Case Report

Use of Anakinra in a Case of Severe Dengue with Refractory Secondary Hemophagocytic Lymphohistiocytosis

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Abstract

Background: Hemophagocytic lymphohistiocytosis (HLH) is a severe life-threatening systemic inflammatory syndrome which may be secondary to infections. It is a potential complication of severe dengue. We report a child with severe dengue with worsening clinical course due to secondary HLH. The refractory course responded to intravenous anakinra (an interleukin-1 blocker) as an add-on therapy. **Clinical Description:** An 11-year-old girl with dengue presented on the 7th day, with progressively worsening clinical condition, having developed multi-organ dysfunction syndrome. **Management and Outcome:** She required mechanical ventilation, hemodialysis, and extracorporeal hemoadsorption therapy. In view of secondary HLH, intravenous immunoglobulin and methylprednisolone were administered, but there was clinical worsening. Hence, anakinra was initiated and improvement was noted in the next 48 hours. The child was finally extubated on day 17 of illness and could be discharged. **Conclusion:** Secondary HLH should be considered early in severe dengue cases with cytopenias, hyperferritinemia, and multi-organ dysfunction and immunotherapy should be initiated without delay. Anakinra is a promising, efficient, therapeutic choice and may have a beneficial role and better prognosis if started early in rapidly worsening HLH.

Keywords: Hypercytokinemia, hyperferritinemia, India, pediatric

Hemophagocytic lymphohistiocytosis (HLH) is characterized by hyperinflammation due to the uncontrolled proliferation of activated lymphocytes and histiocytes secreting large amounts of inflammatory cytokines. The condition may be primary (genetic) or secondary (acquired).[1] Severe dengue may be one of the secondary causes leading to HLH and may require[2,3] intravenous immunoglobulin, or chemotherapy with very few studies exist reporting use of anakinra, an interleukin (IL)-1 blocker, in the treatment of dengue HLH.[4-6] We report the successful outcome of a child with severe dengue complicated with secondary HLH, who was treated with anakinra, an IL-1 blocker.

Clinical Description

An 11-year-old female, appropriately diagnosed at a local hospital, as dengue fever on day 4 of illness, was referred to our center on the 7th day of illness, in view of increasing respiratory distress, tense ascites, and falling blood pressure. This was her second episode of dengue, the previous one 4 years back, which was uneventful. Besides this, the girl did not have any other significant medical or surgical illness in the past. The child was born at term, to a nonconsanguineously married couple, with an uneventful antenatal, natal, and postnatal period. She had achieved her developmental milestones at appropriate ages was immunized for age.

On admission, the child was very lethargic, sick-looking, and dyspneic. She was afebrile, with a heart rate of 150/min, feeble peripheral pulses, prolonged capillary refill time, respiratory rate of 54/min, and SpO2 - 98% on 6 L/min oxygen support by face mask. She was in decompensated circulatory shock with a blood pressure of 66/40 mmHg (<5th centile). There was decreased air entry in bilateral basal lung fields, with tense ascites, liver palpable 6 cm, and spleen 2 cm below costal margin.

Management and Outcome

The child was managed along the lines of dengue shock syndrome and was administered intravenous crystalloid boluses of normal saline, followed by colloids along with

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high-flow oxygen investigations [Table 1] showed hemoglobin of 14.5 g/dL, with leukocytosis, thrombocytopenia, bilirubin total 2.2 mg/dL, and raised liver enzymes and deranged coagulation profile (INR 1.96). Venous blood gas showed pH of 7.21, pCO_2 28, HCO_3 15, and lactic acidosis 8.1. Chest X-ray showed bilateral large pleural effusions. Considering a possibility of secondary HLH, further investigations revealed low fibrinogen, very high ferritin, raised lactate dehydrogenase, raised IL-6 (50 pg/mL), and triglycerides (117 mg/dL). Because of the moribund condition of the child, bone marrow aspiration was not done.

The child thus fulfilled the criteria of HLH as per the guidelines of 2004,[7] secondary to dengue. Intravenous immunoglobulin (2 g/kg) and 500 mg methylprednisolone (MP) were initiated on day 8 of the illness. On day 9, she developed severe acute respiratory distress syndrome with worsening renal functions [Table 1]. She was ventilated with maximal settings (positive end-expiratory pressure of 16 cm H_2O and peak inspiratory pressure of 35 cm H_2O). She underwent continuous veno-venous hemodiafiltration for acute kidney injury. Extracorporeal hemoadsorption therapy for the removal of cytokines was also incorporated. Parenteral MP dose was increased to 1 g and she was started on intravenous meropenem.

On day 10, in view of persistent hyperferritinemia (100,000 ng/mL) and hypercytokinemia (IL-6 of 77 pg/mL) with ongoing multiorgan dysfunction, anakinra (IL-1 blocker) was initiated intravenously at 6 mg/kg/day. Within 48 hours, ventilator settings could be gradually weaned, liver enzymes started improving [Table 1], and serum ferritin levels started decreasing. On day 13 there was resurgence of a fever spike raising the possibility of new-onset sepsis. Stress dose hydrocortisone was substituted for MP, the dose of anakinra was lowered to 2.5 mg/kg/day, antibiotics and antifungals were upgraded to ceftazidime–avibactam and caspofungin. Blood culture after 5 days, however, showed no growth. Anakinra was given for 5 days, the cumulative dose being 20 mg/kg. The child showed signs of recovery, was finally extubated on day 17 of illness, and could be discharged after another 5 days.

Discussion

The above is an interesting report of a child with complicated dengue, with secondary HLH, with a worsening clinical picture, refractory to standard treatment, finally salvaged possibly by administration of IL-1 blocker anakinra along with meticulous management of all associated complications.

Dengue fever is characterized by a febrile phase, followed by an afebrile phase, which may turn into a critical phase with complications such as hemorrhage or shock. Our case presented to us in the critical phase with decompensated shock. In addition, the child was found to have features of secondary HLH, which is a known, but rare complication of dengue.[2,3,8,9] The study of 22 children by Bhattacharya *et al*., and the 5-year retrospective analysis from Malaysia cautioned pediatricians to be watchful for HLH in dengue, because of its high mortality.[10,11] As there is an overlap between features of HLH and dengue, the former may remain elusive.[12] Our case, fulfilled the criteria for HLH, although bone marrow could not be done. The exact pathophysiology leading to HLH in severe dengue is still unknown. Several studies have noted that both the innate and the adaptive immune systems are activated which contribute to cytokine production and HLH. In HLH, the inability to clear the antigenic stimulus results in the perpetuation of the inflammatory stimulus, resulting in uncontrolled hypercytokinemia, sustained macrophage activation, and tissue infiltration.[13] Recently, IL-18 has also been found to be raised in severely ill dengue patients.[14]

Management includes suppression of hyperinflammation in HLH, by corticosteroids and intravenous immunoglobulins. Other therapeutic agents include cyclosporine A, anti-cytokine agents such as etoposide, monoclonal antibodies such as

Table 1: Results of investigations during hospital stay of the child with severe dengue and secondary hemophagocytic lymphohistiocytosis

	Day 7	Day 9	Anakinra (6 mg/kg/day)		Anakinra (2.5 mg/kg/day)			Day 17	Day 22
			Day 10	Day 11	Day 12	Day 13	Day 14		
Hemoglobin (g/L), 11.5–15.5	14.5	8.6	9.7	9.2	11.4	8.8	8.5	8.7	9.2
Hematocrit (%), 35–45	42.0	24.6	28	27		26.2	25.4	26.3	26.0
Total leukocyte count (/mm^3), 5000–13,000	16,700	10,700	9500	10,300	15,200	7400	8000	7000	6200
Platelet count (L/mm^3), 1.5–4.5	0.15	0.44	0.52	0.71	1.36	0.91	0.98	1.01	1.21
Urea (mg/dL), 11–39	28	68	60	48	60	53	54	60	42
Creatinine (mg/dL), 0.3–0.7	0.9	1.9	1.4	1.2	1.4	1.2	0.9	0.8	0.5
AST (SGOT) (U/L), 14–37	10,327	8623	2454		1228		183	127	
ALT (SGPT)) (U/L), 8–29	2674	1438	935		689		142	109	
Ferritin (ng/mL), 7–140	100,000	100,000	100,000	90,605	76,898	46,521	29,079	10,300	4231
Fibrinogen (mg/dL), 200–400	109	216							
LDH (U/L), 110–295	16,502								
IL6 (pg/mL), <7	50	70	77						

AST: Aspartate transaminase, ALT: Alanine transaminase, SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase, LDH: Lactate dehydrogenase, IL-6: Interleukin 6

alemtuzumab and rituximab.[4] Corticosteroids are often used as the first choice for infection-associated HLH.[8,11] Furthermore, intravenous immunoglobulin G is associated with a favorable outcome in dengue associated with HLH.[15]

In our case, clinical deterioration with multiorgan dysfunction, hyperferritinemia, and hypercytokinemia persisted in spite of initial therapy with corticosteroids and IV immunoglobulin, necessitating additional therapy. The benefit of using recombinant human IL-1 receptor antagonist anakinra in secondary HLH is presently supported by several studies in both pediatric and adult patients.[5,6] Anakinra is a recombinant form of human IL-1 receptor antagonist approved for patients with active rheumatoid arthritis.[16] Its use in adult hospitalized patients with SARS-CoV-2 infection, however, did not result in benefit .[17] The short half-life of 4–6 hours also makes it an ideal candidate for treating sepsis patients with features of macrophage activation. In our case, there was a notably significant improvement following the initiation of anakinra.

Conclusion

Secondary HLH should be ruled out timely in severe dengue cases having persistent fever, cytopenias, raised liver enzymes, and hyperferritinemia. Cautious use of corticosteroids and intravenous immunoglobulin may be initiated when HLH is diagnosed in dengue. In refractory cases, immunotherapy with IL blockers such as anakinra may be rewarding.

Lessons learnt

- Severe dengue with multi-organ dysfunction should raise suspicion of secondary HLH
- Timely identification of secondary HLH in severe dengue helps in targeted immunosuppressive treatment
- In refractory cases of severe dengue with HLH, anakinra (an interleukin-1 antagonist) may be effective.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given his consent for images and other clinical information to be reported in the journal. The guardian understands that names and initials will not be published and due efforts will be made to conceal the identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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