e - ISSN - 2349 - 8005

INTERNATIONAL JOURNAL OF ADVANCES IN CASE REPORTS

Journal homepage: www.mcmed.us/journal/ijacr

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS ASSOCIATED WITH DESMOPLASTIC SMALL ROUND CELL TUMOR

Valentina G. Dell'Orto[1] V and Brazzola PL[2*]

[1] Post Graduate, [2] Head Dept of Pediatric Oncology, Reparto di Pediatria, Ospedale Regionale di Bellinzona e Valli – Bellinzona, Switzerland.

Corresponding Author:- **Pierluigi Brazzola**
E-mail: pierluigi.brazzola@eoc.ch

Article Info
Received 15/08/2015
Revised 27/08/2015
Accepted 25/09/2015

Key words:
Hemophagocytic Lymphohistiocytosis (HLH), Desmoplastic small round cell tumor (DRCST), Cryptococcus neoformans.

ABSTRACT
We report on the case of an 18-year-old young woman affected by a desmoplastic small round cell tumor (DRCST) treated with chemotherapy (P6 protocol), surgery and adjuvant radiotherapy. During maintenance therapy, she experienced fever and pancytopenia. Laboratory tests showed: hyperferritinemia, hypertriglyceridemia, high levels of soluble IL-2 receptor (sIL-2r) and in the bone marrow aspirate, an evident hemophagocytosis. Therefore, she was treated for hemophagocytic lymphohistiocytosis (HLH), but she died during therapy.

INTRODUCTION

Desmoplastic small round cell tumor (DRCST) and hemophagocytic lymphohistiocytosis (HLH) are both rare conditions. HLH may have an hereditary aetiology, but could be also linked to an oncological or infectious disease. Patients with a tumor disease could therefore develop an HLH due to their basic condition and the increased risk for various infections. Our patient presented both conditions with evidence of a C. neoformans infection and a recent history and treatment for a DRCST.

Case presentations

An 18-year-old female was diagnosed with an abdominal desmoplastic small round cell tumor (DRCST) positive for t(11:22) (p13:q12) translocations. The initial tumor staging did not show any other involvement and bone marrow biopsy and aspirate were normal.

According to the literature [1, 2] we treated this patient with a multimodality therapy, that had included chemotherapy according to P6 protocol (Table 1), macroscopic total surgical resection (exiting in our case in an ileostomy) with hyperthermic intra-operatory chemotherapy, myeloablative therapy (Table 2) with stem cells rescue, local consolidation radiotherapy (20 times 1,5 Gy/d, a total dose of 30 Gy) followed by maintaining therapy with cyclophosphamide (25 mg/m^2/d) and vinorelbine (60 mg/m^2/d 1/8/15). After radiotherapy a PET FDG-CT-Scan showed no signs of residual disease. Seven months after the end of the P6 protocol, whilst maintaining therapy, normal blood counts and clinical stability of the patient enabled the intervention of ileostomy closure. Two days later, she presented unexplained fever, pancytopenia and bilious vomiting. Blood values showed a severe leukopenia (0,4 G/l), thrombocytopenia at 128 G/l and haemoglobin level of 70 g/l. Empiric antibiotic (meropenem and metronidazole) and antifungal (caspofungin) therapy was started, supported with

5µg/kg/day of G-CSF. In the following days, she presented a persistent pancytopenia (Table 3) and general conditions worsened. Additional blood tests revealed hyperferritinemia (10.233 µg/l), hypertriglyceridemia (2.3 mmol/l), high levels of soluble IL-2 receptor (2228.9 pg/ml) but normal value for fibrinogen (2g/l). A CT-scan of the abdomen showed the presence of ascites but no evidence for a relapse of the DSRCT or splenomegaly. A sample of the observed ascites did not show tumor cells. In the bone marrow aspirate there was clear evidence of hemophagocytosis. Therefore at this point an haemphagocytic limphohistiocytosis was diagnosed and therapy with etoposide and dexamethason was started. Blood cultures, spinal fluid, and ascites were negative for bacterial, viral and fungal infections. The serology for EBV, CMV, parvovirus B19, Herpes virus 6 and 8 were negative. Due to the presence of a tachypnea and appearance of hypoxemia a conventional X-ray of the thorax was performed demonstrating an opacity on the left lung, and the bronchoalveolar lavage was positive for Criptococcus neoformans (growth after 12 days of 3x10^3 CFU/ml).

For this reason the treatment with caspofungin was replaced with liposomal amphotericin B. After initial improvement of the clinical and pulmonary conditions, she experienced sudden clinical worsening with the development of a cardiac tamponade and finally she died from cardiac arrest. The family refused an autopsy and further genetic investigations.

Table 1. Scheduling of the chemotherapy protocol P6

		Days				
Course n.		1	2	3	4	5
1,2,3,6 (HD-CAV)						
Cyclophosphamide	2,1 mg/m^2/die IV	X	X			
Doxorubicine	25 mg/m^2/die IV	X	X	X		
Vincristine	0,67 mg/m^2/die IV	X	X	X		
4,5,7						
Ifosfamide	1,8 mg/m^2/die IV	X	X	X	X	X
Etoposide	100 mg/m^2/die IV	X	X	X	X	X

Kushner et al[1], modified. IV : intravenous

Table 2. Myeloablative schema for the high dose chemotherapy protocol with autologous stem cells reinfusion

Myeloablative regimen		
Thiotepa	300 mg/m^2/die IV	Days -4, -3, -2
Carboplatin	500 mg/m^2/die IV	Days -7, -6, -5
Stem-cells rescue		Days 0

Kushner et al[1]. IV : intravenous

Table 3. Blood values course after ileostomy closure

	Day 1	Day 7	Day 12
Haemoglobin (g/l)	70	77	76
Platelets (G/l)	128	33	55
Leukocytes (G/l)	0,4	4,3	0,6

Day 1: appearance of fever and cytopenia.
Day 12: Diagnostic of HLH

Table 4. Gene mutations related to familial HLH

Gene	**Location**	**Disease**
PRF1	10q21-22	FHL2
UNC13D	17q25	FHL3
STX11	6q24	FHL4
RAB27A	15q21	Griscelli syndrome
STXBP2	19p13	FHL5
Unknown	9q21.3-22	FHL1
SH2D1A	Xq24-26	XLP1
XIAP	Xq25	XLP2/X-linked HLH
LYST	1q24.1-42.2	Chediak-Higashi syndrome

Jordan et al [8]. FHL: Familial hemophagocytic lymphohistiocytosis. XLP: X-linked lymphoproliferative syndrome

DISCUSSION

Desmoplastic small round cell tumor (DSRCT) is a rare aggressive mesenchymal neoplasm. The primary site is commonly the abdomen or pelvis. This tumour is associated with a specific reciprocal translocation t(11:22) (p13;q12) resulting in a fusion of the EWS gene and the WT1 gene, but other chromosomal translocations are described. Despite all possible therapeutic approaches, the prognosis is still very poor today. The multimodal treatment with chemotherapy, surgery and adjuvant radiotherapy is important in order to attempt to improve the patients survival [2-4].

Although DSRST is generally sensitive to chemotherapy and radiotherapy, the response is not long-term lasting. At that time the best literary reported results are with the P6 protocol [4] with a 3 year overall survival of about 29%, but other protocols were also described. The autologous stem cell transplantation (ASTC) was also employed as consolidation therapy in other paediatric high risk solid tumors. The rationale of this approach is to exploit the steep dose response curve observed with other solid tumors, with durable remissions described [4]. The implementation of ASCT in DSMCT is not routinely accepted and sparks controversial debate in the literature [1, 2, 4-7].

Mazuryk et al. [5] described a case of a 19 year old man with an intra-abdominal DSRCT who achieved complete remission after treatment with aggressive surgery, chemotherapy and ASCT. Parenthesis et al. [4] described a case of an 18 year old female in complete remission after stem cell transplantation. Fraser et al. [7], in his series, noted that patients in complete remission at the moment of SCT have a better outcome.

HLH is a systemic immune disease characterized by an uncontrolled activation of the cell-mediated immunity, that primarily involves T-lymphocytes and macrophages [8]. At least five of the following symptoms and signs are required to formulate diagnosis: fever; splenomegaly; cytopenias; hypertriglyceridemia or hypofibrinogenemia; hemophagocytosis in bone marrow, spleen or lymph nodes; low natural killer (NK)-cell activity; hyperferritinemia; high sIL-2r levels. HLH can be primary, most frequent in children, related to an inherited autosomal recessive defined gene mutation involving the functions of NK cells and cytotoxic T cells (Table 4) [8]; or secondary to events like infections, autoimmune diseases, immunodeficiencies or malignancies. The latter form is mostly associated to EBV infections [8-9], but it is also associated to other viral, bacterial or fungal infections [10]. To the best of our knowledge, only one case of HLH associated to cryptococcal infection was reported in literature today [11]. Cryptococcus neoformans is an opportunistic fungus responsible for infections in immunocompromised patients. Inoculum occurs by inhalation and, in general, the first manifestation of the infection is pneumonia. The fungus is neurotrophic, so that a central nervous system dissemination is possible and common. NK cells activity seems to be important in protection against *C. neoformans*. Treatment with Fluconazole or Amphotericin B are the most effective therapies [12].

Malignancy is also an important trigger for secondary HLH (malignancy- associated hemophagocytic syndrome, MAHS) [13]. This has been described primarily in association with lymphoma or T-cell and Nk-cell leukemias, but may be related to other tumors such as germ cell tumors and solid cancers. A hypothesis that could explain MAHS is the secretion of pro-inflammatory cytokines as TNF-α or IL-6 by neoplastic cells. Other factors occurring during malignancy that could trigger HLH, are frequent infections during treatment or immunosuppressive therapy. All these situations can lead to macrophage activation and could be the cause of immune system dysregulation [14]. HLH could be treated according to the protocols HLH-94 or HLH-2004, using dexamethasone, etoposide and cyclosporine A, with intrathecal methotrexate and hydrocortisone for CNS involvement. An allogeneic stem cell transplantation is the gold standard therapy in case of the familial form [13-15]. In the secondary form the treatment of the underlying disease is mandatory [8-12].

CONCLUSION

In this communication we describe two rare conditions (DSRCT and HLH) developed in succession in an 18 year old female. The origin of HLH in our patient remains unclear. In fact, the patient suffered from a tumor disease that could explain the HLH, but at the time of diagnosis there was no evidence of recurrence of the DSRCT and an autopsy could not be performed. Another possible trigger for HLH was the C. neoformans infection, which is described as possible association with HLH [11]. Because of the age of the patient and her previous oncological condition, a primary form of HLH was not initially investigated, even though cases of late onset of familial HLH are described, so that this hypothesis could not be completely excluded. In our case we started treatment for primary HLH in parallel with treatment for C. neoformans. Unfortunately, the parents did not allow further analysis post mortem. In conclusion, in our case, the HLH could be a primary late onset form, or a secondary form triggered by one of the clinical conditions of the patient, and until now only scarcely described.

ACKNOWLEDGEMENT: None

CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

STATEMENT OF HUMAN AND ANIMAL RIGHTS

All procedures performed in human participants were in accordance with the ethical standards of the

institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

REFERENCES

1. Kushner BH, LaQuaglia MP, Wollner N, Cheung N-KV. (1996). Desmoplastic small round-cell tumor: prolonged progression-free survival with aggressive multimodality therapy. *Journal of Clinical Oncology*, 14(5), 1526-1531.
2. Saab R, Khoury JD, Krasin M, Davidoff AM, Navid F. (2007). Desmoplastic Small Round Cell Tumor in Childhood: The St. Jude Children's Research Hospital Experience. *Pediatr Blood Cancer*, 49, 274–279.
3. Kim YS, Cha SJ, Choi YS, Kim BG, Park SJ, Chang IT.(2009). Retroperitoneal desmoplastic small round cell tumor: Pediatric patient treated with multimodal therapy. *World J Gastroenterol*, September 7, 15(33), 4212-4214.
4. Perenthesis JP, Katsanis E, DeFor TE, Neglia JP, Ramsey NKC. (1999). Autologous stem cell transplantation for high-risk pediatric solid tumors. *Bone Marrow Transplantation*, 24, 609-615.
5. Mazuryk M, Peterson AHG, Temple W, Arthur K, Crabtree T, Stewart DA. (1998). Benefit of aggressive multimodality therapy with autologous stem cell support for intra-abdominal desmoplastic small round cell tumor. *Bone Marrow Transplantation*, 21, 961-963.
6. Bertuzzi A, Castagna L, Quagliuolo V, Ginanni V, Compasso S, Magagnoli M, Balzarotti M, Nozza A, Siracusano L, Timofeeva I, Sarina B, Soto Parr H, Santoro A. (2003). Prospective study of high-dose chemotherapy and autologous peripheral stem cell transplantation in adult patients with advanced desmoplastic small round-cell tumor. *British Journal of Cancer*, 89, 1159-1161.
7. Fraser CJ, Weigel BJ, Perentesis JP, Dusenbery DE, DeFor TE, Baker KS, Verneris MR. (2006). Autologous stem cell transplantation for high-risk Ewing's sarcoma and other pediatric solid tumors. *Bone marrow transplantation*, 37, 175-181.
8. Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL. (2011). How I teat hemophagocytic lymphohistiocytosis. *Blood*, 118(15), 4041-4052.
9. Kelly C, Salvi S, McClain K, Hayani A. (2011). Hemophagocytic Lymphohistiocytosis Associated With Precursor B Acute Lymphoblastic Leukemia. *Pediatr Blood Cancer*, 56, 658–660.
10. Rouphale NG, Talati NJ, Vaughan C, Cunnigham C, Moreira R, Gould C. (2007). Infections associated with haemophagocytic syndrome. *Lancet Infectious Disease*, 7, 814-822.
11. Numata K, Tsutsumi H, Wakai S, Tachi N, Chiba S. (1998). A child case of haemophagocytic syndrome associated with cryptococcal meningoencephalitis. *The Journal of Infection*, 36, 118-119.
12. Marr KJ, Jones GJ, Zheng C, Huston SM, Timm-McCann M, Islam A, Berenger BM, Ma LL, Wiseman JC, Mody.CH. (2009). Cryptococcus neoformans directly stimulates perforin production and rearms NK cells for enhanced anticryptococcal microbicidal activity. *Infection and Immunity*, 77(6), 2436-2446.
13. Henter JI, Horne AC, Aricò M, Egeler RM, Filipovich AH, Imashuku S, Ladisch S, McClain K, Webb D, Winiarski J, Janka G. (2007. HLH-2004: Diagnostic and Therapeutic Guidelines for Hemophagocytic Lymphohistiocytosis. *Pediatr Blood Cancer*, 48,124–131.
14. O'Brien MM, Lee-Kim Y, George YI, McClain KL, Twist CJ, Jeng M. (2008). Precursor B-Cell Acute Lymphoblastic leukemia presenting with Hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*, 50, 381-383.
15. Trottestam H, Horne AC, Aricò M. (2011). Chemoimmunotherapy for Hemophagocytic Lymphohistiocytosis: long term results of the HLH-94 treatment protocol. *Blood*, 118 (17), 4577-4584.