Hemophagocytic syndrome in children with acute monoblastic leukemia—another cause of fever of unknown origin

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Abstract

Purpose Intensification of antileukemic treatment and progress in supportive management have improved the survival rates of children with acute myeloid leukemia (AML). However, morbidity and early mortality in these patients are still very high, especially in children with acute monoblastic leukemia (AML FAB M5). Inflammatory syndromes complicating the management of these children after application of cytosine arabinoside and due to hyperleukocytosis at initial presentation have been reported. Hemophagocytic lymphohistiocytosis (HLH) has been described as a serious and life-threatening acute complication during treatment of different oncologic entities; however, data on HLH in children with AML FAB M5 are extremely rare.

Methods A retrospective study of all children with AML FAB M5 treated at our institution between 1993 and 2013 was performed to describe the clinical characteristics of patients who developed an inflammatory syndrome with HLH during oncologic treatment.

Results Three of 10 children developed an inflammatory syndrome with fever, elevation of C-reactive protein, hyperferritinemia, elevation of soluble interleukin-2, and hemophagocytosis during prolonged aplasia following the first cycle of chemotherapy not responding to broad-spectrum antibiotics. No infectious agents could be identified; the initial symptoms occurred 17, 18, and 28 days after diagnosis of AML, respectively. The children immediately responded to dexamethasone; however, the same syndrome was observed again after the second cycle of chemotherapy and, in one patient, also after the third cycle.

Conclusions Treating physicians should be aware of an inflammatory syndrome resembling HLH in children with monoblastic leukemia since this problem might extremely complicate management and supportive care of these children. The co-incidence of monoblastic leukemia with HLH might be explained by cytokines released from the monoblastic leukemic cells themselves.

Keywords Acute monoblastic leukemia · Hemophagocytosis · Inflammatory syndrome

Introduction

During the last decades, the survival of children and adolescents with acute myeloid leukemia (AML) has significantly improved [1–3]. Intensification of antileukemic treatment and better strategies for supportive care have resulted in a 5-year overall survival of 71 % in children treated within the international protocols Acute Myeloid Leukemia-Berlin-Frankfurt-Münster (AML-BFM) 1998 and 2004 [1, 3]. Different prognostic variables have been identified including the French–American–British (FAB) classification, chromosomal abnormalities, Down syndrome, and early response to chemotherapy [1, 2, 4, 5]. However, especially during the first weeks, treatment is still complicated by significant early morbidity including bleeding problems, infections, or even early deaths [3]. Hyperleukocytosis, acute promyelocytic leukemia, and acute monoblastic leukemia (FAB type M5) have been reported as the main risk factors for fatal outcome during the first 2 weeks of induction treatment [3, 6], and an experienced team is needed to provide adequate supportive care in these patients.

Hemophagocytic lymphohistiocytosis (HLH) has been reported as a severe adverse event of antineoplastic treatment in children [7]. Pathogenetically, an acquired dysregulation of the immune system resulting in the release of pro-inflammatory cytokines and excessive activation of hemophagocytic monocytes is discussed.
[7–9]. The HLH Study Group of the Histiocyte Society recently proposed revised diagnostic guidelines for HLH including unexplained fever, cytopenia, hemophagocytosis, hyperferritinemia, high soluble interleukin-2 receptor (sIL2-R), hypertriglyceridemia, and hypofibrinogenemia [8, 9]. Little is known about the possible association between hemophagocytosis and AML FAB M5 and the management of this treatment complication.

Patients and methods

A retrospective chart review was performed of all children for acute monoblastic leukemia treated at our institution between 1993 and 2013. A total of 10 consecutive children were diagnosed; chemotherapy was given according to the international protocols AML-BFM 93 (4 patients) and AML-BFM 2004 (6 patients). Protocol AML-BFM 93 consisted of an 8-day induction: ADE (cytarabine, daunorubicin, etoposide) or AIE (cytarabine, idarubicin, etoposide), followed by HAM (high-dose cytarabine, mitoxantrone), a 6-week consolidation, HAE (high-dose cytarabine, etoposide), and 1 year of maintenance therapy (thioguanine, cytarabine) [3]. Protocol AML BFM 2004 included induction with ADxE (cytarabine, liposomal daunorubicin, etoposide) followed by the cycles HAM, AI-2-CDA (cytarabine, idarubicin, cladribine), HAM (cytarabine, mitoxantrone), HAE, and maintenance therapy [4]. Supportive care included insertion of a tunneled central venous line, forced diuresis, antiemetics, antifungal prophylaxis with liposomal amphotericin B (3 mg/kg/day every third day), antibiotics, parenteral nutrition, and irradiated blood transfusions if necessary. Swabs of all orifices and cultures of stool, urine, and blood were done weekly as well as screening for virus infections including cytomegalovirus (CMV), adenovirus, human herpesvirus-6, parvovirus B19, and Epstein–Barr virus by polymerase chain reaction (PCR) from peripheral blood, urine, and pharyngeal swab specimens.

The characteristics and the clinical course of the 10 patients (6 females, 4 males) with AML FAB M5 are summarized in Table 1. Median age was 12 years (range 2 to 19 years); cytogenetic analysis was done in seven patients revealing translocation (9;11) in six patients and translocation (10;11) in one patient. Four children were treated according to the protocol AML-BFM 93; all of them died due to relapse \( n = 3 \) or intracranial bleeding at initial presentation \( n = 1 \). The remaining six patients received treatment according to the protocol AML-BFM 2004; two of them (patients 5 and 6) underwent successful allogeneic bone marrow transplantation.

HLH was suspected in case of prolonged cytopenia, fever not responding to antibiotic and antimycotic treatment, absence of any proven infection, hemophagocytosis in the bone marrow, hyperferritinemia, and high serum levels of sIL2-R as previously reported [8, 9].

Three of the 10 children with AML FAB M5 and with refractory inflammatory syndrome during the first cycles of chemotherapy fulfilled these criteria and are reported in this retrospective analysis. Informed consent was obtained from the parents or the legal guardians.

Results

Three patients (patients 8, 9, and 10) developed an inflammatory syndrome with high fever, elevation of C-reactive protein (CRP),

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Cytogenetics</th>
<th>Treatment</th>
<th>Complications</th>
<th>Outcome</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>f</td>
<td>11</td>
<td>nt</td>
<td>AML-BFM 93</td>
<td>Sepsis, relapse (day 73)</td>
<td>DOD</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>f</td>
<td>16</td>
<td>t(9;11)</td>
<td>AML-BFM 93</td>
<td>Relapse (day 276)</td>
<td>DOD</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>f</td>
<td>13</td>
<td>t(9;11)</td>
<td>AML-BFM 93</td>
<td>Relapse (day 240)</td>
<td>DOD</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>m</td>
<td>14</td>
<td>nt</td>
<td>AML-BFM 93</td>
<td>Intracranial hemorrhage (day 1)</td>
<td>DOD</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>m</td>
<td>19</td>
<td>t(9;11)</td>
<td>AML-BFM 2004 MUD-BMT</td>
<td>Sepsis, renal failure, gallstones, neuropathy</td>
<td>CR</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>m</td>
<td>10</td>
<td>nt</td>
<td>AML-BFM 2004 MUD-BMT</td>
<td>Delayed engraftment (day 30)</td>
<td>CR</td>
<td>79</td>
</tr>
<tr>
<td>7</td>
<td>f</td>
<td>15</td>
<td>t(9;11)</td>
<td>AML-BFM 2004</td>
<td>–</td>
<td>CR</td>
<td>25</td>
</tr>
<tr>
<td>8</td>
<td>f</td>
<td>11</td>
<td>t(9;11)</td>
<td>AML-BFM 2004</td>
<td>Splenic infarctions, hemophagocytosis, CMV</td>
<td>CR</td>
<td>36</td>
</tr>
<tr>
<td>9</td>
<td>f</td>
<td>2.5</td>
<td>t(10;11)</td>
<td>AML-BFM 2004</td>
<td>Hemophagocytosis</td>
<td>CR</td>
<td>19</td>
</tr>
<tr>
<td>10</td>
<td>m</td>
<td>2</td>
<td>t(9;11)</td>
<td>AML-BFM 2004</td>
<td>Hemophagocytosis</td>
<td>CR</td>
<td>2 still in therapy</td>
</tr>
</tbody>
</table>

BMT bone marrow transplantation, CR complete remission, CMV cytomegalovirus; DOD dead of disease, nt not tested, MUD matched unrelated donor
and prolonged cytopenia affecting ≥2 of 3 lineages in the peripheral blood after the first cycle of chemotherapy (ADxE). Initial white blood cell (WBC) count was 38.3, 10.3, and 2 × 10^9/l, respectively. The interval between start of chemotherapy and onset of fever was 17, 18, and 28 days, respectively. No infectious agents could be detected, and there was no response to broad-spectrum antibiotics and antifungal agents. Blood cultures and screening for virus infections by PCR testing were negative in all three patients. Serum concentrations of ferritin and sIL2-R were extremely increased (Table 2). Additionally, triglyceride levels were elevated and fibrinogen was decreased; thus, hemophagocytosis was suspected. All three patients immediately responded to dexamethasone (0.2 mg/kg/day) with defervescence and normalization of CRP and blood cell counts. Bone marrow aspiration at the beginning of the next cycle of chemotherapy (HAM) showed increased numbers of histiocytes phagocytosing blood cells, confirming the suspected diagnosis of hemophagocytosis. A similar syndrome was observed in all three children during the bone marrow reconstitution after the second chemotherapy (HAM). Two patients (patients 9 and 10) showed a normal recovery phase after the third cycle of chemotherapy (AI-2-CDA) without fever and no need of dexamethasone (DXM) treatment; one of them (patient 10) is still on treatment.

Table 2 gives an overview of laboratory and clinical parameters including fever, cytopenia, the peak serum levels of ferritin, sIL2-R, and CRP in these patients during the first three cycles of chemotherapy. Patient 8 developed HLH again after the third cycle and became positive for CMV by PCR after the fourth cycle. She continued to develop intermittent episodes of CMV reactivation accompanied by fever, cytopenia, and hyperferritinemia during the whole period of antileukemic treatment, so that chemotherapy had to be stopped after 2 months of maintenance therapy. Molecular testing for familiar hemophagocytosis including mutations in the gene encoding perforin and mutations in the gene UNC13D in this patient were negative.

Up to now, these three patients are clinically well and in first remission, and the duration of follow-up is 38, 21, and 4 months, respectively.

**Exemplary case report (patient 8)**

An 11-year-old girl presented with a 2-day history of abdominal pain. Laboratory findings included the following: WBC count 38.3 × 10^9/l (normal 4.4–11.3), hemoglobin 11.9 g/dL (normal 12–15.3), platelets 145 × 10^9/l (normal 140–440), lactate dehydrogenase 851 U/l (normal 120–240), fibrinogen 544 mg/dL (normal 210–400), fibrin degradation products (D-dimer) 9 mg/l (normal <0.59). Abdominal sonography showed multiple hypodense lesions in the spleen compatible with splenic infarctions. The bone marrow (BM) aspirate revealed a nearly 100% infiltration with monocytic blasts that were strongly positive for nonspecific esterase and acid phosphatase. Blast cells expressed CD4, CD56, CD45, CD14, HLA-DR, CD33, CD38, and the translocation (9;11) with the MLL/AF9 fusion gene. Diagnosis of AML Fab M5 was made and treatment according to the protocol AML-BFM 2004 was initiated with the first induction cycle of chemotherapy (ADxE). Supportive care was performed as discussed above. BM aspiration on day 15 revealed aplasia, remission, and hemophagocytosis. On day 17, the patient developed an inflammatory syndrome with high fever and elevation of CRP to 282 mg/l (normal <0.5) in the absence of any detectable infectious agent, which was refractory to antibiotic and antifungal treatment. Screening for virus infections by PCR was negative. Due to additional elevation of ferritin (8,407 ng/ml, normal 24–336) and sIL2-R (10,470 pg/ml, normal <15), diagnosis of HLH was suspected and treatment with DXM (0.2 mg/kg/day) was started. Fever immediately subsided and laboratory parameters normalized. Antileukemic treatment was continued on day 23; however, a similar inflammatory syndrome was observed during bone marrow recovery after the second and third cycles of chemotherapy (HAM and AI-2-CDA), respectively. During the fourth cycle (HAM), CMV was detected by PCR for the first time and was treated with ganciclovir and CMV hyperimmune globulin. The subsequent chemotherapy was complicated by intermittent episodes of CMV reactivation that were accompanied by fever, pancytopenia, elevation of ferritin, and sIL2-R. Several

<table>
<thead>
<tr>
<th>Patient</th>
<th>ADxE</th>
<th>HAM</th>
<th>AI-2-CDA</th>
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<tbody>
<tr>
<td></td>
<td>Ferritin (ng/ml)</td>
<td>sIL2-R (pg/ml)</td>
<td>CRP (mg/l)</td>
</tr>
<tr>
<td>8</td>
<td>8,407</td>
<td>10,470</td>
<td>282</td>
</tr>
<tr>
<td>9</td>
<td>38,129</td>
<td>3,778</td>
<td>94.4</td>
</tr>
<tr>
<td>10</td>
<td>13,080</td>
<td>3,781</td>
<td>58.3</td>
</tr>
</tbody>
</table>

CRP C-reactive protein, sIL2-R soluble interleukin-2 receptor
pulses of DXM in combination with antiviral treatment including ganciclovir, cidofovir, and foscavir were given, and antileukemic therapy had to be stopped after 2 months of maintenance therapy. Molecular testing for familiar hemophagocytosis in this patient was negative; in detail, no mutations in the genes STX11, STXBP2, and UNC13D and no mutation in the gene encoding perforin were found. The patient is now, 3 years after initial diagnosis, in good clinical condition without evidence of residual leukemia.

Discussion

Supportive care of children with AML FAB M5 still remains an enormous therapeutical challenge, since severe complications including infections, coagulopathies, or hyperleukocytosis are frequently seen in these patients [3,6]. In our small series, 3 of 10 children with acute monoblastic leukemia developed an inflammatory syndrome with fever of unknown origin, elevation of CRP, hyperferritinemia, and hemophagocytosis. Primarily, an infection was suspected; however, no infectious agent could be identified, and there was no response to broad-spectrum antibiotics and antifungicides. Viral infection or virus-associated HLH seemed unlikely since virus nucleic acid detection by PCR was negative at weekly monitoring except one positive result for CMV as described above. Another differential diagnosis was the so-called cytarabine syndrome (a spectrum of clinical symptoms including fever, rash, and myalgia) that is frequently seen in children treated with high-dose cytarabine. Median onset of fever in these patients is 28 h (range 20–47 h) after the start of the first cytarabine infusion [10]. In the presented patients, the onset of fever was much later ranging from 17 to 28 days after the start of chemotherapy. An interesting observation was published by Hijiya et al., who reported on five children with acute myelomonocytic or monocytic leukemia who experienced a syndrome with extremely elevated serum concentrations of ferritin and sIL2-R and hemophagocytosis in the bone marrow. These parameters were not evaluated in the study of Hijiya and co-workers. It remains unclear whether some of our supportive care measures like application of liposomal amphotericin and daunorubicin or parenteral nutrition containing soluble lipids might have contributed to the development of HLH in our patients. The question arises whether this inflammatory syndrome was also seen in patients with other subtypes of AML, treated with the same protocols and the same supportive care. During the observation period, a total of 43 patients with AML and with a subtype distinct from M5 were treated in our institution. Only 2 of these 43 patients (4.6 %) developed HLH as previously reported [7], whereas 3 of 10 patients with the M5 subtype (30 %) and hemophagocytosis were observed in the present series, suggesting a predisposition of monoblastic leukemia toward the pathogenesis of HLH. There are two case reports describing two adolescents presenting with primary hemophagocytosis, who were diagnosed for AML FAB M5 several months later [12,13]. Stark et al. reviewed 38 patients with a distinct subtype of AML FAB M4/M5 associated with t(8;16), in whom erythro- or hemophagocytosis by blasts is reported to be a clinical hallmark of the leukemia [14].

Yet, the pathogenetic mechanism causing inflammatory syndromes including hemophagocytosis in patients with monoblastic leukemia remains unclear. In accordance to Hijiya et al., we hypothesize that monoblastic leukemic cells themselves might release pro-inflammatory cytokines. It is well known that a cascade of cytokines is activated by mature histiocytes in patients with familial or secondary hemophagocytic lymphohistiocytosis [8]. One might speculate that similarly to mature histiocytes, leukemic monoblasts also have the ability to induce an environment with high levels of inflammatory cytokines. In some patients, this cytokine release might mimic SIRS with cardiopulmonary complications during acute leukemic cell lysis [11]; in other patients, it might resemble an inflammatory syndrome with hemophagocytosis during recovery from BM aplasia as we observed in our patients. Physicians treating children with AML FAB M5 should be aware of this possible complication by actively searching for HLH parameters to establish adequate supportive care in these patients.

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References
