Hodgkin Lymphoma of the Hepatobiliary Tract

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Abstract

In most cases of classical Hodgkin lymphoma (HL), the neoplastic cells are derived from mature B lymphocytes at the germinal center stage of differentiation. The WHO classification separates nodular lymphocyte-predominant HL from classical HL, the latter subdivided into nodular sclerosis classical HL, lymphocyte-rich classical HL, mixed cellularity classical HL, and lymphocyte-depleted classical HL. All these forms of HL can occur in the hepatobiliary tract, either as rare primary lesions or as secondary manifestations of HL primarily located elsewhere. HL in the liver presents as one of several phenotypes, including miliary lesions, solitary or multiple nodular lesions, large masses, and rare diffuse patterns of involvement. In addition, HL can involve bile ducts and liver-associated lymph nodes with subsequent biliary obstruction mimicking primary bile duct cancer. The histologic presentation of hepatobiliary HD is the same as that in other organs. HL can be associated with several nonneoplastic hepatic alterations. These include a distinct type of vanishing small bile duct disease, granulomatous hepatitis, sclerosing cholangitis, and sinusoidal ectasias mimicking hepatic peliosis.

Introduction

Hodgkin lymphomas (HL) form a group of malignant lymphoproliferative disorders based on a neoplastic expansion mostly of a distinct type of B cells. In more than 98 % of classical HL, the neoplastic cells are derived from mature B cells at the germinal center stage of differentiation. HL presents in the form of several well-defined phenotypes that have an impact on the biology of disease. The principal clinical histologic features, their impact on the natural history of HL, and etiologic issues of HL have been elucidated and reviewed in detail. An outline referring to the history of the HL concept is added at the end of the chapter.

Table 1 2008 WHO histological classification of Hodgkin lymphoma

		ICD-O code
Nodular lymphocyte-predominant Hodgkin lymphoma	(NLPHL)	9659/3
Classical Hodgkin lymphoma	(CHL)	9650/3
Nodular sclerosis classical Hodgkin lymphoma	(NSHL)	9663/3
Lymphocyte-rich classical Hodgkin lymphoma	(LRCHL)	9651/3
Mixed cellularity classical Hodgkin lymphoma	(MCHL)	9652/3
Lymphocyte-depleted classical Hodgkin lymphoma	(LDHL)	9653/3

Selected References (Ziegler 1911; Favre and Croizat 1933; Jackson and Parker 1947; Harrison 1952; Lukes and Butler 1966; Lukes et al. 1966; Cross 1969; Lukes 1971; Jaffe et al. 2001; Thomas et al. 2004; Küppers and Hansmann 2005; Re et al. 2005; Schmitz et al. 2009; Smith 2010; Hjalgrim 2012; Küppers et al. 2012; Carbone et al. 2013; Gobbi et al. 2013; Ansell 2014).

The *WHO histological classification of HL* is shown in Table 1.

Epidemiology

HL accounts for 25–40 % of all lymphomas developing in Caucasians (much rarer in Orientals and persons from underdeveloped countries), with one peak of occurrence in the second to third decades and another in the sixth decade (Nakatsuka and Aozasa 2006). Involvement of the pediatric age group has been recognized early (von Hüttenbrenner 1871; Hübener 1893) and is an important manifestation of HF. The prevalences of the diverse subtypes of HL differ considerably. NLPHL accounts for approximately 5 % of all HL, patients being predominantly male and in the 30–50 years age group. Classical HL accounts for 95 % of all cases and hence is the

main form of HL. Classical HL shows a bimodal age distribution in Western countries, with a first peak at 15–35 years of age and a second peak in late life. NSCHL, the dominant subtype of classical HL, accounts for about 70 % of classical HL in Europe and North America and is more often encountered in resource-rich areas than in resource-poor areas. The incidence of NSCHL is similar in males and females and has its peak at 15–34 years of age. LRCHL is rare and comprises about 5 % of all classical HL. The majority of patients are male, with a higher age than in other forms of classical HL. MCCHL accounts for 20–25 % of classical HL and is more frequent in HIV-infected individuals and in developing countries. Seventy percent of the patients are male, with a mean age at diagnosis of 38 years. LDCHL forms the rarest subtype of classical HL, accounting for less than 1 % of cases in Western countries. Up to 75 % are male, with a median age at diagnosis of 30–37 years. LDCHL is often associated with HIV and is more often found in developing countries.

Epstein-Barr virus (EBV) infection has been associated with an increased risk of HL chiefly in young adults, based on the growing amount of evidence (Hjalgrim et al. 2003). The presence of EBV had a beneficial effect on the length of failure-free survival of patients with classical HL (Krugmann et al. 2003). Classical HL is a rare complication after solid organ transplantation (Hood et al. 1996). Lymphomas resembling HK developing after posttransplant lymphoproliferative disorder ("Hodgkin-like PTLD") have been reported (Stern et al. 2005). The relationship between bona fide posttransplant HL and the intriguing HL-like posttransplant disorders is not yet clarified.

Liver Involvement in Hodgkin Lymphoma

Introduction

Thomas Hodgkin described liver involvement incidentally (Hodgkin 1832); but in a critical analysis of Hodgkin's original cases, the diagnosis of HL involving the liver was accepted in only two cases (Fox 1936). Wilks noted hepatic involvement in 7 of his 13 cases (Wilks 1865). Manifestations of HL, albeit in a highly variable spectrum of patterns, were later reported and discussed many times.

Selected References (Murchison 1869; Barié 1875; Brauneck 1889; Reed 1902; Longcope 1903; Fabian 1911; Ziegler 1911; Rolleston 1912; Barron 1926; Coronini 1928; Gruber 1930; Chevallier and Bernard 1932; Foulon 1932; Hartfall 1932; Wallhauser 1933; Sternberg 1936; Baker and Mann 1939; Goldman 1940; Symmers 1944; Jackson and Parker 1944a, b; Newman and Pushkin 1951; Beatty 1954; Klein 1955; Levitan et al. 1961; Skovsgaard et al. 1982).

Liver involvement is uncommon in HL in early disease, but the incidence increases in the advanced phases of disease, becoming as high as 70 % in certain series (detailed review of the old literature, Wallhauser 1933; Givler et al. 1971; Bagley et al. 1973). In a study of 74 cases, the duration from diagnosis of HL to clinical evidence of liver abnormalities was 1–6 months in 23 %, 7–12 months in 10.8 %, 13–18 months in 10.8 %, and 19–24 months in 12.2 % and was then slowly decreasing as a function of time (Levitan et al. 1961). These data markedly depend on the clinical features, the patterns of liver involvement, and the choice of techniques for assessing liver involvement (radiology, peritoneoscopy, hepatic needle biopsy, autopsy). Direct hepatic involvement in visceral Hl is a frequent event (Cowan and Trounce 1973; Diebold and Temmim 1980; Urbano-Marquez et al. 1981; Kiewe et al. 2004) and may be the presenting manifestation of HL (Trewby et al. 1979). It seems that there is a correlation between splenic involvement and HL manifestations in the liver: The risk of hepatic involvement correlates closely with splenic involvement (Colby et al. 1981), and generally the liver is not involved when the spleen is not tumoral. In a study of 250 exploratory laparotomies for HL, hepatic tumoral localizations were disclosed by liver biopsies in 16 % of the patients with splenic involvement (Diebold and Temmim

1980). There are, however, exceptions to this "rule" where the liver has shown manifestations of HL in the absence of splenic involvement (Glatstein et al. 1969; Aisenberg 1971; Farrer-Brown et al. 1971; Piro et al. 1972; Michel et al. 1973; Spinelli et al. 1975; Fialk et al. 1979; Sulkes et al. 1979; Gordon et al. 1984). Among 472 liver biopsies performed within a large investigation, 11 biopsies from 10 patients (2.4 %) had infiltrates consisting of Reed-Sternberg cells and abnormal histiocytoid cells against the characteristic background of lymphocytes together with neutrophil and eosinophil granulocytes (Skovsgaard et al. 1982). In an autopsy study of 57 cases of malignant lymphoma, hepatic involvement was demonstrated in 67 % of HL versus 56 % in NHL (Okazaki et al. 1985). In another investigation of 112 consecutive patients with malignant lymphoma, hepatic lymphomatous involvement was found more frequently in NHL (16 %) than in HL (8 %) (Sans et al. 1998).

Involvement of the liver by HL often results in hepatomegaly. Hepatomegaly was observed clinically from 2.3 % to 80 % in a series reported before the modern treatment strategies of HL (Murray 1908; Burnam 1926; Uddströmer 1934; Baker und Mann 1939; Goldman 1940; Levitan et al. 1961; Biemer 1984). In a large study of 875 patients with HL, 32.5 % had hepatomegaly, and out of the 122/875 patients autopsied, hepatomegaly amounted to 79.6 % (Levitan et al. 1961). There are differences of opinion regarding the onset of hepatomegaly, some describing it as a sign of the terminal stages of disease (Ackerman and del Regato 1954), whereas others described hepatomegaly as a presenting feature, using the terms "*. . .forme hépatique et forme hépatosplénomégalique de la maladie de Hodgkin*" ("hepatic form and hepatosplenomegalic forms"; Pène 1952; Pène et al. 1955). Considering all types of HL, hepatomegaly seems to be infrequent in early HL and, when present, may represent a nonspecific reactive phenomenon (Biemer 1984). It is more frequently observed in LDCHL (Neiman et al. 1973). Some authors, basing their judgment on autopsy material primarily, claimed that hepatic involvement with organomegaly is a late manifestation of HL (Pène et al. 1955). In later phases of the disease, hepatomegaly can reflect direct, primary or secondary, organ involvement (Chim et al. 2000). Among 308 patients with HL analyzed in a more recent study, hepatomegaly was registered in 34, was more frequently encountered in stages III and IV versus I/II, and was more frequent in MCCHL and LDCHL than in LPCHL and NSCHL (Brinckmeyer et al. 1982).

Hepatic HL can be associated with jaundice and cholestasis. For example, in a study of 421 patients with HL presenting as a cholestatic febrile illness, 7.4 % of liver involvement was found (Cervantes et al. 1996). A icteric/cholestatic complication of HL has already been described in the end-nineteenth century and then in the 20th century (Brauneck 1889; Peiser 1913; Beatty 1954; Mac-Clure et al. 1959; Levitan et al. 1961; Bouroncle et al. 1962; Casirola and Dionigi 1966; Bombara et al. 1970; Barge and Potet 1971; Matsko and Zhukovets 1971; Perera et al. 1974; Piken et al. 1979; Liebermann 1986; Birrer and Young 1987; Marinone et al. 1989; Jansen and van der Lelie 1994; Warner and Whitcomb 1994; Cervantes et al. 1996; Yalcin et al. 1999; Gupta et al. 2002; Opeskin et al. 2003; Omidvari et al. 2004). Peiser described a patient with jaundice and histologic demonstration of HL infiltration mainly of the portal tracts and suggested to compress the small bile ducts as a mechanism of cholestasis (Peiser 1913). Cholestatic hepatitis may be mimicked in situations of massive hepatic infiltration by HL tissue resulting in hepatic failure (Lefkowitch et al. 1985). Cholestasis in patients with HL is sometimes caused by tumorous obstruction of extrahepatic bile ducts, in part also by enlarged perihilar or retroperitoneal lymph nodes (Michalitschke 1919; Diessner und Heck 1958; Razemon et al. 1961; Juniper 1963; Justin-Besançon et al. 1963; Sanbe and Shirato 1966; McNulty 1971; Pariente et al. 1981; Martin et al. 1992; Abe et al. 1997). Other causes of jaundice and/or cholestasis in HL comprise hemolysis, viral hepatitis, and drug toxicity. In the absence of any direct liver involvement by HL, a paraneoplastic cause of cholestasis has also been

postulated (Jansen and van der Leite 1994). The unique cholestatic syndrome caused by intrahepatic ductopenia in HL is discussed in a separate paragraph. HL can present as, or cause, acute hepatic failure (Gunasekaran et al. 1992; Weiner et al. 1994; Tornero et al. 1998; Rowbotham et al. 1998; Vadillo Serrano et al. 2002; Olnes et al. 2003; Vardarelli et al. 2004; Woolf et al. 2008; Hong et al. 2010). In part of these cases, hepatic insufficiency is caused by massive infiltration of the organ by HL (Tornero et al. 1998; Rowbotham et al. 1998; Karmacharya et al. 2014). Fulminant hepatic failure in HL has been described to be a paraneoplastic manifestation of HL (Dourakis et al. 1999), albeit of unknown mechanism.

What Are the Criteria for Involvement of the Liver in HL?

The involvement of the liver in HL is a key element for the success of abdominal pathologic HL staging for harvesting adequate liver samples, including laparoscopy, laparotomy, and/or hepatic needle biopsy, to date more and more assisted by modern imaging techniques. However, liver biopsy is still a standard in the assessment of hepatic involvement by HL, provided a reliable diagnosis can be done in a biopsy sample of the liver. But, as seen in the data given below, the highly variable figures of prevalence suggest, among true variances of involvement, differing types of criteria used to detect bona fide HL in contrast to nonspecific accompanying lesions (see below). Therefore, the question of suitable criteria has been addressed in the literature. In a now classical work by Lukes (1971), biopsies of the liver obtained at laparotomy have revealed three types of lesions: HL of nodular sclerosis, mixed, diffuse fibrosis, and reticular types (in accordance to the then employed nomenclature); the granulomas of uncertain origin (described in more detail in a later paragraph); and portal lymphocytic infiltration associated with proliferation of ductules, also of uncertain origin. Expectedly, difficulties in diagnosing HL mainly arise in small, microscopically detectable lesions. As emphasized by Lukes, the criteria for involvement in case of small hepatic lesions are the same or similar to those for small foci elsewhere. This author proposed that the evidence of a discrete lesion with features of one of the histologic types is essential as well as conclusive evidence of a Reed-Sternberg cell variant, although a diagnostic Reed-Sternberg cell is not required: a large, abnormal mononuclear cell with a huge nucleolus is an acceptable form. Lukes has it that particular caution must be used in interpreting small portal lymphocytic lesions in which there are a few abnormal mononuclear cells (Lukes 1971). It is advisable to perform numerous sections in order to search for the target cells (Dich et al. 1989). In case the large atypical cells are not evidence even after multiple sections, but the infiltrate and the configuration of the lesion nevertheless suggest HL, we propose to denote such lesions, suspicious of HL, not otherwise specified (NOS).

Selected References (Kadin et al. 1970; Givler et al. 1971; Bagley et al. 1972; Kaplan et al. 1973; Abt et al. 1974; Grieco and Cady 1980; Brown et al. 1981; Martin et al. 1982; Jaffe 1987; Pittman et al. 1988; Munker et al. 1995; Gupta et al. 1999; Martinet et al. 2000; Lieberz et al. 2000; Rueffer et al. 2003; van Spronsen and Veldhuis 2003); review Carde 2003.

Primary Hodgkin Lymphoma of the Liver

HL can develop as a primary extranodal disease (Padhi et al. 2012), of which the liver manifestation is an uncommon variant. HL limited to the liver has been rarely reported (Goia 1935; Symmers 1944; Guemes Diaz 1965; Gascard et al. 1970; Khapat'ko and Shestakova 1983; Zaman et al. 1991; Chim et al. 2000; Yokomori et al. 2008; Gota et al. 2009). Based on the biologic nature of HL, it is difficult to distinguish between a putative origin of HL primary to the liver in comparison with a secondary hepatic manifestation of HL originating elsewhere.

Macroscopic Features of the Liver in Hepatic HL Involvement

There have been attempts to classify the hepatic manifestations of HL. Coronini, Gruber, and Foulon distinguished the following types of hepatic involvement by HL: (1) capsular, (2) nodular or granulomatous lesions localized to the portal triad, (3) diffuse, and (4) encroachment upon or invasion of blood vessels (Coronini 1928; Gruber 1930; Foulon 1932).

Hepatic Nodular Manifestations of HL

Nodular involvement is manifest at laparoscopy in the form of white liver spots or nodules (Sans et al. 1998), and the nodular growth pattern is also grossly recognized in larger biopsy specimens (Fialk et al. 1979). In an autopsy study of HL and NHL patients, intrahepatic nodular lesions over 1 cm in diameter were macroscopically identified in 33 % of patients with HL, more frequent than in patients with NHL (22 %; Okazaki et al. 1985). In nodular hepatic HL, hypoechogenic foci have been observed, proved by biopsy to consist of HL tissue (Marjanska-Radziszewska et al. 1996). The macroscopically detectable lesions range in size from miliary foci to large nodules. The miliary pattern is characterized by tiny round lesions of gray to white color (Fraenkel and Much 1910a), easy to be confounded with granulomas. They may be grouped around intrahepatic bile ducts (Peiser 1913). When being cut, they are, however, more consistent than granulomas, and caseification is usually not seen in these small lesions. Similar to the spleen, these small lesions may reveal a characteristic bright color on a darker background, resulting in what has been called a "quartz splinter on granite" pattern (Dietrich 1908). These tiny nodules may grow to numerous, frequently very firm pea-sized lesions, sometimes with ill-defined borders (v. Hüttenbrenner 1871). Larger hepatic nodules may be solitary lesions, reaching up to 5 cm in diameter (Yamasaki 1904), or multiple (Sternberg 1898; Fabian 1911; Meyer 1911; Stahr and Synwoldt 1922; Barge and Potet 1971) and may then resemble metastases of other tumors (Peiser 1913; Russell 1914; Chim et al. 2000), all the more so as, in case they are located in peripheral parts of the liver, they may show a shallow central concavity (Barge and Potet 1971) or, rarely, typical umbilication (Fabian 1911). The coarse nodular manifestations of HL in the liver, resulting in markedly prominent nodular masses, were already recognized by Langhans (Langhans 1872), but intrahepatic tumorous manifestations in HL in progressive, and particularly non- or inadequately treated, disease are highly variegated.

This polymorphous gross picture is illustrated by an autopsy case of non-treated patient with HL, documented by Dr. Greenfield in 1876, showing the complex gross features of liver manifestations in this disease:

> On its (the liver's) surface were seen a number of irregular, somewhat prominent patches, either single or made up of a number of clustered nodules of small size, with surrounding injection. On sections these were found to be irregular infiltrating masses of new growth, which appeared to have become caseous. In addition to these nodules there were very marked thickeling and infiltration of the tela conjunctiva of the portal vein and bile ducts, extending into the liver; and here there were seen small patches or irregularly ramified infiltration of translucent, waxy-yellowish colour, apparently starting at the periphery of the lobules, these, with the caseous masses before described, being the most evident morbid appearances. (Greenfield 1876)

On the cut surface, medium-sized or large nodules are usually well delineated and exhibit a grayish-white, homogeneous, or spotted tissue, sometimes with central necrosis or hemorrhage (Russell 1914) resulting in a grossly visible central concavity (Barge and Potet 1971). Large nodules may be accompanied by much smaller but still grossly detectable foci, a part of which are located to the portal tracts. The large nodules may show a hyperemic and/or hemorrhagic rim of red-blue color (Meyer 1911). In HL lesions of high cellularity, the cut surface is pale gray to gray-red, said to resemble fish meat, and typically bulges (protuberant nodules of Sternberg; Sternberg 1913), whereas sclerosing forms of HL rather reveal a flat and firm cut surface of whitish color.

In case of marked sclerosis, the cut surface has been described to be "dry," and in such situations, the cut surface also reveals furrows and septa dividing the nodule into "acinar-like" compartments (Langhans 1872) or structures resembling "pseudolobules" (so-called secondary tuberculinization; Gilbert and Weil 1900). Intrahepatic septa-like structures have already been described by Masson and thought to follow the geometry of the portal fields ("*on constate que le foie est parcouru par des trainées fibreuses irrégulières qui suivent les bandelettes porte*" ["one notes that the liver is traversed by irregular fibrous tracts following the portal fields"]; Masson 1956). Other reports described that the firm linear lesions, or lesions like beads-on-a-string, seemed to follow the geometry of the intrahepatic bile ducts (Meyer 1911).

Old autopsy reports from the pre-chemotherapy period specify that HL masses in the liver are first smooth and elastic to become more and more firm with time, until the lesions may be very hard (the "hard lymphosarcoma"), producing a screeching sound when being cut with the knife (v. Hüttenbrenner 1871). In case of advanced fibrosclerosis of nodular lesions, these have been reported to resemble syphilitic gummas macroscopically (Jackson and Parker 1944b). This apparent evolution of the lesions, also reported several times in the old literature to occur in lymph nodes and other organs in Hodgkin disease not modified by therapy, is of interest insofar, as sclerosis, now regarded as a subtype of HL, may be part of the natural development of disease ("period of sclerosis"; Masson 1956). Particularly in larger nodules, necrosis may be seen with the naked eye, resulting in yellow-gray or dirty-looking, opaque masses. Dry granular necroses sometimes reminiscent of a caseification necrosis may be encountered and have been reported to form an arborizing network or a geographic pattern (Kaufmann 1909). Rarely, lardous necrotic lesions resembling those in the Hodgkin spleen are seen. The "red porphyry" appearance seen in the spleen involved by HL is not observed in the liver, owing to its different histologic architecture and composition. In lymphocyte-depleted HL, grayish and sometimes numerous nodules are seen scattered throughout the liver (Jackson and Parker 1944b).

Some presentation forms of hepatic HL are characterized by macroscopically yellow lesions caused by a complex mixture of infiltration, necrosis, and accumulation of lipid-laden macrophages (xanthomatous/xanthomatoid reaction). The lesions may present as miliary hepatic micronodules of brown-yellow color (Fraenkel and Much 1910b). One may encounter focal circumscribed cream-colored lesions or yellow streaks along the course of the portal areas (Jackson and Parker 1944b), likely to reflect a distinct pattern of spread of the disease. In case of a xanthomatoid/xanthogranulomatous reaction (accumulation of lipid-laden macrophages), yellow flecks are seen within the nodules or around the nodules in a yellow crescent-like structure, already recognized in other organs in the older literature (Dietrich 1908). This presentation may be modified by hemorrhagic spots or a focal brown discoloration owing to deposition of iron pigment, particularly after treatment. Rarely, the nodules show a greenish hue due to leakage of bile into the lesions. Superficially placed lesions may form confluent beds of coalescing nodules, thus forming plaque-like multinodular tumors that may occupy large areas of the capsular liver surface. The lesions may extend along the lymphatic drainage of the hepatic ligaments in a beads-on-a-string pattern, especially in the region of the round ligament. Although most of nodules have a spheroid shape, lesions with a streak-like or stellate morphology also occur (Hauck 1918; Kaufmann 1922). From the periphery of such nodules, furrows are seen to traverse the adjacent capsule of the liver, probably representing tissue retraction due to scarring. In addition, there may be streaky and in part arborizing lesions seen from the capsular surface of the organ (Sternberg 1913) or inside the organ, where they encircle atrophic parts of the lobular hepatic parenchyma (Langhans 1872). It has been suggested that grossly visible arborizing lesions may take their origin from the connective tissue sheath of portal and/or hepatic venous branches (Langhans 1872).

Diffuse Infiltration of the Liver

In contrast to miliary or macronodular forms, a diffuse pattern of liver infiltration by HL cells is a rare but severe form of disease that can cause fatal hepatic failure (Karmacharya et al. 2014).

Hepatic Capsular Manifestations of HL

These are rare lesions but have already been documented in old autopsy studies (Meyer 1911). In an autopsy study of 112 cases, an exclusively capsular manifestation was found in 2 cases only (Levitan et al. 1961).

Histopathology of Hepatic HL

The reliable diagnosis of HL in a liver biopsy is frequently difficult owing to the small sample size and the scarcity of diagnostic Reed-Sternberg cells and their variants (Gupta et al. 1999). It has, however, been emphasized that a primary diagnosis of HL involving the liver should only be made if diagnostic Reed-Sternberg cells are seen (Jaffe 1987), because nonspecific infiltrates are found in approximately 50 % of liver biopsies from patients with HL (Leslie and Colby 1984). If only a so-called inflammatory component is seen, the liver should not be considered to be involved with HL (Jaffe 1987).

Miliary Lesions

The miliary pattern of HL in the liver is histologically characterized by one of several types of lesions. Frequently, one notes collections consisting of atypical histiocytoid cells with prominent nucleoli, surrounded by small lymphocytes, in the absence of bona fide RS cells. The diagnostic significance of such lesions is questionable but has been proposed as being consistent with HL, provided that diagnostic evidence of the disease is present elsewhere (Kadin et al. 1971). In addition, small hepatic manifestations of HL may frequently defy classification of HL, even in cases where marked fibrosis suggesting nodular sclerosis is present. In a study of 51 *untreated* patients with HL, laparotomy staging revealed small foci of HL in liver biopsies of 9 patients. These lesions were largely confined to portal tracts and only rarely contained typical RS cells; they were registered as "unclassified" Hodgkin lesions (Kadin et al. 1971). Submiliary lesions, usually not detectable with the naked eye, are usually between 100 and 200 mm in size (Skovsgaard et al. 1982). Mixed portal tract infiltrates containing variable numbers of Reed-Sternberg cells and eosinophils are observed (Kiewe et al. 2004).

Portal Tract Infiltration

Portal tract involvement is rather typical for microscopic hepatic manifestations of HL and is characterized by an infiltration of the portal tract spaces by lymphocytes, atypical large mononuclear (nondiagnostic) cells, and diagnostic Reed-Sternberg cells (Chim et al. 2000), the pattern of the diagnostic cells depending on the type of HL. The HL tissue may extend from the portal tracts to the parenchyma of zone 1 (Davey and Doyle 1973). The lesions may then grow to a size to be recognized macroscopically as miliary-like micronodules (Peiser 1913). They can be associated with hepatocyte atrophy or necrosis, hepatocyte necrosis being found in up to 90 % in some studies (Davey and Doyle 1973) and the formation of lesions resembling interface lesions seen in active chronic hepatitis. Reed-Sternberg cells are capable to invade the parenchyma in these destructive lesions. As the lesions progress, the expanding infiltrates in the involved portal tracts may grow to the next portal tract, thus forming what may be called "lymphomatous bridging," and these lesions then become confluent and form larger tumor nodules (Davey and Doyle 1973). The portal tract infiltrate is sometimes accompanied by fibrosis, not only in NSHL lesions. However, a marked fibrosclerotic reaction in the portal triads seems to be more frequent and more prominent in hepatic NSHL. A contribution of eosinophils is regularly seen, also in the interface lesions,

but the density of eosinophil infiltrates is highly variable.

In the absence of diagnostic Reed-Sternberg cells, the combination of lymphocytes, eosinophils, and large atypical nondiagnostic cells in portal tracts should raise the suspicion of involvement by HL. Immunostaining for Reed-Sternberg cell markers may be helpful in these situations in order to uncover cells that are not easily identifiable in H&E sections. In some cases, several foci of HL are arranged in the portal tracts in the form of ductocentric, ringlike, or crescent-like structures that may compress the ducts (Peiser 1913; Coronini 1928). These ductocentric nodules may, in the larger intrahepatic ducts, be associated with fibrosis, resulting in a thick sheath encircling the ducts (Meyer 1911), somewhat resembling advanced primary sclerosing cholangitis. It has been suggested that portal tract infiltrates apparently encroaching upon small, interlobular bile ducts may cause cholestasis/jaundice (Peiser 1913), sometimes even with a clinical presentation simulating acute cholestatic hepatitis (Marinone et al. 1989). Old observation showed that small interlobular bile ducts embedded in HL tissue of portal tracts may resist destruction for longer time periods, epithelial necrosis being rather uncommon (Coronini 1928). Longer-standing involvement of the liver by HL may result in fibrosis of the liver (Mignot et al. 1979).

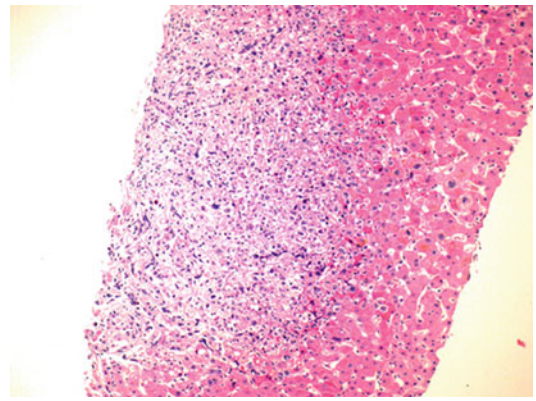

Fig. 1 Liver involvement in Hodgkin disease. A nodule consists of a mixed population of cells, with some large and atypical forms (needle biopsy; hematoxylin and eosin stain)

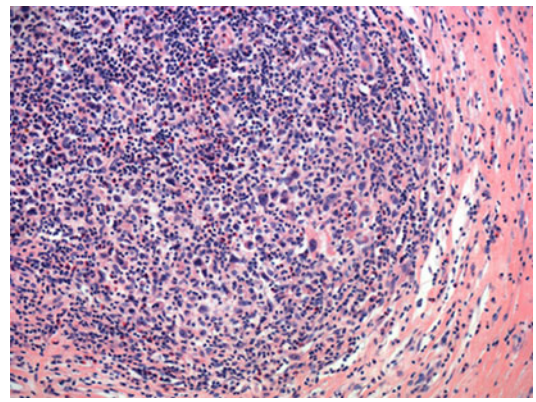

Fig. 2 Hodgkin lymphoma in the liver, mixed cellularity. Within a lymphocytic infiltrate, numerous Hodgkin cells are noted. The nodule is limited by slight fibrosis (hematoxylin and eosin stain)

Nodular Hepatic Lesions of HF

Nodular hepatic lesions histologically consist of dense infiltrates of lymphocytes, macrophages, eosinophils, Hodgkin/Reed-Sternberg cells, and Sternberg giant cells (Figs. 1, 2, 3, 4, and 5). There is recent evidence that giant cells in HL originate from mononucleated progenitors that divide and subsequently re-fuse (Rengstl et al. 2014). Plasma cells and mast cells may also be encountered in the infiltrate. The nodules may coalesce to conglomerates, thus effacing the liver architecture at these places. The cellularity of larger HL nodules is highly variegated, cellular areas and hypocellular, fibrosclerotic areas changing from one place to the other, sometimes interspersed with necroses containing nuclear debris (Russell 1914). Larger nodules are sometimes accompanied by miliary or submiliary foci of HL in their vicinity or may be connected by lymphoma tissue to infiltrated or non-infiltrated portal tracts. In the latter situation, a septal type of fibrosis may ensue, in particular in the nodular sclerosis variant of HL. Large HL nodules sometimes show few lymphocytes in their center, whereas dense lymphocytic infiltrations are seen at their periphery, mainly around small blood vessels (Russell 1914). Large nodules may integrate intrahepatic bile ducts, the contour of the ducts

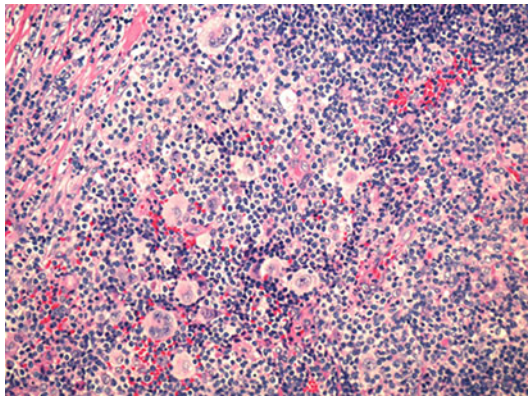

Fig. 3 Hodgkin lymphoma in the liver. Numerous Hodgkin cells and Reed-Sternberg cells are observed (hematoxylin and eosin stain)

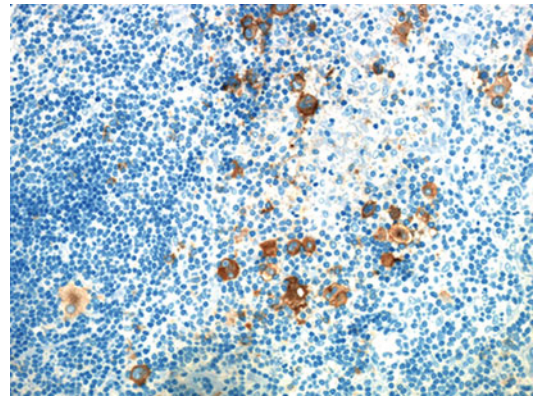

Fig. 5 Hodgkin lymphoma in the liver. Hodgkin cells and Reed-Sternberg cells show positivity for CD15 (CD15 immunostain)

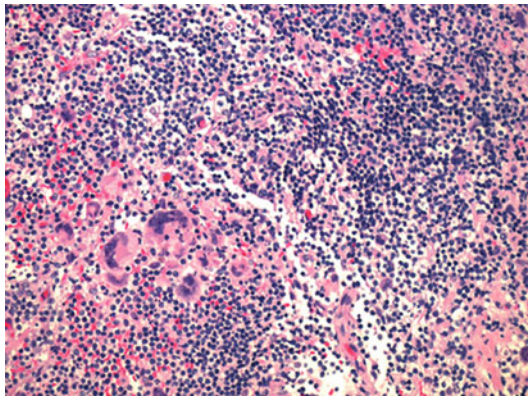

Fig. 4 Hodgkin lymphoma in the liver. In this case, Sternberg giant cells are found (*left half* of figure; hematoxylin and eosin stain)

being visible for some time, ending up with atrophy (with few remnants of cholangiocytes remaining) or even complete duct destruction with substitution by lymphoma tissue. In this situation, bile may leak out of the ducts and stain the HL tissue, particularly in case of lymphoma necrosis (Russell 1914). The neoplastic cell lineage of HL close interacts, within the tumor cell niche, with macrophages and dendritic cells, this interactome regulating a complex immune reaction (review: Tudor et al. 2014).

In addition to intrahepatic bile ducts, intrahepatic portal vein branches may be invaded, sometimes followed by portal vein thrombosis. In an autopsy study, this phenomenon was observed in 23 % of the cases, and this feature tended to occur more frequently with the lymphocyte-depleted type of HL (Davey and Doyle 1973). At the periphery of the nodular lesions, infiltration of hepatic parenchyma may occur, associated with hepatocyte plate atrophy and fatty change of hepatocytes (Russell 1914; Symmers 1944; Sherlock 1955) or even complete destruction of parenchyma. This atrophy has been observed already in old autopsy studies, described, e.g., as hepatocytic "spindle cells" or "spindle-shaped liver cells" (v. Hüttenbrenner 1871). Very rarely, HL may localize to lesions preexisting in the liver, e.g., hepatic angiomas (Toncini and Venzano 1981).

Hilar/Perihilar HL of the Liver and Large Bile Duct Involvement by HL

Involvement of the perihilar hepatic lymph nodes, together with those of the retroperitoneal space and/or the mesentery, causing compression of the large bile duct and thus jaundice, has been described in several reports, sometimes with formation of huge conglomerate masses (Fraenkel and Much 1910a; Meyer 1911; von Jaksch 1913; Weinberg 1917; Michalitschke 1919; Razemon et al. 1961; Martin et al. 1992). Interestingly, these clinical reports describe obstructive

jaundice and in part very large periductal lymphomas, but no prestenotic dilatation of the large hilar bile ducts. On the other hand, Russell described an autopsy case with nodular manifestations of HL in the liver, associated with impressive saccular dilatations of large bile ducts close to the hepatic hilum, these ducts being filled with a dark and viscous bile ("*dilatatio cystica circumscripta ductuum biliferorum*"), whereby some of these cystic structures seemed to follow the larger and infiltrated Glisson's tracts into the liver substance (Russell 1914). Rarely, periductal enlarged lymph nodes involved by HL may bulge into the duct lumen. That enlarged lymph nodes involved by HL exert obstructive effects is exemplified by nonvisualization of the gallbladder in HL of the cystic lymph node (Wee et al. 1970).

Seven patients with direct involvement in the perihilar/hilar tissue compartment were described in detail by Coronini (1928). In two patients, perihilar involvement with biliary obstruction was induced by involvement of hilar/perihilar lymph nodes by HL. In one patient, a perihilar lymphoma had led to kinking of the choledochal duct (Coronini 1928). Direct perihilar tissue involvement was detected in six patients of the extensive analysis of Coronini. Rarely, involvement of the large bile duct close to the hepatic hilum presents in the form of firm and flat nodes developing in the bile duct wall and causing stenosis (Meyer 1911; "Gallengangsgranulomatose"; Coronini 1928), thus clinically mimicking Klatskin's tumor. In other situations, a single bean-sized nodule of HL has been observed in the wall of the choledochal duct (Meyer 1911). Rarely, the entire mucosa of the large bile ducts is seeded by flat tumor nodules, separated from each other by clefts, causing lumenal stenosis (Stahr and Sywolt 1922). Histologically, the latter authors noted that these ductal wall lesions had a transmural extension and were rich in Reed-Sternberg cells, a HL tissue of high cellularity prevailing in the deeper parts of the lesions, while a tissue of lower cellularity was found more close to the mucosal surface. These ductal/periductal nodules may reach 1.5 cm in thickness, encircle the bile ducts, and induce filiform stenosis associated with prestenotic dilatation of the biliary tract (Coronini 1928), sometimes with sacculiform dilatations of the ducts close to the hilum (Russell 1914). Intramural growth of HL tissue in large bile ducts has later been confirmed (Ochoa and Keene 1970; Martin et al. 1992; Abe et al. 1997). In some patients, only duct strictures causing intermittent or persistent obstructive jaundice were found (Diessner and Heck 1958). Fibrotic HL lesions located to the bile ducts may produce imaging features indistinguishable from sclerosing cholangitis (Tartar and Balfe 1990). Biliary and portal vein strictures may also develop following HL therapy (Roberts et al. 2012).

Invasion and Spread of Hodgkin Lymphoma Within the Liver

Invasion of blood vessels and lymphatics by HL has been described by several authors (Reed 1902; Jeanselme and Marchal 1926; Coronini 1928; Callender 1930; Jackson and Parker 1944b; Sayhoun and Eisenberg 1949; Varadi 1960; Rappaport and Strum 1970; Strum et al. 1971; Rappaport et al. 1971; Naeim et al. 1974; Kirschner et al. 1974). But there are also informations in the literature showing the case against (Lamoureux et al. 1973). Rarely, HL reveals a nodal intrasinusoidal invasion pattern mimicking that of anaplastic large cell lymphoma (Lee et al. 2004), suggesting that HL cells can undergo a distinct homing pattern to, and expansion in, specific vascular channels. In the liver, several histopathologic patterns suggest an invasive phenotype of HL. The probably most early phases of involvement, when a specific infiltrate is found to partially occupy the portal tracts, are difficult to judge in regard to invasion, because it is currently still unknown as to how the neoplastic cells of HL reach the liver tissues. It is suggested that the distinct cells circulate in the blood and achieve access to the portal tracts or sinusoidal compartments of the liver by specific homing mechanisms followed by egress of the cells into the extravascular compartments.

In fact, some authors claimed that HL primarily invades the liver within the portal tract spaces

(Schmorl 1922; Sternberg 1936), whereas others proposed that HL extends along the periportal spaces (Fabian 1911; Ziegler 1911) or along the major intrahepatic bile ducts and the portal vein and its branches (Chevallier and Bernard 1932; Sternberg 1936). Spread along the portal tracts is suggested by the typical distribution of xanthomatous yellow streaks that follow the portal course in some cases of hepatic HL (Jackson and Parker 1944b). Dense accumulations of HL infiltrates containing Reed-Sternberg cells may be explained, at least at the beginning of the process, by proliferative expansion of the cells. That the apparently rather dense connective tissues located to the portal tracts allow a rapid infiltration by leukocytes is well known from diverse inflammatory processes (portal hepatitis), illustrating that lymphocytes are potently capable to invade the portal tract space. It may be surmised that the cells of HL can do the same thing, but the mechanisms are not known. On the other hand, expansion of the process beyond the limiting plate and thus into the liver lobules will require invasion rather than proliferative growth alone. Similarly, spread along the intrahepatic bile ducts and blood vessels necessarily involves an invasive phenotype of the neoplastic cells of HL. As described above, Reed-Sternberg cells can be observed within the lumina of hepatic sinusoids, and this will need specific homing and adhesion mechanisms. The fate of such cells in regard to later growth patterns (infiltration of the perisinusoidal space) is not established, but there is some morphologic (and thus indirect) evidence that miliary or submiliary HL growths found within the lobular parenchyma may take their origin from cells primarily settled in the sinusoids.

Invasion of lymph vessels, veins, and arteries by HL has been reported several times (Reed 1902; Jeanselme and Marchal 1926; Coronini 1928; Callender 1930; Jackson and Parker 1944b; Sayhoun and Eisenberg 1949; Varadi 1960). Vascular invasion by HL tissue/cells has been observed in lymph nodes, the incidence of vascular invasion in the original lymph node biopsies being highest in LDHL and decreasing in MCHL, NSHL, and LRCHL (Naeim et al. 1974). It is of importance to note that lymph node vascular invasion is associated more frequently with liver, lung, or bone marrow involvement, either initially or within 1 year in most of the cases analyzed in one study (Strum et al. 1971). Vascular invasion of lymph nodes or the spleen of patients with HL was associated with a high incidence of extranodal organ involvement in other investigations of several hundred tissue samples (Rappaport and Strum 1970; Rappaport et al. 1971). Similarly, HL vascular invasion in the spleen was associated with hepatic and bone marrow involvement, early relapse, and shortened survival (Kirschner et al. 1974). Simonds first noted HL lesions invading the portal vein (Simonds 1926), and this feature was confirmed in later studies (Davey and Doyle 1973). Other types of hepatic vessels have been found to be invaded in an autopsy study (Libansky et al. 1962). The most detailed histopathologic analysis found in the old literature is that of Coronini (Coronini 1928). He described several patterns of vascular lesions occurring in HL, also in the liver. The lesions comprise subendothelial granuloma-like proliferations, associated with endothelial damage, in portal vein branches, a ringlike phlebocentric granulomatosis (granulomatous phlebitis) of portal vein branches resulting in occluding venous thrombosis, and a massively stenosing lymphomatous invasion of large portal vein branches at the liver hilum (lymphomatous phlebopathy), sometimes with accumulation of Reed-Sternberg cells in the markedly thickened portal venous intima. In patients with hilar/perihilar involvement, he also observed an angiodestructive invasion of hepatic artery branches by HL, sometimes with impressive arrosion of the adventitia, a marked granulomatous reaction and/or arterial tissue and tumor necrosis, destruction of the elastica interna, and obliteration of the lumen and with accumulation of Reed-Sternberg cells within the altered media and intima (lymphomatous arteriopathy; Coronini 1928). These hepatic arterial lesions may be associated with necrosis of bile ducts (Coronini 1928), owing to ischemic cholangiopathy/cholangitis.

The neoplastic cells in HL, including cells with the features of Hodgkin and/or Reed-Sternberg cells, can circulate in the peripheral blood (Varadi

1955, 1960; Keiser 1960; Libansky et al. 1962; Hayhoe et al. 1978; Malfitano et al. 1980; Riccardi et al. 1980), sometimes in high numbers leading to what has been termed Reed-Sternberg cell leukemia (Cavalli et al. 1981). The source of these cells is not clear, but it has to be emphasized that peripheral blood mononuclear cells of patients with HL can give rise to permanently growing Hodgkin/Reed-Sternberg cells (Wolf et al. 1996). In regard to the liver, Reed-Sternberg cells have been observed within hepatic sinusoids (Priesel and Winkelbauer 1926; Coronini 1928; Barge and Potet 1971). In his extensive work in hepatic HL involvement, Coronini depicts three large elongated cells located in the sinusoids, most probably representing Sternberg giant cells (Coronini 1928; Fig. 2), a finding which is of interest in the light of target cell homing in HL. A very similar change is depicted in a work published 2 years earlier, again with huge cells with irregular or lobulated nuclei (not representing megakaryocytes) within the sinusoids (Priesel and Winkelbauer 1926). The preparations were from a small child with a generalized lymphomatous disease with numerous hepatic nodules; it is, based on the description, however not certain whether this child had bona fide HL. A convincing figure of Reed-Sternberg cells clearly situated within sinusoids is found in the work of Barge and Potet (Barge and Potet 1971; their Fig. 3).

How Frequent Are HL Infiltrates in the Liver in Extrahepatic HL?

This question has been addressed in rather large number of reports based on autopsies, but using highly variable criteria for identifying HL in the liver, with an incidence range of 10–70 % (Ziegler 1911; Wallhauser 1933; Sternberg 1936; Symmers 1944; Jackson and Parker 1944a; Ackerman and del Regato 1954; Davey and Doyle 1973; Colby et al. 1981). Detailed informations were obtained in a study of 875 patients with HL, 300 (34.3 %) presented with clinical evidence pointing at liver disease such as hepatomegaly and/or abnormal liver function tests. Of this group with clinical signs of liver disease and histologic proof of HL, 112 cases (44 %) were autopsied (Levitan et al. 1961). Of these 122 cases, 74 (66 %) revealed HL involving the liver and 38 (34 %) did not. In the latter group, however, all the livers exhibited some abnormality of major or minor degree. Of the cases with proven hepatic HL involvement, 86.5 % presented with diffuse infiltration, 10.8 % with nodular lesions, and 2.7 % exhibited mixed lesions. Both liver lobes were involved in most cases. Among 59 autopsies of patients with HL, intrahepatic HL was found in 41 or 70 % (Davey and Doyle 1973). In an autopsy study of 80 patients with HL from the time period 1972 to 1977, 54 patients had residual HL, and among 52 of these where the liver was autopsied, 33 had liver involvement (63 %; Colby et al. 1981). Different figures were obtained in liver biopsy studies, likely to be due to an earlier diagnostic approach in comparison with the late stages observed in autopsies. It has been maintained that silent liver involvement can be demonstrated early in the course of the disease by liver biopsy (Pène 1952). In a total of 472 liver biopsies performed in 308 patients with HL, only 2.4 % showed hepatic HL infiltrates consisting of Sternberg-Reed cells and abnormal lymphohistiocytic cells against a background of lymphocytes together with neutrophilic and eosinophilic granulocytes. These infiltrates formed foci of 100–200 mm diameter. This prevalence of bona fide HL involvement is somewhat lower than that in other studies (Rosenberg and Kaplan 1970; Glatstein et al. 1970; Kadin et al. 1971; Abt et al. 1974; Hellman 1974). In a further eight patients of the study of Skovsgaard and coworkers, infiltrates were found that had all the characteristic features of HL except the presence of Sternberg-Reed cells (Skovsgaard et al. 1982). In this large biopsy series, the most frequent finding was lymphocytic infiltration in portal tracts (in 56 % of biopsies), but was of moderate or severe degree in 20 % and 1 % only, respectively. This feature was followed in frequency by focal necrosis (24 %). It has been shown that changes found in liver biopsies taken at the end of staging operations instead at the beginning (a procedure preferred by many surgeons, because no further

manipulations are required) can readily be differentiated from the changes found in HL (Brown et al. 1981).

Is There a Preference of Certain HL Variants to Manifest in the Liver?

This question is difficult to answer due to the fact that the type of lesions found in the liver may or may not correspond to extrahepatic histologic patterns of HL. In an early autopsy study where access to histology was available for 39 cases, it was impossible to classify the intrahepatic HL infiltrates according to then used Lukes classification (Davey and Doyle 1973). This can, at least in part, be due to the phenomenon that extranodal spread, including the liver, is more prevalent in advanced disease and that there is convergence of the morphotypes of HL as a function of progression (Naeim et al. 1974). Nodular lymphocyte-predominant HL (NLPHL; nodular paragranuloma) is different clinically and also in regard to extranodal spread from other variants of HL (Bodis et al. 1997; Diehl et al. 1999). Clinically, most patients present with early stage disease (Ann Arbor I/II; Pappa et al. 1995), but 28 % of patients have presented with advanced stage disease and some of these cases have pursued an aggressive and even fatal clinical course (Hansmann et al. 1984; Trudel et al. 1987). Overall, liver involvement in NLPHL is regarded as rare (Pappa et al. 1995). Of 145 patients with NLPHL, 13 % of the involved sites were extranodal, 4 of them concerning the liver (Hansmann et al. 1984). Among 13 patients with NLPHL (10 with Ann Arbor stage III or IV), four exhibited liver involvement, in two patients with a macroscopic mass; the lesions were focal in two and multifocal in two patients, respectively (Siebert et al. 1995). Among 16 patients with NLPHL, six liver specimens were reviewed (needle or wedge biopsies), four having evidence for NLPHL involvement. None of the involved livers had grossly identifiable lesions. Small to large collections of mature-looking lymphocytes were present in the portal tracts of three of the cases, and varying numbers of LP cells with the immunophenotype typical for NLPHL were also present in this tissue compartment. The fourth case had intralobular and not portal tract involvement, and the numbers of L&H cells and of Reed-Sternberg cells were very low (Chang et al. 1995). The histopathologic differential diagnosis of NLPHL in the liver includes classical HL, T-cell-rich B-cell lymphoma involving the liver (Khan et al. 1993; Fraga et al. 2002), and B-lineage NHL. From a large autopsy study of 122 cases, it turned out that exactly half of the hepatic lesions were what was then termed Hodgkin granuloma (i.e., not LDHL), and of these 82.3 % showed almost exclusive involvement of the portal tracts (Levitan et al. 1961). For LDCHL, liver involvement has been documented by few liver biopsies (Neiman et al. 1973). In the setting of autopsies, liver involvement has been observed in eight out of nine necropsies (Neiman et al. 1973). It seems that portal vein invasion tends to be more frequent in LDCHL (Davey and Doyle 1973).

Hepatic Involvement by Variant Richter's Syndrome

Variant Richter's syndrome can involve the liver (Reddy and Thompson-Arildsen 2010). Hepatomegaly has been described as a feature of this disorder (Brecher and Banks 1990). A progressively enlarged liver has been reported in a patient who developed classical HL 4 years after the diagnosis of Rai stage II (Binet B) chronic lymphocytic leukemia, without liver histology (Nemets et al. 2003). Among nine patients with Richter's syndrome described by Foucar and Rydell, two showed a histology compatible with lymphocyte-depleted HL and were, therefore, likely to be variant Richter's syndrome. At autopsy, one of these two patients exhibited extensive hepatic infiltration with enlarged, confluent portal areas forming actual tumor nodules less than 5 mm in size (Foucar and Rydell 1980).

Differential Diagnosis

Histologically, the main differential diagnoses include lymphomatous lesions that produce cells resembling Hodgkin and Reed-Sternberg cells. These neoplasms mainly include T-cell-rich B-cell lymphoma and so-called Hodgkin-like peripheral T-cell lymphoma/PTCL (Mori et al. 2014). It has been suggested that nodular lymphocyte-predominant HL and T-cell/histiocyte-rich B-cell lymphoma might be endpoints of a spectrum of one disease (Hartmann et al. 2013).

Nonneoplastic Hepatic Manifestations of HL

Vanishing Bile Duct Syndrome in Hodgkin Lymphoma

A syndrome of "idiopathic" intrahepatic cholestasis occurs in some patients with HL, caused by a distinct ductopenic disorder. Secondary intrahepatic ductopenia (vanishing bile duct syndrome; VBDS) usually in the absence of direct HL infiltration of the liver is a rare but critical cause of cholestasis with or without jaundice in patients with HL; the disorder is thought to be a paraneoplastic manifestation of HL and may result in intractable fatal liver damage (review: Nader et al. 2013). Fatal liver failure due to VBDS can ensue despite HD remission (Aleem et al. 2013). The pathogenesis of HL-associated VBDS is not known. That HL as such is in some complex manner involved is supported by the observation that the small bile duct disorder may show resolution following successful therapy of HL (Crosbie et al. 1997). The differential diagnosis of cholestasis in HL due to VBDS/ductopenia comprises nonobstructive HL-associated cholestasis (see above), obstruction due to infiltration of the bile ducts by HL tissue (Ochoa and Keene 1970; Chaudhari et al. 2013), large extrahepatic bile duct obstruction by HL masses (Sanbe and Shirato 1966; McNulty 1971; Pariente et al. 1981; Martin et al. 1992; Abe et al. 1997), and extrahepatic biliary stricture subsequent to radiotherapy of the upper abdomen (Cherqui et al. 1994).

Selected References (Cavalli et al. 1979; Hubscher et al. 1993; Gottrand et al. 1997; de Medeiros et al. 1998; Ludwig 1998; Allory et al. 2000; Rossini et al. 2000; Yusuf et al. 2000; Ozkan et al. 2001; Ripoll et al. 2002; Liangpunsakul et al. 2002; Guliter et al. 2004; Ballonoff et al. 2008; Leeuwenburgh et al. 2008; Pass et al. 2008; Foramiti et al. 2011).

Sclerosing Cholangitis in Hodgkin Lymphoma

Apart from the well-established association with inflammatory bowel disease, primary sclerosing cholangitis (PSC) has been associated with other diseases, which are often cited as single case reports, including HL. Two patterns of bile duct disease resembling sclerosing cholangitis have been described. In the first pattern, fibrosing HL lesions situated in the walls of larger bile ducts produce a radiographic picture mimicking primary sclerosing cholangitis (PSC), with sometimes marked stenosis (Tartar and Balfe 1990; Gupta et al. 2002). The second pattern is characterized by PSC-like larger bile duct alterations in the absence of proven bile duct involvement by malignancy. In the adult age group, a first report concerned three men, of whom one patient had Crohn's disease of the colon. In these three patients, primary sclerosing cholangitis was diagnosed 2, 11, and 17 years before diagnosis of HL, and all three had then advanced biliary cirrhosis prompting referral for liver transplantation (Man et al. 1993). In a pediatric patient with HL involving the liver, biopsy disclosed a morphology compatible with sclerosing cholangitis (Gupta et al. 2002). The pathogenesis of the association of HL and PSC, if this is not a mere coincidence, is unknown. It has been suggested that immune suppression associated with long-standing and advanced liver disease or immunosuppressive drug therapy may predispose PSC patients to HL (Man et al. 1993).

Hepatic Granulomas in Hodgkin Lymphoma

Hodgkin lymphoma (HL) is well known to be associated with a granulomatous reaction in several organs and tissues (Brincker 1970; Kadin et al. 1970, 1971; Goldman 1970; Colby et al. 1981; Brooks 1982; Johnson et al. 1990; Arai et al. 1992), e.g., in the bone marrow, but also in the liver (Atwood et al. 1966; Brinker 1970; Stolzenbach et al. 1976; Sacks et al. 1978; Koene-Bogman 1978; Pak and Friedman 1981; Skovsgaard et al. 1982). In a study of 459 liver biopsies from 308 patients with HL, granulomas were detected in only 2 %, suggesting the rareness of this finding (Skovsgaard et al. 1982). The development of a marked granulomatous reaction can, similar to the situation of NHL, even be a prominent manifestation at the outset of HL (Lerza et al. 2002). In a study of 51 untreated patients, granulomas were detected in otherwise uninvolved tissues in 14 % of the patients (Kadin et al. 1971).

It was at first considered that hepatic granulomas in HL might be an early tissue expression of this neoplasm (Atwood et al. 1966; Brincker 1970); however, there is no evidence for this, with very few exceptions (Goldman 1970). HL, similar to NHL, may masquerade as "idiopathic" liver granulomas (Aderka et al. 1984), so that the presence of hepatic granulomas without clear cause should make one consider HL or NHL. Usually, the granulomas in HL present as noncaseating epithelioid cell nodules with or without a significant lymphocyte seam, but Langhans giant cells are usually sparse or lacking. Central fibrinoid necrosis was occasionally seen, whereas Schaumann and asteroid bodies were not observed (Kadin et al. 1971). A caseating reaction in the granulomas in the absence of mycobacterial infection is exceedingly rare (Johnson et al. 1990). In the liver, HL-associated granulomas are chiefly located to the portal tracts (Kadin et al. 1971). It is established that lymph nodes draining an area harboring malignancy can show epithelioid granulomas, sometimes to a degree histologically mimicking sarcoidosis and reflecting marked macrophage activation in conjunction with a cell-mediated immune reaction directed to tumor antigens (Nadel and Ackerman 1950). There is evidence that at least a part of the granulomas observed in conjunction with HD represent a reaction to oily radiographic contrast media used in lymphangiography (Pak and Friedman 1981), although it has been claimed that the granulomatous lesions in HL do not really resemble reactions to lymphangiography, mainly based on the observation that the heavily lipidized foreign body-type granulomas developing shortly after oily lymphangiography do not occur in HL (Kadin et al. 1970, 1971). But it has been shown that, as a function of time, lipid-rich lipogranulomas with vacuolated cells slowly transform into sarcoid-like granulomas of the type encountered in HL (Pak and Friedman 1981). A sarcoidosis-like granulomatous reaction has been observed following chemotherapy for HL (Merchant et al. 1994). The histiotype of granulomas occurring in HL may rarely deviate from the "standard" granuloma. Very rarely, hepatic granulomas of the liver in HL have been found to be of the caseating type, in the absence of tuberculosis (Johnson et al. 1990). Apart from typical epithelioid granulomas with a variably developed peripheral rim of lymphocytes, the fibrin-ring granuloma-type of lesion has also rarely been encountered in the liver in HL (in 4 % among 23 patients with such granulomas; Marazuela et al. 1991).

Whether the presence of epithelioid granulomas in HL, including granulomas in the liver, is of prognostic significance has been suggested and discussed in few reports, but a conclusive answer to this question requires more and prospective studies (O'Connell et al. 1975; Sacks et al. 1978; Chopra et al. 1995). In a larger analysis of 55 previously untreated patients with HL and associated granulomas, survival and relapse-free survival were significantly different in favor of the granuloma group in comparison with 553 patients without granulomas (Sacks et al. 1978). A later study revisiting the significance of granulomas (with one of the authors of the just mentioned 1978 study), involving 89 HL patients with granulomas and with a longer follow-up, resulted in a different conclusion: after long follow-up, the relapse-free survival advantage was no longer apparent (Abrams et al. 1988).

Lymphoid Hepatic Lobular Infiltration in the Absence of Bona Fide HL Infiltration of the Liver

The presence of lymphoma in the liver at staging may be difficult to confirm histologically when infiltrates are focal and/or nondiagnostic, i.e., without detectable Hodgkin or Reed-Sternberg cells. Focal lymphocytic infiltrations of the liver may, in the otherwise proven presence of HL, suggest hepatic manifestation of this disease. But how frequent are such infiltrates? In a study of wedge and needle liver biopsies from 123 consecutive staging laparotomies for HL, 12 biopsies revealed discrete lobular lymphoid aggregates. In this investigation, there were nine cases of hepatic involvement by HL and one of extensive portal infiltrates by inflammatory cells, but none of these specimens contained the distinctive parenchymal lymphoid aggregates. The lobular aggregates varied from a few lymphocytes clustered within sinusoids to large aggregates entrapping hepatocytes (Leslie and Colby 1984). The nature of these intralobular lymphoid infiltrations has not been clarified so far, but they may represent an immune reaction to unknown, eventually HL-associated antigens.

Nodular Regenerative Hyperplasia of the Liver

Infiltration of the liver substance by HL cells and tissue, associated with complex vascular abnormalities and a deranged blood flow, can result in nodular regenerative hyperplasia/NRH, a recurrent alteration of the liver in HL patients (Lopez et al. 2014).

Hepatic Sinusoidal Changes in Hodgkin Lymphoma

Hepatic sinusoidal dilatation (HSD) is characterized by the widening of sinusoids that may involve the entire liver lobule or predominate in periportal, midzonal, or pericentral areas. Peliosis hepatis, first described in 1916 under this term (Schoenlank 1916), differs from HSD by the formation of intraparenchymal blood-filled spaces ("lakes") without preferential location (Degott and Potet 1984), although there may be transitions or overlaps between the two lesions. Hepatic peliosis is characterized by oval or irregular, multiple blood-filled spaces within the liver parenchyma, the cavities ranging in size from less than 1 mm to several centimeters. In a study of 906 consecutive liver biopsies, sinusoidal dilatation unrelated to passive hepatic congestion was observed in 26 (2.9 %), and in 21 out of 26 the final diagnosis was a neoplastic or granulomatous disease, but in only half of them was there evidence of neoplastic or granulomatous infiltration of the liver (Bruguera et al. 1978). Sinusoidal dilatation (HSD; sinusoidal ectasia) occurring in the context of HL not associated with direct liver involvement has repeatedly been reported (Bain et al. 1982; Bruguera et al. 1987; Kakar et al. 2004). The examination of liver biopsy specimens from 46 patients with HL revealed sinusoidal dilatation with a predominantly centrilobular and mid-lobular localization in 50 %, more frequently in patients with (90 %) than in those without (20 %) systemic symptoms of disease. The prevalence of these alterations was not related to the stage of HL or the existence of hepatic infiltration by HL (Bruguera et al. 1987). From the descriptions, it is difficult to judge whether sinusoidal dilatation fulfilled the criteria of peliosis hepatis, but at least in part of the cases, these lesions may in fact represent, or may evolve to, bona fide peliosis hepatis (Pasquier et al. 1973; Iwai et al. 2002; Kleger et al. 2009), although peliosis in HL has been suggested to be an infrequent association (Bhaskar et al. 1990).

Cytogenetic and Molecular Features

LP cells in NLPHL show clonally rearranged immunoglobulin genes. The variable region of the immunoglobulin heavy chain genes have a high load of somatic mutations. In contrast to other forms of HL, latent EBV infection is consistently absent from LP cells but may be detectable in nonneoplastic lymphocytic bystander cells. In

80 % of NLPHL cases, aberrant somatic gene mutations have been found, involving PAX5, PIM1, RhoH/TTF, and MYC.

In classical HL, HRS cells contain clonal immunoglobulin gene rearrangements in more than 98 % of cases. In rare cases, T-cell receptor gene rearrangements had been detected. HRS cells have lost many of the typical B-cell lineage markers and express a host of aberrant markers. This is in part caused by a downregulation of early B-cell factor 1 (EBF1), a major B-cell transcription factor (Bohle et al. 2013). The transcription factor NF-kappaB is constitutively activated in HRS cells. There is recent evidence that HL is associated with genetic variations at both HLA and non-HLA loci, including loci at 2p16, 5q31, 6p31, 8q24, and 10p14. A susceptibility locus for HL is on chromosome 19p13.3, involving TCF3 (or E2A), a regulator of B- and T-cell lineage commitment (Cozen et al. 2014).

Both proliferation and survival of HL Reed-Sternberg cells require this activity, which is comprised of the p50 and relA subunits. It was shown that EBV-negative Reed-Sternberg cells reveal enhanced expression of NF-kappaB2/p52 and RelB-containing NF-kappaB DNA-binding activity and that CD30 triggers the noncanonical NF-kappaB activation pathway. Hodgkin cells and Reed-Sternberg cells display a disturbed cell cycle regulation with an abnormality short G1 phase (Tzankov et al. 2005). The p18INK4c gene, encoding a cyclin-dependent kinase (CDK) inhibitor interfering with the Rb-kinase activity of CDK6/CDK4, is silenced in HL through epigenetic promoter hypermethylation (Sanchez-Aguilera et al. 2004). Epigenetic inactivation of the putative tumor suppressor with proapoptotic activity, RASSF1 A, has been found in HL (Murray et al. 2004). Mutations of the JAK regulator SOC-1 occur and are associated with nuclear STAT5 accumulation in HRS cells. As discussed above, overexpression of CD30 is a typical feature of neoplastic cells in HL. CD30 is a member of the tumor necrosis factor/nerve growth factor receptor superfamily and is the receptor of the cytokine, CD30 ligand (CD30L; Gruss and Herrmann 1996). CD30 is expressed transiently on activated B and T cells and constitutively on several B- and T-cell NHLs and on HL. The major CD30 functions include participation in negative selection of thymocytes, costimulation of activated T cells, isotype switching of B cells, and regulation of the effector activity of cytotoxic lymphocytes. CD30 is expressed in Reed-Sternberg cells, and increased levels of serum CD30 are observed in HL patients and are a marker for predicting poor prognosis and poor treatment response. In fact, the CD30 antigen has been characterized as a marker for both primary and cultured Reed-Sternberg cells, but this antigen is also expressed in cells of anaplastic large cell lymphoma and of Burkitt lymphoma. Persistent expression of high levels of CD30 in HL cells, and in particular Reed-Sternberg cells, is thought to play a central role in growth regulation of the neoplastic cells involved. Reed-Sternberg cells, in contrast to cells of anaplastic large cell lymphoma, coexpress CD30 and CD30 ligand, suggesting an autocrine CD30L-CD30 cytokine receptor loop (Hsu and Hsu 2000). The differential expression patterns of downstream components of the CD30 signaling pathway, in particular TRAF1 and c-Rel, may prove a useful adjunct in distinguishing cases of classical HL from morphologically and immunophenotypically similar lymphomas (Rodig et al. 2005). CD30-mediated signals are involved in lymphoid cell homing to lymph nodes, and affect, in a complex network, apoptosis in that CD30 on the one hand upregulates Fas, death receptor 3, and TNF-related apoptosis-inducing ligand and on the other hand upregulates TNFR-associated factor 1 and cellular inhibitor of apoptosis 2, protecting cells from certain types of apoptosis (Muta et al. 2000). It has been found that expression of CD30 by neoplastic cells in HL is associated with inhibition of proliferation and activation of T cells (Su et al. 2004). Proteins that function in signaling events downstream of activated CD30 are also expressed in neoplastic cells of classical HL, including TRAF1 and activated c-Rel (Rodig et al. 2005), and CD30 ectodomain shedding affecting its biologic activity is mediated by TNF-alpha converting enzyme (TACE), is dependent on the availability of the

cysteine-rich domains (CRD) 2 and 5 of the CD30 ectodomain (Hansen et al. 2004), and is increased by depletion of cellular cholesterol and of lipid rafts (von Tresckow et al. 2004). TACE is itself a metalloproteinase, and inhibitors of this enzyme therefore affect the turnover of CD30 (Hansen et al. 2002).

Role of EBV Infection

HL is more often seen in patients with EBV infection (Khan 2006; Kapatai and Murray 2007; Martin et al. 2011; review: Mohamed et al. 2014). The highest frequency of EBV gene expression in HRS cells is found in MCCHL (around 75 %) and the lowest incidence in NSCHL (10–40 %). In Western countries, the EBV strain 1 prevails, whereas strain 2 prevails in resource-poor areas. EBV-encoded latent membrane protein 1 (LMP-1) gene exhibiting deletion mutants is highly associated with HIV-related HL, and these mutants accumulate in RS cells (Guidoboni et al. 2005). From a genome-wide association study of 1200 classical HL patients, it resulted that there were associations between EBV-positive classical HL and genetic variants within the class I region and between EBV-negative classical HL and the rs6903608 locus within the class II region, the latter association being confined to NSCHL (Urayama et al. 2012). In pediatric HL, tumor-associated macrophages are associated with EBV, suggesting that the macrophage microenvironment in pediatric classical HL is different from that of HL in adults (Barros et al. 2012). EBV contributes to the growth and survival of HRS cells. Expression of EBNA1 is associated with downregulation of the TGF-beta target gene, protein tyrosine phosphatase receptor kappa (PTPRK), conferring increased growth and survival to HRS cells (Flavell et al. 2008). EBV infection also affects the recruitment of accessory cells of HL tissue. Expression of the EBV-encoded EBV nuclear antigen 1 in HL neoplastic cells mediates the upregulation of the chemokine CCl20 and the migration of regulatory T cells (Baumforth et al. 2008).

Mechanisms Involved in Growth, Apoptosis, Invasion, and Spread of HL Cells

The Mummified Reed-Sternberg and Hodgkin Cells and Mechanisms of Para-apoptosis/Apoptosis in Hodgkin Lymphoma

The presence of degenerative or regressive changes occurring in the large neoplastic cells in HL had already been noted by Reed and by Sternberg, and these features were later specified in more detail (Jackson and Parker 1944b; Cross 1969; Lorenzen et al. 1997), in one instance described under the term "selective apoptotic necrosis (SAN)" (Kodousek et al. 1992). The phenomenon represents distinct stages of a cellular death process including para-apoptosis and apoptosis of Hodgkin/Reed-Sternberg cells, although it is established that the neoplastic cells in HL are characterized by a remarkable resistance to certain apoptotic stimuli. Histologically, the tissues of HL contain Reed-Sternberg cells with a condensed and markedly eosinophilic or amphophilic cytoplasm and basophilic and condensed nuclei lacking chromatin marginalization, termed mummified cells (Lorenzen et al. 1997). In certain stages of this decay process, the cells may be triangular or elongated. Although the nuclear chromatin undergoes condensation, the tortuous nuclear contour is retained for longer time periods. Similarly, immunoreactivity for CD30 and/or CD15 is retained in what has been termed para-apoptosis, while these markers are negative in cells with classical signs of apoptosis (Lorenzen et al. 1997). Para-apoptosis (nonclassical apoptosis) is a specific morphologic type of programmed, non-necrotic cell death, characterized by cytoplasmic vacuolization, condensed chromatin (but not early margination of the chromatin), and swollen mitochondria. In contrast to classical apoptosis, surface blebbing and the formation of typical apoptotic bodies do not occur (Asher et al. 1995). It seems that para-apoptosis is driven by an alternative caspase-9 activity that is Apaf-1-independent (Sperandio et al. 2000). Para-apoptosis, in addition to Hodgkin and Reed-Sternberg cells, has been observed

in several other cell systems, including lymphocytes (Asher et al. 1995) and the megakaryocyte lineage (Houwerzijl et al. 2004). It is sometimes noted that apoptosis and para-apoptosis are seen in classical HL, but in fact they may occur in any type and subtype of HL (Cross 1969). In a detailed study, the lowest incidence of mummified cells was found in NLPHL ("paragranuloma"), significantly different from the mixed cellularity subtype (Lorenzen et al. 1997). Mummified cells ("mummy cells") do not seem to exhibit DNA fragmentation, but the apoptotic cells are strongly reactive by in situ end labeling of DNA fragments (Benharroch et al. 1996, 1998), while abortive mitoses and nuclear DNA fragmentation were observed in CD30-reactive large cells of HL (Leoncini et al. 1996).

What are the mechanisms of apoptosis and para-apoptosis in HL? Several proteins known to regulate apoptosis and protection from apoptosis show an increased expression in HL tissue and/or Reed-Sternberg cells, including CD95/Fas (Vassallo et al. 2003; although the neoplastic cells show a remarkable resistance to Fas), Bcl-2 (Lauritzen et al. 1999; Kanavaros et al. 2000; Van Spronsen et al. 2000; Vassallo et al. 2003; Kim et al. 2003; Garcia et al. 2003; Kim et al. 2004), Bcl-x (Schlaifer et al. 1996; Chu et al. 1999; Lauritzen et al. 1999; Vassallo et al. 2003; Garcia et al. 2003; Kim et al. 2004), Bax (Brousset et al. 1996; Kanavaros et al. 2000; Vassallo et al. 2003), Bak (Brousset et al. 1999), CD40 ligand (Metkar et al. 2001), Mcl-1 (Vassallo et al. 2003), p53 protein and p53-binding protein MDM2 (Chilosi et al. 1994; Lauritzen et al. 1999), survivin (Garcia et al. 2003), and caspases (Smolewski et al. 2000). Bcl-2 protein reactivity is not usually found in NLPHL (Algara et al. 1991), but is observed in other types of HL to variable degrees (Gupta et al. 1994). Less is so far known about key mechanisms driving para-apoptosis which is an important pathway for the generation of typical mummified cells occurring in HL. A recent study has shown that IGFIR (insulin-like growth factor I receptor), as well as the IGFIR intracytoplasmic domain, induces non-apoptotic programmed cell death characterized by cytoplasmic vacuolation and resistance to apoptosis inhibitors, and this process requires transcription and the de novo synthesis of proteins. IGFIR-induced cell death is mediated by caspase-9 which is, as such, an inducer of apoptosis via cleavage and activation of caspase-3 zymogen and possibly other caspase zymogens, but in para-apoptosis, the caspase-9 effects are different from those in apoptosis owing to the effects of the caspase inhibitors, BAF, p53 protein, and XIAP (Sperandio et al. 2000).

What is the potential role of pro- and antiapoptotic mechanisms in the striking resistance of HL neoplastic cells to apoptosis? Deregulation of some of the factors seems to mediate rescue from apoptosis. There are differences in the expression patterns of Bcl-2 mRNA and Bcl-2 protein (Hell et al. 1995). HL-derived cell lines are resistant to Fas-mediated apoptosis and thus behave differently in comparison with normal germinal center B cells that are eliminated via a Fas pathway. The rescue mechanisms are not yet fully known, but Reed-Sternberg cells, although expressing Fas, exhibit a low frequency of Fas gene mutations, and part of these mutations may impair Fas/CD95 function in apoptotic pathways (Muschen et al. 2000; Maggio et al. 2003). Although expressed in HL cells, Fas does not seem to significantly affect apoptosis in these cells, because an inhibitor protein, cellular FLICE (FADD-like IL-1beta-converting enzyme)-inhibitory protein (c-FLIP), is expressed in the cells as well and protects them from autonomous Fas-mediated death (Dutton et al. 2004; Mathas et al. 2004). Inhibition of Fas-mediated apoptosis in Reed-Sternberg cells also seems to be mediated by constitutional expression of the Fas inhibitor operational in germinal B-cell survival, c-FLIP, in HL cells (Thomas et al. 2002). Furthermore, in regard to caspase effectors of apoptosis, one study did not find significant cytoplasmic staining for caspase-3 and caspase-8 in Reed-Sternberg cells (Xerri et al. 2000), whereas others did (Smolewski et al. 2000). The role of caspase activity in the light of the relative apoptosis resistance of at least some populations of neoplastic cells in HL is complex and is modified by other effectors. Cytochrome c fails to stimulate caspase-9 and

caspase-3 activation in HL-derived B cells, which is due to high level expression of the X-linked inhibitor of apoptosis (XIAP), apoptosis protease-activating factor-1, and caspase-3 being complexed (Kashkar et al. 2003). The expression of CD40 ligand in HL cells has been suggested to rescue these cells from apoptosis (Metkar et al. 2001). Soluble stem cell factor which interacts with the c-kit receptor expressed by Reed-Sternberg cells was able to partially rescue these cells from apoptosis (Aldinucci et al. 2002). On the other hand, some mechanisms seem to promote apoptosis of HL cells and therefore to be involved in pathways leading to mummified cells. Apoptosis of the neoplastic cells in HL is related to the expression of the cdk inhibitor, p27KIP1, suggesting that the p27 and possibly also the p21 pathways are involved in protection from apoptosis in HL (Kolar et al. 2000). The frequent expression in Reed-Sternberg cells of the proapoptotic proteins, Bax (Brousset et al. 1996) and Bak (Brousset et al. 1999), may be an important feature in the pathogenesis of mummified cells.

At least some of these factors seem to be correlated with the biology of disease. For example, a high percentage of Reed-Sternberg cells expressing Bcl-2 protein is associated with treatment failure and subsequent poor survival in young patients with nodular sclerosing HL (Van Spronsen et al. 2000). The simultaneous expression of Bcl-2, Mcl-1, and EBV-associated LMP-1 was shown to significantly and independently be correlated with excellent survival in classical HL (Vassallo et al. 2003). High numbers of active caspase 3-positive Reed-Sternberg cells predict a favorable clinical outcome (Dukers et al. 2002), although the action of caspases in these cell systems is complex, as briefly discussed above.

In contrast to pathogenic pathways promoting apoptosis in neoplastic HL lineages, there are mechanisms prolonging survival of these cells. Telomerase expression and telomere lengthening and inhibition of apoptosis by NF-kappaB expression and inhibitor of NF-kappaB mutations have been suggested to play a role in the possible immortalization of Hodgkin and Reed-Sternberg cells (Emmerich et al. 2003; Zheng et al. 2004). Survival of HL cells is also promoted by a Jagged1-activated Notch1 signaling pathway (Jundt et al. 2002).

Invasion and Spread

It may be anticipated that, similar to other malignant neoplasms, invasion and spread of HL cells markedly depend on cell-to-matrix interactions, all the more so as HL is characterized by a complex mixture of neoplastic cell lineages and nonneoplastic reactive tissues. It is well established that hematologic neoplasms derive from cell systems with an innate capacity of the expression of enzymes acting on the extracellular matrix, particularly metalloproteinases and gelatinases. MMP-9 levels are substantially increased in HL (Thorns et al. 2003; Hazar et al. 2004), and in HL, MMP-9 has been shown to be linked to an adverse prognosis (Kuittinen et al. 2002), similar to NHL (Sakata et al. 2004), suggesting a pathogenic effect promoting tumor cell spread in the matrix. It has been found that proteins associated with EBV (being involved in the development of HL) may affect the expression of metalloproteinase-9. This is of interest insofar as EBV, and specifically its LMP-1, seems to induce other invasion and metastasis factors, such as type IV collagenase, cyclooxygenase-2, and VEGF (Wakisaka and Pagano 2003). In fact, several reports have described an upregulating effect of LMP-1 on the expression of metalloproteinase-9 (Yoshizaki et al. 1998, 1999; Takeshita et al. 1999; Horikawa et al. 2000; Yoshizaki 2002; Wang et al. 2002). However, no correlation between the EBV status in HL and the expression of MMP-9 was found in another investigation (Flavell et al. 2000).

HL tissue also expresses proteins counteracting metalloproteinases, in particular tissue inhibitors of metalloproteinases (TIMPs), similar to NHL (Kuittinen et al. 2003). Expression of TIMP-1 has been detected in Reed-Sternberg cells and found to be an autocrine and paracrine survival factor, but also to be immunodepressant via inhibition of T-cell-mediated cytotoxicity (Oelmann et al. 2002). It has been shown that

the expression of TIMP-1 protein is strongly associated with the nodular sclerosis subtype and the existence of a bulky tumor in HL, while the expression of TIMP-2 is correlated with the occurrence of B symptoms, suggesting that TIMP-1 may promote growth of HL and linked to increased connective tissue turnover, whereas TIMP-2 may correlate with systemic effects of the disease (Pennanen et al. 2004). On the other hand, the expression of MMPs is induced by the extracellular MMP inducer (EMMPRIN). It was found that EMMPRIN and TIMP-1 were co-expressed in two thirds of HL (Thorns et al. 2002, 2003) and the interplay of these two factors may modulate the MMP activity in spread of HL. MMPs are also integrated in a complex network of other proteins, including CD30 that is expressed by a set of HL cells. It has been shown that CD signaling affects lymphoid cell trafficking and homing to lymph nodes (Muta et al. 2000). Furthermore, CD30 affects, via mediation of ICAM-1 upregulation, lymphocyte cluster formation in lymphoid tissues (lymphocyte self-aggregation; Nam et al. 2002). Apart from metalloproteinases, distinct components of the extracellular matrix (ECM) itself and cell surface molecules interacting with the ECM seem to affect the spreading mechanisms of HL cells. Syndecan-1 (CD 138) is a cell surface proteoglycan belonging to the syndecan family of cell surface transmembrane heparan sulfate proteoglycans participating in proliferation, cell migration, and cell-matrix interactions and thus is a multifunctional regulator of cell behavior within the microenvironment of normal cells and several tumors (Dhodapkar and Sanderson 1999; Conejo et al. 2000). Specifically, syndecan-1 has anti-invasive properties dependent on an invasion regulatory domain within the core protein (Langford et al. 2005). The cell-matrix relationship by syndecan-1 is also mediated by its ectodomain regulating alpha(v)beta(3) integrin activity (Beauvais et al. 2004), and shed ecodomains exert a proteolytic activity observed in a wound healing model of mice overexpressing syndecan-1 (Elenius et al. 2004). It is also involved in osteoprotegerin-induced chemotaxis in peripheral blood monocytes. The proteoglycan also makes part of mechanisms controlling vascular development, in that ephrinB2 and EphB4, its cognate receptor, upregulate syndecan-1 in inflammatory angiogenesis (Yuan et al. 2004). Syndecan-1 is associated with post-germinal center and terminal B-cell differentiation and is expressed by Reed-Sternberg cells (Carbone et al. 1997), but only in distinct subtypes of HL: it is not expressed by nodular sclerosis HL, but is, together with Bcl-6, expressed in classical mixed HL (Carbone et al. 1998); furthermore, the syndecan-1+MUM1/IRF4+Bcl-6- phenotype characterized HIV-HL (Carbone et al. 2001). In B-cell NHL, the expression of one of the hyaluronidases, HYAL2, acting on the substrate hyaluronan, was related with tumor aggressiveness (Bertrand et al. 2005), and it may be anticipated that this pathway is also active in the spread of HL.

The spread of HL is, furthermore, affected by the composition and amount of stroma and the local vascular geometry and thus by angiogenesis. The stromal response, which is a dominant feature in the NSHL subtype, is at least in part regulated by TGF-beta that is chiefly expressed in the nodular sclerosis variants (Kadin et al. 1990). It has been documented that vascular endothelial growth factor (VEGF) is expressed in HL (Foss et al. 1997) and specifically by neoplastic Hodgkin/Reed-Sternberg cells in HL but also by nonneoplastic cells (in particular macrophages) located to the stroma (Doussis-Anagnostopoulou et al. 2002)

History of the Hodgkin Disease Concept

Several synonyms of this disease were previously recognized, part of them integrating the observation that the progressive lymph node disorder was not associated with leukemia (lymphogranulomatosis maligna, lymphomatosis granulomatosa, malignant lymphogranuloma, pseudoleukemia, fibromyeloid medullary reticulosis, Paltauf-Sternberg disease, Hodgkin-Paltauf-Sternberg disease, Sternberg disease, Bonfils' disease, Bonfils' syndrome, Hodgkin granuloma, Hodgkin

syndrome, Pel-Ebstein fever, anemia sive cachexia lymphatica, cachexie sans leucémie, adénie, lymphadenoma, lymphome ganglionnaire anémique, progressive multiple lymph node hyperplasia, malignant aleukemic lymphadenoma). This goes back on a series of seminal reports describing the disorder (Hodgkin 1832; Bonfils 1857; Wilks 1865; Greenfield 1876; Pel 1885; Ebstein 1887; Paltauf 1897; Sternberg 1898; Fraenkel and Much 1910b). Thomas Hodgkin (1798–1866) was an English physician and pathologist. In 1825 he was elected member of the Royal College of Physicians in London, was appointed to a position as physician to The London Dispensary (comparable to present emergency unit), and became the curator of the pathology Museum at Guy's Hospital Medical School. Here, he started his career as a leading pathologist of his time and in 1827 became the first reader in England lecturing on pathological anatomy. He discovered the biconcavity of erythrocytes and the cross-striation of skeletal myocytes, but is of course best known for the description of the disease now bearing his name (Hodgkin 1832). At Guy's Hospital in London, Hodgkin was a colleague of Richard Bright and Thomas Addison. Unfortunately for him, he was denied professional advancement, and he later devoted most of his time to issues of social medicine, predominantly the medical problems of the poor and unprivileged, specifically American Indians and natives of black Africa. He was one of the founders of the British and Foreign Aborigines Protection Society, the later British and Foreign Anti-Slavery Society. Up to now, the seven original preparations of Hodgkin lymphogranulomatosis are kept in Guy's Hospital in London. The later analysis of these cases confirmed the diagnosis of the now Hodgkin disease in three of the seven, one designated as "cancer cerebriformis."

Carl Sternberg (Carl von Sternberg; 1872–1935) was working as assistant of pathology in the Viennese Rudolfspital, where he was influenced by professor Richard Paltauf (1858–1924). Several years after the first world war, where he earned great reputation for fighting for soldiers' rights, he became full professor in Vienna in 1926. His main research concerned tuberculosis and leukemia. In 1898, he published his work (in a Journal edited in Prague) on what is now known as Hodgkin disease, but regarded by him as a special form of tuberculosis ("*eigenartige Tuberkulose des lymphatischen Apparates*"), and described one of the cellular hallmarks of this disease (review: Sternberg 1936). HL, early thought to be a variant of tuberculosis, was then named, Sternberg disease or Paltauf-Sternberg lymphogranuloma, until Pappenheim coined the term lymphogranulomatosis.

Although Hodgkin and Sternberg are in the center of the recognition of the disease in question, others have contributed much to our understanding of Hodgkin disease. Another British physician, Samuel Wilks, independently described the same disease and with greater precision (Wilks 1856). But he recognized Hodgkin's priority and named the disease for Hodgkin in an article in Guy's Hospital Reports entitled "Cases of enlargement of the lymphatic glands and spleen (or, Hodgkin's disease) with remarks" (Wilks 1865). There is some evidence that a disease possibly representing Hodgkin disease was already described by Malpighi and Morgagni (in Birch-Hirschfeld 1878). Marcello Malpighi (1628–1694) is said to have described lesions corresponding to Hodgkin disease in 1666 (Malpighi 1666). Giovanni Battista Morgagni (1682–1771) presents a description of a disorder likely to be Hodgkin disease in his famous work entitled *De Sedibus et Causis Morborum per Anatomen Indagatis* (On the seats and causes of diseases investigated by anatomy) (Morgagni 1761). The view of Sternberg that HL may represent a unique form of tuberculosis was put into question several years after his descriptions only. Chiari had observed in several patients that the "granulomatous disease" can progress into a sarcomatous growth, with diffuse infiltration of organs adjacent to the lymph nodes initially involved, and already remarked that, in this situation, the cellularity of the lesions may increase (cited in Dietrich 1908), and these observations were confirmed later, leading to the term "granuloma-like sarcoma of lymph nodes" (Dietrich 1908).

An interesting history also relates to the giant cell that is such a typical feature of Hodgkin disease (the Reed-Sternberg cell). These characteristic giant and/or multinuclear cells were already registered by early authors (v. Hüttenbrenner 1871; Langhans 1872; Greenfield 1878; Dreschfeld 1891; Hübener 1893; Gilbert and Weil 1900; Dietrich 1908). Langhans, in his description of what was then termed "hard lymphosarcoma" (i.e., sclerosing forms of Hodgkin disease), noted scattered large cells with 2 or 3, and sometimes many more, nuclei of irregular shape ("*Hie und da finden sich zerstreut grössere dunkelkörnige Zellen, etwa von der Grösse der Schleimkörper, mit 2, 3 auch mehr Kernen, und ferner wahre Riesenzellen, grosse Haufen von dunkelkörniger Zellsubstanz mit 10, 20 Kernen, von länglich unregelmässiger Gesta*lt"). These cells do not represent the reactive multinuclear giant cells also detected by Langhans, but in fact a first description of the later Reed-Sternberg cell (Langhans 1872). Langhans refers, in his work, to a similar observation by v. Hüttenbrenner (1871), who described "multinuclear protoplasmic masses (giant cells)" and "*myeloplaques à plusieurs noyaux*." The striking giant cells were reported again in 1878 (Greenfield 1878). In his autopsy study on HL patients, Greenfield described the cells observed in enlarged lymph nodes as follows: "There were a large number of multinucleated cells adherent to the trabeculae, well seen on washing away the lymph cells. These multinucleated cells, containing from 4 to 8 or 12 nuclei, were often collected in clusters in the parts of the gland especially where the fibrous change was progressing" (Greenfield 1878). In his Fig. 2 (a drawing by the author), the typical large nuclei with the characteristic prominent nucleolus are nicely depicted. It is seen that this author already recognized that the cells in question occur in clusters, what is typical for certain variants of HL. Hübener described, based on the autopsy of a 5-year-old girl with typical HL, large cells in involved lymph nodes, characterized by the presence of two or more nuclei (Hübener 1893). The detailed description of the characteristic cells occurring in HL was performed by Sternberg (Sternberg 1898). Four years later appeared the work of Dorothy Reed Mendenhall (1874–1964) who not only produced more relevant information on the unique cells types but also separated Hodgkin disease from tuberculosis (Reed 1902). The so-called lacunar Reed-Sternberg cells chiefly observed in the nodular sclerosis variant of HL and characterized by cytoplasmic retraction in formalin-fixed samples have probably first been described in 1900 (Gilbert and Weil 1900; "*la très grosse majorité (des cellules) sont constituées par un gros noyau arrondi ou ovalaire, très clair, vésiculeux, que l'hématéine teinte à peine en violet clair et qui présente un ou deux nucléoles; on ne constate presque pas de protoplasme autour de ce noyau*"; the large majority of the cells exhibit a large, roundish, or ovoid nucleus, very clear, vesicular, that the hematein hardly stains violet, and that show one or two nucleoli; one detects almost no cytoplasm around these nuclei). A further characteristic feature in HL is the presence of a distinct type of Hodgkin cell apoptosis, resulting in so-called mummified cells (see below). It seems that this feature was first recognized in 1910 already. In an autopsy case of HL ("Sternberg's so-called peculiar tuberculosis of the lymphatic system") Graetz found large and giant cells in the bone marrow (with indented, reniform, or lobulated nuclei), part of these cells showing "marked pycnosis or other signs indicating cell decay" (Graetz 1910).

References

Abe H, Kubota K, Makuuchi M (1997) Obstructive jaundice secondary to Hodgkin's disease. Am J Gastroenterol 92:526–527

Abrams J, Pearl P, Moody M, Schimpff SC (1988) Epithelioid granulomas revisited: long-term follow-up in Hodgkin's disease. Am J Clin Oncol 11:456–460

Abt AB, Kirschner RH, Belliveau RE, O'Connell MJ, Sklandky BD, Greene WH, Wiernik PH (1974) Hepatic pathology associated with Hodgkin's disease. Cancer 33:1564–1571

Ackerman LV, del Regato JA (1954) Cancer: diagnosis, treatment and prognosis, 2nd edn. Mosby, St. Louis

Aderka D, Kraus M, Avidor I, Sidi Y, Weinberger A, Pinkhas J (1984) Hodgkin's and non-Hodgkin's lymphomas masquerading as "idiopathic" liver granulomas. Am J Gastroenterol 79:642–644

Aisenberg AC (1971) Letter. Ann Intern Med 75:322
Aldinucci et al (2002) http://www.ncbi.nlm.nih.gov/pubmed/12199785
Aleem A, Al-Katari M, Alsaleh K, AlSwat K, Al-Sheikh A (2013) Vanishing bile duct syndrome in a Hodgkin's lymphoma patient with fatal outcome despite lymphoma remission. Saudi J Gastroenterol 19:286–289
Algara et al (1991) http://www.ncbi.nlm.nih.gov/pubmed/1916688
Allory Y, Metreau J, Zafrani E (2000) Paraneoplastic vanishing bile duct syndrome in a case of Hodgkin's disease (in French). Ann Pathol 20:52–55
Ansell SM (2014) Hodgkin lymphoma: 2014 update on diagnosis, risk-stratification, and management. Am J Hematol 89:771–779
Arai N, Hara A, Umeda M, Sirai T (1992) Hodgkin's disease presenting with fever of unknown origin associated with granulomas of the bone marrow (in Japanese). Rinsho Ketsueki 33:1252–1256
Asher E, Payne CM, Bernstein C (1995) Evaluation of cell death in EBV-transformed lymphocytes using agarose gel electrophoresis, light microscopy and electron microscopy. II. Induction of non-classic apoptosis ("para-apoptosis") by tritiated thymidine. Leuk Lymphoma 19:107–119
Atwood WG, Miller RC, Nelson CT (1966) Sarcoidosis and the malignant lymphoreticular diseases. Arch Dermatol 94:144–151
Bagley CM, Roth JA, Thomas LB, Devita VT (1972) Liver biopsy in Hodgkin's disease. Clinicopathologic correlations in 127 patients. Ann Intern Med 76:219–225
Bagley CM, Thomas LB, Johnson RE, Chretien PB, de Vita VT (1973) Diagnosis of liver involvement by lymphoma: results in 96 consecutive peritoneoscopies. Cancer 31:840–847
Bain BJ, Chong KC, Coghlan SJ, Roberts SJ (1982) Hepatic sinusoidal ectasia in association with Hodgkin's disease. Postgrad Med J 58:182–184
Baker C, Mann WN (1939) Hodgkin's disease. A study of 65 cases. Guy's Hosp Rep 89:83–107
Ballonoff A, Kavanagh B, Nash R, Drabkin H, Trotter J, Costa L, Rabinovirch R (2008) Hodgkin lymphoma-related vanishing bile duct syndrome and idiopathic cholestasis: statistical analysis of all published cases and literature review. Acta Oncol 47:962–970
Barge J, Potet F (1971) Anatomopathological study of the liver in Hodgkin's disease (in French). Presse Med 79:565–568
Barié E (1875) Lymphadénie sans leucémie; hypertrophie généralisée des ganglions lymphatiques, tumeurs lymphoides du foie, de la rate, des reins, du coeur, de la peau, etc. Bull Soc Anat (Paris) 50(3 ser):711–719
Barron M (1926) Two rare cases of Hodgkin's disease: (a) chronic relapsing fever of Pel-Ebstein type; (b) Hodgkin's disease with extensive cutaneous manifestations. Arch Pathol (Chicago) 2:616
Barros MH, Hassan R, Niedobitek G (2012) Tumor-associated macrophages in pediatric classical Hodgkin lymphoma: association with Epstein-Barr virus, lymphocyte subsets, and prognostic impact. Clin Cancer Res 18:3762–3771
Baumforth KR, Birgersdotter A, Reynolds GM, Wei W, Kapatai G, Flavell JR, Kalk E, Piper K et al (2008) Expression of the Epstein-Barr virus-encoded Epstein-Barr virus nuclear antigen 1 in Hodgkin's lymphoma cells mediates up-regulation of CCL20 and the migration of regulatory T cells. Am J Pathol 173:195–204
Beatty (1954) http://www.ncbi.nlm.nih.gov/pubmed/113150006
Beauvais DM, Burbach BJ, Rapraeger AC (2004) The syndecan-1 ectodomain regulates alphavbeta3 integrin activity in human mammary carcinoma cells. J Cell Biol 167:171–181
Benharroch D, Prinsloo I, Goldstein J, Brousset P, Kachko L, Gopas J (1996) A comparison of distinct modes of tumor cell death in Hodgkin's disease using morphology and in situ DNA fragmentation. Ultrastruct Pathol 20:497–505
Benharroch D, Brousset P, Goldstein J, Gopas J (1998) Mummified Hodgkin cells and apoptosis. J Pathol 185:116
Bertrand P, Courel MN, Maingonnat C, Jardin F, Tilly H, Bastard C (2005) Expression of HYAL2 mRNA, hyaluronan and hyaluronidase in B-cell non-Hodgkin lymphoma: relationship with tumor aggressiveness. Int J Cancer 113:207–212. 8
Bhaskar KV, Joshi K, Banerjee CK, Rao RK, Verma SC (1990) Peliosis hepatis in Hodgkin's disease: an infrequent association. Am J Gastroenterol 85:628–629
Biemer JJ (1984) Hepatic manifestations of lymphomas. Ann Clin Lab Sci 14:252–260
Birch-Hirschfeld FV (1878) Leukämie und Pseudoleukämie, Hodgkinsche Krankheit. in: Gerhardts Handbuch der Kinderkrankheiten, Band 3, pp 301, 339
Birrer MJ, Young RC (1987) Differential diagnosis of jaundice in lymphoma patients. Semin Liver Dis 7:269–277
Bodis S, Kraus MD, Pinkus G, Silver B, Kadin ME, Canellos GP, Shulman LN, Tarbell NJ, Mauch PM (1997) Clinical presentation and outcome in lymphocyte-predominant Hodgkin's disease. J Clin Oncol 15:3060–3066
Bohle V, Döring C, Hansmann ML, Küppers R (2013) Role of early B-cell factor 1 (EBF1) in Hodgkin lymphoma. Leukemia 27:671–679
Bombara R, Cassi E, Pagliano F, Visca U (1970) On jaundice during hemoblastosis. Hodgkin's granuloma (in Italian). Minerva Med 61:4600–4660
Bonfils EA (1857) Quelques réflexions sur un cas d'hypertrophie ganglionaire générale: avec fistules lymphatiques et avec cachexie, sans leucémie. Clermont
Bouroncle BA, Old JW, Vazques AG (1962) Pathogenesis of jaundice in Hodgkin's disease. AMA Arch Intern Med 110:872–883
Brauneck H (1889) Ueber einen Fall von multipler Lymphombildung (Hodgkin'scher Krankheit), welcher unter hohem Fieber, Icterus und Nephritis zum Tode führte. Dtsch Arch Klin Med 44:297–310

Brecher, Banks (1990) http://www.ncbi.nlm.nih.gov/pubmed/1689938

Brincker H (1970) Epithelioid-cell granulomas in Hodgkin's disease. Acta Pathol Microbiol Scand A 78:19–32

Brinckmeyer LM, Skovsgaard T, Thiede T, Vesterager L, Nissen NI (1982) The liver in Hodgkin's disease – I. Clinico-pathological relations. Eur J Cancer Clin Oncol 18:421–428

Brooks JJ (1982) Granulomas in Hodgkin's disease. Hum Pathol 13:87

Brousset P, Benharroch D, Krajewski S, Laurent G, Meggetto F, Rigal-Huguet F, Gopas J, Prinsloo I et al (1996) Frequent expression of the cell death-inducing gene Bax in Reed-Sternberg cells of Hodgkin's disease. Blood 87:2470–2475

Brousset P, Krajewski S, Schlaifer D, Reed JC, Delsol G (1999) Detection of the cell death-inducing protein BAK in Reed-Sternberg cells of Hodgkin's disease. Leuk Lymphoma 34:581–584

Brown R, Gillett R, Stansfeld A, Irving M (1981) The timing of liver biopsy during staging laparotomy for Hodgkin's disease. Clin Oncol 7:99–103

Bruguera M, Aranguibel F, Ros E, Rodes J (1978) Incidence and clinical significance of sinusoidal dilatation in liver biopsies. Gastroenterology 75:474–478

Bruguera M, Caballero T, Carreras E, Aymerich M, Rodes J, Rozman C (1987) Hepatic sinusoidal dilatation in Hodgkin's disease. Liver 7:76–80

Burnam CF (1926) Hodgkin's disease, with especial reference to its treatment by irradiation. J Am Med Assoc 87:1445–1452

Callender GR (1930) The lymphatic tumor registry report. Am J Pathol 5:519

Carbone A, Gloghini A, Gattei V, Degan M, Improta S, Aldinucci D, Canzonieri V, Perin T, Volpe R et al (1997) Reed-Sternberg cells of classical Hodgkin's disease react with the plasma cell-specific monoclonal antibody B-B4 and express human syndecan-1. Blood 89:3787–3794

Carbone A, Gloghini A, Gaidano G, Franceschi S, Capello D, Drexler HG, Falini B, Dalla-Favera R (1998) Expression status of BCL-6 and syndecan-1 identifies distinct histogenetic subtypes of Hodgkin's disease. Blood 92:2220–2228

Carbone A, Gloghini A, Larocca LM, Capello D, Pierconti F, Canzonieri V, Tirelli U, Dalla-Favera R, Gaidano G (2001) Expression profile of MUM1/IRF4, BCL-6, and CD138/syndecan-1 defines novel histogenetic subsets of human immunodeficiency virus-related lymphomas. Blood 97:744–751

Carbone A, Spina M, Gloghini A, Ponzoni M, Doglioni C, Tirelli U (2013) Nodular lymphocytic predominant Hodgkin lymphoma with non-invasive or early invasive growth pattern suggests an early step of the disease with a highly favorable outcome. Am J Hematol 88:161–162

Carde P (2003) Staging Hodgkin's lymphoma: why and how? Haematologica 88:1176–1181

Casirola G, Dionigi R (1966) Jaundice in malignant granuloma. Clinical and statistic studies and etiopathogenic remarks (in Italian). Haematologica 51:817–835

Cavalli G, Casali AM, Lambertini F, Busachi C (1979) Changes in the small biliary passages in the hepatic localization of Hodgkin's disease. Virchows Arch A Pathol Anat Histol 384:295–306

Cavalli P, Cazzola M, Gobbi PG, Gorini M, Malfitano A, Riccardi A, Ascari E (1981) Reed-Sternberg cell leukaemia. Tumori 67:63–70

Cervantes F, Briones J, Bruguera M, Font C, Grau JM, Rozman C, Montserrat E (1996) Hodgkin's disease presenting as a cholestatic febrile illness: incidence and main characteristics in a series of 421 patients. Ann Hematol 72:357–360

Chang KL, Kamel OW, Arber DA, Horyd ID, Weiss LM (1995) pathologic features of nodular lymphocytes predominance Hodgkin's disease in extranodal sites. Am J Surg Pathol 19:1313–1324

Chaudhari D, Khan S, Saleem A, Taylor T, Teddy T, Reddy C, Borthwick T, Young M (2013) Obstructive jaundice as an initial manifestation of non-Hodgkin lymphoma: treatment dilemma and high mortality. Case Rep Med 2013:259642

Cherqui D, Palazzo L, Piedbois P, Charlotte F, Duvoux C, Duron JJ, Fagniez PL, Valla D (1994) Common bile duct stricture as a late complication of upper abdominal radiotherapy. J Hepatol 20:693–697

Chevallier P, Bernard J (1932) La maladie de Hodgkin. Masson, Paris

Chilosi M, Doglioni C, Menestrina F, Montagna L, Rigo A, Lestani M, Barbareschi M, Scarpa A et al (1994) Abnormal expression of the p53-binding protein MDM2 in Hodgkin's disease. Blood 84:4295–4300

Chim et al (2000) http://www.ncbi.nlm.nih.gov/pubmed/11042525

Chopra R, Rana R, Zachariah A, Mahajan MK, Prabhakar BR (1995) Epithelioid granulomas in Hodgkin's disease – prognostic significance. Indian J Pathol Microbiol 38:427–433

Chu WS, Aguilera NS, Wei MQ, Abbondanzo SL (1999) Antiapoptotic marker Bcl-X (L), expression on Reed-Sternberg cells of Hodgkin's disease using a novel monoclonal marker, YTH-2H12. Hum Pathol 30:1065–1070

Colby TV, Hoppe RT, Warnke RA (1981) Hodgkin's disease at autopsy: 1972–1977. Cancer 47:1852–1862

Conejo JR, Kleeff J, Koliopanos A, Matsuda K, Zhu ZW, Goecke H, Bicheng N, Zimmermann A et al (2000) Syndecan-1 expression is up-regulated in pancreatic but not in other gastrointestinal cancers. Int J Cancer 88:12–20

Coronini C (1928) Ueber das Paltauf-Sternberg'sche Lymphogranulom, mit besonderer Berücksichtigung der veränderungen des verdauungsschlauches und solcher an der Leberpforte mit und ohne Gelbsucht. Zugleich ein Beitrag über lymphogranulomatöse Gefässveränderungen. Beitr Pathol Anat 80:405–478

Cowan R, Trounce JR (1973) Hodgkin's disease and the liver. Guys Hosp Rep 122:221–230
Cozen W, Timofeeva MN, Li D, Diepstra A, Hazelett D, Delahaye-Sourdeix M, Edlund CK et al (2014) A meta-analysis of Hodgkin lymphoma reveals 19p13.3 TCF3 as a novel susceptibility locus. Nat Commun 5:3856
Crosbie OM, Crown JP, Nolan NP, Murray R, Hegarty JE (1997) Resolution of paraneoplastic bile duct paucity following successful treatment of Hodgkin's disease. Hepatology 26:5–8
Cross JM (1969) Hodgkin's disease: histological classification and diagnosis. J Clin Pathol 22:165–182
Davey FR, Doyle WF (1973) Hepatic alterations in Hodgkin's disease. N Y State J Med 73:1981–1986
De Medeiros BC, Lacerda MA, Telles JE, da Silva JA, de Medeiros CR (1998) Cholestasis secondary to Hodgkin's disease: report of 2 cases of vanishing bile duct syndrome. Haematologica 83:1038–1040
Degott C, Potet F (1984) Peliosis hepatis and sinusoidal dilatation. Arch Anat Cytol Pathol 32:296–300
Dhodapkar MV, Sanderson RD (1999) Syndecan-1 (CD138) in myeloma and lymphoid malignancies: a multifunctional regulator of cell behavior within the tumor microenvironment. Leuk Lymphoma 34:35–43
Dich NH, Goodman ZD, Klein MA (1989) Hepatic involvement in Hodgkin's disease. Clues to histologic diagnosis. Cancer 64:2121–2126
Diebold J, Temmim L (1980) Anatomo-pathologic study of biopsies taken in 250 exploratory laparotomies for Hodgkin's disease (in French). Ann Anat Pathol (Paris) 25:341–352
Diehl V, Sextro M, Franklin J, Hansmann ML, Harris N, Jaffe E, Poppema S, Harris M, Franssila K et al (1999) Clinical presentation, course, and prognostic factors in lymphocyte-predominant Hodgkin's disease and lymphocyte-rich classical Hodgkin's disease: report from the European Task Force on Lymphoma Project on lymphocyte-predominant Hodgkin's disease. J Clin Oncol 17:776–783
Diessner GR, Heck FJ (1958) Intermittent obstructive jaundice in Hodgkin's disease: report of a case. J Lancet 78:99–102
Dietrich D (1908) Ueber granulomartiges Sarkom der Lymphdrüsen. Deut Med Wochenschr 27:1188–1189
Dourakis SP, Tzemanakis E, Deutsch M, Kafiri G, Hadziyannis SJ (1999) Fulminant hepatic failure as a presenting paraneoplastic manifestation of Hodgkin's disease. Eur J Gastroenterol Hepatol 11:1055–1058
Doussis-Anagnostopoulou IA, Talks KL, Turley H, Debnam P, Tan DC, Mariatos G, Gorgoulis V, Kittas C, Gatter KC (2002) Vascular endothelial growth factor (VEGF) is expressed by neoplastic Hodgkin-Reed-Sternberg cells in Hodgkin's disease. J Pathol 197:677–683
Dreschfeld J (1891) Ein Beitrag zur Lehre von den Lymphosarkomen. Dtsch Med Wochenschr 42:1175–1177
Dukers DF, Meijer CJ, ten Berge RL, Vos W, Ossenkoppele GJ, Oudejans JJ (2002) High numbers of active caspase 3-positive Reed-Sternberg cells in pretreatment biopsy specimens of patients with Hodgkin disease predict favorable clinical outcome. Blood 100:36–42
Dutton A, O'Neil JD, Milner AE, Reynolds GM, Starvzynski J, Crocker J, Young LS, Murray PG (2004) Expression of the cellular FLICE-inhibitory protein (c-FLIP) protects Hodgkin's lymphoma cells from autonomous Fas-mediated death. Proc Natl Acad Sci U S A 101:6611–6616
Ebstein W (1887) Das chronische Rückfallsfieber, eine neue Infektionskrankheit. Berl Klin Wochenschr 24:565–568
Elenius V, Gotte M, Reizes O, Elenius K, Bernfield M (2004) Inhibition of the soluble syndecan-1 ectodomains delays wound repair in mice overexpressing syndecan-1. J Biol Chem 279:41928–41935
Emmerich F, Theurich S, Hummel M, Haeffker A, Vry MS, Dohner K, Bommert K, Stein H, Dorken B (2003) Inactivating I kappa B epsilon mutations in Hodgkin/Reed-Sternberg cells. J Pathol 201:413–420
Fabian E (1911) Die Lymphogranulomatosis (Paltauf-Sternberg). Zbl f Allg Pathol Pathol Anat 22:145–186
Farrer-Brown G, Bennett MH, Harrison CV, Millett Y, Jelliffe AM (1971) The pathological findings following laparotomy in Hodgkin's disease. Br J Cancer 25:449–457
Favre M, Croizat A (1933) L'sadénie éosinophilique prurigène. Ann Dermat Syph 7:1918–1991
Fialk MA, Jarowski CI, Coleman M, Mouradian J (1979) Hepatic Hodgkin's disease without involvement of the spleen. Cancer 43:1146–1147
Flavell JR, Baumforth KR, Williams DM, Lukesova M, Madarova J, Noskova V, Prochazkova J et al (2000) Expression of the matrix metalloproteinase 9 in Hodgkin's disease is independent of EBV status. Mol Pathol 53:145–149
Flavell JR, Baumforth KR, Wood VH, Davies GL, Wei W, Reynolds GM, Morgan S, Boyce A et al (2008) Down-regulation of the TGF-beta target gene, PTPRK by the Epstein-Barr virus encoded EBNA1 contributes to the growth and survival of Hodgkin lymphoma cells. Blood 111:292–301
Foramiti S, Biondini E, Bigolin T, Pasca S, Rossi P (2011) Vanishing bile duct syndrome in non-Hodgkin lymphoma: a case report. Minerva Med 102:345–349
Foss HD, Araujo I, Demel G, Klotzbach H, Hummel M, Stein H (1997) Expression of vascular endothelial growth factor in lymphomas and Castleman's disease. J Pathol 183:44–50
Foucar, Rydell (1980) http://www.ncbi.nlm.nih.gov/pubmed/6770990
Foulon P (1932) A propos de quelques lésions extra-ganglionnaires de la lymphogranulomatöse. Ann Anat Path 9:725–744
Fox H (1936) Remarks on microscopical preparations made from some of the original tissue described by Thomas Hodgkin, 1832. Guy's Hosp Rep 86:11–16

Fraenkel E, Much H (1910a) Ueber die Hodgkin sche Krankheit [Lymphomatosis granulomatosa], insbesondere deren Aetiologie. Zschr Hyg Inf Krankh 67:160–199

Fraenkel E, Much H (1910b) Bemerkungen zur Aetiologie der Hodgkinschen Krankheit und der Leukaemia lymphatica. Münch Med Woschenschr 57:685–687

Fraga M, Sanchez-Verde L, Forteza J, Garcia—Rivero A, Piris MA (2002) T-cell/histiocyte-rich large-B-cell lymphoma is a disseminated aggressive neoplasm: differential diagnosis from Hodgkin's lymphoma. Histopathology 41:216–229

Garcia JF, Camacho FI, Morente M, Fraga M, Montalban C, Alvaro T, Bellas C, Castano A et al (2003) Hodgkin and Reed-Sternberg cells harbor alterations in the major tumor suppressor pathways and cell-cycle checkpoints: analyses using tissue microarrays. Blood 101:681–689

Gascard E, Ferrara A, Bizzari A (1970) Hepatic localization of Hodgkin's disease (apropos of a case simulating amebic abscess of the liver) (in French). Mars Med 107:605–615

Gilbert A, Weil E (1900) De la tuberculisation secondaire des ganglions néoplasiques. Arch Med Exp 12:257–268

Givler RL, Brunk SF, Hass CA, Gulesserian HP (1971) Problems of interpretation of liver biopsy in Hodgkin's disease. Cancer 28:1335–1342

Glatstein E, Guernsey JM, Rosenberg SA, Kaplan HS (1969) The value of laparotomy and splenectomy in the staging of Hodgkin's disease. Cancer 24:709–718

Glatstein E, Trueblood HW, Enright LP, Rosenberg SA, Kaplan HS (1970) Surgical staging of abdominal involved in unselected patients with Hodgkin's disease. Radiology 97:425–432

Gobbi PG, Ferreri AJ, Ponzoni M, Levis A (2013) Hodgkin lymphoma. Crit Rev Oncol Hematol 85:216–237

Goia I (1935) Contributions à la forme hépatique de la lymphogranulomatose maligne. Sang 9:367–374

Goldman LB (1940) Hodgkin's disease; an analysis of 212 cases. J Am Med Assoc 114:1611–1616

Goldman RL (1970) Granulomas in Hodgkin's disease. N Engl J Med 283:1410

Gordon CD, Sidawy MK, Talarico L, Kondi E (1984) Hodgkin's disease in the liver without splenic involvement. Arch Intern Med 144:2277–2278

Gota VS, Purandare NC, Gujral S, Shah S, Nair R, Rangarajan V (2009) Positron emission tomography/computerized tomography evaluation of primary Hodgkin's disease of liver. Indian J Cancer 46:237–239

Gottrand F, Cullu F, Mazingue F, Nelken B, Lecomte-Houcke M, Farriaux JP (1997) Intrahepatic cholestasis related to vanishing bile duct syndrome in Hodgkin's disease. J Pediatr Gastroenterol Nutr 24:430–433

Graetz F (1910) Fur Kenntnis von Sternbergs sog. "eigenartiger Tuberkulose des lymphatischen Apparates. Beitr z Klin Tuberk 15:110–132

Greenfield WS (1876) A case of lymphadenoma with tumours in the skin. Lancet 1:740

Greenfield WS (1878) Specimens illustrative of the pathology of lymphadenoma and leukocythaemia. Trans Pathol Soc London 29:272–304

Grieco MB, Cady B (1980) Staging laparotomy in Hodgkin's disease. Surg Clin North Am 60:369–379

Gruber GB (1930) Spezielle Infektionsfolgen der Leber. IX. Lymphogranulomatose. In: Henke F, Lubarsch O (eds) Handbuch der speziellen pathologischen Anatomie, vol 5, Part I. Springer, Berlin, pp 604–615

Gruss HJ, Herrmann F (1996) CD30 ligand, a member of the TNF ligand superfamily, with growth and activation control CD30+ lymphoid and lymphoma cells. Leuk Lymphoma 20:397–409

Guemes Diaz F (1965) Hepatic lymphogranuloma (in Spanish). Rev Esp Enferm Apar Dig 24:1210–1218

Guidoboni M, Ponzoni M, Caggiari L, Lettini AA, Vago L, De Re V, Gloghini A, Zancai P, Carbone A, Boiocchi M, Dolcetti R (2005) Latent membrane protein 1 deletion mutants accumulate in Reed-Sternberg cells of human immunodeficiency virus-related Hodgkin's lymphomas. J Virol 79:2643–2649

Guliter S, Erdem O, Isik M, Yamac K, Uluoglu O (2004) Cholestatic liver disease with ductopenia (vanishing bile duct syndrome) in Hodgkin's disease: report of a case. Tumori 90:517–520

Gunasekaran TS, Hassall E, Dimmick JE, Chan KW (1992) Hodgkin's disease presenting with fulminant liver disease. J Pediatr Gastroenterol Nutr 15:189–193

Gupta RK, Lister TA, Bodmer JG (1994) The t(14;18) chromosomal translocation and Bcl-2 protein expression in Hodgkin's disease. Leukemia 8:1337–1341

Gupta RK, Gospodarowicz MK, Lister TA (1999) Clinical evaluation and staging of Hodgkin's disease. In: Mauch PM, Armitage JO, Diehl V, Hoppe RT, Weiss LM (eds) Hodgkin's disease, 2nd edn. Lippincott Williams and Wilkins, Philadelphia, pp 223–240

Gupta A, Roebuck DJ, Michalski AJ (2002) Biliary involvement in Hodgkin's disease. Pediatr Radiol 32:202–204

Hansen HP, Matthey B, Barth S, Kisseleva T, Mokros T, Davies SJ, Beckett RP, Foelster-Holst R, Lange HH, Engert A, Lemke H (2002) Inhibition of metalloproteinases enhances the internalization of anti-CD30 antibody Ki-3 and the cytotoxic activity of Ki-3 immunotoxin. Int J Cancer 98:210–215

Hansen HP, Recke A, Reineke U, Von Tresckow B, Borchmann P, Von Strandmann EP, Lange H, Lemke H, Engert A (2004) The ectodomain shedding of CD30 is specifically regulated by peptide motifs in its cysteine-rich domains 2 and 5. FASEB J 18:893–895

Hansmann ML, Zwingers T, Boske A, Loffler H, Lennert K (1984) Clinical features of nodular paragranuloma (Hodgkin's disease, lymphocyte predominance type, nodular). J Cancer Res Clin Oncol 108:321–330

Harrison CV (1952) Benign Hodgkin's disease (Hodgkin's paragranuloma). J Pathol Bacteriol 64:513–518

Hartfall SJ (1932) Hodgkins disease of the lung. Guy's Hosp Rep 82:55–74
Hartmann S, Döring C, Jakobus C, Rengstl B, Newrzela S, Tousseyn T, Sagaert X, Ponzoni M et al (2013) Nodular lymphocyte predominant Hodgkin lymphoma and T cell/histiocyte rich large B cell lymphoma – endpoints of a spectrum of one disease? PLoS One 8:e78812
Hauck K (1918) Ein Beitrag zur Kenntnis der Lymphogranulomatose. Zbl f Allg Pathol Pathol Anat 29:225–232
Hayhoe FG, Burns GF, Cawley JC, Stewart JW (1978) Cytochemical, ultrastructural and immunological studies of circulating Reed-Sternberg cells. Br J Haematol 38:485–490
Hazar B, Polat G, Seyrek E, Bagdatoglglu O, Kanik A, Tiftik N (2004) Prognostic value of matrix metalloproteinases (MMP-2 and MMP-9) in Hodgkin's and non-Hodgkin's lymphoma. Int J Clin Pract 58:139–143
Hell K, Lorenzen J, Fischer R, Hansmann ML (1995) Hodgkin cells accumulate mRNA for bcl-2. Lab Invest 73:492–496
Hellman S (1974) Current studies in Hodgkin's disease. N Engl J Med 290:894–898
Hjalgrim H (2012) On the aetiology of Hodgkin lymphoma. Dan Med J 59:B4485
Hjalgrim H, Askling J, Rostgaard K, Hamilton-Dutoit S, Frisch M, Zhang JS, Madsen M, Rosdahl N et al (2003) Characteristics of Hodgkin's lymphoma after infectious mononucleosis. N Engl J Med 349:1324–1332
Hodgkin T (1832) On some morbid appearances of the absorbent glands and spleen. Medico-Chir Trans (London) 17:68–114 (reprint: Med Classics 1:741–770, 1937)
Hong FS, Smith CL, Angus PW, Crowley P, Ho WK (2010) Hodgkin lymphoma and fulminant hepatic failure. Leuk Lymphoma 51:947–951
Hood IM, Mahendra P, McNeil K, Marcus RE (1996) Hodgkin's disease after cardiac transplant: a report of two cases. Clin Lab Haematol 18:115–116
Horikawa T, Yoshizaki T, Sheen TS, Lee SY, Furukawa M (2000) Association of latent membrane protein 1 and matrix metalloproteinase 9 with metastasis in nasopharyngeal carcinoma. Cancer 89:715–723
Houwerzijl EJ, Blom NR, van der Want JJ, Esselink MT, Koornstra JJ, Smit JW, Louwes H et al (2004) Ultrastructural study shows morphologic features of apoptosis and para-apoptosis in megakaryocytes from patients with idiopathic thrombocytopenic purpura. Blood 103:500–506
Hsu PL, Hsu SM (2000) Autocrine growth regulation of CD30 ligand in CD30-expressing Reed-Sternberg cells: distinction between Hodgkin's disease and anaplastic large cell lymphoma. Lab Invest 80:1111–1119
Hübener M (1893) Ein Fall von malignem Lymphom. Dtsch Zschr f Chir 37:368–372
Hubscher SG, Lumley MA, Elias E (1993) Vanishing bile duct syndrome: a possible mechanism for intrahepatic cholestasis in Hodgkin's lymphoma. Hepatology 17:70–77
Iwai M, Muramatsu A, Tanaka S, Morikawa T, Mori T, Harada Y, Okanoue T, Horishi M, Suyama Y, Kashima K (2002) Macroscopic and microscopic findings of livers in malignant hepatologic disorders, biopsied under peritoneoscopy. J Clin Gastroenterol 35:262–265
Jackson H, Parker F (1944a) Hodgkin's disease; I, general considerations. N Engl J Med 230:1–8
Jackson H, Parker F (1944b) Hodgkin's disease. II. Pathology. N Engl J Med 231:35–44
Jackson H, Parker F (1947) Hodgkin's disease and allied disorders. Oxford University Press, New York
Jaffe ES (1987) Malignant lymphomas: pathology of hepatic involvement. Semin Liver Dis 7:257–268
Jaffe ES, Harris NL, Stein H, Vardiman JW (2001) Pathology and genetics of tumours of haematopoietic and lymphoid tissues. World Health Organization Classification of Tumours. IARC Press, Lyon
Jansen PL, van der Lelie H (1994) Intrahepatic cholestasis and biliary cirrhosis associated with extrahepatic Hodgkin's disease. Neth J Med 44:99–102
Jeanselme E, Marchal G (1926) Commentaires sur un cas de maladie de Hodgkin à évolution aigue. Ann Med 20:1–26
Johnson et al (1990) http://www.ncbi.nlm.nih.gov/pubmed/2227301
Jundt F, Anagnostopoulos I, Forster R, Mathas S, Stein H, Dorken B (2002) Activated Notch1 signaling promotes tumor cell proliferation and survival in Hodgkin and anaplastic large cell lymphoma. Blood 99:3398–3403
Juniper K (1963) Prolonged severe obstructive jaundice in Hodgkin's disease. Gastroenterology 44:199–204
Justin-Besançon L, Laroche C, Nenna A, Etienne JP (1963) Jaundice caused by choledochal obstruction in Hodgkin's disease. Surgical by-pass (in French). Sem Hop 39:2571–2574
Kadin ME, Donaldson SS, Dorfman RF (1970) Isolated granulomas in Hodgkin's disease. N Engl J Med 283:859–861
Kadin ME, Glatstein E, Dorfman RF (1971) Clinicopathologic studies of 117 untreated patients subjected to laparotomy for the staging of Hodgkin's disease. Cancer 27:1277–1294
Kadin ME, Agnarsson BA, Ellingsworth LR, Newcom SR (1990) Immunohistochemical evidence of a role for transforming growth factor beta in the pathogenesis of nodular sclerosing Hodgkin's disease. Am J Pathol 136:1209–1214
Kakar S, Kamath PS, Burgart LJ (2004) Sinusoidal dilatation and congestion in liver biopsy: is it always due to venous outflow impairment ? Arch Pathol Lab Med 128:901–904
Kanavaros P, Stefanaki K, Vlachonikolis J, Eliopoulos G, Kakolyris S, Rontogianni D, Gorgoulis V, Georgoulias V (2000) Expression of p53, p21/waf1, bcl-2, bax, Rb and Ki67 proteins in Hodgkin's lymphomas. Histol Histopathol 15:445–453
Kapatai, Murray (2007) http://www.ncbi.nlm.nih.gov/pubmed/18042690

Kaplan HS, Dorfman RF, Nelsen TS, Rosenberg SA (1973) Staging laparotomy and splenectomy in Hodgkin's disease: analysis of indications and patterns of involvement in 285 consecutive, unselected patients. Natl Cancer Inst Monogr 36:291–301

Karmacharya P, Bhandari N, Aryal MR, Pandit AA, Pathak R, Ghimire S, Shrestha P et al (2014) Before it crumbles: fulminant hepatic failure secondary to Hodgkin's lymphoma. J Comm Hosp Intern Med Perspect 4:25821

Kashkar H, Haefs C, Shin H, Hamilton-Dutiot SJ, Salvesen GS, Kronke M, Jurgensmeier JM (2003) XIAP-mediated caspase inhibition in Hodgkin's lymphoma-derived B cells. J Exp Med 198:341–347

Kaufmann E (1909) Lehrbuch der speziellen pathologischen Anatomie. Kapitel "Lymphogranulomatose", de Gruyter, Berlin, pp. 158–161

Kaufmann E (1922) Lehrbuch der speziellen pathologischen Anatomie, 7th edn, vol 1, de Gruyter, Berlin, p 205

Keiser G (1960) Tumor cell migration into peripheral blood in malignant tumors of the lymphatic and reticular system (in German). Acta Haematol 23:29–46

Khan G (2006) Epstein-Barr virus and the germinal center B cells. Exp Hematol 34:695–696

Khan SM, Cottrell BJ, Millward-Sadler GH, Wright DH (1993) T-cell-rich B-cell lymphoma presenting as liver disease. Histopathology 23:217–224

Khapat'ko TS, Shestakova NN (1983) Primary liver Hodgkin's disease (in Russian). Vrach Delo 8:98–100

Kiewe P, Korfel A, Loddenkemper C, Fischer L, Jahnke K, Notter M, Muhr-Wilkenshoff F, Stein H, Thiel E (2004) Unusual sites of Hodgkin's lymphoma: case 3. Cholemic nephrosis in Hodgkin's lymphoma with liver involvement. J Clin Oncol 22:4230–4231

Kim LH, Eow GI, Peh SC, Poppema S (2003) The role of CD30, CD40 and CD95 in the regulation of proliferation and apoptosis in classical Hodgkin's lymphoma. Pathology 35:428–435

Kim LH, Nadarajah VS, Peh SC, Poppema S (2004) Expression of Bcl-2 family members and presence of Epstein-Barr virus in the regulation of cell growth and death in classical Hodgkin's lymphoma. Histopathology 44:257–267

Kirschner RH, Abt AB, O'Connell MJ, Sklansky BD, Greene WH, Wiernik PH (1974) Vascular invasion and hematogenous dissemination of Hodgkin's disease. Cancer 34:1159–1162

Kleger A, Bommer M, Kunze M, Klaus J, Leithaeuser F, Wegener M, Adler G, Dikopoulos N (2009) First reported case of disease: peliosis hepatis as cardinal symptom of Hodgkin's lymphoma. Oncologist 14:1088–1094

Klein F (1955) Ueber einen Fall von akut verlaufender Lymphogranulomatose. Zbl Allg Pathol Pathol Anat 93:19–27

Kodousek R, Ticha V, Tichy M (1992) Selective apoptotic necrosis (SAN) of H/R-S cells in malignant lymphogranuloma, and their immunoreactivity with antinuclear antibodies. Scr Med 65:225–230

Koene-Bogman J (1978) Granulomas and the diagnosis of Hodgkin's disease. N Engl J Med 299:553

Kolar Z, Flavell JR, Ehrmann J, Rihakova P, Macak J, Lowe D, Crocker J, Vojtesek B, Young LS, Murray PG (2000) Apoptosis of malignant cells in Hodgkin's disease is related to expression of the cdk inhibitor p27KIP1. J Pathol 190:604–612

Krugmann J, Tzankov A, Gschwendtner A, Fischhofer M, Greil R, Fend F, Dirnhofer S (2003) Longer failure-free survival interval of Epstein-Barr virus-associated classical Hodgkin's lymphoma: a single-institution study. Mod Pathol 16:566–573

Kuittinen O, Soini Y, Turpeenniemi-Hujanen T (2002) Diverse role of MMP-2 and MMP-9 in the clinicopathological behavior of Hodgkin's lymphoma. Eur J Haematol 69:205–212

Kuittinen O, Apaja-Sarkkinen M, Turpeenniemi-Hujanen T (2003) Gelatinases (MMP-2 and MMP-9), TIMp-1 expression and the extent of neovascularization in aggressive non-Hodgkin's lymphomas. Eur J Haematol 71:91–99

Küppers R, Hansmann ML (2005) The Hodgkin and Reed/Sternberg cell. Int J Biochem Cell Biol 37:511–517

Küppers R, Engert A, Hansmann ML (2012) Hodgkin lymphoma. J Clin Invest 122:3439–3447

Lamoureux KB, Jaffe ES, Berard CW, Johnson RE (1973) Lack of identifiable vascular invasion in patients with extranodal dissemination of Hodgkin's disease. Cancer 31:824–825

Langford JK, Yang Y, Kieber-Emmons T, Sanderson RD (2005) Identification of an invasion regulatory domain within the core protein of syndecan-1. J Biol Chem 280:3467–3473

Langhans TH (1872) Das maligne Lymphosarkom (Pseudoleukämie). Virchows Arch 54:509–537

Lauritzen AF, Moller PH, Nedergaard T, Guldberg P, Hou-Jensen K, Ralfkiaer E (1999) Apoptosis-related genes and proteins in Hodgkin's disease. APMIS 107:636–644

Lee SS, Ryoo BY, Park YH, Park S, Kim MS, Park KH, Kim CW (2004) Hodgkin lymphoma with unusual intrasinusoidal pattern of infiltration. Leuk Lymphoma 45:2135–2141

Leeuwenburgh I, Lugtenburg EP, van Buuren HR, Zondervan PE, de Man RA (2008) Sever jaundice, due to vanishing bile duct syndrome, as presenting symptom of Hodgkin's lymphoma, fully reversible after chemotherapy. Eur J Gastroenterol Hepatol 20:145–147

Lefkowitch JH, Falkow S, Whitlock RT (1985) Hepatic Hodgkin's disease simulating cholestatic hepatitis with liver failure. Arch Pathol Lab Med 109:424–427

Leoncini L, Spina D, Close P, Megha T, Pacenti L, Tosi P, Pileri S, De Vivo A, Kraft R, Laissue JA, Cottier H (1996) Abortive mitoses and nuclear DNA fragmentation in CD30+ large cells of Hodgkin's disease. Leuk Lymphoma 22:119–124

Lerza R, Schenone E, Barsotti BP, Botta M, Arboscello E, Truini M, Bogliolo G, Pannacciulli I (2002) Epithelioid granulomas as main clinical manifestation at the outset of non-Hodgkin's lymphoma: report of two cases. Oncol Res 13:55–59

Leslie KO, Colby TV (1984) Hepatic parenchymal lymphoid aggregates in Hodgkin's disease. Hum Pathol 15:808–809

Levitan R, Henry T, Diamond D, Lloyd-Cravier LD (1961) Jaundice in Hodgkin's disease. Am J Med 30:99–111

Liangpunsakul S, Kwo P, Koukoulis GK (2002) Hodgkin's disease presenting as cholestatic hepatitis with prominent ductal injury. Eur J Gastroenterol Hepatol 14:323–327

Libansky J, Bednar B, Buzek J (1962) Sternberg cells (Reed cells) in the peripheral blood in a patient with Hodgkin's disease. Neoplasma 9:411–428

Liebermann DA (1986) Intrahepatic cholestasis due to Hodgkin's disease. An elusive diagnosis. J Clin Gastroenterol 8:304–307

Lieberz D, Sextro M, Paulus U, Franklin J, Tesch H, Diehl V (2000) How to restrict liver biopsy to high-risk patients in early-stage Hodgkin's disease. German Hodgkin's Lymphoma Study Group. Ann Hematol 79:73–78

Lopez R, Barrera L, Vera A, Andrade R (2014) Concurrent Hodgkin lymphoma and nodular regenerative hyperplasia on an explanted liver with clinical diagnosis of alcoholic cirrhosis at University Hospital fundacion santa fe de Bogota. Case Rep Pathol 2014:193802

Longcope WT (1903) On the pathological history of Hodgkin's disease, with a report of a series of cases. Bull Ayer Clin Lab 1:4–76

Lorenzen J, Thiele J, Fischer R (1997) The mummified Hodgkin cell: cell death in Hodgkin's disease. J Pathol 182:288–298

Ludwig J (1998) Idiopathic adulthood ductopenia: an update. Mayo Clin Proc 73:285–291

Lukes RJ (1971) Criteria for involvement of lymph node, bone marrow, spleen, and liver in Hodgkin's disease. Cancer Res 31:1755–1767

Lukes RJ, Butler JJ (1966) The pathology and nomenclature of Hodgkin's disease. Cancer Res 26:1063–1081

Lukes RJ, Butler JJ, Hicks EB (1966) Natural history of Hodgkin's disease as related to its pathologic picture. Cancer 19:317–344

Mac-Clure E, Lemos C, Ferreira CS, Leme MA (1959) Considerations on the pathogenesis of jaundice in Hodgkin's disease: presentation of two cases with hepatocanalicular jaundice (in Portuguese). Hospital (Rio J) 56:59–80

Maggio EM, Van den Berg A, De Jong D, Diepstra A, Poppema S (2003) Low frequency of FAS mutations in Reed-Sternberg cells of Hodgkin's lymphoma. Am J Pathol 162:29–35

Malfitano A, Cazzola M, Cavalli P, Gobbi PG, Gorini M, Ascari E, Perugini S (1980) Morphological and cytochemical studies of circulating Hodgkin's and Reed-Sternberg cells. Basic Appl Histochem 24:101–107

Malpighi M (1666) De viscerum structura exercitatio anatomica. Bologna

Man KM, Drejet A, Keeffe EB, Garcia-Kennedy R, Imperial JC, Esquivel CO (1993) Primary sclerosing cholangitis and Hodgkin's disease. Hepatology 18:1127–1131

Marazuela M, Moreno A, Yebra M, Cerezo E, Gomez-Gesto C, Vargas JA (1991) Hepatic fibrin-ring granulomas: a clinicopathologic study of 23 patients. Hum Pathol 22:607–613

Marinone G, Lazzari R, Pellizzari F, Marinone MG (1989) Acute cholestatic Hodgkin's lymphoma: an unusual clinical picture. Haematologica 74:293–296

Marjanska-Radziszewska J, Zawila K, Ciesla E (1996) A case of Hodgkin's disease with an uncommon clinical course. Predominant localization in the liver (in Polish). Przegl Lek 53:830–832

Martin JK, Clark SC, Beart RW, ReMine WH, White WL, Ilstrup DM (1982) Staging laparotomy in Hodgkin's disease: Mayo Clinic experience. Arch Surg 117:586–591

Martin KR, Moore TJ, Wright RA (1992) Obstructive jaundice secondary to primary biliary involvement with Hodgkin's disease. Am J Gastroenterol 87:1194–1195

Martin P, Gomez-Lozano N, Montes S, Salas C, Provencio M, Bellas C (2011) Epstein-Barr virus in the germinal centres of adenopathies affected by classic Hodgkin lymphoma. Histopathology 59:349–352

Martinet O, Bettschart V, Scholl B, Suter M (2000) Value of laparoscopic staging for Hodgkin disease. Surg Laparosc Endosc Percutan Tech 10:335–337

Masson P (1956) Tumeurs humaines. Histologie, diagnostics et techniques. Librairie Maloine, Paris, p 272

Mathas S, Lietz A, Anagnostopoulos I, Hummel F, Wiesner B, Janz M, Jundt F, Hirsch B, Johrens-Leder K et al (2004) c-FLIP mediates resistance of Hodgkin/Reed-Sternberg cells to death receptor-induced apoptosis. J Exp Med 199:1041–1052

Matsko GF, Zhukovets AV (1971) Jaundice in lymphogranulomatosis in children (in Russian). Pediatriia 50:40–43

McNulty JG (1971) Diagnosis of extrahepatic jaundice in Hodgkin's disease. Br Med J 4:26–27

Merchant TE, Filippa DA, Yahalom J (1994) Sarcoidosis following chemotherapy for Hodgkin's disease. Leuk Lymphoma 13:339–347

Metkar SS, Manna PP, Anand M, Naresh KN, Advani SH, Nadkarni JJ (2001) CD40 ligand – an anti-apoptotic molecule in Hodgkin's disease. Cancer Biother Radiopharm 16:85–92

Meyer O (1911) Beiträge zur Klinik, Pathogenese und pathologischen Anatomie des malignen Granuloms. Frankfurt Zschr Pathol 8:343–400

Michalitschke G (1919) Lymphogranulomatose und Ikterus. Wien Med Wochenschr 14:685–687

Michel J, Ardichvili D, Somerhausen M, Kenis Y, Heuson JC (1973) Hodgkin's disease with massive hepatic involvement and uninvolved spleen. Eur J Cancer 9:701–702

Mignot J, Bergue A, Baviera E, Malod-Panisset A (1979) Quantitative study of hepatic fibrosis i Hodgkin's disease (in French). Pathol Biol (Paris) 27:229–232

Mohamed G, Vrzalikova K, Cader FZ, Vockerodt M, Nagy E, Flodr P, Yap LF, Diepstra A et al (2014) Epstein-Barr virus, the germinal centre and the development of Hodgkin's lymphoma. J Gen Virol 95:1861–1869

Morgagni GB (1761) De sedibus et causis morborum per anatomen indagatis libri quinque, 2 vols, venice, typog. Remondiniana, 3 vols. edition in 1779, Yverdon (Ebroduni in Helvetia)

Mori D, Matsuishi E, Akashi M, Shibaki M, Hirano T, Ide M, Tsutsumi Y, Tsukiji H, Gondo H (2014) Hodgkin-like peripheral T-cell lymphoma (PTCL) with preserved Hodgkin-like lesions at autopsy: a case report with an interesting clinical course. Pathol Res Pract. doi:10.1016/j.prcp.2014.08.016

Munker R, Stengel A, Stabler A, Hiller E, Brehm G (1995) Diagnostic accuracy of ultrasound and computed tomography in the staging of Hodgkin's disease. Verification by laparotomy in 100 cases. Cancer 76:1460–1466

Murchison C (1869) "Lymphatic new formations" in the liver, with enlargement of the spleen and persistent jaundice, in a child aged 12. Trans Pathol Soc London 20:198–203

Murray GR (1908) Lymphadenoma. In: Allbutt C, Rolleston HD (eds) A system of medicine, vol 4, Part I. Macmillan, London, pp 459–481

Murray PG, Qiu GH, Fu L, Waites ER, Srivastava G, Heys D, Agathanggelou A, Latif F, Grundy RG et al (2004) Frequent epigenetic inactivation of the RASSF1A tumor suppressor gene in Hodgkin's lymphoma. Oncogene 23:1326–1331

Muschen M, Re D, Brauninger A, Wolf J, Hansmann ML, Diehl V, Küppers R, Rajewski K (2000) Somatic mutations of the CD95 gene in Hodgkin and Reed-Sternberg cells. Cancer Res 60:5640–5643

Muta H, Boise LH, Fang L, Podack ER (2000) CD30 signals integrate expression of cytotoxic effector molecules, lymphocyte trafficking signals, and signals for proliferation and apoptosis. J Immunol 165:5105–5111

Nadel EM, Ackerman LV (1950) Lesions resembling Boeck's sarcoid in lymph nodes draining an area containing a malignant neoplasm. Am J Clin Pathol 20:952–957

Nader K, Mok S, Kalra A, Harb A, Schwarting R, Ferber A (2013) Vanishing bile duct syndrome as a manifestation of Hodgkin's lymphoma: a case report and review of the literature. Tumori 99:e164–e168

Naeim F, Waisman J, Coulson WF (1974) Hodgkin's disease: the significance of vascular invasion. Cancer 34:655–662

Nakatsuka S, Aozasa K (2006) Epidemiology and pathologic features of Hodgkin lymphoma. Int J Hematol 83:391–397

Nam SY, Cho KS, Heo YM, Ha JC, Kim YH, Keun YH, Han HP, Kim HM, Podack ER (2002) Regulation of lymphocyte clustering by CD30-mediated ICAM-1 up-regulation. Cell Immunol 219:38–47

Nemets et al (2003) http://www.ncbi.nlm.nih.gov/pubmed/14959863

Neiman et al (1973) http://www.ncbi.nlm.nih.gov/pubmed/4688713

Newman B, Pushkin W (1951) Acute fulminating Hodgkin's disease. J Am Med Assoc 146:335–337

Ochoa JI, Keene WR (1970) Obstructive jaundice in Hodgkin's disease due to infiltration of the biliary ducts. J Fla Med Assoc 57:21–23

O'Connell MJ, Schimpff SC, Kirschner RH, Abt AB, Wiernik PH (1975) Epithelioid granulomas in Hodgkin disease. A favorable prognostic sign? JAMA 233:886–889

Oelmann E, Herbst H, Zuhlsdorf M, Albrecht O, Nolte A, Schmitmann C, Manzke O, Diehl V et al (2002) Tissue inhibitor of metalloproteinases 1 is an autocrine and paracrine survival factor, with additional immune-regulatory functions, expressed by Hodgkin/Reed-Sternberg cells. Blood 99:258–267

Okazaki A, Niibe H, Mitsuhashi N, Ito J, Nakajima N, Saito Y, Tamaki Y, Nagai T, Machinami R, Sakata N (1985) CT and pathologic studies on detecting hepatic involvement of malignant lymphoma (in Japanese). Gan No Rinsho 31:494–500

Olnes M, Alli P, Freedman A, Auster M, Erlich R (2003) Hematologic malignancies with extramedullary spread of disease. Case 3. Extra-nodal Hodgkin's disease presenting as rapidly progressive liver failure. J Clin Oncol 21:1890–1891

Omidvari SH, Khojasteh HN, Mohammadianpanah M, Monabati A, Mosalaei A, Ahmadloo N (2004) Long-term pruritus as the initial and sole clinical manifestation of occult Hodgkin's disease. Indian J Med Sci 58:250–252

Opeskin K, Burke M, McCaffrey G, Nandurkar H (2003) Hodgkin's disease associated cholestasis in a man with thymoma. Pathology 35:349–351

Ozkan A, Yoruk A, Celkan T, Apak H, Yildiz I, Ozbay G (2001) The vanishing bile duct syndrome in a child with Hodgkin disease. Med Pediatr Oncol 36:398–399

Padhi S, Paul TR, Challa S, Prayaga AK, Rajappa S, Raghunadharao D, Sarangi R (2012) Primary extra-nodal non Hodgkin lymphoma: a 5 year retrospective analysis. Asian Pac J Cancer Prev 13:4889–4895

Pak HY, Friedman NB (1981) Pseudosarcoid granulomas in Hodgkin's disease. Hum Pathol 12:832–837

Paltauf R (1897) Lymphosarkom (Lymphosarkomatose, Pseudoleukämie, Myelom, Chlorom). Ergebn Allg Pathol Pathol Anat Menschen Tiere 3:652–691

Pappa VI, Norton AJ, Gupta RK, Wilson AM, Rohatiner AZ, Lister TA (1995) Nodular type of lymphocyte

predominant Hodgkin's disease. A clinical study of 50 cases. Ann Oncol 6:559–565
Pariente D, Cornud F, Grenier P, Degos F, Nahum H (1981) Involvement of the common bile duct in Hodgkin's disease: report of three cases (in French). Sem Hop 57:2027–2030
Pasquier J, Pauchard J, Lesbros F, Descos L, Feroldi J, Scotto J (1973) Hodgkin's disease with principal hepatic localization and peliosis lesions. Apropos of a case (in French). Sem Hop 49:2301–2304
Pass AK, McLin VA, Rishton JR, Kearney DL, Hastings CA, Margolin JF (2008) Vanishing bile duct syndrome and Hodgkin disease: a case series and review of the literature. J Pediatr Hematol Oncol 30:976–980
Peiser H (1913) Zur Kasuistik der akuten Lymphogranulomatose. Med Klin 42:1719–1721
Pel PK (1885) Zur Symptomatologie der sogenannten Pseudo-Leukämie. Berl Klin Wochenschr 22:3–7
Pène P (1952) Foie et lymphogranulomatose de Hodgkin. Gaz Med Fr 59:1245–1250
Pène P, du Paquier P, Alium F, Pène JA (1955) Forme hépatosplénomégalique prédominante de la maladie de Hodgkin. Bordeaux Chir 2:93–94
Pennanen H, Kuittinen O, Soini Y, Turpeenniemi-Hujanen T (2004) Clinicopathological correlations of TIMP-1 and TIMP-2 in Hodgkin's lymphoma. Eur J Haematol 72:1–9
Perera DR, Greene ML, Fenster LF (1974) Cholestasis associated with extrabiliary Hodgkin's disease. Report of three cases and review of four others. Gastroenterology 67:680–685
Piken EP, Abraham GE, Hepner GW (1979) Investigation of a patient with Hodgkin's disease and cholestasis. Gastroenterology 77:145–147
Piro AJ, Hellman S, Moloney WC (1972) The influence of laparotomy on management decisions in Hodgkin's disease. Arch Intern Med 130:844–848
Pittman CE, Buss DH, Sterchi JM (1988) Detection of liver involvement in Hodgkin's disease. J Surg Oncol 38:265–266
Priesel A, Winkelbauer A (1926) Placentare Uebertragung des Lymphogranulomas. Virchows Arch Pathol Anat Physiol Klin Med 262:749–765
Rappaport H, Strum SB (1970) Vascular invasion in Hodgkin's disease: its incidence and relationship to the spread of the disease. Cancer 25:1304–1313
Rappaport H, Strum SB, Hutchison G, Allen LW (1971) Clinical and biological significance of vascular invasion in Hodgkin's disease. Cancer Res 31:1794–1798
Razemon P, Salembier Y, Meignie P (1961) Compression of the bile ducts by adenopathies in Hodgkin's disease (in French). Arch Mal Appar Dig Mal Nutr 50:374–376
Re D, Thomas RK, Behringer K, Diehl V (2005) From Hodgkin's disease to Hodgkin lymphoma: biological insights and therapeutic potential. Blood 105:4553–4560
Reddy N, Thompson-Arildsen MA (2010) Hodgkin's lymphoma: Richter's transformation of chronic lymphocytic leukemia involving the liver. J Clin Oncol 28: e543–e544
Reed D (1902) On the pathological changes in Hodgkin's disease, with especial reference to its relation to tuberculosis. Johns Hopkins Hosp Rep (Baltimore) 10:133–196
Rengstl B, Rieger MA, Newrzela S (2014) On the origin of giant cells in Hodgkin lymphoma. Community Integr Biol 7:e28602
Riccardi A, Montecucco CM, Cresci R, Mazzini G, Ascari E, Perugini S (1980) Cytokinetic studies on circulating neoplastic cells of Hodgkin's disease. Basic Appl Histochem 24:109–120
Ripoll C, Carretero L, Sabin P, Alvarez E, Marrupe D, Banares R (2002) Idiopathic cholestasis associated with progressive ductopenia in two patients with Hodgkin's disease (in Spanish). Gastroenterol Hepatol 25:313–315
Roberts KJ, Brown R, Patel JV, Toogood GJ (2012) Biliary and portal vein strictures following treatment of Hodgkin's lymphoma. Ann R Coll Surg Engl 94: e225–e226
Rodig SJ, Savage KJ, Nguyen V, Pinkus GS, Shipp MA, Aster JC, Kutok JL (2005) TRAF1 expression and c-Rel activation are useful adjuncts in distinguishing classical Hodgkin lymphoma from a subset of morphologically or immunophenotypically similar lymphomas. Am J Surg Pathol 29:196–203
Rolleston HD (1912) Diseases of the liver, gallbladder and bile-ducts, 2nd edn. Macmillan, London
Rosenberg SA, Kaplan HS (1970) Hodgkin's disease and other malignant lymphomas. Calif Med 113:23–28
Rossini MS, Lorand-Metze I, Oliveira GB, Souza CA (2000) Vanishing bile duct syndrome in Hodgkin's disease: case report. Sao Paulo Med J 118:154–157
Rowbotham D, Wendon J, Williams R (1998) Acute liver failure secondary to hepatic infiltration: a single centre experience of 18 cases. Gut 42:576–580
Rueffer U, Sieber M, Stemberg M, Gossmann A, Josting A, Koch T, Grotenhermen F, Diehl V, German Hodgkin's Lymphoma Study Group (GHSG) (2003) Spleen involvement in Hodgkin's lymphoma: assessment and risk profile. Ann Hematol 82:390–396
Russell BRG (1914) Drei bemerkenswerte Fälle von Lymphogranulomatose. Ziegler's Beitr Pathol Anat 58:516–553
Sacks EL, Donaldson SS, Gordon J, Dorfman RF (1978) Epithelioid granulomas associated with Hodgkin's disease: clinical correlations in 55 previously untreated patients. Cancer 41:562–567
Sakata K, Satoh M, Someya M, Asanuma H, Nagakura H, Oouchi A, Nakata K, Kogawa K, Koito K et al (2004) Expression of matrix metalloproteinase 9 is a prognostic factor in patients with non-Hodgkin lymphoma. Cancer 100:356–365
Sanbe K, Shirato E (1966) Case of common bile duct obstruction caused by Hodgkin's disease (in Japanese). Nippon Rinsho 24:1139–1142
Sanchez-Aguilera A, Delgado J, Camacho FI, Sanchez-Beato M, Sanchez L, Montalban C et al (2004) Silencing of the p18INK4c gene by promoter

hypermethylation in Reed-Sternberg cells in Hodgkin lymphomas. Blood 103:2351–2357
Sans M, Andreu V, Bordas JM, Llach J, Lopez-Guillermo-A, Cervantes F, Bruguera M, Mondelo F et al (1998) usefulness of laparoscopy with liver biopsy in the assessment of liver involvement at diagnosis of Hodgkin's and non-Hodgkin's lymphomas. Gastrointest Endosc 47:391–395
Sayhoun PF, Eisenberg S (1949) Hodgkin's disease, histopathological and clinical classification with radiotherapeutic response. Am J Roentgenol 61:369–379
Schlaifer D, Krajewski S, Rigal-Huguet F, Laurent G, Pris J, Delsol G, Reed JC, Brousset P (1996) Bcl-x gene expression in Hodgkin's disease. Leuk Lymphoma 23:143–146
Schmitz R, Stanelle J, Hansmann ML, Küppers R (2009) Pathogenesis of classical and lymphocyte-predominant Hodgkin lymphoma. Annu Rev Pathol 4:151–174
Schmorl K (1922) Case presentation before the Gesellschaft für Natur und Heilkunde zu Dresden, on 20 March 1922. Münch Med Wochenschr 69:908
Schoenlank FW (1916) Ein Fall von Peliosis hepatis. Virchows Arch [A] 222:358–364
Sherlock S (1955) Diseases of the liver and biliary system. Blackwell, Oxford
Siebert JD, Stuckey JH, Kurtin PJ, Banks PM (1995) Extranodal lymphocyte predominance Hodgkin's disease. Clinical and pathologic features. Am J Clin Pathol 103:485–491
Simonds JP (1926) Hodgkin's disease. Arch Pathol (Chicago) 1:394–430
Skovsgaard T, Brinckmeyer LM, Vesterager L, Thiede T, Nissen NI (1982) The liver in Hodgkin's disease – II. Histopathologic findings. Eur J Clin Oncol 18:429–435
Smith LB (2010) Nodular lymphocyte predominant Hodgkin lymphoma. Diagnostic peals and pitfalls. Arch Pathol Lab Med 134:1434–1439
Smolewski P, Niewiadomska H, Los E, Robak T (2000) Spontaneous apoptosis of Reed-Sternberg and Hodgkin cells; clinical and pathological implications in patients with Hodgkin's disease. Int J Oncol 17:603–609
Sperandio S, de Belle I, Bredesen DE (2000) An alternative, nonapoptotic form of programmed cell death. Proc Natl Acad Sci U S A 97:14376–14381
Spinelli P, Beretta G, Bajetta E, Tancini G, Castellani R, Rilke F, Bonadonna G (1975) Laparoscopy and laparotomy combined with bone marrow biopsy in staging Hodgkin's disease. Br Med J 4:554–556
Stahr H, Sywoldt I (1922) Ueber Lymphogranulomatose, insbesondere an den grossen Gallengängen. Med Klin (Berlin) 18:404–409
Stern M, Herrmann R, Rochlitz C, Dirnhofer S, Pless M (2005) A case of post-transplant lymphoproliferative disease presenting as CD20-expressing, Epstein-Barr-virus positive Hodgkin lymphoma. Eur J Haematol 74:267–270
Sternberg C (1898) Ueber eine eigenartige, unter dem Bilde der Pseudoleukämie verlaufende Tuberkulose des lymphatischen Apparates. Zschr Heilkunde (Prague) 19:21–90
Sternberg C (1913) XIII. Leber, Gallenblase und Gallenwege, Pankreas. In: Aschoff L (ed) Pathologische Anatomie. Ein Lehrbuch für Studierende und Aerzte, 3rd edn. Gustav Fischer, Jena, p 893
Sternberg C (1936) Lymphogranulomatose und Reticuloendotheliose. Ergebn AllgPathol Pathol Anat 30:1–76
Stolzenbach G, Garbrecht M, Mertelsmann R, Kastendieck H (1976) Coincidence of Hodgkin's disease and epithelioid-cell granulomatosis in liver and spleen (in German). Dtsch Med Wochenschr 101:709–711
Strum SB, Allen LW, Rappaport H (1971) Vascular invasion in Hodgkin's disease: its relationship to involvement of the spleen and other extranodal sites. Cancer 28:1329–1334
Su CC, Chiu HH, Chang CC, Chen JC, Hsu SM (2004) CD30 is involved in inhibition of T-cell proliferation by Hodgkin's Reed-Sternberg cells. Cancer Res 64:2148–2152
Sulkes A, Benjamin RS, Luna MA (1979) Liver replacement with Hodgkin's disease, lymphocyte-depletion type, with an uninvolved spleen. Eur J Cancer 15:373–377
Symmers D (1944) Clinical significance of the deeper anatomic changes in lymphoid diseases. Arch Intern Med 74:163–171
Takeshita H, Yoshizaki T, Miller WE, Sato H, Furukawa M, Pagano JS, Raab-Traub N (1999) Matrix metalloproteinase 9 expression is induced by Epstein-Barr virus latent membrane protein 1 C-terminal activation regions 1 and 2. J Virol 73:5548–5555
Tartar VM, Balfe DM (1990) Lymphoma in the wall of the bile ducts: radiologic imaging. Gastrointest Radiol 15:53–57
Thomas RK, Kallenborn A, Wickenhauser C, Schultze JL, Draube A, Vockerodt M, Re D, Diehl V, Wolf J (2002) Constitutive expression of c-FLIP in Hodgkin and Reed-Sternberg cells. Am J Pathol 160:1521–1528
Thomas RK, Re D, Wolf J, Diehl V (2004) Part I: Hodgkin's lymphoma – molecular biology of Hodgkin and Reed-Sternberg cells. Lancet Oncol 5:11–18
Thorns C, Feller AC, Merz H (2002) EMMPRIN (CD 174) is expressed in Hodgkin's lymphoma and anaplastic large cell lymphoma. An immunohistochemical study of 60 cases. Anticancer Res 22:1983–1986
Thorns C, Bernd HW, Hatton D, Merz H, Feller AC, Lange K (2003) Matrix-metalloproteinases in Hodgkin lymphoma. Anticancer Res 23:1555–1558
Toncini C, Venzano C (1981) Localization of Hodgkin's lymphoma in hepatic angiomas (in Italian). Pathologica 73:827–829
Tornero C, Laparra E, Jimenez A, Ricart C, Pastor A, Rull S (1998) Acute hepatic failure and Hodgkin's disease (in Spanish). An Med Interna 15:654–655
Trewby PN, Portmann B, Brinkley DM, Williams R (1979) Liver disease as presenting manifestation of Hodgkin's disease. Q J Med 48:137–150

Trudel MA, Krikorian JG, Neiman RS (1987) Lymphocyte predominance Hodgkin's disease: a clinicopathologic reassessment. Cancer 59:99–106

Tudor CS, Bruns H, Daniel C, Distel LV, Hartmann A, Gerbitz A, Buettner MJ (2014) Macrophages and dendritic cells as actors in the immune reaction of classical Hodgkin lymphoma. PLoS One 9:e114345

Tzankov A, Zimpfer A, Went P, Maurer R, Pileri SA, Geley S, Dirnhofer S (2005) Aberrant expression of cell cycle regulators in Hodgkin and Reed-Sternberg cells of classical Hodgkin's lymphoma. Mod Pathol 18:90–96

Uddströmer M (1934) On the occurrence of lymphogranulomatosis (Sternberg) in Sweden 1915–1931 and some considerations as to its relation to tuberculosis. Acta Tuberc Scand (Suppl 1):1–225

Urayama KY, Jarrett RF, Hjalgrim H, Diepstra A, Kamatani Y, Chabrier A, Gaborieau V, Boland A et al (2012) Genome-wide association study of classical Hodgkin lymphoma and Epstein-Barr virus status-defined subgroups. J Natl Cancer Inst 104:240–253

Urbano-Marquez A, Grau Junyent JM, Sala M, Estruch R, Bruguera M, Rozman C (1981) Hodgkin's disease presenting as a hepatic disease. Report of two cases (in Spanish). Med Clin (Barc) 76:255–258

Vadillo Serrano M, Las Heras G, Badia F, Puig I (2002) Hodgkin's disease presenting as severe acute liver failure (in Spanish). Med Clin (Barc) 119:677

Van Spronsen DJ, Veldhuis GJ (2003) New developments in staging and follow-up of patients with Hodgkin's lymphoma. Neth J Med 61:278–284

Van Spronsen DJ, Peh SC, Vrints LW, van Imhoff GW, Poppema S (2000) Clinical drug-resistant nodular sclerosing Hodgkin's lymphoma is associated with decreased bcl-2 expression in the surrounding lymphocytes and with increased bcl-2 expression in the Reed-Sternberg cells. Histopathology 37:420–426

Varadi S (1955) Hodgkin's disease: specific findings in sternal puncture material. Br J Haematol 1:184–188

Varadi S (1960) Reed-Sternberg cells in the peripheral blood and bone marrow in Hodgkin's disease. Br J Med 1:1239–1243

Vardarelli E, Dundar E, Aslan V, Gulbas Z (2004) Acute liver failure due to Hodgkin's lymphoma. Med Princ Pract 13:372–374

Vassallo J, Metze K, Traina F, de Sousa CA, Lorand-Metze I (2003) The prognostic relevance of apoptosis-related proteins in classical Hodgkin's lymphomas. Leuk Lymphoma 44:483–488

Von Hüttenbrenner A (1871) Zwei Fälle von harten Lymphomen bei Kinder. Jahrb Kinderheilk 4:157–165

Von Jaksch R (1913) Klinische Beiträge zur Kenntnis der Lymphogranulomatose. Dtsch Arch Klin Med 3:503–529

Von Tresckow B, Kallen KJ, von Strandmann EP, Borchmann P, Lange H, Engert A, Hansen HP (2004) depletion of cellular cholesterol and lipid rafts increases shedding of CD30. J Immunol 172:4324–4331

Wakisaka N, Pagano JS (2003) Epstein-Barr virus induces invasion and metastasis factors. Anticancer Res 23:2133–2138

Wallhauser A (1933) Hodgkin's disease. Arch Pathol 41:522–562

Wang C, Deng X, Li X, Gu H, Yi W, Wenig X, Xia L, Cao Y (2002) Matrix metalloproteinase 9 expression is induced by Epstein-Barr virus LMP1 via NF-kappa B or AP-1 signaling pathway in nasopharyngeal carcinoma cells (in Chinese). Zhongghua Zhong Liu Za Zhi 24:9–13

Warner AS, Whitcomb FF (1994) Extrahepatic Hodgkin's disease and cholestasis. Am J Gastroenterol 89:940–941

Wee GC, Hagen G, Torres A, Shieber W (1970) Hodgkin's disease of the cystic node as a cause of nonvisualization of the gallbladder. Am J Gastroenterol 54:272–276

Weinberg F (1917) Lymphogranuloma tuberculosum. Zschr Klin Med 85:99–166

Weiner G, Hoew SE, Mallory A (1994) hepatic failure from Hodgkin0s disease in a patient with HIV infection. J Clin Gastroenterol 18:88–89

Wilks S (1856) Cases of a peculiar enlargement of the lymphatic glands frequently associated with disease of the spleen. Guys Hosp Rep 2:114

Wilks S (1865) Cases of enlargement of the lymphatic glands and spleen (or, Hodgkin's disease) with remarks. Guys Hosp Rep 11:56

Wolf J, Kapp U, Bohlen H, Kornacker M, Schoch C, Stahl B, Mucke S, von Kalle C, Fonatsch C et al (1996) Peripheral blood mononuclear cells of a patient with advanced Hodgkin's lymphoma give rise to permanently growing Hodgkin-Reed Sternberg cells. Blood 87:3418–3428

Woolf KM, Wei MC, Link MP, Arber DA, Warnke RA (2008) Nodular-lymphocyte-predominant Hodgkin lymphoma presenting as fulminant hepatic failure in a pediatric patient: a case report with pathologic, immunophenotypic, and molecular findings. Appl Immunohistochem Mol Morphol 16:196–201

Xerri L, Palmerini F, Devilard E, Defrance T, Bouabdallah R, Hassoun J, Birg F (2000) Frequent nuclear localization of ICAD and cytoplasmic co-expression of caspase-8 and caspase-3 in human lymphomas. J Pathol 192:194–202

Yalcin S, Kars A, Sokmensuer C, Atahan L (1999) Extrahepatic Hodgkin's disease with intrahepatic cholestasis: report of two cases. Oncology 57:83–85

Yamasaki M (1904) Zur Kenntnis der Hodgkin'schen Krankheit und ihres uebergangs in Sarkom. Zschr Heilkde 25:268

Yokomori H, Kaneko F, Sato A, Takeuchi H, Tahara K, Motoori T, Sekiguchi Y, Mori S, Tamaru J et al (2008) Primary hepatic presentation of Hodgkin's lymphoma: a case report. Hepatol Res 38:1054–1057

Yoshizaki T (2002) Promotion of metastasis in nasopharyngeal carcinoma by Epstein-Barr virus latent membrane protein-1. Histol Histopathol 17:845–850

Yoshizaki T, Sato H, Furukawa M, Pagano JS (1998) The expression of matrix metalloproteinase 9 is enhanced by Epstein-Barr virus latent membrane protein 1. Proc Natl Acad Sci U S A 95:3621–3626

Yoshizaki T, Sato H, Murono S, Pagano JS, Furukawa M (1999) Matrix metalloproteinase 9 is induced by the Epstein-Barr virus BZLF1 transactivator. Clin Exp Metastasis 17:431–436

Yuan K, Hong TM, Chen JJ, Tsai WH, Lin MT (2004) Syndecan-1 up-regulated by ephrinB2/EphB4 plays dual roles in inflammatory angiogenesis. Blood 104:1025–1033

Yusuf MA, Elias E, Hubscher SG (2000) Jaundice caused by the vanishing bile duct syndrome in a child with Hodgkin lymphoma. J Pediatr Hematol Oncol 22:154–157

Zaman et al (1991) http://www.ncbi.nlm.nih.gov/pubmed/1885082

Zheng B, Georgakis GV, Li Y, Bharti A, McConkey D, Aggarwal BB, Younes A (2004) Induction of cell cycle arrest and apoptosis by the proteasome inhibitor PS-341 in Hodgkin disease cell lines is independent of inhibitor of nuclear factor-kappaB mutations or activation of the CD30, CD40, and RANK receptors. Clin Cancer Res 10:3207–3215

Ziegler K (1911) Die Hodgkinsche Krankheit. Gustav Fischer Verlag, Jena