Secondary Biphenotypic Acute Leukemia Following Rosai-Dorfman-Disease A Coincidence?

Sekundäre biphänotypische akute Leukämie nach Rosai-Dorfmann-Erkrankung – eine Ko-Inzidenz?

**ABBREVIATIONS**

- RDD: Rosai-Dorfman-Disease
- TP53: Tumor protein p53
- CNS: Central nervous system
- Dexa: dexamethasone
- ESR: Erythrocyte sedimentation rate
- IC-2: Initial Course 2 of LCH-registry Therapy (Vinblastine and Prednisolone)
- LCH-registry International Collaborative Treatment Protocol for Children and Adolescents with Langerhans Cell Histiocytosis
- LDH: Lactate dehydrogenase
- MRD: Minimal residual disease
- MRI: Magnetic resonance imaging
- N-LCH: Non-Langerhans cell histiocytosis
- Nel: Nelarabine
- Cyt: Cytarabine
- Eto: Etoposide
- Dara: Daratumomab

**Introduction**

Non-Langerhans cell histiocytosis (N-LCH) comprises a spectrum of proliferative disorders of histiocytes, macrophages and dendritic cells. There is a wide spectrum of benign or malignant, localized or multifocal/systemic manifestations. One subgroup of N-LCH is the Rosai-Dorman-Disease (RDD), also called sinus histiocytosis with massive lymphadenopathy, which is generally a benign and self-limiting disease. RDD is characterized by a reactive proliferation of macrophages showing emperiploesis and expression of S100 protein (Abla O et al. Blood. 2018; 131: 2877–90; Classen CF et al. Klin Padiatr. 2016; 228: 294–306). Here, we present the case of a 6-year old male patient who was diagnosed with multifocal extranodal RDD developing a secondary biphenotypic, treatment-resistant leukemia during treatment and partial response of N-LCH.

An association to hemato-lymphoid malignancies or immune diseases is suspected, but has not been validated so far. There are few reports of children suffering from NHL, Hodgkin-Disease or Leukemia who developed a secondary histiocytosis after treatment (Classen CF et al. Klin Padiatr. 2016; 228: 294–306). Here, we present the case of a 6-year old male patient who was diagnosed with multifocal extranodal RDD developing a secondary biphenotypic, treatment-resistant leukemia during treatment and partial response of N-LCH.

**Case Description**

At the age of 4 years and 10 month, our patient was diagnosed with Rosai-Dorfman-Disease by lymph-node and skin biopsy with manifestations cervical, mediastinal, pulmonary, renal and bone (Fig. 1a–c). This led to an upper venous congestion. Furthermore, papular skin lesions could be found. He was initially treated with two cycles of Methylprednisolone pulse therapy due to the multifocal extranodal disease. Restaging after 3 weeks showed progressive disease, so chemotherapy according to the Initial Course- 2 of International Collaborative Treatment Protocol for Children and Adolescents with Langerhans Cell Histiocytosis was initiated, consisting of vinblastine and prednisone. As disease control was not sufficient after one cycle methotrexate and 6-mercaptopurine were added in accordance with the registry committee. A partial response of local masses to chemotherapy could be seen in the MRI-control after 7 weeks of therapy. The patient was in excellent clinical condition without relevant restrictions.

Fifteen months after diagnosis, the patient presented in reduced general condition with diffuse abdominal pain. Ultrasound revealed splenomegaly, MRI showed several splenic infarctions (Fig. 1d). Whereas ESR and C-
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Bone marrow puncture on point time 2 of the protocol detected for the first time a second atypical promyelocytic blast population (CD34 neg, low expression of CD117 and TdT) besides the known lymphoblastic cells, so that a biphenotypic leukemia was suspected. Cytogenetic and molecular genetic aberrations (t(4;7), t(14;16), del(9)) could be seen. As lymphoblasts showed CD34 + expression, in an off label use of daratumomab, a specific antibody, was administered (2 cycles, 500 mg/m²). After two cycles, again leukemic blast crisis was documented. As a next step, a modified therapy with cytarabine and mitoxantrone was started. However, the increase of leukocytes and blast crisis could not be controlled (Fig. 2). The patient died three months after diagnosis of secondary leukemia.

Hypothesizing that RDD and the secondary leukemia could be based on the same malignant clone/precursor or on a cancer predisposition syndrome, whole-exome-sequencing of a saliva sample and a blood sample (leukemic cells) were performed in addition. Saliva analysis showed a pathogenic splice site variant affecting the MLH1 gene (c.790 + 1 G > A, p.?), which was also detected in the blood sample. Furthermore, sequencing results of leukemic cells revealed a pathogenic variant in the TP53 gene (c.844C > T p.[Arg282Trp]) also being detected low-frequently in the saliva sample. Both mutated genes constitute well-known cancer predisposition genes, as they are causative for different hereditary cancer-predisposing syndromes, including Lynch and Li-Fraumeni syndrome. For further discrimination whether the secondary leukemia and the RDD are genetically related, a DNA sample of initial RDD diagnosis was examined according to the MLH1 and TP53 mutational status. Both sequence variants could not be detected in the RDD sample. Finally, we could not prove a genetically association of these both diseases. Moreover, the sequencing data do not point to a germline MLH1 mutation.

Discussion

Diagnosis and management of RDD has been lately discussed, but etiology, prognosis, diagnostic markers and relation to other diseases still are not completely understood. An association of Non-LCH with malignant hematologic neoplasm has been reported in a few cases, suggesting that this is more than a coincidence (Classen CF et al. Klin Padiatr. 2016; 228: 294–306; Zanelli M et al. Int J Surg Pathol. 2019; 27: 396–8; Bonometti A et al. J Cutan Pathol. 2021; 48: 637–43; Park IS et al. Korean J Intern Med. 2012; 27: 459–62; Castro EC et al. Pediatr Dev Pathol. 2010; 13: 225–37; Ambati S et al. Pediatr Blood Cancer. 2008; 51: 433–5; Allen MR et al. Med Pediatr Oncol. 2001; 37: 150–2; Rodig SJ et al. Am J Hematol. 2008; 83: 116–21). In most cases, leukemia preceded Non-LCH or occurred at the same time. Furthermore, a MAP2K1-driven mixed histiocytosis with Langerhans cell histiocytosis, Rosai-Dorfman-Destombes disease, and Erdheim-Chester disease features and cutaneous involvement, progressing to a fatal and clonally-related acute myeloid leukemia has been described (Bonometti A et al. J Cutan Pathol. 2021; 48: 637–43). This report is a rare case of acute leukemia following RDD as a secondary malignancy in a child. Since therapy related secondary malignancy after treatment of RDD with low dose MTX (20 mg/m²/week) and 6-mercaptopurine (50 mg/m²/day) has not been described previously, we suspect leukemia to be rather an association with histiocytosis than a secondary, treatment-related malignoma.

This remarkable case, especially because of its switch to biphenotypic leukemia (from a pre-T-ALL (CD2, CD10, cyCD3 and CD99) to

![Fig. 2](image_url) Leucocyte and blast count versus time since diagnosis. Treatment modification according to diagnosis and therapy response. DEXA, dexamethasone; NEL, nelarabine; CYT, cytarabine; ETO, etoposide, DAR, daratumomab. BMP, bone marrow puncture.
a second atypic promyelocytic blast population (CD34 neg, low expression of CD117 and TdT) after day 78 of treatment), illustrates how important a better understanding and a central collection of clinical courses of Non-LCH are. In our case a common marker of cell lines of histiocytosis and leukemic blasts - as described in literature (Bonometti A et al. J Cutan Pathol. 2021; 48: 637–43; Park IS et al. Korean J Intern Med. 2012; 27: 459–62; Scott DW et al. Cornell Vet. 1979; 69: 176–97; Venkataraman G et al. Am J Surg Pathol. 2010; 34: 589–94), has not been found. As we could not detect a genetic tumor relevant mutation, an association between these both diseases can only be hypothesis, not confirmed. Further studies are necessary to identify genetic and molecular markers that can prove the association of Non-LCH with leukemia as well as predicting the progression to a malignant haematologic disease.

Summarizing our demonstrated case, we could find a therapy refractory acute leukemia in a patient treated for Rosai-Dorfmann disease. Even if we did not confirm an association between those two diseases an association with Rosai Dorfmann disease to other hematologic diseases seems likely, as there are several case reports in Rosai Dorfmann patients with other hematological diseases. Since pathogenesis remains unclear, molecular genetic examinations in those patients will help to advance the understanding of the disease and will help to detect possible innovative therapy strategies and disease associations.

Contributor’s Statement

AT, VW contribution to study concept and design and drafting or revising the manuscript. KS, KE, KM, SH performed genetical analysis and interpretation of data CB, AB performance and interpretation of radiologic images and designed figure 1. PGS, CH, CFC, ME and MW: drafting or revising the manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

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