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Bilateral Primary Adrenal Non-Hodgkin's Lymphoma – A Case Report and Review of the Literature

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Abstract
Primary adrenal non-Hodgkin's lymphoma (PAL) is a rare neoplastic disease. Clinical symptoms are often related to the presence of lymphoma or adrenal insufficieny. Diagnostic strategies include endocrine evaluation, imaging studies and histopathological examination. In case of suspicious PAL, percutaneous CT or US-guided needle biopsy is recommended to rapidly establish diagnosis before starting chemotherapy. We report about an 84-year-old male who presented with significant weight loss and chronic lumbar pain. Abdominal CT scans revealed bilateral masses highly suggestive of malignancy. After open bilateral adrenalectomy with abdominal lymphadenectomy, histological examination showed bilateral PAL. Five months after surgery, the patient died due to progressive tumor disease.

Key words: Primary adrenal lymphoma (PAL); bilateral adrenal masses; abdominal non-Hodgkin's lymphoma, adrenalectomy

Introduction

The adrenal gland is a frequent site of neoplastic disease. Adrenal masses occur in about 9% of the entire population [1]. Neoplastic involvement of the adrenal gland may result from primary tumors originating from the adrenal cortex or the adrenal medulla. However, the incidence of these tumors is rather low. Adrenal glands are more frequently the site of metastatic disease caused by primary carcinomas [1, 2, 3].

Primary adrenal non-Hodgkin's lymphoma (PAL) is a rare neoplastic disease with about 116 reports in the literature (Table 1), so far. Most of these tumours are highly aggressive, and their treatment is still not satisfactory. Therapeutic modalities include multi-agent chemotherapy, surgery followed by chemotherapy and/or radiation therapy and central nervous system (CNS) prophylaxis [4, 5]. Usually, the prognosis of PAL patients is fatal with early death occuring during chemotherapy. However, complete and partial remissions with a longer mean duration of survival have been reported in some cases [1-9]. Generally, poor prognosis seems to result partially from delays in diagnosis. Therefore the overall survival seems to be dependant on the ability to establish diagnosis early in order to start adequate therapy without any time delay and to avoid serious and potentially fatal complications. Unfortunately there are no pathognomonic symptoms or diagnostic features to distinguish PAL form other benign or malignant adrenal disease preoperatively. Confirmation diagnosis can only be based on histopathological examination. We describe the case of an 84-year-old male patient with PAL followed by a systemic review of literature to determine epidemiology, histopathology, treatment and outcome of this entity.

Case Report

An 84-year-old male in good physical condition presented with a six-month history of significant weight loss and lumbar pain. The medical history revealed arterial hypertension, absolute arrhythmia due to atrial fibrillation and chronic obstructive pulmonary disease, but no past history of carcinoma.

Physical examination, electrocardiogram and plain radiography of the chest were unremarkable except for signs of cardiac and pulmonary disease. Laboratory investigations showed normochromic, normocytic anaemia, as well as increased CRP and lactat dehydrogenase serum levels. Esophagogastroduodenoscopy and colonoscopy were both inconspicuous. Abdominal ultrasonography (US) revealed splenomegaly and large bilateral adrenal masses without lymphadenopathy. By means of contrast-enhanced CT scan, the left adrenal gland was measured to a maximum of 4 x 4 x 5cm, the right adrenal gland to 10 x 8 x 8cm (Fig. 1). The 2-[(18)F] fluoro-2-deoxyglucose (FDG)-PET scan depicted an intense FDG accumulation in both adrenal glands without abnormal FDG uptake in extraadrenal regions (Fig.1). Thoracic CT scan excluded any hilar or mediastinal lymphadenopathy.

Initially, bilateral phaeochromocytomas were suggested considering the 10-year history of arterial hypertension. However, all serum hormones and fractionated urinary catecholamines were within normal ranges. Because of the large diameter both non-hyperfunctioning masses were highly suggestive of malignancy, so that fine needle aspiration (FNA) biopsy was

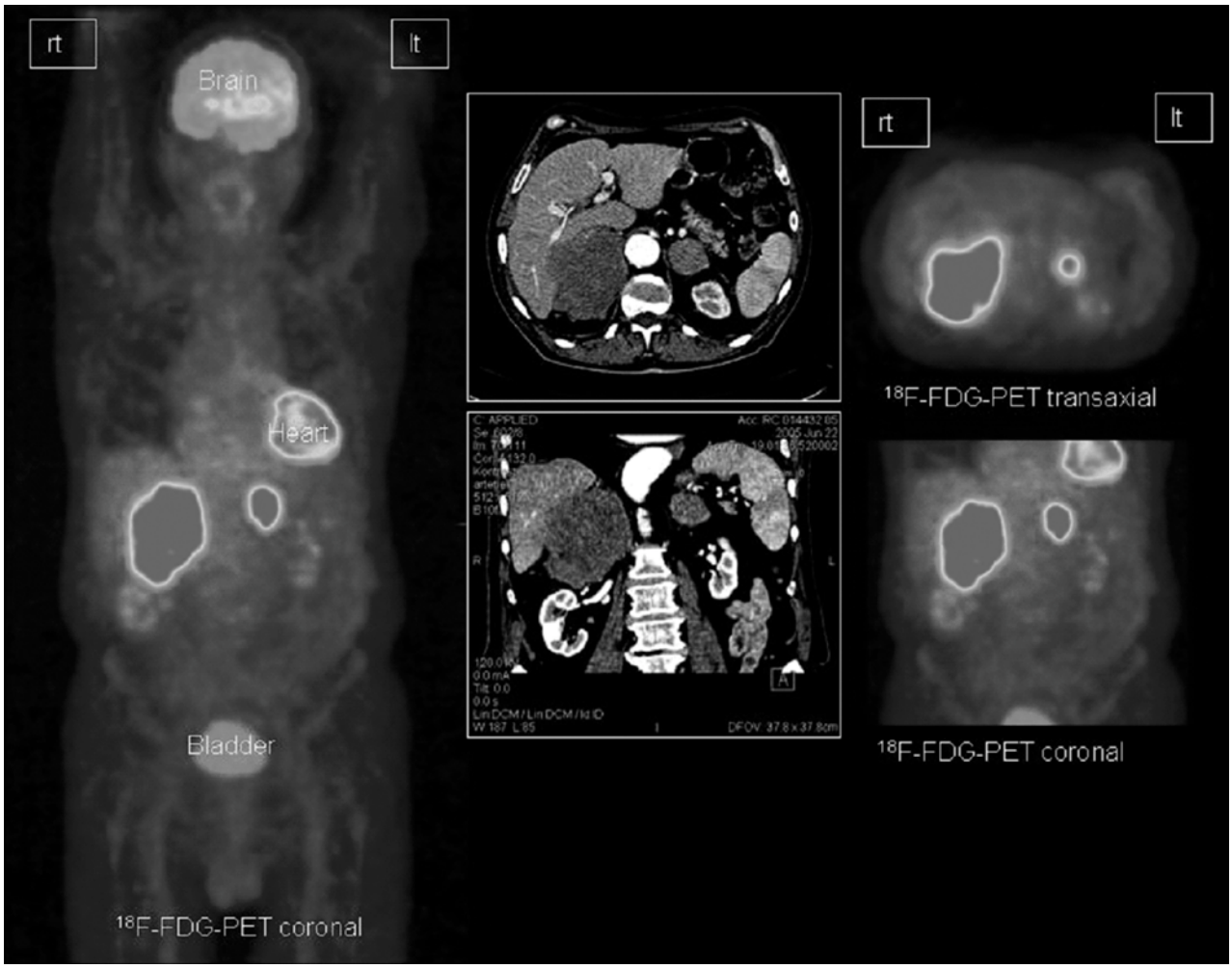

Fig. 1. Axial and sagittal PET CT scan. Intense FDG uptake in bilateral adrenal masses. The right adrenal mass is bigger than the left. There are no areas of abnormal FDG uptake.

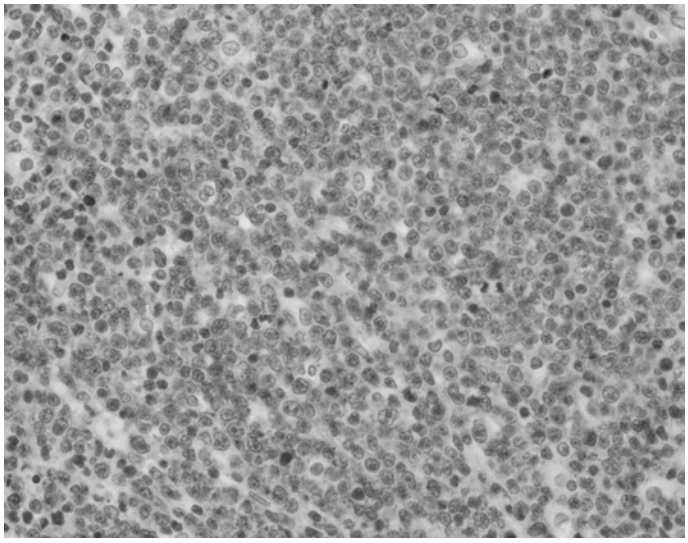

Fig. 2. Primary adrenal lymphoma diagnosed by CD 20 lymphocytic immunophenotyping (C; magnification 40x).

avoided and open bilateral adrenalectomy with abdominal lymphadenectomy was performed. Histopathological examination revealed the infiltration of both adrenal glands by sheets of large monomorphic lymphoid cells suggesting a large cell non-Hogkin's (NHL) lymphoma. Lymphocytic immunophenotyping showed positive expressions of common leukocyte antigen CD 45 and B-cell marker of CD 20 (Fig. 2), but no expression of T-cell markers CD 43 and CD 45 RO. The tumor cells were negative for Epstein-Barr

virus (EBV) latent membrane protein-1 (LMP-1) and EB encoded RNA (EBER). The lymphoma was classified as a diffuse large B-cell type according to the World Helath Organization Classification [10]. The patient could be discharged at day 12 after surgery in good physical condition, and adjuvant chemotherapy therapy was already planned. However, the patient suddenly worsened two months postoperatively, and died another four weeks later because of disseminated progressive disease and cardiopulmonary failure.

Discussion

Primary bilateral adrenal non-Hodgkin lymphoma (PAL) as described in this case report should be considered as a distinct entity characterized by unique clinical and radiological features. Whereas secondary involvement of the adrenal gland with NHL occurs in nearly 25% of patients during the course of disease, PAL represents only 3% of extranodal lymphomas [1, 5, 11]. We reviewed the English and non-English literature from 1961 till 2006 and found 116 cases reported. PAL occurs in mostly elder patients (mean age 61.3 years, range 17-89 years) with a male:female ration of 2:1 (Table 1, 2). At time of diagnosis, nearly 78% of those cases reveal a bilateral adrenal involvement with a median maximum diameter of 70 mm (range 15-180 mm) (Table 1, 2) [3, 4, 5]. About 88% of PAL cases are B cell lymphomas. Only 7 reports (6,4 %) describe T cell lymphomas (Table 1, 2) [12-17]. The most common histology is the diffuse large-cell B cell lymphoma (68%. Table 1). Less common types are the small-cell (6.4%, including cleaved-cell and non-cleaved-cell) lymphoma, the mixed small- and large-cell (4.5 %), and the undifferentiated lymphoma (Table 1, 2) [3, 4, 5].

As human adrenal glands do not contain any lymphoid tissue, it is suggested that PAL arises from previous autoimmune adrenalitis. It seems to derive from haemopoietic tissue within a single adrenal gland and to gravitate to the microenvironment of the contralateral gland [4, 9, 18]. Immune dysfunction is described to be the most important predisposing factor. According to a review on 55 cases of PAL by Wang et al. in 1998, 4% of patients suffered from human immunodeficiency virus (HIV) infection, 13% from concommittant autoimmune diseases, and 15% showed a past history of carcinoma. The data also implicates, that Epstein-Barr virus may be a possible causative agent in genesis of PAL [4, 8]. Moreover recent molecular analyses indicate, that mutations of the p53 gene (53%) and the c-kit gene (71%) may play an additional role in adrenal lymphomagenesis [4, 8].

The clinical symptoms of PAL are quite variable. They are often related to the presence of lymphoma or adrenal insufficiency. Typically, PAL patients show a low incidence of extra-adrenal disease and absence of leucemia [4, 5]. Skin pigmentation, gastrointestinal symptoms, profound fatigue, hypotension and Addison's disease due to adrenal insufficiency occur in 50% of cases [3-5, 9, 19]. Systemic symptoms as fever and weight loss may be associated with local lumbar pain [3, 4]. Uncommon symptoms are reported as autoimmune haemolytic anaemia or thrombocytopenia, severe and diffuse skin hitching, hypercalcaemia or unusual involvement of extranodal organs such as eye, thyroid gland, pituitary gland, or testicles [3, 4, 6, 19]. The incidence of CNS involvement is determined by the extent and proliferation of the disease.

Differential diagnosis of PAL includes primary tumors originating from the adrenal cortex or medulla as well as metastases from other malignant neoplasms, i.e. lung cancer, melanoma, leukemia, kidney and ovarian carcinoma [1, 2]. Contrast-enhanced CT is considered to be the most appropriate imaging tool to distinguish benign from malignant adrenal lesions. Tumor size and growth as well as attenuation thresholds have been proposed to be important criteria of malignancy [2, 5, 20-22]. CT demonstrates a complex mass with diffuse involvement of the gland and variable density of the lesion, often comprising cystic components due to areas of haemorrhage, cystic degeneration or necrosis [1, 5]. On MRI, PAL appears hypointense on T1 weighted images and heterogenously hyperintense on T2 weighted images. Lesions show a strong contrast enhancement with delayed washout after injection of paramagnetic contrast [2, 5]. Abdominal US largely depends on operator skills as well as tumor diameter, and cannot be recommended for the differentiation between benign and malignant masses [2, 5]. PET is proposed for staging and detecting recurrences of adrenal malignomas. But data are still insufficient to justify the application of PET for diagnosis of clinically inapparent masses beyond clinical studies [2]. All in all, there are no pathognomonic symptoms or diagnostic features to distinguish PAL form other benign or malignant adrenal tumors. Therefore percutaneous punch or FNA biopsies under US or CT guidance can be recommended in case of suspicious PAL to establish diagnosis and start chemotherapy without time delay. Nevertheless, FNA cannot be approved as a standard procedure in the diagnostic workflow for suspicious adrenal masses considering the risk of metastatic spread of cancer cells and the fact that benign cytological diagnosis does not exclude malignancy [2, 3].

Therapeutic modalities of PAL patients include fluid and adrenocortical hormone replacement, combination chemotherapy, surgery followed by chemotherapy and/or radiation therapy and CNS prophylaxis [4, 5]. In general, surgery of adrenal tumours should be considered in patients with functioning cortical tumours. Regarding non-functioning masses, recommendations for treatment mainly refer to the tumour size. Up to date, lesions >6 cm show a higher risk of primary adrenocortical carcinoma (25%) and should be excised by open procedure, as performed in the present case [2, 23, 24]. A close follow–up or laparoscopic adrenalectomy is the reasonable approach for intermediate sized tumours between 4 and 6 cm. In case of increase in size or suspicion of malignancy, adrenalectomy should be strongly considered [2, 22, 23]. Clinically inapparent lesions <4 cm without any criteria of malignancy are generally not resected and should be followed up closely [2, 23, 24].

Surgical resection as a solitary treatment in PAL patients is associated with a poor outcome. Nevertheless, surgical debulking of PAL in addition to chemotherapy may result in improved survival [5]. The regimes of

Table 1. Details of clinicopathologic findings in patients with PAL reported as case reports or in reviews in the English and non-English literature.

Year	Author	Article	Case	Age [years]	Gender	Major diameter [mm]	Site	Therapy	Follow-up [months]	Outcome	Pathology
1997	Pimentel M. [14]	CR	1	42	m	NA	BL	C	4	D	diffuse large T-cell
	Baudard M. [25]	CR	1	61	f	NA	BL	NA	NA	NA	NA
	Truong B. [26]	CR	1	38	m	100	UL	C	24	CR	diffuse large B-cell NHL
	Nasu M. [27]	CR	1	55	m	NM	BL	C	8	D	diffuse large B-cell NHL
	Al-Fiar F. [28]	CR	1	61	f	NM	BL	C	11	D	diffuse large B-cell NHL
	Kubo M. [29]	CR	1	61	m	NM	BL	C	1	D	NHL
	Levy N. [12]	CR	1	77	m	NM	BL	None	0.25	D	diffuse large B-cell NHL
		CR	1	89	f	NM	BL	None	0.5	D	diffuse large B-cell NHL
		CR	1	60	m	NM	BL	C	7	D	diffuse large B-cell NHL
		CR	1	77	M	NM	BL	C	2	D	small non-cleaved B-cell
		CR	1	70	m	NM	BL	None	0.75	D	T-cell NHL
1998	Wang J. [8]	CR	1	46	m	25	UL	none	0.5	D	diffuse large B-cell NHL 39 large cell
		R								7 CR	4 mixed and small cell
	Wang J. [8]	1961-1996	55	65 (39-89)	38 m, 17 f	3-17	40 BL, 15 UL		max 26	13 PR 35 D	6 smal cel 5 NHL 1 T-cell NHL
	May [13]	CR	1	59	m	80	UL	S	96	CR	Centroblastic T-cell NHL
1999	Lee K. [30]	CR	1	54	m	50 / 70	BL	S	NS	SR	diffuse large B-cell NHL
	Hsu C. [31]	CR	1	64	f	100 / 100	BL	C (CVP)	4	D	diffuse large B-cell NHL
	Salvatore J. [32]	CR	1	27	m	50 / 90	BL	C (CHOP)	52	CR	B-cell NHL
	Wu H. [33]	CR	1	64	f	120 / 80	UL	C (CHOP)	12	CR	B-cell NHL
	Takai K. [34]	CR	1	72	f	81 / 64	BL	S	72	CR	diffuse large B-cell NHL
	Cavanna L. [35]	CR	1	78	m	100	UL	C (CHOP)	12	CR	B-cell NHL
	Yanamoto E. [36]	CR	1	63	m	NA	BL	S	72	CR	diffuse large B-cell NHL
	Fearon P.[37]	CR	1	57	m	NM	UL	S	12	CR	diffuse large B-cell NHL
2000	Frankel W. [38]	CR	1	62	f	150 / 40	BL	S	23	CR	anaplastic large B-cell NHL
	Clemens [39]	CR	1	62	m	30 / 50	BL	C	NM	NM	diffuse large B-cell NHL
	Ellis R. [18]	CR	1	74	f	100	BL	C (CHOP)	1	D	B-cell NHL
	Suga [40]	CR	1	73	f	65 / 48	BL	C (CVP)	6	P	diffuse large B-cell NHL
	Yamashita [41]	CR	1	62	f	NM	BL	C	NM	NM	diffuse large B-cell NHL
	Kuyama [42]	CR	1	69	f	NA	BL	C (CHOP)	50	CR	diffuse mixed B-cell NHL
2001	Ludvik R. [43]	CR	1	76	m	100	UL	C (CHOP)	6	D	B-cell-NHL
	Mermershtain W. [44]	CR	1	60	m	60 / 40	BL	C (CHOP)	14	D	diffuse large B-cell NHL
	Viswanathan V. [45]	CR	1	56	f	60 / 30	BL	NM	NM	NM	diffuse large B-cell NHL

Table 1 (continued).

Year	Author	Article	Case	Age [years]	Gender	Major diameter [mm]	Site	Therapy	Follow-up [months]	Outcome	Pathology
2002	Hahn J. [46]	CR	1	61	m	58 / 68	BL	C	NM	PR	diffuse large B-cell NHL
	Schocket L. [47]	CR	1	71	m	NA	BL	C	84	CR	diffuse large B-cell NHL
	Lu J. [48]	CR	1	80	m	NA	UL	S	16	D	B-cell-NHL
	Brink [49]	CR	1	50	m	NA	BL	C	12	CR	centroblastic centrocytic B-cell NHL
2003	Grigg A. [4]	CR	1	55	m	102	BL	C	6	D	diffuse large B-cell-NHL
		CR	1	58	f	75	BL	C(CHOP)	6	CR	follicular grade II B- cell NHL with diffuse areas
	Wang F. [16]	CR	1	59	f	90 / 80	BL	S	6	D	B-cell-NHL
	Yoon L. [50]	CR	1	NA	NA	NA	UL	C	NA	CR	diffuse large B-cell NHL
	Fukushima A. [6]	CR	1	66	f	50 / 30	BL	S	12	D	diffuse large B-cell NHL
	Rezgui-Marhoul L. [51]	CR	1	NA	NA	NA	NA	NA	NA	NA	NA
	Tumino S. [3]	CR	1	66	f	81 / 45	BL	C	NM	D	diffuse large B-cell NHL
	Nishikawa N. [52]	CR	1	NM	NM	NM	BL	NM	NM	NM	NM
2003	Xu et al. [17]	CR	1	NM	m	NM	BL	S	3	D	T-cell NHL
		CR	1	NM	m	NM	BL	S	3	D	diffuse large B-cell NHL
		CR	1	NM	f	NM	BL	C	2 cycles	D	diffuse large B-cell NHL
	Gillett [53]	CR	1	86	m	NM	BL	C	10	CR	diffuse large B-cell NHL
2004	Devaux M. [54]	CR	1	NA	NA	NA	UL	NA	NA	NA	NA
	Zar T. [55]	CR	1	NA	NA	NA	NA	NA	NA	NA	NA
	Mantzios G. [7]	CR	1	80	m	90 / 100	BL	C (CVP)	2	D	Burktitt-like Lymphoma
	Singh D. [56]	CR	1	47	m	60	UL	C (CHOP)	3 cycles	PR	diffuse large B-cell NHL
		CR	1	55	f	150 / 100	BL	C (CHOP)	7	D	diffuse large B-cell NHL
	Zargar H. [9]	CR	1	50	f	37 / 22	BL	S	NM	NM	NHL
	Terpos E. [19]	CR	1	77	M	70 / 50	BL	C (CHOP)	1	D	diffuse large B-cell NHL
2005	Kumar R. [5]	CR	1	67	M	42 / 39	BL	C	NM	CR	Diffuse large B-cell NHL
	Mizoguchi Y. [57]	CR	1	17	m	NM	BL	NM	NM	D	Natural killer cell lymphoma
2006	Tsai W. [15]	CR	1	42	f	52 / 45	BL	C (CHOP)	2	D	T-cell NHL
	Li Y. [58]	CR	1	58	f	76 / 65	BL	NM	NM	NM	B-cell NHL
		CR	1	38	m	NM	BL	NM	NM	NM	B-cell NHL
	Zhang L. [59]	CR	1	NA	NA	180 / NM	BL	NA	NA	NA	NA
	Libe R. [60]	CR	1	70	f	15 / NM	BL	S	NM	CR	B-cell NHL

(CR = case report, R = review; m=maskulin, f = feminin; UL = unilateral, BL = bilateral; C = Chemotherapy, S = Surgery; D = death, CR= complete remission, PR= partial remission, NM = not mentioned, NA = article not available)

Table 2. Clinical findings in patients with PAL reported as case reports or in reviews in the English and non-English literature.

Variable	N	
Gender (n = 109)	Male	71 (65.1%)
	Female	38 (34.9%)
Age (n = 107) [year]	Mean	61.26
	Range	17-89
Adrenal lesions (n = 114)	Unilateral	26 (22,8%)
	Bilateral	88 (77,2 %)
Major tumor diameter (n = 33) [mm]	Mean	70.75
	Range	15-180
Histopathology (n = 109)	**B-cell NHL**	**96 (88,1%)**
	Diffuse large B-cell NHL	74 (67.9%)
	Mixed small and large cell NHL	5 (4.5%)
	Small cell (cleaved/non-cleaved) NHL	7 (6.4%)
	B-cell-lymphoma not specified	10 (9.1 %)
	T-cell-lymphoma	**7 (6.4%)**
	NHL not specified	**4 (3.7%)**
	Others	**2 (1.8%)**
Primary therapy (n = 71)	Surgery	20 (28.1%)
	Chemotherapy	47 (66.2%)
Survival time [months]	Mean	15.26
Outcome (n = 102)	Range	0.25 -96
	Death	64 (62.7%)
	Complete remission	22 (21.6%)
	Partial remission	16 (15.7%)

Total: n = 116 patients; Others = Natural killer cell lymphoma, Burktitt-like Lymphoma

chemotherapy used include CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), CHOP in combination with Rituximab, CHO (cyclophosphamide, doxorubicin, vincristine), CVP (vincristine, prednisone) or MACOP (cyclophosphamide, doxorubicin, prednisone, methotrexate, bleomycin). According to a review published by Kumar et al., one third of the patients achieved a partial or complete remission during chemotherapy with a mean duration of survival of 34 + 32 months [5]. Nevertheless, many PAL patients deceased due to tumour recurrence or severe infections within one year after diagnosis. We found information on primary treatment in 71 (61.2%) of the cases reported. 47 (66%) of the patients received chemotherapy and 20 (28%) received surgery. Information on response on treatment and outcome was available in 102 (87.9%) patients. 64 (62.7%) patients had died, 22 (21.6%) patients showed complete and 16 (15.7%) patients showed partial remission. Mean overall-survival rate was 15.3 months (Table 1).

Regarding adjuvant therapy, CNS prophylaxis including intrathecal methotrexate and hydrocortisone applications may reduce the incidence of CNS recurrence and improve long-term survival in patients with aggressive NHL [4]. It should be considered in cases with increased LDH serum levels, a high/intermediate or high-risk International Progostic Index and an involvement of more than one extranodal site including bone marrow [4].

Conclusion

In case of suspicious bilateral adrenal non-functioning masses and rapidly progressive adrenal insufficiency PAL should also be considered for differential diagnosis. Diagnostic strategies include endocrine evaluation, imaging studies and histopathological examination. Percutaneous CT or US-guided needle biopsy is recommended to establish diagnosis before starting chemotherapy. In single cases, open bilateral adrenalectomy with abdominal lymphadenectomy is another diagnostic option. Chemotherapy and/or radiation therapy seem to be associated with a better outcome of PAL patients.

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