Haemophagocytic lympho-histiocytosis: A rare initial presentation of microscopic polyangiitis in a three-year-old girl

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Introduction

Microscopic polyangiitis (MPA) is a childhood onset anti-neutrophilic cytoplasmic antibody (ANCA) associated vasculitis (AAV)[1,2]. AAV predominantly affects small blood vessels[2,3]. AAVs are distinguished from other small vessel vasculitis by the absence of immune deposits[2]. Other AAVs are granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA) and renal limited ANCA vasculitis[1,2]. MPA is distinguished from GPA and EGPA by the absence of granuloma formation and the presence of necrotising vasculitis[2]. Renal involvement, in the form of necrotising glomerulonephritis is one of the common manifestations of MPA[3]. Other clinical manifestations common to all AAVs include fever, fatigue, weight loss, arthralgia, rhinosinusitis, cough, dyspnoea and urinary abnormalities[3]. Prodromal symptoms can last for weeks to months without evidence of specific organ involvement[3,4]. Although these diseases have been reported in all age groups, they most commonly manifest in older adults[5]. In the paediatric age group, GPA has been reported more frequently than MPA and EGPA[1,6,7]. Haemophagocytic lympho-histiocytosis (HLH) is extremely rare in MPA. A systematic review involving 117 papers, 421 with autoimmune/rheumatic patients did not find HLH association with MPA[8]. We present a 3-year-old girl with the diagnosis of MPA who presented initially as HLH.

Case report

A 3-year-old girl first presented to us with fever and maculopapular rash over the face and upper limbs of 15 days duration. She also had polyarthralgia. She had no premorbid condition and no significant past history. Development and immunization were age appropriate. Examination revealed fever of 103°F, bilateral cervical lymphadenopathy, hepatomegaly of 4cm, splenomegaly of 4cm, maculopapular rash over the face and neck (Figure 1A), and palatal ulcer (Figure 1B**)**. Rashes were also observed over bilateral upper limbs. Other systemic examination was normal.

Investigations showed pancytopenia [haemoglobin (Hb): 7.4g/dl, total leucocyte count (TLC): 4500 cells/mm^3, monocytes: 4%, platelet count (PC): 136,000/mm^3)]. She was treated with packed red blood cell (PRBC) transfusion and antibiotics. Though the transfusion trigger for PRBC is Hb of 7g% or lower, in this child, considering the overall general condition, persistent tachycardia and tachypnoea during afebrile period, we transfused PRBC. Detailed work up for infectious aetiology, including tuberculosis, rickettsial fever, brucellosis, typhoid fever and influenza was negative. Parvovirus infection was not considered as it was not a pure red cell aplasia. We did not consider infectious mononucleosis because of absence of axillary lymphadenopathy, and the normal monocyte count. Bone marrow examination showed no evidence of infiltration. Antinuclear antibody (ANA) profile was negative. Serum ferritin (>2000ng/ml) and triglycerides (237mg/dl) were elevated. Lactate dehydrogenase (LDH) was 816 IU/L. A diagnosis of infection associated HLH was considered as 5 out of 8 criteria were fulfilled. She was started on intravenous corticosteroids. She responded to treatment, fever subsided and rash decreased. She was discharged after 12 days on alternate day oral prednisolone (0.5mg/kg).

She was under regular follow up. The organomegaly and rash subsided. Five months later, she presented with recurrence of rash, abdominal distension, cough, fever and arthralgia. Rash involved face, upper limbs, chest, abdomen and lower limbs. Clinical examination showed multiple oral ulcers (Figure 1C), generalised maculopapular rash (Figure 1D**)**, generalised lymphadenopathy, hepatomegaly of 5 cm and splenomegaly of 4cm. Other system examination was normal.

Investigations showed bicytopenia (Hb: 7.1g/dl, TLC: 5400 cells/mm^3, monocytes: 5%, PC: 105,000/mm^3), elevated erythrocyte sedimentation rate (ESR): 74mm/1st hour, LDH: 571U/L, ferritin (276ng/ml) and triglycerides (295mg/dl). Urinalysis showed proteinuria and microscopic haematuria. Twenty-four urine protein was 51mg/m^2/hour. Detailed autoimmune work up showed ANCA positivity with perinuclear type fluorescence (p-ANCA). Skin biopsy showed perivascular lymphocytic infiltration suggestive of MPA (Figure 1E). She was started on oral prednisolone (2mg/kg/day), cyclophosphamide (2mg/kg/day) and other supportive treatment. Dose of prednisolone was tapered after 6 weeks and cyclophosphamide was given for 3 months. Parents were counselled regarding the nature of the disease and advised regular follow up. During follow up she achieved complete remission with resolution of rash (Figure 1 F).

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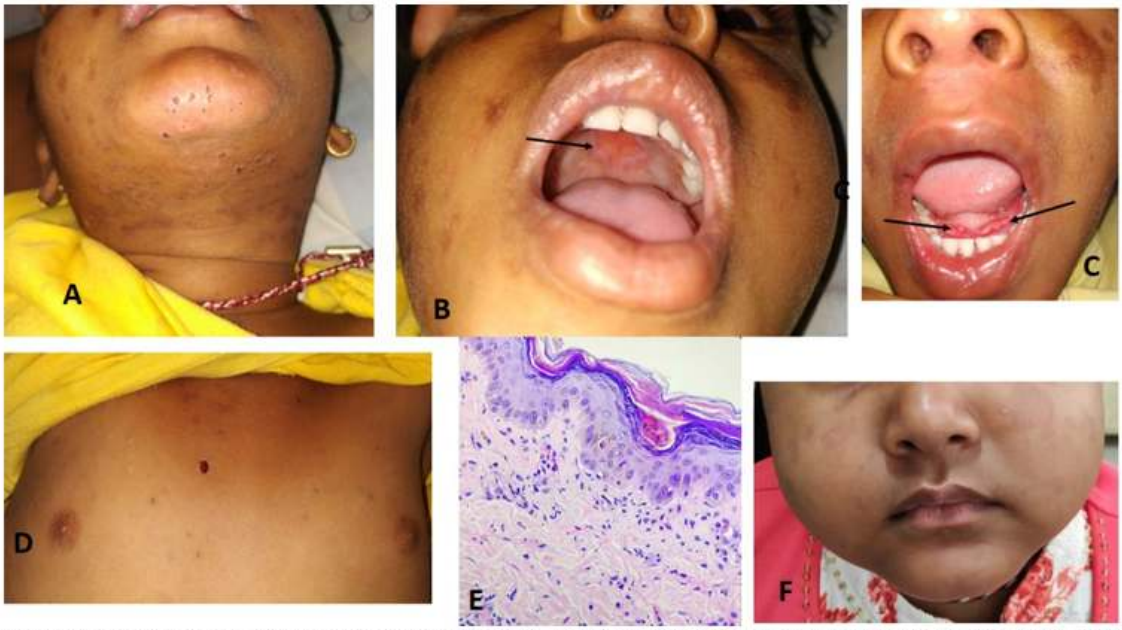

Figure 1: ***A) Maculopapular rash over face and neck, B) palatal ulcer, C) Multiple oral ulcers, D) Generalised maculopapular rash, E) Skin biopsy showed perivascular lymphocytic infiltration suggestive of MPA, F) Resolved rashes over face at follow up***

Discussion

HLH complicating MPA has been rarely described especially in the paediatric age group. HLH results from non-specific activation of macrophages in bone marrow and lymphoid organs leading to haemophagocytosis of blood cells and production of high amounts of pro-inflammatory cytokines[6,7]. It can be primary or secondary to infections, malignancies or autoimmune conditions[6]. In the present case, the diagnosis of secondary HLH was made as 5 out of 8 criteria required for the diagnosis were fulfilled: fever, splenomegaly, bicytopenia, hypertriglyceridaemia and hyperferritinaemia[7]. HLH sometimes may be atypical, have an insidious course and may not fulfil all criteria always[7]. It is also possible that a number of patients are likely develop one or more of the diagnostic criteria later during the disease course[7]. The triglyceride level in the present case, though high, is lower than the cut-off level of 265mg/dL. We did not repeat this level as other criteria were strongly suggestive of HLH in the clinical context. A study from USA found triglycerides >265 mg/dL only in 39% of proven HLH cases[9]. Authors further reported triglycerides in the range of 49-812mg/dL in same patients. The bone marrow aspirate also may not show haemophagocytosis always as in the present case. Serial bone marrow aspirates over time could help in such a scenario[7]. We could not do further bone marrow aspiration in the present case. However, the primary aetiology was considered as infection due to the rare occurrence of AAVs in that age group and also the rare association of HLH with MPA. The association between HLH and autoimmune systemic diseases has been described in a systematic review in descending order as: juvenile idiopathic systemic arthritis, lupus, Still's disease, Kawasaki disease, dermatomyositis, rheumatoid arthritis, periarteritis nodosa, sarcoidosis, Sjogren syndrome, ankylosing spondylitis, Behcet disease, sharp syndrome and GPA. There was no case of MPA found in this review[8].

HLH secondary to autoimmune disorders usually responds to treatment of the primary condition. Corticosteroids are useful in controlling the activity of HLH with transient effect[10]. In the present case, the child initially responded to corticosteroids. She did not have renal manifestations of MPA at presentation. Five months after the onset of disease, she presented with features of nephrotic syndrome along with characteristic skin rash and oral ulcers and was diagnosed to have MPA with renal involvement. The combination of glucocorticoids and cyclophosphamide has been recommended for the treatment of MPA[11]. Daily oral low-dose cyclophosphamide has been associated with a lower rate of relapse on long-term follow-up[12]. In the present case, the child responded well to treatment with oral corticosteroids and cyclophosphamide and was found to be asymptomatic at 6 months follow-up.

In conclusion, HLH secondary to autoimmune disorders usually responds to treatment of the primary condition. Corticosteroids are useful in controlling the activity of HLH with transient effect. HLH associated with MPA responds well to cyclophosphamide.

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