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

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

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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

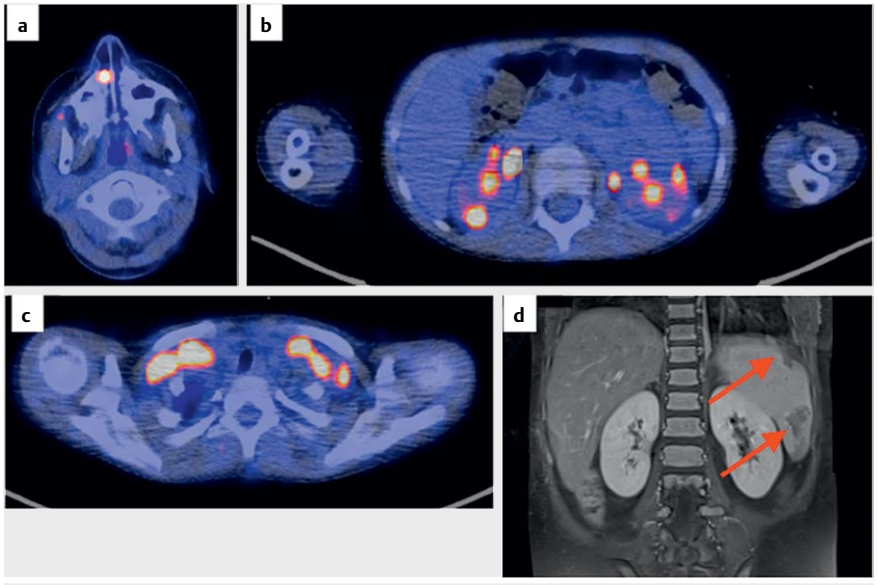
Non-Langerhans cell histiocytosis (N-LCH) comprises a spectrum of proliferative disorders of histiocytes, macrophages and dendritic cells. There is a wide spectrum of benign or malignant, localized or multifocal/systemic manifestations. One subgroup of N-LCH is the Rosai-Dorman-Disease (RDD), also called sinus histiocytosis with massive lymphadenopathy, which is generally a benign and self-limiting disease. RDD is characterized by a reactive proliferation of macrophages showing emperipolesis and expression of S100 protein (Abla O et al. *Blood*. 2018; 131: 2877–90; Classen CF et al. *Klin Padiatr*. 2016; 228: 294–306; Papo M et al.. *Curr Oncol Rep*. 2019; 21: 62). Immunohistochemically the cells are typically positive for S100, CD68-PGM1 and CD163, but negative for langerin, clusterin, CD1a and BRAF. Clinical characteristic are bilateral, painless, cervical lymph node enlargement with or without B-symptoms. 30–40 % of patients show extranodal involvement including cutaneous (10 %), CNS (< 5 %), head and neck (11 %), intrathoracic (2 %), kidney, gastrointestinal, bone and hematologic manifestations.

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 .

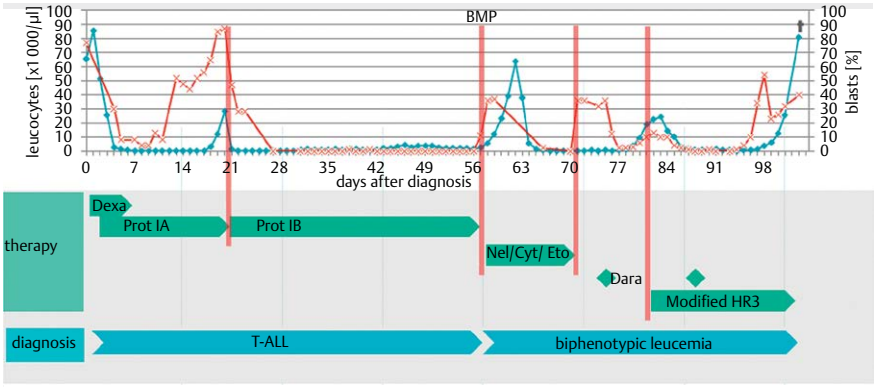
Case Description

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, pulmonal, 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 -



▶ **Fig. 1** FDG-PET-CT showing initial manifestations of RDD: nasal (**a**), renal (**b**) and supraclavicular lymph node manifestations (**c**). MR showing splenic infarctions (**d**).



▶ **Fig. 2** Leucocyte and blast count versus time since diagnosis. Treatment modification according to diagnosis and therapy response. Dexa, dexamethasone; Nel, nelarabine; Cyt, cytarabine; Eto, etoposide, Dara, daratumomab. BMP, bone marrow puncture.

reactive protein showed values within the normal range, LDH was increased (3450 U/l) and blood count showed hyperleukocytosis (max 124.000/µl leukocytes) with 77 % leukemic blasts (L1). Leukemic blasts showed expression of CD2, CD10, cyCD3 and CD99, suitably with pre-T-ALL. Molecular genetics could not detect rearrangements, especially no bcr/abl, MLL rearrangements or TEL-AML1. Because of additional hyperfibrinolysis with disseminated intravascular coagulation, the lumbar puncture and bone marrow puncture were postponed. CNS Status 2a with 7 % blasts, defined as negative (overall cell number 1/µl) could be diagnosed on day 14 of therapy.

Treatment according to AEIOP-BFM ALL 2017 registry was started immediately with dexamethasone. Because of further increasing leucocyte count, cyclophosphamide was given at days 2 and 3 in addition, followed by vincristine, daunorubicin and asparaginase at day 8 und 15. Reduction of blasts was detected on day 8 in peripheral blood (leukocytes 150/µl; 4 % blasts) but already on day 21 of protocol IA another blast crisis occurred (Leucocytes 28.660/µl; 85 % blasts). Protocol IB was therefore started earlier on day 21, including cyclophosphamide, cytarabin,6-mercaptopurine and intrathecal methotrexate. As another blast crisis occurred after protocol IB with 37 % blast (cytomorphologic MRD- 89 %) an individual experimental therapy consisting of nelarabine, cytarabine and etoposide was attempted, but leukemia remained refractory (▶ **Fig. 2**).

Bone marrow puncture on time point 2 of the protocol detected for the first time a second atypic 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 CD38 + 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 leucocytes and blast crisis could not be controlled (▶ **Fig. 2**). The patient died three month after diagnosis of secondary leukemia.

Hypothezing that RDD and the secondary leukemia could be based on the same malignant clone/precursor or on a cancer predispostion 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.844 C > 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[1], 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*

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.

Authors

Anne Thieme[1], Katja Maurus[2], Karen Ernestus[2], Steffen Hirsch[3], Kathrin Schramm[3], Clemens Wirth[4], Andreas Buck[5], Christoph Härtel[6], Paul G. Schlegel[7], Matthias Eyrich[1], Mathias Woelfl[8], Carl Friedrich Classen[9], Verena A. Wiegering[1]

Affiliations

1 Department of Pediatrics, University Hospital Wuerzburg, Wuerzburg, Germany
2 Department of Pathology, University of Würzburg, Wuerzburg, Germany
3 Hopp Children's Cancer Center Heidelberg (KiTZ) and German Cancer Research Center (DKFZ) University Hospital Heidelberg, University Hospital Heidelberg Medical Clinic, Heidelberg, Germany
4 Institute of Radiology, University Hospital Würzburg, Würzburg, Germany
5 Department of Nuclear Medicine, University of Würzburg, Wuerzburg, Germany
6 Pediatric, Klinikum der Universität Würzburg, Wurzburg, Germany
7 Childrens Hospitals, University of Würzburg, 97080, Germany
8 Department of pediatric hemato-oncology, University Clinic of Würzburg, Wuerzburg, Germany
9 Pediatric Oncology and Hematology, University Children's Hospital Rostock, Rostock, Germany

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Correspondence

Dr. Verena A. Wiegering
University Hospital Wuerzburg
Department of Pediatrics
Josef-Schneiderstr. 2
97080 Wuerzburg
Germany
Tel.: + 49/931/20127 728,
Fax: + 49/931/20127 730
wiegering_v@ukw.de

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