Pediatric Anaplastic Large Cell Lymphoma with Concomitant Involvement of Spine and Central Nervous System: A Case Report and Review of Literature

Giulia A. Restivo 1,*, Lara Mussolin 2,3,*, Paolo D’Angelo 4,*, Angela Trizzino 4, Salvatore Ialuna 5, Elena Sabattini 6,*, Cristina Gallo 7, Angelo Toscano 8, Elisa Carraro 2,*, Marta Pillon 2,*, and Piero Farruggia 4

Abstract: Anaplastic large cell lymphoma (ALCL) is a histological subtype of non-Hodgkin lymphoma, largely characterized by anaplastic lymphoma kinase (ALK) positivity, resulting from the chromosomal translocation t(2;5). We report a pediatric case of ALK-positive ALCL with primary concomitant involvement of bone and central nervous system (CNS); thereafter, a literature review about pediatric primary bone and primary CNS ALCL was conducted. According to the analyzed data, our case is unique because it is characterized by the contemporary involvement of the spine and CNS. During and after chemotherapy, our patient was monitored by detecting minimal residual disease (MRD) through the analysis of fusion transcript nucleophosmin-ALK. MRD assessment, not only in bone marrow but also in peripheral blood, seems to be a very powerful tool for predicting the prognosis of pediatric ALCL patients, as already described in the literature. Moreover, as shown in our case, it could be used during the follow-up for early recognition of relapse.

Keywords: anaplastic large cell lymphoma; minimal residual disease; central nervous system; bone

1. Introduction

Anaplastic large cell lymphoma (ALCL) is a T/NK-cell or null-cell phenotype non-Hodgkin lymphoma (NHL); in most cases, it is characterized by the expression of nucleophosmin (NPM)-anaplastic lymphoma kinase (ALK) fusion protein, resulting from the chromosomal translocation t(2;5)(p23;q35) and causing the hyperactivation of ALK [1]. It can involve nodes and extranodal sites [2]; both primary bone and primary central nervous system (CNS) localizations are extremely rare. Here we describe a pediatric case of extranodal ALCL with bone and CNS involvement, focusing also on a follow-up strategy for disease monitoring; furthermore, a review of the literature about these unusual sites of disease onset was performed.

2. Materials and Methods

In ALCL, reverse transcriptase-polymerase chain reaction (RT-PCR) for fusion transcript NPM-ALK is used to detect the level of disease dissemination. Through this highly...
sensitive technology, it is feasible to determine minimal disseminated disease (MDD), defined as the presence of NPM-ALK mRNA in bone marrow (BM) and/or peripheral blood (PB) at the time of the diagnosis, and minimal residual disease (MRD), defined as the presence of NPM-ALK mRNA in BM and/or PB during and after therapy. In our case, total RNA was isolated from mononuclear or nuclear BM or PB samples by standard methods. Complementary DNA (cDNA) synthesis was performed with 1 µg total RNA, random hexamers and superscript II reverse transcriptase (Invitrogen, Carlsbad, CA). NPM-ALK cDNA was amplified using a qualitative PCR reaction with a sensitivity of 10^-5.

We performed a review of English literature about pediatric ALCL with bone and/or CNS involvement; only those with adequate clinical details were included. Firstly, a PubMed, Scopus, and Web of Science (WOS) search, including as keywords “anaplastic large cell lymphoma” AND “bone” revealed 15 articles, concerning 17 patients aged less than 18 years with primary bone ALCL. Another search using as keywords “anaplastic large cell lymphoma” AND “central nervous system” retrieved 19 papers, regarding 23 cases of primary CNS ALCL in children and adolescents.

3. Case Report

A previously healthy 9-year-old boy came to our attention for back pain, lasting more than 2 months, with no other symptoms; he had been treated with physiotherapy and anti-inflammatory drugs. On clinical examination, the boy was well-appearing, complaining of moderate back pain at the lumbar level. Complete blood count, lactate dehydrogenase, uric acid, C-reactive protein, and erythrocyte sedimentation rate were in the normal range. Spine magnetic resonance imaging (MRI) showed a signal alteration at the D12-L2 level (with a wedge-shaped D12 body) characterized by hypointensity at T1-weighted and hyperintensity at T2-weighted sequences; furthermore, an abnormal tissue involving medullary canal and neural foramina was appreciated at the D11-L1 level (Figure 1). Cerebral, thorax, and abdominal CT were of normal appearance. The boy underwent an open biopsy, and the histological diagnosis was ALCL, CD30+, ALK+, EMA+, perforin+, associated with numerous histiocytes CD68PGM1+. Positron emission tomography/computed tomography (PET-CT) showed high fluorodeoxyglucose (FDG) uptake at D11-L2 level, with spinal cord involvement. Lumbar puncture revealed the presence of 66 T-lymphoblasts/µL in the cerebrospinal fluid (CSF) and bone marrow aspirate was positive for NPM-ALK transcript, detected by qualitative RT-PCR. The patient was treated with six courses of chemotherapy according to the AIEOP LNH-97 protocol for ALCL, high-risk group, with CNS involvement (Table 1) [3]. MRD in bone marrow and peripheral blood was negative just after the first course of chemotherapy. PET-CT, performed after the second chemotherapy block, showed a complete metabolic response, confirmed also at the end of treatment. Spine MRI performed 2 weeks after stop-therapy demonstrated complete disappearance of both D12-L1 lesions and tissue proliferation in the D11-L1 region, with the persistence of mild signal alteration, without any contrast enhancement, at the L2 level only (Figure 2). During the follow-up, the boy was also monitored by the analysis of MRD in peripheral blood every month for the first three months, then every two months up to one year from the stop-therapy: NPM-ALK transcript was never detected. The patient is in clinical, radiological, and molecular remission at 12 months after the end of treatment.
Table 1. Therapy courses according to AIEOP LNH-97 protocol for ALCL, risk group R3, with CNS involvement.

| Cycle     | Drugs and Dosage                                                                 |
|-----------|----------------------------------------------------------------------------------|
| Prephase  | DEX 5 mg/m²/day orally Days 1-2, DEX 10 mg/m²/day orally Days 3–5, CPX 200 mg/m²/day IV (1 h) Days 1,2, MTX + ARA-C + PRED 12 mg + 30 mg + 10 mg IT Day 1 |
| 1. Cycle AA | DEX 10 mg/m²/day orally or IV Days 1–5, MTX 5 g/m²/day IV Day 1, IFO 800 mg/m²/day IV (1 h) Days 1–5, ETP 100 mg/m²/day IV (2 h) Days 4,5, ARA-C 150 mg/m² every 12 h IV (1 h) Days 4,5, VCR 1.5 mg/m²/day (max 2 mg) IV Day 1, MTX + PRED 12 mg + 10 mg IT Days 1,3, MTX + ARA-C + PRED 12 mg + 30 mg + 10 mg IT Day 5 |
| 2. Cycle BB | DEX 10 mg/m²/day orally or IV Days 1–5, MTX 5 g/m²/day IV Day 1, CPX 200 mg/m²/day IV (1 h) Days 1–5, DOXO 25 mg/m²/day IV (4 h) Days 4,5, VCR 1.5 mg/m²/day (max 2 mg) IV Day 1, MTX + PRED 12 mg + 10 mg IT Days 1,3, MTX + ARA-C + PRED 12 mg + 30 mg + 10 mg IT Day 5 |
| 3. Cycle CC | DEX 20 mg/m²/day orally or IV Days 1–5, ETP 100 mg/m²/day every 12 h IV (2 h) Days 3–5, ARA-C 3 g/m³ every 12 h IV (3 h) Days 1,2, VDS 3 mg/m²/day (max 5 mg) IV Day 1, MTX + PRED 12 mg + 10 mg IT Days 1,3, MTX + ARA-C + PRED 12 mg + 30 mg + 10 mg IT Day 5 |
| 4. Cycle AA | DEX 10 mg/m²/day orally or IV Days 1–5, MTX 5 g/m²/day IV Day 1, IFO 800 mg/m²/day IV (1 h) Days 1–5, ETP 100 mg/m²/day IV (2 h) Days 4,5, ARA-C 150 mg/m² every 12 h IV (1 h) Days 4,5, VCR 1.5 mg/m²/day (max 2 mg) IV Day 1, MTX + PRED 12 mg + 10 mg IT Days 1,3, MTX + ARA-C + PRED 12 mg + 30 mg + 10 mg IT Day 5 |
| 5. Cycle BB | DEX 10 mg/m²/day orally or IV Days 1–5, MTX 5 g/m²/day IV Day 1, CPX 200 mg/m²/day IV (1 h) Days 1–5, DOXO 25 mg/m²/day IV (4 h) Days 4,5, VCR 1.5 mg/m²/day (max 2 mg) IV Day 1, MTX + PRED 12 mg + 10 mg IT Days 1,3, MTX + ARA-C + PRED 12 mg + 30 mg + 10 mg IT Day 5 |
| 6. Cycle CC | DEX 20 mg/m²/day orally or IV Days 1–5, ETP 100 mg/m²/day every 12 h IV (2 h) Days 3–5, ARA-C 3 g/m³ every 12 h IV (3 h) Days 1,2, VDS 3 mg/m²/day (max 5 mg) IV Day 1, MTX + PRED 12 mg + 10 mg IT Days 1,3, MTX + ARA-C + PRED 12 mg + 30 mg + 10 mg IT Day 5 |

Abbreviations: DEX: dexamethasone; CPX: cyclophosphamide; IV: intravenous; MTX: methotrexate; ARA-C: cytarabine; PRED: prednisolone; IT: intrathecal; VCR: vincristine; IFO: ifosfamide; ETP: etoposide; DOXO: doxorubicin; VDS: vindesine.

Figure 1. Spine MRI at onset: wedge-shaped D12 vertebral body and abnormal tissue proliferation with involvement of medullary canal at L1-L2 level.
Figure 2. Spine MRI after treatment: complete disappearance of both D12 lesion and tissue proliferation with persistence of mild signal alteration at L2 level.

4. Discussion

ALCL represents about 10–15% of NHL in children [2]. It generally arises from abdominal or mediastinal lymph nodes; primary bone and CNS involvement is very rare.

After a review of English literature, we identified 17 cases of pediatric primary bone ALCL (Table 2) [4–18]. The median age of onset was 10 years and 82% (14/17) were male. Multifocal and unifocal bone lesions were identified in 7 (41%) and 10 (59%) children, respectively. Twelve patients (70.5%) presented with axial skeleton involvement, as either unique site of disease or in association with extremities lesions. The most frequently involved bones were pelvis (5/17), neurocranium (4/17), and femur (4/17); four children (23.5%) presented with multiple vertebral lesions and only one patient with bone marrow involvement. The clinical diagnosis was often challenging because of multiple possible differential diagnoses (i.e., Langerhans cell histiocytosis, neuroblastoma, osteosarcoma, Ewing sarcoma, and other sarcomas) [19]. All patients were treated with different chemotherapy regimens (three cases also received radiotherapy and one also autologous bone marrow transplantation). Thirteen patients (76.5%) achieved complete remission, 3 children (2 with multifocal disease) died for disease progression, and in 1 patient, the outcome was not specified. These clinical data are summarized in Table 3.

Interestingly, according to one of the largest studies that investigated 225 pediatric ALCL patients, children with bone lesions seem to have a better prognosis compared to patients without bone disease [20].
### Table 2. Characteristics of reported pediatric patients with primary bone ALCL.

| Reference          | Age/Sex | Bones Sites                  | BM/CSF | ALK     | Therapy       | Survival |
|--------------------|---------|------------------------------|--------|---------|---------------|----------|
| Chan et al., 1991 [4] | 8y/F    | Parietal, cervical column, ribs, left humerus, right femur | Neg/neg | NS      | CT            | Alive    |
| Edwards et al., 1993 [5] | 14y/M   | Vertebral column, sacrum, pelvis, ribs, left scapula, left femur | Neg/neg | NS      | CT            | Alive    |
| Ishizawa et al., 1995 [6] | 14y/F   | Temporal, sternum, pelvis | Neg/neg | NS      | CT + RT       | Dead     |
| Nagasaka et al., 2000 [7] | 4y/M    | Right radius, right tibia | Neg/neg | Pos     | CT + HSCT     | Dead     |
| Parker et al., 2001 [8]  | 11y/M   | Frontal                     | Neg/neg | Pos     | CT            | Alive    |
| Postovsky et al., 2001 [9] | 5y/M    | Right fibula                | Neg/neg | NS      | CT            | Alive    |
| Biasotti et al., 2002 [10] | 16y/NS  | Parietal                    | Neg/neg | Pos     | CT            | Alive    |
| Gianelli et al., 2002 [11] | 14y/M   | Pelvis                      | Neg/neg | NS      | NS            | Alive    |
| Bakshi et al., 2006 [12] | 3y/M    | Sacrum                      | Pos/neg | Pos     | CT            | Alive    |
|                      | 9y/M    | Right femur                 | Neg/neg | Pos     | CT            | Dead     |
|                      | 14y/M   | Left fifth rib              | Neg/neg | Pos     | CT            | Alive    |
| Mounasamy et al., 2006 [13] | 8y/M    | Right humerus               | Neg/neg | Pos     | CT            | Alive    |
| Chow et al., 2007 [14]  | 10y/M   | Lumbar vertebral column     | Neg/ND | NS      | CT + RT       | Alive    |
| Ng et al., 2007 [15]    | 13y/M   | Right scapula               | Neg/neg | Pos     | CT            | Alive    |
| Mika et al., 2012 [16]  | 13y/M   | Pelvis                      | Neg/neg | Pos     | NS            | NS       |
| Hue et al., 2018 [17]   | 3y/M    | Left and right femur, pelvis | Neg/neg | Pos     | CT            | Alive    |
| Barik et al., 2019 [18] | 7y/M    | Right calcaneus             | Neg/neg | Pos     | CT + RT       | Alive    |

**Abbreviations:** ALCL: Anaplastic large cell lymphoma; BM: bone marrow involvement; CSF: cerebrospinal fluid; ALK: anaplastic lymphoma kinase transcript; y: years; NS: not specified; CT: chemotherapy; RT: radiotherapy; HSCT: hematopoietic stem cells transplantation; ND: not done.

CNS involvement in children with ALCL is also extremely rare, both as primary and secondary localization: in an international study of systemic childhood ALCL [21], CNS disease was recognized in only 2.6% of cases, most of them being secondary involvement. After a review of English literature, we identified 23 pediatric cases of primary CNS ALCL (Table 4) [21–38]. Age ranged from 23 months to 18 years (median 11 years). Intracerebral mass, meningeal disease, and involvement of both cerebrum and meninges were found in 11/23 (48%), 3/23 (13%), and 6/23 (26%) patients, respectively; in 1 child, ALCL was localized in both the brain and spinal cord and in 2 other patients, the CNS site of disease was not specified. In 2 out of 11 patients with intracerebral lesions [26,38], a skull bone invasion was appreciated. Lymphoma cells were found in 7 (41%) infants in whom CSF analysis was performed. In only 2 patients [28,32], a lymph nodal involvement was present. Several therapeutic approaches have been used with details available in 21 out of 23 patients: 7 patients (30%) were treated with chemotherapy and radiotherapy, 4 (19%) with chemotherapy only, 1 (5%) with radiotherapy only, 2 (9.5%) with chemotherapy and surgery, 3 (14%) with chemotherapy, radiotherapy, and surgery, 2 (9.5%) with chemotherapy followed by autologous stem cell transplant and 1 (5%) with chemotherapy, radiotherapy, and autologous bone marrow transplantation; one child was untreated because he died immediately after the diagnosis. Outcome details are available in 20 out of 23 patients: complete remission (median follow-up 5.2 years, range 1.3–9 years) was achieved in 14 patients (70%), and 6 children (30%) died. In Table 5, these clinical findings are summarized.
Table 3. Main features of pediatric primary bone ALCL.

| Total Cases | 17 | % |
|-------------|----|---|
| Age (years) median/mean | 10/9.8 | - |
| Sex | | |
| Male | 14 | 82 |
| Female | 2 | 12 |
| Not reported | 1 | 6 |
| Sites | | |
| Unifocal, axial | 8 | 47 |
| Unifocal, extremity | 4 | 23.5 |
| Multifocal | 5 | 29.5 |
| Treatment | | |
| CT only | 11 | 64.5 |
| CT + RT | 3 | 17.5 |
| CT + HSCT | 1 | 6 |
| Not reported | 2 | 12 |
| Outcome | | |
| CR | 13 | 76.5 |
| Dead | 3 | 17.5 |
| Not reported | 1 | 6 |

Abbreviations: CT: chemotherapy; RT: radiotherapy; HSCT: hematopoietic stem cells transplantation; CR: complete remission.

Table 4. Characteristics of reported pediatric patients with primary CNS ALCL.

| Reference | Age/Sex | CNS Disease | CSF | ALK | Therapy | Survival |
|-----------|---------|--------------|-----|-----|---------|----------|
| Havlioglu et al., 1995 [22] | 4y/F | Intracerebral + spinal | Pos | NS | CT | Alive |
| Buxton et al., 1998 [23] | 10y/F | Intracerebral | NS | NS | SURG + RT + CT | Dead |
| Abdulkader et al., 1999 [24] | 13y/M | Intracerebral | Neg | Pos | CT | Dead |
| George et al., 2003 [25] | 17y/M | Meningeal | NS | Pos | RT | Alive |
| | 18y/M | Intracerebral + meningeal | NS | Pos | CT + RT | Alive |
| Rupani et al., 2005 [26] | 17y/M | Intracerebral (with skull bone invasion) | NS | Pos | CT + RT | Dead |
| Abla et al., 2006 [27] | 6y/F | NS | NS | NS | CT + HSCT | Alive |
| | 7y/M | NS | Pos | NS | CT + RT | Alive |
| Karikari et al., 2007 [28] | 4y/M | Intracerebral + meningeal | Neg | Pos | CT + RT | Alive |
| Merlin et al., 2008 [29] | 13y/M | Meningeal | Pos | Pos | CT + RT | Dead |
| Ozkaynak et al., 2009 [30] | 9y/M | Intracerebral + meningeal | Pos | Pos | CT + RT + HSCT | Alive |
| Shah et al., 2010 [31] | 2y/M | Intracerebral + meningeal | Neg | Pos | SURG + CT | Alive |
| Thangarajh et al., 2012 [32] | 11y/M | Intracerebral + meningeal | Neg | Pos | NS | NS |
A recent paper, investigating prognostic factors in a cohort of 420 ALCL patients aged <22 years treated according to the international ALCL99 trial [40], revealed that histological small cell/lymphohistiocytic (SC/LH) pattern and positive MDD were significantly associated with higher risk of treatment failure in multivariate analysis. Furthermore, CNS disease is more often associated with high-risk features, but so far, it could not be considered an independent prognostic factor [21]. In addition, as reported by Del Baldo et al. [41], initial CNS involvement seems to be associated with higher risk of CNS relapse. Thus, special care should be taken in the follow-up of patients with primary CNS disease.

ALCL is characterized in more than 80% of children and adolescents by the fusion gene NPM-ALK [42], derived from the translocation t(2;5); its RNA transcript can be detected by RT-PCR in BM and PB, with high concordance between these biological samples [43]. Early assessment of MRD, before the second course of chemotherapy, seems to be able to identify patients with high relapse risk and inferior survival [44]: both event-free survival (EFS) and overall survival (OS) of MDD-positive/MRD-negative are significantly higher compared with that of persistent positive MRD patients [44]. Our patient was MDD-positive at onset; after the first chemotherapy block, MRD assessment resulted negative in both BM and PB, showing a good response to treatment and a favorable outcome, as confirmed by persistent complete clinical and molecular remission 12 months after the end of treatment.

Table 5. Main features of pediatric primary CNS ALCL patients.

| Reference                          | Age/Sex      | CNS Disease                        | CSF | ALK   | Therapy       | Survival |
|------------------------------------|--------------|------------------------------------|-----|-------|---------------|----------|
| Williams et al., 2013 [21]         | NS/NS        | Intracerebral                      | Pos | Pos   | CT + RT       | Alive    |
|                                    | NS/NS        | Intracerebral                      | Neg | NS    | CT + RT       | Alive    |
|                                    | NS/NS        | Intracerebral                      | Neg | NS    | CT            | Alive    |
| Furuya et al., 2014 [33]           | 11y/M        | Intracerebral + meningeal          | Neg | Pos   | SURG + CT + RT| Alive    |
| Kim et al., 2014 [34]              | 10y/F        | Intracerebral                      | Pos | Pos   | CT            | NS       |
| Dunbar et al., 2015 [35]           | 10y/NS       | Intracerebral                      | Neg | Pos   | CT + HSCT     | Alive    |
| Kuntegowdenahalli et al., 2015 [36]| 18y/M        | Meningeal                          | Neg | Pos   | SURG + CT + RT| NS       |
| Feng et al., 2020 [37]             | 8y/M         | Intracerebral                      | Pos | Pos   | NS            | Dead     |
| Lee et al., 2020 [38]              | 12y/M        | Intracerebral (with skull bone invasion) | Neg | Pos   | SURG + CT     | Alive    |
| Liu et al., 2020 [39]              | 12y/M        | Intracerebral                      | NS  | Pos   | Untreated     | Dead     |

Abbreviations: CNS: central nervous system; CSF: cerebrospinal fluid; ALK: anaplastic lymphoma kinase transcript; y: years; NS: not specified; CT: chemotherapy; SURG: surgery; RT: radiotherapy; HSCT: hematopoietic stem cells transplantation.
Table 5. Cont.

| Treatment                  | Total Cases | %   |
|----------------------------|-------------|-----|
| CT + RT                    | 7           | 30.5|
| CT only                    | 4           | 17.5|
| CT + RT + surgery          | 3           | 13  |
| CT + surgery               | 2           | 9   |
| CT + HSCT                  | 2           | 9   |
| RT only                    | 1           | 4   |
| CT + RT + HSCT             | 1           | 4   |
| No therapy                 | 1           | 4   |
| Not reported               | 2           | 9   |

| Outcome                   | Total Cases | %   |
|----------------------------|-------------|-----|
| CR                         | 14          | 61  |
| Dead                       | 6           | 26  |
| Not reported               | 3           | 13  |

**Abbreviations:** CT: chemotherapy; RT: radiotherapy; HSCT: hematopoietic stem cells transplantation; CR: complete remission.

Our case report confirms the relevant role of MDD and MRD monitoring during treatment and follow-up of pediatric patients affected by ALCL. MDD and MRD assessed on BM and/or PB have already been confirmed to be independent prognostic factors [43,44]. Tailored treatment based on MRD is becoming a reality for patients with ALK-positive ALCL. Furthermore, MRD at the end of treatment could identify high-risk patients for whom consolidation therapy could be added to prevent relapse and increase the chances of survival in children who are at a very high risk of relapse [44]. Next-generation sequencing-based methods may represent new opportunities for minimal disease evaluation in childhood ALCL and other lymphoma subtypes [45]. Up to now, MRD has not been studied to evaluate if it can replace bioptic procedures or post-therapy radiological disease monitoring. Further studies are needed to assess the predictive role of MRD in the follow-up period.

5. Conclusions

ALCL is an uncommon type of lymphoma in childhood. Bone and/or CNS involvement are very rare, with only few case reports described in the literature. According to the analyzed data, our patient, who presented contemporary involvement of the spine and CNS, is unique; two other ALCL children with concomitant bone and CNS involvement were reported, but in both patients, lymphoma started as cerebral mass with secondary skull involvement. With the limits of a case report, it seems that a treatment based on intensive chemotherapy can be effective in obtaining and maintaining a complete remission; furthermore, the availability of a disease marker, the NPM-ALK transcript, in a biological sample that is easy to collect, i.e., PB, greatly simplifies the disease monitoring in these patients.

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