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ORIGINAL ARTICLE

Comparison of clinical diagnoses and autopsy findings in 54 cases with lymphoid neoplasms

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Abstract

There are few systematic analyses on autopsy findings of patients with lymphoid neoplasms. Autopsy cases with ($n = 54$) and without ($n = 50$) lymphoid neoplasms were compared for this study. Neoplasms found were B cell lymphomas ($n = 30/54$, 56%), plasmacytomas ($n = 15/54$, 28%), T cell lymphomas ($n = 7/54$, 13%), Hodgkin lymphomas ($n = 2/54$, 3%) and solid tumours ($n = 7/54$, 13%). In the control group, 12/50 (24%) cases had solid tumours. Autopsy alone identified the previously unknown lymphoid neoplasm in 10/54 (18%) cases, whilst only 1/50 (2%) previously unknown carcinoma was found in the control group. Cardiac/respiratory failure was the most frequent cause of death in the lymphoid neoplasm group ($n = 35/54$, 65%) as well as in the control group ($n = 36/50$, 72%). In 8/54 (15%) cases with lymphoid neoplasms and 5/50 (10%) control cases, class I discrepancies were found. This study shows the high rate of autopsy-verified lymphoid neoplasms and unrecognised co-morbidities.

Keywords Autopsy · Post-mortem examination · Lymphoma · Plasmacytoma

Introduction

The diagnosis of lymphomas and plasmacytomas is a routine procedure during a patient's life time and there rarely is a demand for autopsy after patients have died. In case of severely ill patients, however, death may occur before a diagnosis has been established and autopsy can reveal previously unknown tumours and complications which led to death. It is well known that the rate of discrepancies between clinical diagnosis and autopsy findings is approximately 10–30%. However, the rate of autopsies decreases constantly [1, 2]. There are few systematic studies on autopsy-verified causes of death in patients with lymphoid neoplasms. Some studies are more than 25 years old and do not reflect modern diagnostic procedures and therapy options [3–6]. More recent studies seem to be biased by their inclusion criteria, e.g. a particular organ involvement or only post-transplant lymphoproliferative diseases (PTLD) [7–9]. Most of these studies have no control group without haematological neoplasms. The aim of the current study was to provide a more general characterisation. Thus, all types of lymphoid neoplasms as well as a control group were included. From our experience, autopsies are often rejected because the clinical diagnosis is "death due to lymphoma/plasmacytoma". By addressing clinically relevant questions, we intended to provide a rationale for initiating an autopsy, even if a lymphoid neoplasm had already been diagnosed. Therefore, the underlying study was designed to focus mainly on the cause of death and its association with the lymphoid neoplasm. A further objective was to analyse if certain subtypes of lymphoid neoplasms are more often diagnosed by autopsy than others. Finally, we aimed to evaluate the frequency of discrepancies of clinical and post-mortem diagnoses.

Materials and methods

Study cohort

Data was collected from autopsy reports from the archive of the Institute of Pathology at Hannover Medical School

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(MHH) within an arbitrary time interval (2006–2016). The retrospective study was approved by the local ethics committee (no. 2893-2015). Inclusion criteria (n total = 104): either present at autopsy or history of any lymphoid neoplasm (n = 54/104). A control group without lymphoid neoplasms (n = 50/104) was matched by age. Exclusion criteria for both were myeloid neoplasms.

Autopsies were performed in a standardised fashion [10] and included cranial, thoracic and abdominal preparations and macroscopic inspection. In all cases, heart, lungs, liver, spleen, gastrointestinal tract, kidneys and vertebral bone marrow were histologically evaluated (minimum of 15 tissue samples, haematoxylin and eosin as standard staining, Elastica van Gieson for lung tissues, periodic acid-Schiff for lung and kidney tissues, iron staining for lung, liver and spleen tissues, Giemsa for bone marrow tissues). In cases with tumour formation, bleeding or suspicious cervical/supraclavicular, paraaortal and inguinal lymphadenopathy (> 1 cm), additional histology was applied. Immunohistochemistry and PCR were used if applicable.

Analysis of data

The following parameters were analysed: age, sex, body height, body and organ weights, pathological findings, type of lymphoid neoplasm, any other solid tumour, time between diagnosis of lymphoid neoplasm and death, immunosuppression/transplantation status and cause of death. We took into account that death is a multifactorial process which is influenced by different co-morbidities, therapy modalities and therapy durations in each individual patient. We re-evaluated all available clinical notes and subdivided all cases according to the most probable leading cause of death: failure of central nervous system, heart, lung, liver or kidney function, sepsis or haemorrhage/non-cardiac infarction. Sepsis was diagnosed only in cases with histologic septicopyaemic lesions. If more than one organ system was involved, the most severe pathologic condition was classified as the leading cause of death. Direct cause of death by the lymphoid neoplasm was defined as infiltration of tumour cells or amyloidosis in the organ with the leading failure of function.

For evaluation of the discrepancy between clinical diagnosis and autopsy findings, cases were grouped according to the Goldman criteria [11]: (i) class I error, misdiagnosis that may have affected survival and probably would have required alteration of treatment; (ii) class II error, misdiagnosis that did not affect survival and would not have required alteration of treatment; (iii) congruent or almost congruent clinical diagnosis and autopsy findings (including class III/IV errors, missed minor diagnoses unrelated to the disease course).

Statistical analyses of age and organ weights were performed with Prism 5.0 (GraphPad Software, San Diego, CA, USA).

Results

Tumour subtypes and risk factors in patients with lymphoid neoplasms

Lymphoid neoplasms were mainly B cell lymphomas (B-NHL) and plasmacytomas and less often high-grade T-NHL and Hodgkin lymphomas (Table 1). Comparison of organ weights revealed no differences between the lymphoid neoplasm and control groups ($p > 0.05$).

In the lymphoid neoplasm group, 6/54 (11%) had an infection with human immunodeficiency virus (HIV; n = 5/6 high-grade B-NHL, n = 1/6 plasmacytoma). In the control group, there was 1/50 (2%) patient with HIV infection (Table 2).

In total, 4/54 (7%) patients underwent transplantation before manifestation of a lymphoid neoplasm, but only three were classified as monomorphic PTLD (diffuse large B cell lymphomas after lung transplantation in two patients and bone marrow transplantation in a patient with aplastic anaemia). In one liver-transplanted patient, an Epstein-Barr virus (EBV)-negative low-grade B-NHL manifested that was classified as incidental and not as monomorphic PTLD according to the WHO classification [12].

Solid tumours

In addition to lymphoid neoplasms, solid tumours manifested in 7/54 (13%) patients. Of these cases, 4/7 had remission of carcinomas and 3/7 had tumours at autopsy, including two metastatic carcinomas and one unusual collusion tumour (HIV-positive patient with EBV-positive high-grade B-NHL in combination with an EBV-negative low grade smooth muscle actin-positive spindle cell tumour in the lung) (Table 1, Fig. 1).

In the control group, 12/50 (24%) cases had solid tumours: of these 4/12 with residual (apT3/4) or metastatic carcinomas at autopsy and the rest with an apT0 stage (Table 1).

Frequency of clinically inapparent, suspected and known lymphoid neoplasms

In the lymphoma cohort, a total of 10/54 (18%) cases were primarily diagnosed by autopsy findings: high-grade B-NHL (n = 6; including 1/6 intravascular lymphoma), low-grade B-NHL (n = 2), T-NHL (n = 1) and Hodgkin lymphoma (n = 1) (Table 1, Fig. 1).

In 15/54 cases, a lymphoid neoplasm had been suspected shortly before death (≤ 1 month) and the diagnosis was verified by autopsy: high-grade B-NHL (n = 4; including 1/4 intravascular lymphoma), plasmacytomas (n = 7; 3/7 with clinically known amyloidosis) and T-NHL (n = 4). In one patient, a Hodgkin lymphoma was diagnosed one week before death in lymph node and spleen specimens, but no residual tumour

Table 1 Known neoplasms versus diagnosis of clinically unknown neoplasms at autopsy

	Cases with lymphoid neoplasms ($n = 54$)			Control cases ($n = 50$)		
	Tumour diagnosis (n)			Tumour diagnosis (n)		
	At autopsy	≤ 1 month before death	> 1 month before death (median, range)	At autopsy	≤ 1 month before death	> 1 month before death
Low-grade B-NHL, $n = 10$	2	0	8 (66 months, 5–236 months)	–	–	–
High-grade B-NHL, $n = 20$	6 (see legend, #1)	4	10 (15.5 months, 3–144 months; remission at autopsy, $n = 5/10$)	–	–	–
Plasmacytoma, $n = 15$	0	7	8 (37 months, 3–199 months)	–	–	–
T-NHL, $n = 7$	1	4	2 (3 and 63 months; both remission at autopsy)	–	–	–
Hodgkin lymphoma, $n = 2$	1	1 (remission at autopsy)	0	–	–	–
Lung carcinoma	0	0	0	1 (see legend, #2)	2 (remission at autopsy, $n = 1/2$)	1 (9 months)
GI/hepatic carcinoma	0	2 (remission at autopsy, $n = 1/2$)	1 (21 months)	1 (see legend, #2)	5 (remission at autopsy, $n = 3/5$)	1 (2 months; remission at autopsy)
Gynaecologic/urologic carcinoma	0	0	2 (20 and 72 months; both remission at autopsy)	0 0	0	1 (36 months; remission at autopsy)
Other tumours (see legend)	1	0	1 (48 months; remission at autopsy)	0	0	1 (2 months; remission at autopsy)

Regarding high-grade B-NHL: In one patient (#1), a low-grade B-NHL was known since 34 months but at autopsy, a transformation into an intravascular high-grade B-NHL was found (see Fig. 1). Lymphoma group, carcinomas: Three low-grade B-NHL patients with breast carcinoma (apT0, apM0), oesophageal carcinoma (apT0, apM0) or colon carcinoma (apT0, apM1-HEP); two plasmacytoma patients with renal cell carcinoma (apT0, apM0) or oesophageal carcinoma (apT3, apM1-HEP). Control group, carcinomas: Two patients with lung squamous cell carcinomas (apT4, apM1; apT0, apM1); one patient with two simultanious carcimomas (#2), a lung squamous cell carcinoma (apT4, apM1) and a hepatocellular carcinoma (apT1, apM0); one patient with lung non-small cell adenocarcinoma (apT0, apM0); two patients with biliary duct or gall bladder carcinomas (apT3, apM0; apT0, apM0); two patients with oesophageal or pancreatic carcinomas (both apT0, apM0); one patient with appendiceal carcinoma (apT4, apM0); one patient with cervical carcinoma (apT0, apM0). Lymphoma group, other tumours: One HIV patient with high-grade B-NHL and low grade spindle cell tumour (at autopsy); one patient with plasmacytoma and no residual tumour after resection of bilateral ovarian serous border line tumours. Control group, other tumours: One patient with no residual tumour after resection of pituitary adenoma

Table 2 Clinico-pathologic characteristics

	Cases with lymphoid neoplasms ($n = 54$)	Control cases ($n = 50$)
Sex (female/male)	12/42 (22%/78%)	16/34 (32%/68%)
Age	median 57.5 years (range 24–84 years)	median 61.5 years (range 31–82 years)
HIV (see legend)	6/54 (11%)	1/50 (2%)
Transplantation before tumour	4/54 (7%)	6/50 (12%)
Tumour diagnosis at autopsy	10/54 (18%)	1/50 (2%)
Tumour diagnosis ≤ 1 month before death	16/54 (30%)	7/50 (14%)
Tumour diagnosis > 1 month before death	28/54 (52%; median 37 months, range 3–236 months)	4/50 (8%; median 9 months, range 1.5 months to ~ 3 years)

Lymphoid neoplasm group, virus infection: hepatitis C virus (HCV, $n = 2/54$, one with HIV coinfection), hepatitis B virus (HBV, $n = 1/54$). Control group, virus infection: HCV ($n = 1/50$), HBV ($n = 1/50$ with HIV coinfection)

was found at autopsy. Therefore, the frequency of tumour diagnosis ≤ 1 month before death was 30% ($n = 16/54$).

In 28/54 (52%) cases, the lymphoid neoplasms were known for > 1 month (median 37 months, range 3–236 months): high-grade B-NHL ($n = 10$; including previously diagnosed low-grade B-NHL with secondary transformation into a intravascular high-grade B-NHL, which was verified at autopsy), low-grade B-NHL ($n = 8$; 2/8 with clinically known amyloidosis), plasmacytomas ($n = 8$) and T-NHL ($n = 2$).

In the previously mentioned case of a HIV patient, in addition to a high-grade B-NHL, a previously unknown low grade spindle cell tumour was diagnosed at autopsy ($n = 1/54$, 2%), whilst the other six solid tumours were known for a median of 20.5 months (range < 1–72 months) before death.

In control cases, 1/50 (2%) previously unknown metastatic lung carcinoma (apT4, apM1) with simultaneous hepatocellular carcinoma (apT1, apM0) was found at autopsy (clinically suspected pneumonia). The other 11 tumours were known for median < 1 month (range < 1 month to ~ 3 years; $n = 9/11$ died within ≤ 2 months after oncological surgical procedure) (Table 1). One patient without a tumour had a known AA type amyloidosis.

Treatment and remission status in patients with known lymphoid neoplasms

A specific therapy was applied in 20/54 patients with lymphoid neoplasms. In 3/20 patients with lymphoid neoplasm diagnosed shortly before death (≤ 1 month), chemotherapy had been initiated. In 17/20 cases with lymphoid neoplasm diagnosed > 1 month, rituximab with chemotherapy or chemotherapy alone had been administered. In 4/17 of these patients, stem cell transplantation had been performed. In eight patients, no residual lymphoid neoplasms were detectable at autopsy (5/8 high-grade B-NHL, 2/8 T-NHL, 1/8 Hodgkin lymphoma).

Correlation of cause of death with lymphoma localisation

The most frequent cause of death was cardiac/respiratory failure for the lymphoid neoplasm group ($n = 35/54$, 65%) as well as for the control group ($n = 36/50$, 72%) (Table 3).

In the lymphoma group, patients with cardiac failure ($n = 20$) included 3/20 cases with cardiac lymphoma manifestation (two intravascular high-grade B-NHL and one T-NHL) and 3/20 with cardiac amyloidosis. In 3/15 cases with respiratory failure, lymphoid tumour cells infiltrated the lungs. Additional characteristics regarding organ failure and lymphoid tumour cell infiltration are shown in supplementary table 1.

Discrepancy between clinical diagnoses and autopsy findings

Within the lymphoma group and the control cohort, clinical diagnoses were congruent to the autopsy findings in 21/54 (39%) and 26/50 (52%) of cases, respectively.

In 25/54 (46%) patients with lymphoid neoplasms and 19/50 (38%) control cases, class II discrepancies were noted.

In 8/54 (15%) cases with lymphoid neoplasms and 5/50 (10%) control cases, class I discrepancies were found. In the lymphoma group, these consisted of four high-grade B-NHL and each one low-grade B-NHL, plasmacytoma, T-NHL and Hodgkin lymphoma case (Table 3; supplementary table 2).

Discussion

In 18% of the study group, autopsy alone identified the clinically unknown or suspected lymphoid neoplasm, whilst only 2% of previously unknown solid tumours were found primarily by autopsy. It would be expected that indolent low-grade lymphomas are more frequently found as a coincidental disease in autopsies and that organ weights of liver and spleen are higher in patients with lymphomas. In contrast to this, few cases with low-grade lymphomas were newly diagnosed post-mortem and control cases had similar organ weights. Among the 26/54 patients who died shortly before further diagnostic evaluation could be performed or succumbed shortly after diagnosis within ≤ 1 month, we noted that 58% ($n = 15/26$) suffered from high-grade B- or T-NHL. This is concordant to another recently published study (supplementary table 3) [13]. It could be possible that in those cases, a higher

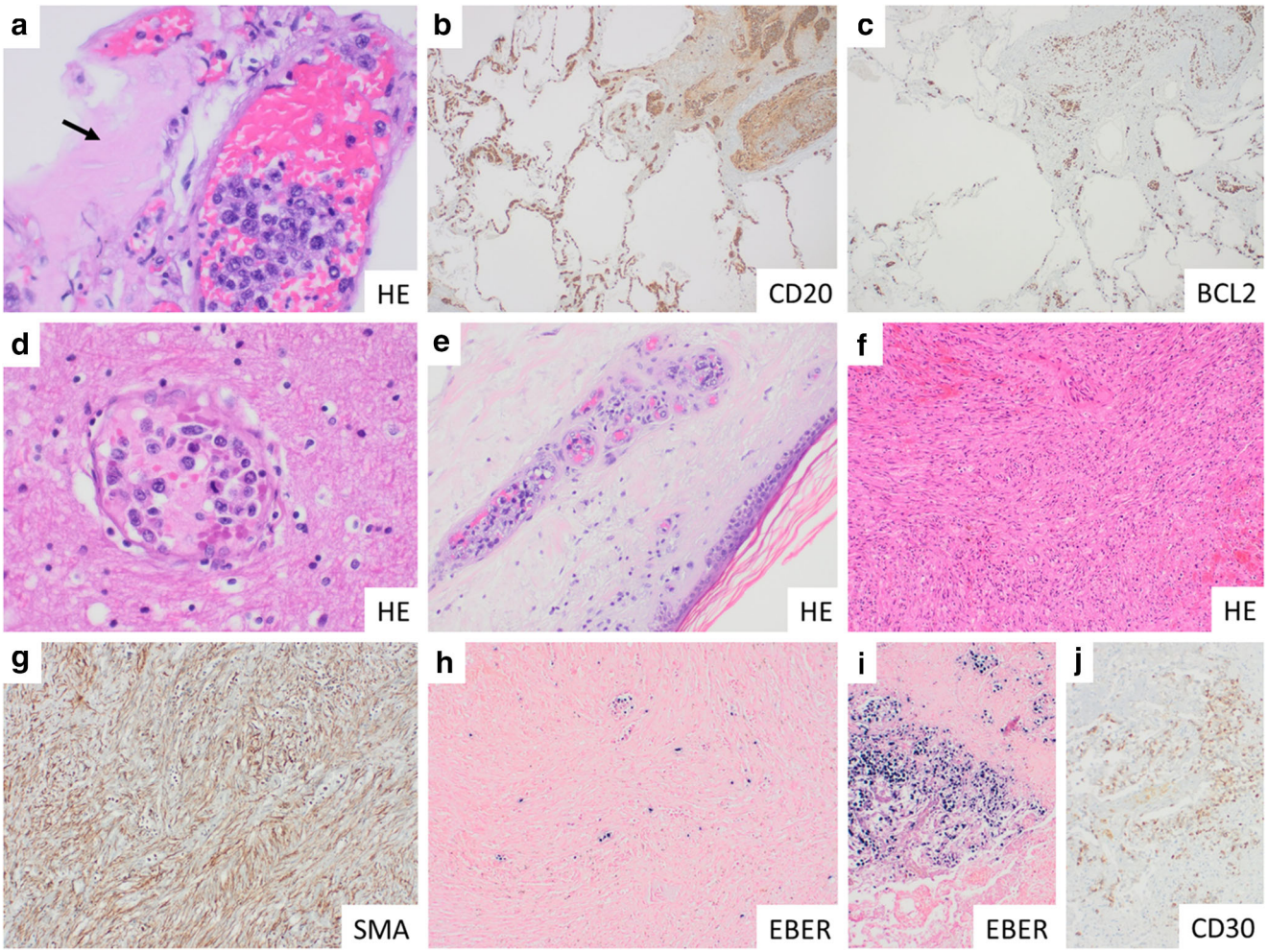

Fig. 1 Previously unknown tumours, diagnosed at autopsy. **a**–**e** In this patient, a B-CLL was known since 34 months, and short before death, a tuberculosis was suspected. Autopsy revealed no residual low-grade B-NHL and no pneumonia but a rare intravascular high-grade B-NHL. Intravascular manifestation in the lungs was associated with acute alveolar oedema (arrow), which indicated acute left ventricular cardiac failure (**a**; magnification × 400). Tumour cells co-expressed CD20 (**b**; × 40), BCL2 (**c**; × 40), partially CD5, partially BCL6 and were negative for CD23 and EBER. In addition, intravascular tumour cells were found in the brain (**d**; × 400), skin (**e**; × 100), gut and kidneys. Note the typical lack of extravascular tumour cell infiltration in all images. **f**–**j** In a HIV patient, a high-grade B-NHL was known since 4 months and the patient succumbed to mycobacterial sepsis with septic lesions in bone marrow and spleen. A previously unknown pulmonary low grade mesenchymal spindle tumour was diagnosed at autopsy (**f**; × 40). Due to autolytic changes, further subclassification was limited, but spindle cells were positive for smooth muscle actin (**g**; × 40) and negative for caldesmon, desmin, CD34, CD31 and EBER (**h**; × 40). At the edge of the spindle cell tumour, the high-grade B cell lymphoma manifested, which was positive for EBER (**i**; × 40), CD30 (**j**; ×40) and lambda, but negative for CD20. Note the intermingled EBER+ lymphoma cells between the spindle cells in image **h**

demand for initiating an autopsy was seen in order to clarify the cause of rapid deterioration.

In two recent studies on autopsy findings in lymphoma patients, respiratory failure manifested often (*n* total = 52/63, 83%; supplementary table 3) [13, 14]. Comparison of autopsy findings in patients with lymphomas or acute myeloid leukaemias revealed no major differences; acute respiratory failure manifested in 88% and 85% of cases, respectively [14]. The majority of cases with clinical diagnosis of acute respiratory failure had autopsy-verified lung lesions such as pneumonia (~ 40–45%), tumour infiltration (~ 20–25%) and thromboembolism (~ 10–15%) [14]. However, some had myocardiac lesions, such as cardiac tumour cell infiltration (~ 10%) [14]. In our cohort, pneumonia was the main cause of lung damage, both in lymphoma and non-lymphoma cases with respiratory failure. Several decades ago, two autopsy studies showed that infections are the main cause of death for patients with several subtypes of lymphoid neoplasms (*n* total = 121/246, 49%) [5, 15]. In another study, which included 156 autopsies from solid organ-transplanted patients and PTLD manifestation, infection was the cause of death in 41% of cases [9]. These included bronchopneumonia, aspergillosis and gastrointestinal infections but few cases with sepsis (4%) [9]. In our cohort, septic

Table 3 Discrepancy between clinical diagnosis and autopsy findings

	Cases with lymphoid neoplasms ($n = 54$)				Control cases ($n = 50$)			
	Autopsy finding	Class I discrepancy	Class II discrepancy	Congruent clinical diagnosis	Autopsy finding	Class I discrepancy	Class II discrepancy	Congruent clinical diagnosis
Cardiac failure (cardiac infiltration by tumour cells, cardiac amyloidosis)	20 (3/20, 3/20)	3/20, 15%	11/20, 55%	6/20, 30%	21 (0/21, 1/21)	2/21, 9.5%	6/21, 28.5%	13/21, 62%
Respiratory failure (pulmonary infiltration by tumour cells)	15 (3/15)	3/15, 20%	8/15, 53%	4/15, 27%	15 (1/15)	2/15, 13%	9/15, 60%	4/15, 27%
Hepatic failure (hepatic infiltration by tumour cells)	6 (2/6)	0	4/6, 67%	2/6, 33%	6 (0/6)	0	2/6, 33%	4/6, 67%
Brain damage (brain infiltration by tumour cells)	1 (1/1)	0	1/1, 100%	0	4 (0/4)	0	2/4, 50%	2/4, 50%
Sepsis (bacterial, fungal)	8 (5/8, 3/8)	1/8, 12.5%	1/8, 12.5%	6/8, 75%	4 (2/4, 2/4)	1/4, 25%	0	3/4, 75%
Intestinal bleeding or infarction (intestinal amyloidosis)	4 (2/4)	1/4, 25%	0	3/4, 75%	0	0	0	0

Lymphoid neoplasm group: class I discrepancy ($n = 8/54$, 15%), class II discrepancy ($n = 25/54$, 46%), congruent clinical diagnosis ($n = 21/54$, 39%). Control group: class I discrepancy ($n = 5/50$, 10%), class II discrepancy ($n = 19/50$, 38%), congruent clinical diagnosis ($n = 26/50$, 52%)

inflammation was relatively rare, too. It has to be taken into consideration that sepsis is a relatively common clinical diagnosis in severely ill patients and that these patients are usually treated accordingly. We restricted the diagnosis of sepsis as the leading cause of death to those cases with septicopyogenic lesions at autopsy. Regarding sepsis, sepsis-like clinical presentation can be masked by a previously unknown lymphoma [16].

It can be assumed that the decrease of autopsies is caused by different factors. Many clinicians do not see the need for autopsies or are afraid that treatment errors could be detected retrospectively [17–21]. The misunderstanding regarding the role of non-legal autopsy is that it serves not to find treatment errors but to clarify which major co-morbidities manifested and to correlate clinical findings with autopsy findings. Based on previous autopsy studies, a general rate of class I discrepancies of 2–20% has to be expected [17–21]. In cases with lymphoid neoplasms, we found a rate of 15% ($n = 8/54$). In a recent autopsy study with a similar number of lymphoma cases, the rate of class I discrepancies was higher (25%; $n = 12/48$) [14]. In some instances advanced disease stages and co-morbidities could be major factors that make diagnoses and differential diagnoses of lymphoid neoplasms difficult during life time. One reason for missing a relevant diagnosis could be that organ biopsies during life time may not have been performed if the risk of complications appeared to be unreasonably high. In addition, biopsies may be non-diagnostic. As discussed by van de Louw et al., the diagnostic yield of lung biopsies could be up to 80% but has to be balanced with a complication rate of up to 30% [14]. Another diagnostic difficulty is manifestation of extremely rare lymphoid neoplasms, e.g. intravascular high-grade B-NHL [22]. The characteristic pattern of intravascular infiltration, which usually lacks tissue infiltration, can be misinterpreted or overlooked, particularly in small biopsies [22]. Intravascular lymphoma cells can lead to increased intravascular obstructions and consecutive cardiopulmonary stress, which can mimic many other neurologic, dermatologic and cardiopulmonary diseases, e.g. respiratory distress [22]. In general, a considerable number of patients with intravascular lymphomas are diagnosed post-mortem by autopsy [22] and all three cases in our cohort were diagnosed at autopsy or shortly before death.

Whilst misdiagnosis may have lead to alteration of therapy, it has to be considered that not all patients may have benefited from this. In patients who are severely ill, it is questionable if modification of therapy would generally be applicable and effective. In addition, therapies have particular side effects which may be fatal, e.g. post-therapy bowel perforation after anti-lymphoma therapy [23]. Another example is the rare

manifestation of an intravascular lymphoma, which generally has a poor prognosis even after ante-mortem diagnosis and therapy [22]. On the one hand, this shows that autopsy can identify class I errors. On the other hand, this does not mandatorily imply a long-lasting survival if the diagnosis was established during a patient`s life time.

In summary, the rationale for initiating an autopsy in patients with suspected lymphoid neoplasms is the relatively high rate of post-mortem-identified diagnoses. Most patients succumbed to complications that were not directly related to the lymphoid neoplasm, and high-grade lymphomas are more often diagnosed shortly before or after death via autopsy than other lymphoid neoplasms. The frequency of class I discrepancies between clinical diagnosis and autopsy findings was 15% in our cohort, which is within the range of previously reported autopsy studies.

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Contributions LA and KH conceived and designed the study. LA collected data and reviewed the literature. LA and KH analysed data. LA, HK and KH wrote, edited and reviewed the manuscript. All authors gave final approval for publication. KH takes full responsibility for the work as a whole, including the study design, access to data and the decision to submit and publish the manuscript.

Compliance with ethical standards

Retrospective evaluation of archived tissues and related data (ethics committee, MHH, no. 2893-2015).

Conflict of interest The authors declare that they have no conflict of interest.

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