFD has only been described in one adult case [22], while mumps virus-associated HLH has been described in only two adult case reports [23,24]. Synchronous KFD and HLH have been described in several case reports [2-7], but never in association with mumps virus infection in a previously immunized child, as seen in our patient. The incidence of mumps has been reduced by high rates of immunization. However, outbreaks have been reported even in populations who received the recommended two doses of the vaccine [25].

In 2008 an outbreak of mumps in well-immunized college students in Kansas suggested that vaccine-induced protection waned over time [26]. Furthermore, mumps infection of multiple fully-immunized 13 to 17 year old boys who were attending Orthodox Jewish schools has been reported [27]. The nature of this educational setting indicated that intense face to face exposure facilitated transmission and overcame vaccine-induced protection in these individuals [27]. A diagnosis of acute mumps infection in the present case was based upon the presence of clinical parotitis at presentation, identification of a location of potential exposure and the demonstration of a strongly positive IgM antibody level that decreased over time. The histopathology of the patient's lymph node demonstrated KFD. Finally, the criteria for a diagnosis of HLH were met.

Because our patient was diagnosed with KFD and HLH only 5 years after his second mumps immunization, and had no history of being in an environment similar to that described by Barskey et al. [27], the presence of an underlying primary immune dysfunction was considered. The patient's NK cell number and function was monitored for over one year after his full recovery from KFD and HLH, and remained abnormally low. A search for genetic variants that might explain our patient's persistently decreased NK cell function demonstrated a single allele sequence variant of unclear significance in the MUNC13-4 gene, and a heterozygous mutation in the MEFV gene. There are no reports of either of these two alone being associated with either HLH or KFD. A literature search revealed a single case of a patient with an established diagnosis of Familial Mediterranean Fever (FMF) due to compound heterozygous MEFV mutations (M694V/E148Q) and associated with Crohn's disease that developed fatal HLH [30]. It is possible that the combination of our patient's single missense variant of MUNC13-4 and the heterozygous MEFV variant together may have contributed to his disease manifestation. Although still uncertain in humans, there is, however, recent convincing evidence that heterozygous biallelic mutations can cause an HLH-like condition in a murine model. Stated another way, heterozygous mutations among different HLH-associated genes add up, resulting in an increased risk of developing HLH. The HLH-associated genes tested in the murine model were PRF1, STX11, and RAB27A. MUNC13-4, however, was not tested [31,32]. That mumps virus infection alone has been reported to trigger either KFD or HLH in only three individuals [22-24] suggests that there is a strong genetic component that predisposed our patient to develop this degree of inflammatory response. It is important to consider HLH and KFD in a persistently febrile child with adenopathy. In addition, documentation of a complete immunization record may provide a false sense of security in situations where an individual patient may not be protected because of waning immunity or the presence of subtle immunodeficiency. To our knowledge, this is the first case report documenting mumps virus causing both KFD and HLH in a previously immunized child.

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