Tumors of the Langerhans Cell System

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Contents

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DOI 10.1007/978-3-319-26956-6_100

Abstract

Langerhans cell histiocytosis (LCH) is a rare proliferative disorder of bone marrow-derived antigen-presenting cells that home to diverse organs and tissues, predominantly the skin. LCH is a rare disease that mainly manifests in the pediatric age group, with several in part overlapping phenotypes. Clinically and morphologically, LCH is divided into unifocal LCH, single-system LCH, multifocal LCH, multiorgan/disseminated LCH, Langerhans cell sarcoma, and Langerhans tumors. All forms and variants are characterized by a progressive and monoclonal proliferation of medium-sized, CD1a-reactive, and langerin-/CD207-reactive cells that often contain Birbeck granules. Langerhans cell infiltrates are regularly accompanied by infiltrates of eosinophils, lymphoid cells, and macrophages. Lesions with a high density of eosinophils were previously termed eosinophilic granuloma. Hepatobiliary involvement in LCH presents with a characteristic spectrum of lesions that include a disseminated form, focal forms (microscopic and macroscopic), and a form associated with bile ducts (LCH cholangiopathy). A small subset of Langerhans cell proliferations present as tumorous lesions or Langerhans cell sarcoma. In addition to LCH, there are a group of so-called self-healing Langerhans cell and related disorders that can involve the hepatobiliary tract.

Langerhans Cell Histiocytosis (LCH)

ICD-O code 9751/3

Introduction

Langerhans cell histiocytosis (LCH) is a rare proliferative disorder of bone marrow-derived antigen-presenting cells that tend to chiefly infiltrate the skin, but also other organs and tissues, including the bone marrow, bone, liver, spleen, lymph nodes, gastrointestinal tract, lungs, and hypophysis (Arico and Egeler 1998; Broadbent et al. 1994; Herzog and Tubbs 1998; Ladisch 1998; Allen and McClain 2007; Windebank and Nanduri 2009; Abla et al. 2010; Minkow 2011; Munir et al. 2012; Xu et al. 2012a; Gadner et al. 2013; Haupt et al. 2013; Collin et al. 2015; El Demellawy et al. 2015). Synonymous terms that are currently regarded as obsolete are histiocytosis X, eosinophilic granuloma, Letterer-Siwe disease, Hand-Schüller-Christian disease, Langerhans cell granulomatosis, type II histiocytosis, and nonlipid reticuloendotheliosis (Komp 1987; Favara et al. 1997). These older terms reflect the first clinical descriptions of LCH and its variants by Hand (1893, 1921), by Schüller (1915), by Christian (1919), and later by Letterer (1924) and Siwe (1933), resulting in considerable confusion in nomenclature until it was recognized that the disease in each of these clinical syndromes was components of a spectrum of disease involving the LC (Lichtenstein 1953; Lieberman et al. 1969; Broadbent et al. 1994).

Epidemiology

The estimated incidence of LCH is approximately five per one million population per year. Most cases are diagnosed in the pediatric age group. LCH has a clear predilection for males (M/F = 3.7:1) and chiefly occurs in whites of northern European descent, being rare in blacks. LCH can be clustered within families, with high concordance in monozygotic twins, but there is no evidence for vertical transmission. LCD occurs in the neonatal period, where it is associated with a poor prognosis (Gee et al. 2013). In very rare instances, LCH can present as congenital disorder, sometimes with placental involvement (Terry et al. 2013).

Clinical Features

The clinical presentation and biology of LCH are highly heterogeneous and range from unifocal manifestations with an apparently self-limited course to multifocal and chronic, complex organ manifestations to rapidly progressing and fatal,

disseminated leukemia-like forms. LCH can be localized to a single site, multiple sites within a single system, or more disseminated and multisystemic. The solitary or unifocal form mainly involves bones and adjacent soft tissues and less commonly the skin, lung, lymph nodes, and other organs. Multifocal LCH is typically a bone disease, with involvement of the periosseous tissue. Preferential involvement sites in multisystemic LCH comprise the bone marrow, spleen, bone, skin, and liver. Interestingly, kidneys and gonads are very uncommonly involved. Clinically, solitary/unifocal lesions prevail in older children and adults and typically present as lytic bone defects. In skull base involvement, diabetes insipidus is common. Multisystem involvement predominantly occurs in infants and small children and is characterized by a febrile illness with skin, bone, and visceral lesions and cytopenia.

Classifications of LCH

What renders histopathologic diagnosis and classification difficult is the fact that the clinical heterogeneity is reflected in a broad spectrum of morphological lesions, heterogeneous themselves in regard to a given patient and her or his age and genetic background, the organ localization, the time point of examination, and the stage of disease, lesions that histologically sometimes do not appear to have something to do with a proliferative LC disorder. The criteria for a definitive diagnosis of LCH have been worked out and published in 1987 (Writing Group of the Histiocyte Society 1987); they are not further discussed here. Differential organ and tissue involvement has led to the definition of several subtypes, e.g., *unifocal LCH* (formerly, eosinophilic granuloma), *single-system LCH* (almost a third in one large study; Arico et al. 2003), and *multisystem/multiorgan/disseminated disease*. Pulmonary LCH (PLCH) is an important member of single-system LCH, being clearly distinct from systemic multiorgan LCH (Yousem et al. 2001; Sundar et al. 2003). A further variant of single-system LCH seems to be soft tissue solitary LCH (al-Abbadi et al. 1997).

Table 1 Working classification of Langerhans cell histiocytosis

Unifocal LCH (with or without marked eosinophilia, in the latter case corresponding to the former "eosinophilic granuloma")
Single-system LCH
Multifocal LCH (including manifestations corresponding to the former Hand-Schüller-Christian disease)
Multiorgan/disseminated LCH (acute, subacute; including manifestations corresponding to the former Letterer-Siwe disease)
Langerhans cell sarcoma
Langerhans cell tumors

Multisystem LCH covers syndromes originally denoted as Hand-Schüller-Christian disease and Letterer-Siwe disease, distinct by the rapidity of disease progression and by the involved organ/tissue spectrum, but an individual patient with multisystem LCH may present with signs intermediate between these apparent entities (Kato et al. 1981; Iupati and Chander 2006; Cugati et al. 2011). In the present chapter, the *working classification of LCH* summarized in Table 1 is used.

Langerhans cell tumors and Langerhans cell sarcomas are discussed in a separate paragraph.

General Morphologic Features of Langerhans Cell Histiocytosis

In principle, LCH is a progressive and apparently monoclonal proliferation of CD1a-positive cells, at least part of them containing Birbeck granules. "Langerhans cell granules" have already been reported for LCH then termed "subacute disseminated histiocytosis of Letterer-Siwe" in 1968 (Gianotti et al. 1968). The cells are medium sized (10–15 μm) of oval shape, lacking dendritic processes, with a slightly eosinophilic cytoplasm and grooved, folded, lobulated, or indented nuclei with fine chromatin and inconspicuous nucleoli. These cells are embedded in a cellular background with variable numbers of macrophages (in part multinucleated forms), eosinophils, neutrophils, and lymphocytes. Plasma cells are sparse. Eosinophils are sometimes very numerous, especially in solitary/unifocal bone lesions (the former

"eosinophilic granuloma"). Such lesions may contain eosinophilic abscesses with Charcot-Leyden crystals. Ultrastructurally, cells of LCH contain Birbeck granules, zipper-like structures with a tennis racquet shape, measuring 200–400 nm in length and 33 nm in width. Birbeck granules originate from subdomains of endosomal recycling compartments that consist of disks of two limiting membranes separated by leaflets with periodic zipper-like striations. Immunohistochemically, cells in LCH are strongly reactive for CD1a, langerin, and S100 protein. Langerin (CD207) is a trimeric C-type lectin that functions as a antigen receptor and in pathogen capture via the recognition of glycan motifs by three carbohydrate recognition domains (CRDs) (Muñoz-Garcia et al. 2015). Langerin recognizes hyaluronic acid on dendritic cells and is involved in the morphogenesis of Langerhans cell Birbeck granules (Chabrol et al. 2015). In addition, the tumor cells are positive for CD68, HLA-DR, and vimentin. LCs in LCH can express matrix metalloproteinase-9 (MMP-9), mostly co-expressed in cells that are also CD68+ and associated with recurrence of lesions (Zyada 2009).

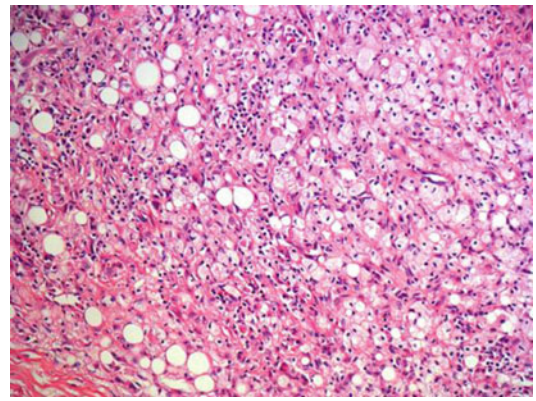

Fig. 1 Langerhans cell histiocytosis of the liver. Medium-sized to large cells have infiltrated the steatotic liver tissue (hematoxylin and eosin stain)

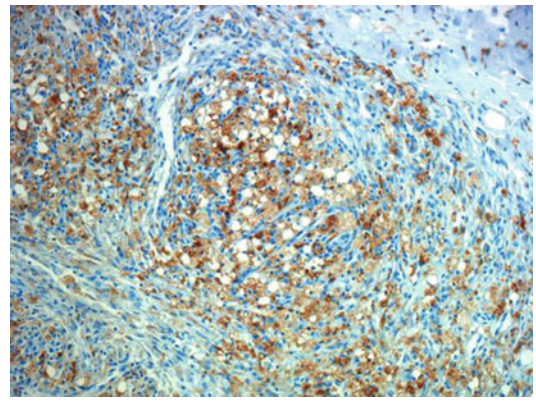

Fig. 2 Langerhans cell histiocytosis of the liver. Most of the neoplastic cells are reactive for CD1a (CD1a immunostain)

Liver Involvement in Langerhans Cell Histiocytosis

Introduction

In LCH, the liver is commonly involved, albeit with a rather broad spectrum of manifestations reflecting the different biologic phenotypes of LCH, including those with marked contribution of eosinophils (Figs. 1, 2, 3, 4, 5, and 6 and Table 2). Liver infiltration can sometimes cause massive hepatomegaly (Trochtenberg and Dessypris 1990). In multisystemic LCH, liver dysfunction may be the first clinical presentation (Liu et al. 2012). The morphology and immunophenotypes of LC in LCH of the liver are, in principle, similar to that of normal LC. For example, cells of LCH contain, albeit to variable degrees, Birbeck granules, a finding known since 1973 (Nezelof et al. 1973). However, LC in LCH expresses a phenotype of an LC apparently "fixed" at an earlier stage of activation, the cells being functionally defective in antigen capture and presentation and being very different in regard to tissue distribution and homing features (Chu and Jaffe 1994).

Selected References Avery et al. (1957), Parker and Lichtenstein (1963), Grosfeld et al. (1976), Leblanc et al. (1981), Jones et al. (1981), Favara (1981, 1996), Favara et al. (1983), Thompson et al. (1984), Sisto et al. (1987), Pirovino et al. (1988), Iwai et al. (1988), Heyn et al. (1990), Stieber et al. (1990), Concepcion et al. (1991), Squires et al. (1993), Granot et al. (1994), Debray et al. (1994), Finn and Jaffe

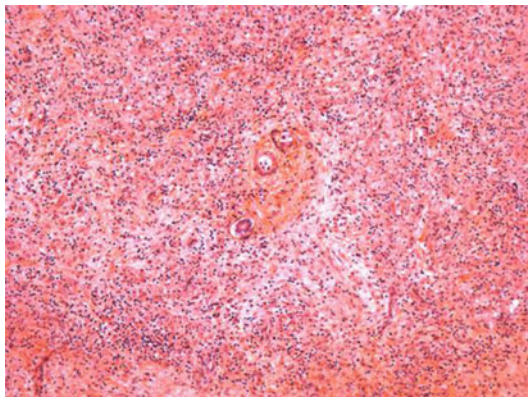

Fig. 3 Variant of Langerhans cell histiocytosis of the liver with xanthomatous cells and significant fibrosis. Variants with this phenotype were termed Hand-Schüller-Christian disease (hematoxylin and eosin stain)

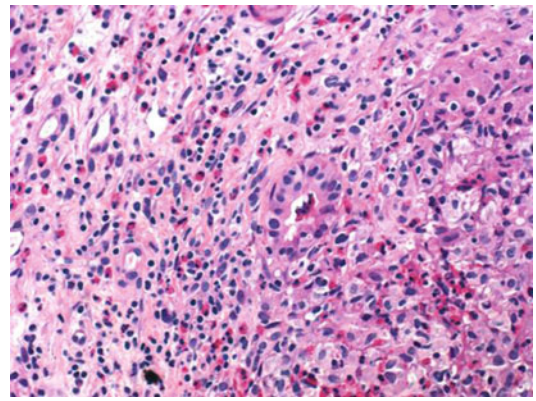

Fig. 5 Eosinophilic granuloma of the liver at higher magnification. The infiltrate is dominated by eosinophils, Langerhans cells, and lymphocytes. Eosinophils have invaded an interlobular bile duct, which is injured (eosinophilic cholangiopathy, hematoxylin and eosin stain)

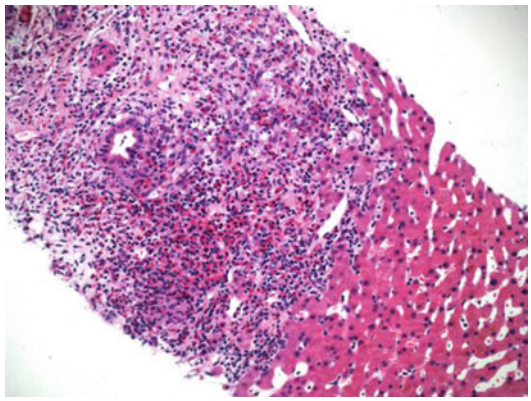

Fig. 4 Eosinophilic granuloma of the liver as a variant of Langerhans cell histiocytosis. In this biopsy, dense infiltrates of eosinophils, atypical round cells, and lymphocytes occupy an enlarged portal tract (hematoxylin and eosin stain)

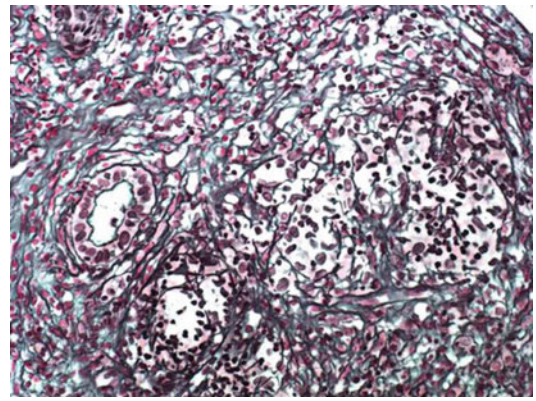

Fig. 6 Eosinophilic granuloma of the liver. The infiltrate is associated with increased reticulin fiber density. A small damaged bile duct is seen to the left (Gomori silver stain)

(1997), Kaplan et al. (1999), Guthery and Heubi (2001), Jaffe (2004), Chaudhary et al. (2006), Konno et al. (2007), Savva-Bordalo and Freitas-Silva (2008), Abdallah et al. (2011), and Ma et al. (2012).

Classifications of Hepatic LCH

There are several propositions to classify hepatic LCH, based on various criteria (Table 2).

Portal Tract/Bile Duct Involvement

Pretreatment liver biopsies show several lesions, a considerable part of the changes being nonspecific. In a study on 20 patients with LCH, pretreatment evaluation of liver tissues revealed various abnormalities of the portal tracts in 19/20 specimens, including "triaditis," small bile duct proliferation, variable fibrosis with infiltration of "histiocytes," and liver cirrhosis. One patient showed a granulomatous lesion (Heyn et al. 1990). In this study, patients with larger livers and hepatic dysfunction tended to exhibit

Table 2 Classifications of hepatic Langerhans cell histiocytosis

Clinicopathologic classification
I. Disseminated form (with or without sinusoidal spread)
II. Focal forms
1. Focal LC infiltration, microscopic pattern
2. Nodular LCH of the liver
3. Granulomatous hepatopathy
III. LCH cholangiopathy (in particular, sclerosing cholangitis)
IV. Posttransplant manifestations and associations of LCH
V. Paraneoplastic manifestations of LCH
Pathologic/pathogenic classification (Kaplan et al. 1999, modified)
A. Portal area/bile duct infiltration by LC causing:
Cholangionecrosis
Periductal sclerosis with or without LC ("PSC-like")
Ductopenia
Chronic cholestasis
Fibrosis/secondary biliary cirrhosis/atrophy-hypertrophy complex (AHC)
B. Sinusoidal infiltration
C. Disseminated infiltration
D. Multifocal infiltration with tumor-like lesions
E. Focal granulomatoid lesions (including "eosinophilic granuloma")
F. Secondary sclerosing cholangitis
G. Other liver manifestations

more marked histologic anomalies in the portal tracts, however, with considerable overlap. It turned out that patients showing fibrohistiocytic changes or cirrhosis initially were more likely to have continuing or progressive liver disease, although the liver histology was not diagnostic for LCH (Heyn et al. 1990). Triaditis was also observed in the majority of cases in another study (Favara 1996). In case of more advanced involvement of the liver, focal aggregates of LC (microscopic pattern) are observed in a polymorphous background of mature eosinophils, lymphocytes, neutrophils, and plasma cells (Kaplan et al. 1999). Specific LC infiltrates may be cholangiocentric, forming dense collections of cells surrounding damaged bile ducts (Favara 1996), or in the form of apparently random acinar "histiocytic" lesions (Favara 1996). Ductocentric LCH can result in progressive portal tract fibrosis or septal fibrosis (Arakawa et al. 1994). Involvement of the bile ducts with LCH may result in biliary wall calcification (Caruso et al. 2008). LCH may be associated with cholelithiasis and bile duct dilatation (Caruso et al. 2009).

Sinusoidal Infiltration

In part of cases of hepatic LCH, the CD1a-reactive tumor cells are found within the sinusoidal lumina, either as single cells or small clusters or groups of cells. This infiltration pattern can be associated with atrophy of hepatocyte plates.

Disseminated Infiltration

Relatively few data are available on the liver pathology in multisystemic/disseminated LCH, and in some of the published observations, it is difficult to judge as to what form of LCH one really deals with. In contrast to the chronic disseminated form of LCH (the former Hand-Schüller-Christian disease; Fig. 3), disseminated LCH is known to show an acute or subacute course. In the pediatric age group, the most impressive manifestation of disseminated LCH is the disorder characterized by a severe illness, a distinctive and frequently hemorrhagic skin rash, a low-grade fever, a leukemia-like blood change, and a massive hepatosplenomegaly with or without ascites, jaundice, lymphadenomegaly, soft tissue edema, and gingival necrosis, i.e., what has previously been termed Letterer-Siwe disease or "acute nonlipid disseminated reticuloendotheliosis" (see below; Batson et al. 1955; Komp 1987). Liver manifestations have been reported in the literature (Childers and Price 1954; Batson et al. 1955). In an autopsy case (two-and-a-half-year-old child with "classical" presentation of Letterer-Siwe disease), the enlarged liver showed numerous nodular projections on the capsular surface, a greenish-yellow color, and a firm consistency. Microscopy revealed an increased amount of connective tissue in the portal tracts associated with ductular proliferations, portal tract infiltrates of mononuclear

cells and small lymphocytes, and signs of cholestasis (Childers and Price 1954). The disease manifestations depend on the stage of disease, i.e., florid lesions with tissue damage together with highly cellular infiltrates being more prominent in early phase disease, while the portal tract lesions described in the case of Childers and Price reflect longer-standing disease.

Multifocal Infiltration with Tumor-like Lesions

LCH can produce focal infiltrations growing in the form of nodules, termed nodular LCH of the liver, but this type of manifestation is much rarer than the disseminated form (Foschini et al. 1995; Levy et al. 1998; Cavazza et al. 1999; Rice and Wyatt 2000; Yagita et al. 2001). In this situation, the liver substance is partially replaced by a hypercellular tissue forming lobulated, poorly demarcated nodules surrounded by fibrous tissue . The nodular lesions can clinically and radiologically resemble a primary hepatic malignancy and thus be misdiagnosed as liver cancer (Ma et al. 2014). The diameter of the nodules ranges from 1 mm to a few centimeters. In very few instances, only one hepatic nodule had been detected (Rice and Wyatt 2000). The infiltrate nodules may encroach upon small intrahepatic bile ducts (Parker and Lichtenstein 1963), but focal LCH confined to a bile duct has also been found (Finn and Jaffe 1997). Multifocal or disseminated hepatic LCH is mainly seen in patients who also show significant involvement of other organs and tissues and can present similar to multiple hepatic metastases (Hara et al. 1988; Guilarte Lopez-Manas et al. 1997). On the other hand, multiple tumor-like lesions at imaging may also be caused by marked periportal fibrosis in hepatic LCH (Arakawa et al. 1994).

Focal Granulomatoid Lesions (Including "Eosinophilic Granuloma")

Rarely, hepatic lesions in the context of LCH may contain numerous eosinophils, thus reflecting what previously has been termed eosinophilic granuloma, either unifocal or multifocal (the former Hand-Schüller-Christian disease; Parker and Lichtenstein 1963). Hepatic eosinophilic granuloma and other solitary liver lesions in LCH may radiologically be confounded with metastatic cancer (Saito et al. 2008). Hepatic lesions representing unifocal LCH may contain numerous lipid-laden macrophages in addition to eosinophils ("xanthomatous eosinophilic granuloma"; Fione and Rizzo 1959), leading to differential diagnostic problems with respect to other xanthomatous hepatic lesions such as those occurring in some lipidoses and in obstructive cholestasis. In an autopsy of a patient with multifocal LCH of the former Hand-Schüller-Christian type (chronic disseminated form of LCH), the liver was enlarged (1,900 g) and showed yellow flecks scattered about the parenchyma (Parker and Lichtenstein 1963). Histologically, the liver displayed marked cholestasis with formation of bile lakes, rounded portal tracts with fibrosis and ductular proliferations, and histiocyte-containing nodules (sometimes impinging upon bile ducts and producing florid duct lesions), containing in addition to histiocyte-like cells lipid-laden macrophages, but only few eosinophils, whereas a previous biopsy had shown eosinophil-rich nodules. This observation illustrates the transitional or overlapping features of LCH, lesions at one time point looking like the eosinophil-rich variant of focal LCH (eosinophilic granuloma) and showing at a later time point the features of xanthomatous lesions. Hence, an initial histologic diagnosis of eosinophil focal LCH or eosinophilic granuloma may result in the erroneous judgment that one deals with a benign process, what may then not be the case.

Langerhans Cell-Induced Secondary Sclerosing Cholangitis

A distinctive situation is obstructive cholestasis caused by secondary sclerosing cholangitis (SSC) in hepatic LCH (Leblanc et al. 1981; Thompson et al. 1984; Squires et al. 1993; Kaplan et al. 1999; Hadzic et al. 2000; Romao et al. 2002;

Lee et al. 2011). As in other forms of SSC, SSC due to LCH can result in secondary biliary cirrhosis. In a study of nine cases of LCH of the liver, four of the patients had SSC with visible infiltration of the ductal compartment with LC, but in two other patients, SSC was not associated with directly visible involvement of the ducts with LC (Kaplan et al. 1999). In children, LCH is probably a cause of SSC almost as frequent as SSC related to inflammatory bowel disease (Mieli-Vergani and Vergani 2001; Sabib et al. 2011). The pathogenesis of SSC in hepatic manifestations of LCH has not been clarified. In particular, infiltration of the bile ducts walls or the periductal tissues by LCH cells may be sparse. In five explanted livers with marked destructive cholangitis, CD1a staining revealed a small number of LCs in the choledochal wall in only one specimen (Braier et al. 2002). Conversely, there are highly unusual situations where marked infiltration of a hepatic duct in LCH has caused features clinically suggesting biliary atresia (Heitner et al. 1978). Furthermore, LCH of the eosinophilic granuloma type can produce highly cellular and micronodular lesions impinging upon the bile ducts, associated with florid duct lesions and focal-sectorial bile duct destruction (Parker and Lichtenstein 1963). The fibrotic response centered around the bile ducts results in a sonographic pattern characterized by hypoechoic or hyperechoic lesions, the hypoechoic changes probably corresponding to periportal inflammation (Chan et al. 1997).

Histologically, intrahepatic bile ducts show ductocentric fibrosis of varying cellularity, most of the infiltrate cells found in this periductal compartment consisting of lymphocytes, with variable contributions of macrophages (including epithelioid forms), plasma cells, and eosinophil granulocytes. Similar to SSC of other etiologies, lymphocytes and macrophages can reveal an intimate relation to bile ducts (Parker and Lichtenstein 1963), invade the normal-looking or already damaged biliary epithelium, with sectorial bile duct destruction, or infiltrate form micronodules impinging upon small bile ducts. The abnormal infiltration can be associated with portal tract fibrosis, sometimes with ductular proliferation (Parker and Lichtenstein 1963). In most situations, LC is only detectable when using immunohistochemistry (in particular CD1a), LC being recognized as single cells or small groups of cells intermingled with other cell types within the fibrotic areas. Usually, LC is not seen to invade the epithelial duct lining, even though this may occur. The array of these lesions has been put together to form two lesion groups, i.e., (a) small bile duct infiltration and destruction, producing clinicopathologic features of chronic cholestasis reminiscent of primary sclerosing cholangitis, and (b) destructive cholangitis of larger bile ducts, producing cystic dilatation and/or bile extravasation (Kaplan et al. 1999).

Biology of Disease

The clinical course strongly depends on stage of disease at presentation. Patients with solitary/unifocal disease have a 99 % or greater survival, while infants with multisystemic disease have a mortality of more than 60 %. Treatment strategies in LCH are based on the distribution pattern of disease and unifocality versus multifocality versus multisystemic disease. Low-risk organs include the skin, bone, lymph nodes, pituitary gland, and CNS. High-risk organs for unfavorable outcome are the bone marrow, lung, spleen, and liver involvement. The involution of lesions in some forms of LCH is well known, albeit multisystem variants can take a rapidly fatal course (Mosterd et al. 2008). In multisystem LCH (MS-LCH), reactivation is a frequent and early event, but involvement of risk organs at reactivation is rare and mortality is minimal. But reactivations have been shown to increase the risk for permanent consequences by about twofold (Minkow et al. 2008). The incidence of reactivation correlates with the stage of disease at diagnosis (Pollono et al. 2007). The spontaneous regression of lesions in single-system disease (and eventually in infantile self-healing forms) may be caused by apoptosis through the Fas/Fas-L pathway (Peng et al. 1999; Petersen et al. 2003).

On the other hand, LCH occurs in conjunction with, or is sometimes followed by, malignant

neoplasias involving a cell lineage different from LC. Examples of synchronous or metachronous neoplastic disorders comprise B-cell lymphoma (Almanaseer et al. 1986), T-cell lymphoblastic lymphoma (Li and Borowitz 2001; Rodig et al. 2008), splenic lymphomas (Llamas-Velasco et al. 2012), and Hodgkin's disease (Karadeniz et al. 1991; Ibarrola de Andres et al. 1999; Park et al. 2012). LCH has also been observed in conjunction with Erdheim-Chester disease (Pineles et al. 2011).

Cytogenetic and Molecular Features

Monoclonality and, hence, neoplastic features seem to be present in many, but not all, forms of LCH, clonality, i.e., having been identified in solitary lytic bone lesions, in multisystem disease of infancy, and in the intermediate form of the disease that usually has multisystem involvement and chronic course (Willman 1994; Willman et al. 1994; Yu et al. 1994; Badalian-Very et al. 2013), whereas the majority of cases with PLCH have been shown to be nonclonal lesions (Yousem et al. 2001). It has also been proposed that LCH may represent a reactive condition, possibly induced by immune stimulation (Bank et al. 2003). The clonal features of Langerhans cells may be related to elevated expression of p53, c-myc, and H-ras, the p53-p21 pathway and the p16-Rb pathway being activated (Schouten et al. 2002), and distinct deleted chromosomal segments, the highest frequency of LOH being found in chromosomes 1p and 7 (Murakami et al. 2002). As the abnormal dendritic histiocytes in LCH express elevated levels of tumor necrosis factor-alpha (TNF-alpha), IFN-gamma, GM-CSF, IL-1, and leukemia inhibitory factor (LIF), increased cytokine levels may contribute to the expansion of the cells, and polymorphisms of the TNF-alpha promoter in LCH could increase the production of that particular cytokine (Wu and McClain 1997), even though polymorphisms of the TNF-alpha promoter have not been detected in a more recent study (McClain et al. 2003). Tumor cells in LCH differ from normal epidermal LC in their transcription profile, in that they selectively express the Notch ligand Jagged 2, and are the only dendritic cells that express both Notch ligand and its receptor, suggesting the presence of a unique Notch signaling pathway in LCH cells (Hutter et al. 2012).

There is recent evidence that variably differentiated cells in LCH carry the BRAFV600E and BRAF600DLAT gene mutations (Badalian-Very et al. 2010; Sahm et al. 2012; Satoh et al. 2012; reviews: Badalian-Very et al. 2012, 2013), indicating that these mutations are somatic mutants enriched in LCH CD1a + cells. In BRAF V600E-negative LCH, a high prevalence of recurrent, mutually exclusive somatic MAP2K1 mutations was detected (Brown et al. 2014), supporting an important role for ERK (extracellular signal-regulated kinase) activation in pathogenic pathways involved in LCH (Chakraborty et al. 2014). There is evidence that MAPK activation in self-renewing hematopoietic progenitors cells can induce disseminated and high-risk disease, while MAPK activation in a more differentiated committed myeloid lineage promotes low-risk disease, shedding more light on the cells of origin of LCH (Collin et al. 2015).

Liver Manifestations of Eosinophilic Granuloma, Hand-Schüller-Christian Disease, and Abt-Letterer-Siwe Disease: What Is the Relationship with Modern LCH?

As specified above, these terms and the entities behind them are today obsolete; the disorders have been identified as related manifestations of a single nosologic entity, i.e., LCH (Lichtenstein 1953; Lieberman et al. 1969). In the context of the improvement of classification, based on increased knowledge regarding the cell involved, this is on the one hand a progress. On the other hand, the price that had to be paid is a certain loss of valuable information, mainly in regard to the understanding of excellent clinical and pathologic observations found in the older literature, specifically relating to liver involvement. In this paragraph, some informations pertinent to the liver and extractable from "historical" reports are

briefly summarized (historical reviews: Komp 1987; Coppes-Zantinga and Egeler 2002).

Originally, some of the "entities" discussed in this paragraph made part of what was called "nonlipid reticuloendothelioses" and defined to include Hand-Schüller-Christian disease (HSCD), eosinophilic granuloma of the bone, and acute disseminated reticuloendotheliosis (Letterer-Siwe disease, LSD). HSCD is characterized by the triad, diabetes insipidus, exophthalmos, and defects in membranous bones (Smith 1864; Hand 1893; Kay 1905; Schüller 1915; Christian 1919). Later reports put emphasis on the intriguing finding that the cells found in HSCD frequently accumulated considerable amounts of lipid ("lipoid histiocytosis," "lipoid granulomatosis"), resulting in the concept that the disorder might have something to do with a genuine lipid storage disease (Weidman and Freeman 1924). In contrast, acute forms of pediatric LCH do not usually show these features and thus were initially called "acute *nonlipid* disseminated reticuloendotheliosis" (Batson et al. 1955). Schüller, who appears in the eponym HSCD, described peculiar skull defects related to LCH and coined them "geographic skull defects (i.e., 'Landkartenschädel' in German)" (Schüller 1915). Later, he further discussed the lesions employing the term "dysostosis hypophysaria" (Schüller 1926). Henry Asbury Christian (1876–1951) had read the article of Schüller and, based on his own observations, thought that the disease in question was hypophyseal in origin, but apparently failed to recognize Dr. Hand's case of polyuria as being part of the same syndrome (Komp 1987). The cell type involved in these disorders, i.e., the LC, was detected during the same time period by the then 21-year-old medical student, Paul Langerhans (1847–1888), who studied medicine under Haeckel and Virchow and described in his 1869 thesis in the rabbit pancreas the structures that later became the islets of Langerhans, an eponymic term created by Edouard Laguesse (Coppes-Zantinga and Egeler 2002). The identification of skin dendritic cells (LC) was based on Cohnheim's gold chloride staining technique (Langerhans 1868).

The pathway to the concept of "eosinophilic granuloma" is rather complex as well. Two early reports independently documented, in the same year and in the same volume of the American Journal of Pathology patients with solitary bone lesions rich in both histiocytes and eosinophils (Lichtenstein and Jaffe 1940; Otani and Ehrlich 1940). "Unifocal" eosinophilic granuloma (UFEG), which is now classified as unifocal LCH, not only develops in bones but also in visceral organs including the liver. UFEG is its original description denotes the most benign disorder in the spectrum of LCH (review: Duncan et al. 1988). "Multifocal eosinophilic granuloma (MFEG)," proposed as a replacement for the designation formerly known as Hand-Schüller-Christian disease (HSCD) (Krutchkoff and Jones 1984), may also manifest in the liver. In contrast to UFEG/unifocal LCH, MFEG/HSCD is a chronic disorder with a complex manifestation pattern and a highly variable histology, including the participation of eosinophils, markedly depending on the manifestation site (Kaufman et al. 1976). In the liver, MFEG/HSCD presents in the form of multifocal lesions and displays a multifaceted infiltrate with or without numerous eosinophils, with or without easily detectable LC, and with or without lipid-laden macrophages or giant cells (Parker and Lichtenstein 1963). As the terms imply, a dense infiltrate of eosinophils should characterize these lesions. However, there are instances where unifocal LCH (the "new" entity) is poor in eosinophils, suggesting that unifocal LCH is heterogeneous (Papasozomenos 1999). This not only confers difficulties in histopathologic diagnosis but also has an impact on the pathogenesis of the lesion patterns associated with LCH.

The study of older reports on acute or subacute, rapidly progressive or even fulminant forms of LCH is fruitful insofar as one may obtain carefully collected clinical informations and pathology data from a pre-chemotherapy era. What has previously been termed Letter-Siwe disease (Abt-Letterer-Siwe disease; aleukemic reticulosis; Letterer 1924) is a highly impressive and catastrophic disorder mainly occurring in infants and children, fetal and congenital presentations also

being known (Shuangshoti and Seksarn 1987; Yu et al. 1990; Valde et al. 1993). Letterer reported an acute fulminant non-leukemic disorder of the Aschoffian reticuloendothelial system in a 6-month-old child (Letterer 1924). Nine years later, Siwe reported a further case (Siwe 1933) and formulated the diagnostic criteria of the disease. The eponymic term, Letterer-Siwe disease, goes back to Arthur Frederick Abt, an American physician. Together with Denenholz, he discussed the issue of so-called reticuloendothelioses by proposing the term Letterer-Siwe disease (Abt and Denenholz 1936). Hence, the disorder was sometimes called "Abt-Letterer-Siwe disease." A disseminated visceral involvement, including the liver, is a striking feature in many patients ("disseminated visceral histiocytosis X"; Landing 1987). The involvement of bona fide LC has been documented in at least part of the cases (Ruco et al. 1988). Lipid-laden histiocytes can also occur in the Letterer-Siwe type of LCD (Kawai et al. 1978), similar to MFEG/HSCD.

Langerhans Cell Tumors and Langerhans Cell Sarcoma

Introduction

A small subset of Langerhans cell neoplasms present as isolated mass lesions rather than a diffusely growing process. These Langerhans cell tumors (LCTs) have been proposed to be classified into two distinctive groups: (a) typical LCT consisting of cells found in classical Langerhans cell histiocytosis and (b) a sarcomatous form (Langerhans cell sarcoma, LCS) (Warnke et al. 1995; Lieberman et al. 1996; Pileri et al. 2002). The diagnosis of both lesions requires the detection of expression of both CD1a and S-100 protein, but there is frequently also expression of some histiocyte markers, such as CD68 and some focal, weak expression of lysozyme, the latter staining being clearly less than in histiocytic sarcoma and eventually being due to background staining or staining by infiltrating normal histiocytes/macrophages. Staining for CD35 or CNA.42 (Pileri et al. 2002); the transcription factor PU.1 (Muirhead et al. 2009); the phosphatidylserine receptors T-cell immunoglobulin mucin proteins 3 and 4 (Dorfman et al. 2010); langerin, fascin, DEC-205, and DC-SIGN (Orii et al. 2010); and CD163 (hemoglobin scavenger receptor) (Nguyen et al. 2005) has been described.

Langerhans Cell Tumors (LCTs)

Solitary or multiple circumscribed tumors consisting of Langerhans cells have seldom been observed in several organs and tissues, including the skin (Ricciardo et al. 2011) and the hepatobiliary tract. Multiple LCTs of the liver have been observed (Guilarte Lopez-Manas et al. 1997; Cavazza et al. 1999; Yagita et al. 2001) and in part suggested the existence of hepatic metastases of colorectal cancer. LCT has been found as a mass causing extrahepatic biliary obstruction in children, probably originating from periductal lymph nodes or lymph nodes situated near the porta hepatis (Chen et al. 1989). In rare instances, massive periportal fibrosis of the liver caused by hepatic Langerhans cell histiocytosis mimicked multiple liver tumors on CT and MR images (Arakawa et al. 1994).

Langerhans Cell Sarcoma (LCS)

ICD-O code 9756/3

Introduction

Langerhans cell sarcoma (LCS, synonyms: dendritic/histiocytic sarcoma, Langerhans cell type; malignant Langerhans cell tumor, MLCT; true histiocytic neoplasm of Langerhans cell type; malignant histiocytosis X) is a rare malignant dendritic cell neoplasm with a Langerhans cell phenotype and a highly aggressive biology (high grade), tending to disseminate throughout the body and leading to death usually within 1 year. This tumor has to be distinguished from LCH (Imamura et al. 1971; Henderson and Sage 1973; Wood et al. 1984; Delabie et al. 1991;

Tani et al. 1992; Favara et al. 1997; Itoh et al. 2001; Misery et al. 2003). It seems that at least part of the cases of LCS correspond to what has been reported in the literature "Letterer-Siwe disease of the adult" (Vollum 1979; Wells 1979). A particularly aggressive subset of LCS is positive for CD56/N-CAM (Kawase et al. 2005).

Morphology

LCS is composed of pleomorphic neoplastic cells, with nuclei having clumped chromatin and large nucleoli. Part of the cells display the diagnostically important complex grooves of LCH cells. The mitotic rate is usually high, with more than 50 mitotic figures per 10 HPFs. Ultrastructurally, Birbeck granules are present. Typical LCS has an immunohistochemical profile being CD1a/langerin/S100 +. Exceptionally, T-cell markers are expressed, e.g., CD3 (Xu et al. 2012b). LCS cells can express some members of the B7 superfamily, including B7-H1, B7-H3, and B7-H4, co-expressed with signals from the T-cell immunoglobulin and mucin-domain (TIM)-containing molecules, i.e., TIM-1, TIM-3, and TIM-4 (Li et al. 2013).

Epidemiology

LCS is a very uncommon neoplasm that almost exclusively occurs in adults, with a female predominance. The median age at diagnosis is 39 years (range 10–72 years). The most common sites of LCS are the skin and soft tissues, often with multiorgan involvement (lung, lymph nodes, spleen, bone, and liver). Rarely, LCS initially presents as a single-organ disorder, e.g., in the lung (Langfort et al. 2009) or in the thyroid (Kitahama et al. 1996).

Liver Involvement

As LCS may involve the liver, this lesion is discussed here in some more detail. In the patients described so far, the disease usually started in the skin in the form of erythematous nodules of up to a few centimeter diameter, followed by diffuse or nodular spread within the body. LCS exhibits overtly malignant cytologic features and marked, sometimes, extreme cellular pleomorphism (similar to histiocytic sarcoma), but cells with grooved nuclei are generally detected (Pileri et al. 2002). The cell involved exhibits immunohistochemical features typical for abnormal LC (CD1a and S-100 protein), and Birbeck granules have been detected (Wood et al. 1984). The cells of LCS express B7, a member of a group of proteins involved in the immunoescape of cancer cells (Li et al. 2012).

Multisystem involvement in LCS, including jaundice and infiltration of the liver, has been reported (Wood et al. 1984; Itoh et al. 2001; Kawase et al. 2005). In the patient described by Wood and coworkers (1984), autopsy of a patient with rapidly fatal MLCT revealed massive tumor infiltration of the liver; the neoplastic cells were identical to those detected in the earlier skin biopsies, many showing extremely large, multilobulated nuclei, looking like "bunches of grapes." Numerous mitoses were seen, and the eosinophilic cytoplasm was rather scanty. The neoplastic cells in this case exhibited typical Birbeck granules (Wood et al. 1984). LCS can arise in the gallbladder and involve locoregional lymph nodes (Zhao et al. 2009).

Biology of Disease

LCS is a high-grade tumor with rapid progression, still bearing a mortality of more than 50 %. LCS can undergo leukemic transformation (Sumida et al. 2008). The neoplasm may develop in the setting of other neoplasms. It can arise from Langerhans cell histiocytosis (Lee et al. 2006) and sometimes occurs on a background of other hematologic malignancies. LCS has been observed following ALL (Castro et al. 2010). A common clonal origin of an acute B-lymphoblastic leukemia and an LCS has been observed, suggesting evidence for hematopoietic plasticity (Ratei et al. 2010). LCS and dendritic cell tumors can occur in conjunction with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), suggesting a transdifferentiation of CLL/SLL B cells to a dendritic or

Langerhans tumor cell lineage (Shao et al. 2011). LCS was found to arise from hairy cell leukemia (Muslimani et al. 2012).

Spontaneously Regressing/Involuting "Histiocytic" Disorders (So-Called Autoinvolutive Disorders)

Introduction

Several regressing or self-healing disorders involving an expansion of Langerhans cells or still ill-defined "histiocytic" cells have been identified, mainly in infants and children (Jang et al. 2000). Based on the data in the literature, a classification of these disorders is emerging, but not yet settled (Jang et al. 2000). The reason for the difficulties arising in the attempt at creating reliable categories is based on the fact that older investigations did not yet have access to modern cell typing and that terms such as "histiocytosis X" have been used to identify disorders with some clinical resemblance but quite different cells involved (Ferrando et al. 1982; Coldiron et al. 1988; Oranje et al. 1988; Contreras et al. 1990; Kolde and Bonsmann 1992; Gianotti et al. 1993; Hernandez-Martin et al. 1997; Campourcy et al. 1997; Hashimoto et al. 1999; Wee et al. 2000).

Classification

A preliminary classification is presented in Table 3. What seems to be established is that self-healing, and most frequently congenital or infantile, "histiocytoses" can involve Langerhans cells or cells with a histiocyte phenotype, the latter lacking Birbeck granules (Oranje et al. 1988).

Table 3 Working classification of self-healing Langerhans cell and non-Langerhans cell "histiocytic" disorders

Langerhans cell* "*histiocytic*" *disorders
Congenital self-healing Langerhans cell histiocytosis (CSHLCH), Hashimoto-Pritzker type (including variants with epidermotropism, pagetoid variants)
Solitary congenital self-healing Langerhans cell histiocytosis (SCSHLCH)
Self-healing childhood histiocytosis X of the Illig-Fanconi type (Illig-Fanconi disease)
Benign regressing histiocytosis of the Langerhans cell type
Non-Langerhans cell* "*histiocytic*" *disorders (*non-X histiocytoses*, *non-X histiocytic syndromes*)
Congenital self-healing non-Langerhans cell histiocytosis
Acquired regressive cutaneous non-Langerhans cell histiocytosis of infancy
Generalized eruptive histiocytosis (GEH, possible variants with regressive course: generalized lichenoid juvenile xanthogranuloma, benign cephalic histiocytosis)
Juvenile xanthogranuloma
Xanthoma disseminatum
Scalloped cell xanthogranuloma

Self-Healing Langerhans Cell Histiocytosis: A Complex Spectrum of Diseases

Self-healing Hashimoto-Pritzker LCH (Hashimoto-Pritzker disease; congenital self-healing histiocytosis/reticulohistiocytosis, CSHH/CSHR; congenital self-healing Langerhans cell histiocytosis, CSHLCH) is a rare variant of LCH originally described in 1973 (Hashimoto and Pritzker 1973). Since, several terms have been employed to denote this disorder, including reticulohistiocytosis of benign evolution, autoinvolutive congenital reticulosis, congenital self-healing reticulohistiocytosis, childhood self-healing histiocytosis X, congenital self-healing histiocytosis, and Hashimoto-Pritzker disease (Laugier et al. 1975; Mascaro et al. 1978; Bonifazi et al. 1982; Berger et al. 1986; Hashimoto et al. 1986; Pujol et al. 1988; Cambazard et al. 1988; Larralde et al. 1999). CSHLCH is characterized by neonatal onset, with purple or necrotic nodular lesions, rare visceral manifestations, spontaneous regression within the first 3 months of life, and an overall histology similar or identical to that of LCH, albeit with less Birbeck granules. Apart from multiple lesions, solitary variants have also been observed (Masouye et al. 1990; Shy et al. 1996; Tay et al. 1998; Walia et al. 2004; Kapur et al. 2007; Belhadjali et al. 2008; Sankilampi et al. 2008;

Hatakeyama et al. 2009). Unusual cases showed involvement of monozygotic twins (Ersoy-Evans et al. 2006) or late-onset disease, e.g., in an 8-year-old girl (Nakahigashi et al. 2007). Rarely, CSHLCH presents as a blistering eruption (Higgins et al. 1994), with hemorrhagic bullae (Inuzuka et al. 2003) or with papulovesicular, herpes-like lesions (Morgan and Callen 2001), and a variant with marked epidermotropism of the abnormal Langerhans cells, with a pagetoid growth pattern, has been reported (Hashimoto et al. 1999). As skin lesions of CSHLCH may contain large numbers of mast cells, Darier's sign typical for mastocytosis can ensue (Butler et al. 2001). The infiltrating cells show, at electron microscopic examination, a complex cytoplasmic structure, with myelinoid inclusions, laminated profiles, and so-called vermiform bodies but only few Birbeck granules (Laugier et al. 1975; Bonifazi et al. 1982; Kanitakis et al. 1988; Larralde et al. 1999). It has to be emphasized that not all patients clinically presenting with CSHLCH will follow a favorable course. The disorder may, in its early phases, mimic congenital LCH, and the outcome may then be dismal (Longakter et al. 1994; Larralde et al. 2003).

Solitary Congenital Self-Healing Langerhans Cell Histiocytosis

SCSHLCH is a very rare congenital disorder characterized by single (solitary) cutaneous Langerhans cell lesions that show self-healing (Chun and Song 1992; Dorjsuren et al. 2011; Wheller et al. 2013; Yurkovich et al. 2013). One variant of SCSHLCH revealed a combine immunohistochemical phenotype, cells being both CD1a+ and S100+ (Tardio et al. 2013).

Self-Healing Childhood Histiocytosis X (Illig-Fanconi Disease)

Illig-Fanconi disease is a rare cutaneous self-healing Langerhans cell histiocytosis restricted to the pediatric age group. Clinically, the skin lesions are characterized by few, small, translucent, and confluent papules, sometimes purpuric. This histology is that of LCH, ultrastructurally with the presence of Birbeck granules (Ferrando et al. 1982; Calero et al. 1986).

Self-Healing Non-Langerhans Cell "Histiocytic" Disorders

Self-healing non-Langerhans cell, or non-X, histiocytoses constitute a group of disorders that share clinical manifestations and are characterized by proliferations of histiocyte-like cells or macrophages in the absence of evidence for Langerhans cell histiocytosis (Zelger et al. 1996). The diseases present as in part nodular cutaneous infiltrates consisting of cells with a histiocytic phenotype, being reactive for Leu M3 and HLA-DR, but CD1 – and Leu-6 – negative and lacking Birbeck granules (Oranje et al. 1988; Kodet et al. 1991). The cutaneous forms can occur as congenital lesions or as acquired regressive skin lesions.

Generalized eruptive histiocytosis/histiocytoma (GEH) is a rare and self-healing non-Langerhans cell histiocytosis, clinically characterized by recurrent crops of papules that appear in a symmetrical fashion on the face, trunk, and arms. The disorder occurs both in children and adults. GEH may represent an early undifferentiated stage of various histiocytic disorders (Winkelmann and Müller 1963; Stables and Mackie 1992; Wee et al. 2000; Seward et al. 2004). Benign cephalic histiocytosis is histologically similar to juvenile xanthogranuloma and generalized eruptive histiocytosis (Gianotti et al. 1993), but chiefly involves the head and the neck (Jih et al. 2002).

Liver Involvement in Self-Healing Histiocytosis Syndromes (Except Juvenile Xanthogranuloma and Xanthoma Disseminatum)

Congenital Self-Healing Langerhans Cell Histiocytosis (Hashimoto-Pritzker Disease)

CSHLCH may rarely involve inner organs, e.g., involvement of the lung (Chunharas et al. 2002) or infiltration of the eye (Zaenglein et al. 2001). Hepatomegaly has been encountered in CSHLCH

(Chunharas et al. 2002). In a female newborn with CSHLCH, liver ultrasonography revealed hypoechoic lesions with blurred borders, suggested to represent liver involvement with this form of histiocytosis (Parentin et al. 2011). In one patient with Hashimoto-Pritzker disease and marked cutaneous involvement, multisystem disease with involvement of the liver, bone marrow, lymph nodes, and lung was noted (Mandel et al. 2014).

Benign Regressing Histiocytosis

Benign regressing histiocytosis of the Langerhans cell type has been reported to manifest in the liver. In an adult patient, the disease presented in the form of multiple hepatic nodules varying in size from 0.5 to 1 cm, histologically composed of clusters of polygonal to roundish, S100-protein-positive cells with granular, eosinophilic cytoplasm and vesicular nuclei with central folding, admixed with an infiltrate of eosinophils and lymphocytes. At EM examination, no Birbeck granules were detectable. The liver nodules spontaneously disappeared within a relatively short time period (Foschini et al. 1995).

Juvenile Xanthogranuloma

In normolipemic juvenile xanthogranuloma (JXG, synonym: naevoxantho-endothelioma) and its variants, cutaneous accumulations of histiocytes lacking Birbeck granules and without the immunohistochemical features of Langerhans cells occur. JXG was first described as a clinicopathological entity, in 1905 (Adamson 1905) and 1912 (McDonagh 1912), but Virchow had already described a child with cutaneous xanthomas in 1871. JXG is the only more common non-Langerhans cell histiocytosis (Burgdorf and Zelger 1996; Hernandez-Martin et al. 1997; Dehner 2003; Janssen and Harms 2005; Sivapirabu et al. 2011) and is, in most instances, a benign disorder of infancy and early childhood characterized by yellowish cutaneous nodules that spontaneously regress over months to years.

Very few cases of typical JXG have been observed in the adult age group (Jain et al. 2011; Narvaez-Moreno et al. 2013). The most common skin lesions are classified as either solitary versus multiple or a "small nodular form" versus a "large nodular form," but other manifestations comprise keratotic, lichenoid, pedunculated, subcutaneous, clustered, plaque-like, giant, eruptive, disseminated, or disseminated clustered lesions (Sidwell et al. 2005; Aparicio et al. 2008; Kaur et al. 2008). In the vast majority of children, JXG is usually limited to the skin, but systemic forms occur (Chang 1999; Jain et al. 2011). JXG is currently thought to be a proliferative disorder of dendrocytes, possibly dermal dendrocytes (Kraus et al. 2001), i.e., a "dendritic cell-related histiocytosis." However, the cellular infiltrate is mixed, consisting of monocytoid and macrophage-like forms, epithelioid and foamy macrophages, Touton giant cells, lymphocytes, plasma cells, eosinophils, and spindle cells of two forms (dendritic and fusiform) (Tahan et al. 1989). Although JXG is classified as a non-Langerhans cell histiocytosis, very rare "overlap disorders" have been observed, e.g., LCH preceding the development of JXG, possibly caused by therapy-induced modulation of cell differentiation (Bains and Parham 2011), or LCH accompanying JXG as a deep-seated process (Tran et al. 2008).

Histologically, JXG is characterized by lipid-laden, foamy macrophages (foamy histiocytes) in upper parts of the dermis. These cells have centrally placed, bland nuclei of the macrophage type, usually without visible mitotic activity. These cells are intermingled with Touton giant cells, lymphocytes, and eosinophils. Touton cells ("xanthelasmic giant cells") were described in 1885 by Karl Touton, who was active as a specialist in dermatology and venereal diseases in Wiesbaden, Germany, where he also had duties as physician in a spa ("Badearzt") (Touton 1885; review: Aterman et al. 1988). Apart from this "classical" form, a hypolipidized or nonlipidized form also exists, showing a more diffuse pattern of infiltration, with or without rare Touton cells, and a mitotic activity that is somewhat higher than in the "classic" form. This phenotype has been termed mitotically active xanthogranuloma

(Batista et al. 2012; Ngendahayo and de Sant Aubain 2012).

The etiology and pathogenesis of JXG are not known. As the lesions can regress, a reactive process has been suggested, but at least one study showed a clonal bone marrow proliferation with a distinct abnormal karyotype, in the absence of leukemia (Maly et al. 2012). Clonality in another case has been demonstrated via the HUMARA technique (Janssen et al. 2007). JXG can be associated with certain other disease entities. An association between JXG and juvenile myelomonocytic leukemia, with or without neurofibromatosis type 1, has been recognized in more than 20 cases (Cooper et al. 1984; Shin et al. 2004; Cham et al. 2010; Al Ghamdi and Al Suwaidan 2010; Arachchillage et al. 2010; Raygada et al. 2010). JXG has been found in association with Wiskott-Aldrich syndrome (Jesenak et al. 2013).

JXG rarely presents with systemic involvement (systemic juvenile xanthogranuloma, "deep juvenile xanthogranuloma"), with involvement of diverse inner organs, including the central nervous system (sometimes with multiple cerebral lesions), heart, lung, kidney, bone marrow, and liver (Fig. 7). Involvement of the liver has been reported several times, also in the setting of neonatal systemic xanthogranulomatosis (Diard et al. 1982; de Graaf et al. 1992; Di Blasi et al. 1993; Guthrie and Arthur 1994; Freyer et al. 1996; Favara 1996; Dehner 2003; Chantranuwat 2004; Nakatani et al. 2004; Cabrera et al. 2005; Janssen and Harms 2005; Unuvar et al. 2007; Yeh et al. 2007; Azorin et al. 2009; Patel et al. 2010; Fan and Sun 2011). Among 34 children with various forms of systemic JXG, the median age was 0.3 years; 8/34 had involvement of the liver/spleen (Freyer et al. 1996). In a large study on 174 patients, visceral manifestations were identified in 5 % of the patients (Dehner 2003). Neonates with systemic JXG can develop severe and sometimes fatal liver disease associated with fever, jaundice, hepatomegaly, ascites, and giant cell neonatal hepatitis in addition to xanthogranulomas in the liver and other visceral sites (Hu et al. 2004; Chantorn et al. 2008; Azorin et al. 2009; Papadakis et al. 2012). Severe congenital systemic JXG with liver failure has been observed in monozygotic twins (Chantorn et al. 2008). Massive liver involvement in neonatal disseminated JXG with progressive cholestasis, marked hepatic infiltration, and portal hypertension may require liver transplantation (Haughton et al. 2008). Hepatic manifestation of JXG may be associated with hypergammaglobulinemia (de Graaf et al. 1992). Indirect liver changes consist of obstructive jaundice, e.g., in case the manifestations of JXG develop in the pancreatic head (Prasil et al. 1999).

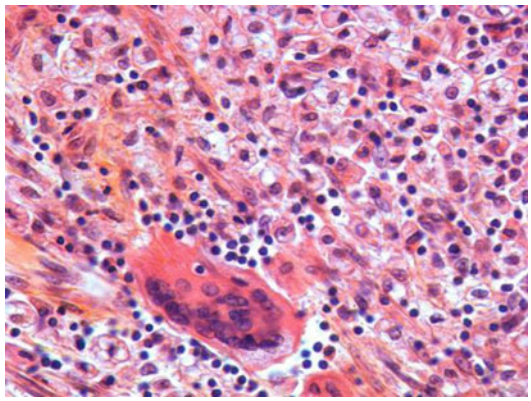

Fig. 7 Juvenile xanthoma in the liver. The lesion is characterized by foamy xanthomatous cells, but can also contain Touton-type giant cells (hematoxylin and eosin stain)

In severe liver involvement, hepatomegaly develops, and yellow nodules are seen on the liver surface at laparoscopy (Di Blasi et al. 1993). The cell types prevailing in extracutaneous sites consist of mononuclear (monocytoid) cells and spindle cells (arranged in fascicles or in a storiform pattern), whereas Touton giant cells are less common or even lacking. The portal tracts may be crowded with lipid-laden foamy macrophage-like cells or spindled nonlipidized cells (Dehner 2003; Haughton et al. 2008), and focal granulomatous lesions may be present (Favara 1996). The immunophenotype of these cells is characterized by uniform positivity for vimentin, CD68, and factor XIIIa, while S-100 protein and CD1a are consistently negative (Dehner 2003; Janssen and Harms 2005). The hepatic manifestations of JXG may be accompanied by syncytial giant cell hepatitis in neonates

and infants (Dehner 2003). In case of JXG-induced fulminant infantile hepatic failure, autopsy showed marked hepatomegaly, the organ containing extensive irregular nodular tumor infiltrates centered around blood vessels and portal tracts. Histologically, interlobular bile ducts were encircled by JXG tissue, but biliary epithelium was not infiltrated. The tumor cells consisted of a population of plump histiocytoid and spindle-shaped forms. Touton cells were present but rare. The process had infiltrated the lumen of hepatic vein, the veins sometimes being nearly completely occluded by tumor. There were signs of infantile syncytial giant cell hepatitis (Hu et al. 2004).

Xanthoma Disseminatum

Xanthoma disseminatum (XD, disseminated xanthoma, Montgomery syndrome) is a rare benign non-Langerhans cell histiocytic disorder in older children and adults of unknown etiology and pathogenesis. In 60 % of cases of XD, the age of onset has been between 5 and 25 years, men being affected twice as common as females (Altman and Winkelmann 1962). XD was first described in 1938 (Montgomery and Osterberg 1938), is characterized by the development of cutaneous xanthomas, and typically involves the skin of the flexor skinfolds and eyelids or a mucocutaneous disorder but may also affect inner organs, including the eye, CNS, pituitary gland, peripheral nerves, skeletal system, respiratory tract, kidney, pancreas, uterus, and gastrointestinal tract.

Involvement of the respiratory tract, complicated by dyspnea, life-threatening obstruction, and eventually asphyxiation, is the most recognized cause of morbidity in XD (Altman and Winkelmann 1962; Caputo et al. 1995; Ferrando et al. 1998; Davies et al. 2000). XD is usually not associated with hyperlipidemia. The biology of disease of XD is commonly benign, but visceral manifestations can cause morbidity and mortality (reviews: Ringel and Moschella 1962; Weiss and Keller 1993; Alexander et al. 2005). Caputo and coworkers (1995) identified three clinical patterns of XD. In the first pattern, skin lesions are persistent and continue unabated in patients who are otherwise in good health. The second form is characterized by spontaneous regression of lesions after many years (self-healing form). The third form, the rarest variant, exhibits systemic involvement, including the CNS and other organs. Involvement of the hypothalamo-pituitary region often causes diabetes insipidus. In a minority of patients with XD, malignant lymphoma has developed as a late complication (Battaglini and Olsen 1984; Shoo et al. 2008). Histologically, the foamy histiocytes/macrophages (xanthoma cells) form clusters and then develop into plaques or nodular lesions, the infiltrate being mostly situated in the upper and mid dermis. These cells are CD68+, but are negative for S-100 protein and CD1a, and lack Birbeck granules (Zelger et al. 1992; Weiss and Keller 1993; Ferrando et al. 1998; Caputo et al. 2003). The histiocytic infiltrate may contain Touton giant cells. Non-foamy histiocytes and lymphocytes may also occur (Caputo et al. 2003).

In a minority of patients, XD can involve the liver, with formation of nodular lesions of fatlike low density on CT images, consisting of xanthoma cells (Woollons and Darley 1998). A 32-year-old female patient with XD associated with diabetes insipidus and progressive CNS and ocular involvement revealed an echo-dense liver and gallbladder polyposis. A liver biopsy showed steatosis and foamy histiocytes in portal tracts (Knobler et al. 1990). Liver involvement was suspected in a child having XD with systemic manifestations in the skeleton and marrow cavities (Calverly et al. 1995). Hepatic steatosis has been observed in XD (Celic et al. 2004).

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