

---

# Histiocytic Disorders

---

Oussama Abla • Gritta Janka  
Editors

# Histiocytic Disorders

*Editors*

Oussama Abla  
University of Toronto  
The Hospital for Sick Children  
Toronto, Ontario, Canada

Gritta Janka  
Pediatric Hematology and Oncology  
University Medical Center Hamburg  
Eppendorf  
Hamburg, Germany

ISBN 978-3-319-59631-0      ISBN 978-3-319-59632-7 (eBook)  
<https://doi.org/10.1007/978-3-319-59632-7>

Library of Congress Control Number: 2017958965

© Springer International Publishing AG 2018

This work is subject to copyright. All rights are reserved by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed.

The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

The publisher, the authors and the editors are safe to assume that the advice and information in this book are believed to be true and accurate at the date of publication. Neither the publisher nor the authors or the editors give a warranty, express or implied, with respect to the material contained herein or for any errors or omissions that may have been made. The publisher remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Printed on acid-free paper

This Springer imprint is published by Springer Nature  
The registered company is Springer International Publishing AG  
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

---

## Preface

As the second textbook on “histiocytic disorders” is about to be published, the world of histiocytoses has never been more exciting and challenging at the same time. Exceptional advances in molecular and cellular biology have led to rapid changes in diagnostic and therapeutic modalities and have revolutionized the way we view most histiocytic disorders today. Once considered to be disorders of immune regulation, Langerhans cell histiocytosis (LCH) and Erdheim-Chester disease (ECD) are now considered as inflammatory myeloid neoplasms thanks to the discovery of BRAF-V600E and MAP2K mutations in two-thirds of these patients. One of the most important priorities of this textbook is to discuss the new genomic findings in all histiocytic neoplasms and related disorders and to shed more light on the new pathophysiological and genetic findings in hemophagocytic lymphohistiocytosis (HLH). The 2016 revised classification of histiocytic disorders will also be explained, and this will take into account all the most recent molecular and genomic findings merged with clinical categories.

This book will include four sections: the first one is dedicated to the pathology of all histiocytic disorders and is written by the top two world pathology experts on histiocytoses; section 2 is dedicated to LCH in children and adults, central nervous system (CNS) LCH, and first-line treatment of pediatric and adult LCH as well as treatment of refractory and relapsed LCH, with chemotherapy and BRAF inhibitors as well as new hematopoietic stem cell transplantation (HSCT) modalities, with an updated chapter on late effects after LCH. The third section is dedicated to HLH, in particular its diagnostic and clinical features, genetics and pathophysiology, with dedicated chapters on CNS-HLH, EBV-related HLH, malignancy-associated HLH, and macrophage-activation syndrome (MAS). These are followed by chapters on frontline treatment, treatment of refractory/relapsed HLH, HSCT and novel therapies, and finally adult HLH. Section 4 includes the uncommon histiocytic disorders with dedicated chapters on juvenile xanthogranuloma (JXG) and JXG-like disorders, ECD, Rosai-Dorfman disease (RDD), and malignant histiocytoses.

All chapters were written by distinguished experts in each field. We would like to take this opportunity to thank all of them for their efforts and time but also to thank several junior physicians who assisted these experts on specific chapters. We are also very grateful for the editorial assistance of Andy Kwan in New York and of Rahul Kumar Sharma in India, who have shown extraor-

dinary dedication and patience in managing the flow of many manuscripts, figures, and permissions.

We hope this book will serve as a comprehensive and updated tool for all pediatric and adult hematologists, oncologists, immunologists, pathologists, and trainees who will be looking after patients with histiocytic disorders.

Toronto, Canada  
Hamburg, Germany

Oussama Abla, MD  
Gritta Janka, MD, PhD

---

# Contents

## Part I Pathology of Histiocytic Disorders

- 1 Pathology of Histiocytic Disorders and Neoplasms and Related Disorders . . . . . 3**  
Jennifer Picarsic and Ronald Jaffe

## Part II Langerhans Cell Histiocytosis (LCH)

- 2 Biology and Genomics of LCH and Related Disorders . . . . . 53**  
Barrett J. Rollins
- 3 Epidemiology and Clinical Manifestations of Langerhans Cell Histiocytosis in Children . . . . . 73**  
Etai Adam, Rima Jubran, and Sheila Weitzman
- 4 Central Nervous System Langerhans Cell Histiocytosis . . . . . 87**  
Milen Minkov, Jennifer Picarsic, and Karoly Lakatos
- 5 First-Line Treatment of Pediatric Langerhans Cell Histiocytosis . . . . . 103**  
Carlos Rodriguez-Galindo and Cor van den Bos
- 6 Treatment of Relapsed and Refractory Langerhans Cell Histiocytosis in Children . . . . . 119**  
Oussama Abla, Carlos Rodriguez-Galindo, and Paul Veys
- 7 Adult Langerhans Cell Histiocytosis . . . . . 139**  
Michael Girschikofsky and Abdellatif Tazi
- 8 Late Effects of Langerhans Cell Histiocytosis and the Association of LCH with Malignancy . . . . . 155**  
Vasanta Nanduri, Lilibeth R. Torno, and Riccardo Haupt

## Part III Hemophagocytic Lymphohistiocytosis (HLH)

- 9 Classification, Clinical Manifestations, and Diagnostics of HLH . . . . . 173**  
Jana Pachlopnik Schmid, Benjamin Volkmer, and Stephan Ehl

<b>10</b>	<b>CNS Involvement in HLH (CNS-HLH)</b> .....	189
	AnnaCarin Horne and Karin Beutel	
<b>11</b>	<b>Genetics and Pathogenesis of Hemophagocytic Lymphohistiocytosis</b> .....	197
	Geneviève de Saint Basile, Despina Moshous, and Alain Fischer	
<b>12</b>	<b>Hemophagocytic Lymphohistiocytosis Associated with Malignancies and with Epstein-Barr Virus</b> .....	215
	Kai Lehmborg, Fumihiro Ochi, Kim E. Nichols, and Eiichi Ishii	
<b>13</b>	<b>Macrophage Activation Syndrome in Rheumatic Diseases (MAS-HLH)</b> .....	233
	Alexei A. Grom, AnnaCarin Horne, and Fabrizio De Benedetti	
<b>14</b>	<b>Treatment of Newly Diagnosed HLH and Refractory Disease</b> .....	247
	Jan-Inge Henter, Rebecca A Marsh, and Tatiana von Bahr Greenwood	
<b>15</b>	<b>Hematopoietic Cell Transplantation and Novel Therapies in Hemophagocytic Lymphohistiocytosis</b> .....	265
	K. Scott Baker and Michael B. Jordan	
<b>16</b>	<b>HLH in Adults</b> .....	275
	Paul La Rosée and Rafal Machowicz	
 <b>Part IV Rare Histiocytic Disorders: Non-Langerhans Cell Histiocytosis</b>		
<b>17</b>	<b>Juvenile Xanthogranuloma and Related Non-LCH Disorders</b> .....	293
	Francesco Ceppi and Oussama Abla	
<b>18</b>	<b>Erdheim-Chester Disease</b> .....	313
	Eli L. Diamond	
<b>19</b>	<b>Rosai–Dorfman Disease</b> .....	339
	Oussama Abla and Jennifer Picarsic	
<b>20</b>	<b>Malignant Histiocytoses</b> .....	361
	Eric Jacobsen, Oussama Abla, and Johannes Visser	
	<b>Index</b> .....	383

---

## Contributors

**Oussama Abl, MD** Department of Pediatrics, Division of Hematology/Oncology, Hospital for Sick Children and University of Toronto, Toronto, ON, Canada

**Etai Adam, MD** The Children's Center for Cancer and Blood Diseases, Children's Hospital Los Angeles, Los Angeles, CA, USA

**Tatiana von Bahr Greenwood, MD** Childhood Cancer Research Unit, Department of Women's and Children's Health, Karolinska Institutet, and Theme of Children's and Women's Health, Karolinska University Hospital, Stockholm, Sweden

**Fabrizio De Benedetti, MD** Ospedale Pediatrico Bambino Gesù, Rome, Italy

**Karin Beutel, MD** Pediatric Hematology and Oncology, Children's Hospital München-Schwabing, Städtisches Klinikum München and University Hospital München Rechts der Isar, Technical University München, München, Germany

**Cor van den Bos, MD** Emma Children's Hospital/Academic Medical Center, Department of Pediatric Oncology, Amsterdam, The Netherlands

**Francesco Ceppi, MD** Department Woman-Mother-Child, Divisions of Pediatric Oncology and Hematology, University Hospital of Lausanne, Lausanne, Switzerland

**Eli L. Diamond, MD** Department of Neurology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

**Stephan Ehl, MD** Center for Chronic Immunodeficiency, University Medical Center Freiburg, University of Freiburg, Freiburg, Germany

**Alain Fischer, MD, PhD** INSERM UMR1163, Paris, France  
Paris Descartes University-Sorbonne Paris Cité, Imagine Institute, Paris, France

Paediatric Immunology and Hematology Department, Necker Children's Hospital, AP-HP, Paris, France  
Collège de France, Paris, France



**Michael Girschikofsky, MD** Internal Medicine I, (Hemostasis, Hematology and Stem Cell Transplantation and Medical Oncology), Ordensklinikum Linz - Elisabethinen Hospital, Linz, Austria

**Alexei A. Grom, MD** Cincinnati Children's Hospital Medical Center, Division of Rheumatology, Cincinnati, OH, USA

**Riccardo Haupt, MD** Epidemiology and Biostatistics Unit, Istituto Giannina Gaslini, Genoa, Italy

**Jan-Inge Henter, MD, PhD** Childhood Cancer Research Unit, Department of Women's and Children's Health, Karolinska Institutet, and Theme of Children's and Women's Health, Karolinska University Hospital, Stockholm, Sweden

**AnnaCarin Horne, MD, PhD** Pediatric Rheumatology Clinic and Childhood Cancer Research Unit, Karolinska universitets sjukhuset and Karolinska Institutet, Stockholm, Sweden

**Eiichi Ishii, MD** Department of Pediatrics, Ehime University Graduate School of Medicine, Toon, Ehime, Japan

**Eric Jacobsen, MD** Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

**Ronald Jaffe, MB, BCh** Department of Pathology, University of Pittsburgh School of Medicine, Magee Women's Hospital of UPMC, Pittsburgh, PA, USA

**Michael B. Jordan, MD** Divisions of Immunobiology and Bone Marrow Transplantation and Immune Deficiency, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, OH, USA

**Rima Jubran, MD** The Children's Center for Cancer and Blood Diseases, Children's Hospital Los Angeles, Los Angeles, CA, USA

**Karoly Lakatos, MD** St. Anna Children's Hospital, Department of Pediatrics and Adolescent Medicine, Medical University of Vienna, Vienna, Austria

**Kai Lehmberg, MD** Department of Pediatric Hematology and Oncology, University Medical Center Hamburg Eppendorf, Hamburg, Germany

**Rafal Machowicz, MD, MSc** Department of Hematology, Oncology and Internal Diseases, Medical University of Warsaw, Warsaw, Poland

**Rebecca A. Marsh, MD** Division of Bone Marrow Transplantation and Immune Deficiency, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

**Milen Minkov, MD, PhD** International LCH Study Reference Center, CCRI, St. Anna Kinderkrebsforschung, Department of Pediatrics and Adolescent Medicine, Medical University of Vienna, Vienna, Austria  
St. Anna Children's Hospital, Department of Pediatrics and Adolescent Medicine, Medical University of Vienna, Vienna, Austria

**Despina Moshous, MD, PhD** INSERM UMR1163, Paris, France  
Paris Descartes University-Sorbonne Paris Cité, Imagine Institute, Paris, France

Paediatric Immunology and Hematology Department, Necker Children's Hospital, AP-HP, Paris, France

**Vasanta Nanduri, MD, MRCP, FRCPCH** Department of Paediatrics, Watford General Hospital, Watford, WK, UK

**Kim E. Nichols, MD** Department of Oncology, St. Jude Children's Research Hospital, Memphis, TN, USA

**Fumihiko Ochi, MD** Department of Pediatrics, Ehime University Graduate School of Medicine, Toon, Ehime, Japan

**Jennifer Picarsic, MD** Department of Pathology, University of Pittsburgh School of Medicine, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, USA

Department of Pathology, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, USA

**Carlos Rodriguez-Galindo, MD** Departments of Global Pediatric Medicine and Oncology, St. Jude Children's Research Hospital, Memphis, TN, USA

**Barrett J. Rollins, MD, PhD** Department of Medical Oncology, Dana-Farber Cancer Institute, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

**Paul La Rosée, MD** Klinik für Innere Medizin II, Klinikstr. 11, Schwarzwald-Baar-Klinikum, Villingen-Schwenningen, Germany

**Geneviève de Saint Basile, MD, PhD** INSERM UMR1163, F-75015, Paris, France

Paris Descartes University-Sorbonne Paris Cité, Imagine Institute, Paris, France

Centre d'Etudes des Déficits Immunitaires, Assistance Publique-Hôpitaux de Paris, Hôpital Necker, Paris, France

**Jana Pachlopnik Schmid, MD, PhD** Division of Immunology, University Children's Hospital, University of Zurich, Zurich, Switzerland

**K. Scott Baker, MD, MS** Clinical Research Division, Fred Hutchinson Cancer Research Center, Department of Pediatrics, University of Washington, Seattle, WA, USA

**Abdellatif Tazi, MD, PhD** Publique-Hôpitaux de Paris, Saint-Louis Hospital, National Reference Center for Histiocytoses, Pulmonary Department, Paris, France

University Paris Diderot, Sorbonne Paris Cité, Inserm UMR-1153 (CRESS), Biostatistics and Clinical Epidemiology Research Team (ECSTRA), Paris, France

**Lilibeth R. Torno, MD** After Cancer Treatment Survivorship Program,  
Children's Hospital of Orange County, Orange, CA, USA

**Paul Veys, MBBS, FRCP, FRCPath, FRCPCH** Blood and Bone  
Marrow Transplantation Unit, Great Ormond Street Hospital for Children,  
London, UK

**Johannes Visser, MB, ChB** Cambridge University Hospitals NHS  
Foundation Trust, Addenbrooke's Hospital, Cambridge, UK

**Benjamin Volkmer, PhD** Division of Immunology, University Children's  
Hospital, University of Zurich, Zurich, Switzerland

**Sheila Weitzman, MB, BCh, FCP(SA), FRCP(C)** Division of  
Haematology and Oncology, Department of Paediatrics, The Hospital for  
Sick Children, University of Toronto, Toronto, ON, Canada

Histiocytic Disorders

Abla, O.; Janka, G. (Eds.)

2018, XII, 392 p. 96 illus., 74 illus. in color., Hardcover

ISBN: 978-3-319-59631-0