Urologic Oncology: Seminars and Original Investigations 37 (2019) 531.e17–531.e25

UROLOGIC ONCOLOGY

Clinical-Testis cancer

Noncaseating granulomatous diseases in germ cell cancer patients—A single-center experience

Lars Henning Schmidt, M.D.[a,*], Sebastian Huss, M.D., Prof.[b], Christoph Schuelke, M.D.[c], Arik Schulze, M.D.[a], Georg Evers, M.D.[a], Christoph Schliemann, M.D., Prof.[a], Anna Hansmeier, M.D.[a], Bengt Schilling, M.D.[d], Berit Lauterbach[a], Peter Barth, M.D., Prof.[b], Karsten Wiebe, M.D.[e], Dennis Goerlich, Ph.D.[f], Wolfgang E. Berdel, M.D., Prof.[a], Gerald Puehse, M.D.[d,1], Michael Mohr, M.D.[a,1]

[a] *Department of Medicine A, Hematology, Oncology and Pulmonary Medicine, University Hospital Muenster, Muenster, Germany*
[b] *Gerhard-Domagk-Institute of Pathology, University Hospital Muenster, Muenster, Germany*
[c] *Department of Clinical Radiology, University Hospital of Muenster, Muenster, Germany*
[d] *Department of Urology, University Hospital Muenster, Muenster, Germany*
[e] *Division of Thoracic Surgery and Lung Transplantation, Department of Cardiothoracic Surgery, University Hospital of Muenster, Muenster, Germany*
[f] *Institute of Biostatistics and Clinical Research, Westfaelische Wilhelms-University Muenster, Muenster, Germany*

Received 18 November 2018; received in revised form 5 March 2019; accepted 10 March 2019

Abstract

Objectives: In patients with testicular Germ Cell Tumors (GCT) noncaseating granulomatous diseases such as Sarcoid Like Lesions (SLL) or Sarcoidosis can mimic metastasis due to hilar or mediastinal lymphadenopathy. Due to the clinical and prognostic impact, exclusion of malignant diseases is mandatory.

Material and methods: Retrospectively, data from 636 GCT patients, who were seen in the course of tumor surveillance/follow-up were collected. Focus was put on the detection of tumor relapse vs. noncaseating granulomatous reactions. For the differential diagnosis of thoracic lymphadenopathy or pulmonary infiltrates either bronchoscopy (e.g., endobronchial ultrasound-guided transbronchial needle aspiration, endobronchial ultrasound-guided transbronchial needle aspiration) or thoracic surgery was performed. Both GCT patients with either tumor relapse or coexisting SLL were compared to GCT patients without SLL and tumor relapse.

Results: Twenty-nine patients suffered from suspected tumor relapse. Whereas thoracic relapses were suspected in 15 patients on chest computed tomography, thoracic relapse was confirmed in 5 cases by open surgery. In 2 cases open surgery yielded reactive lymphadenitis, and in 8 cases SLL was diagnosed either *via* EBUS-TBNA ($n = 7$) or thoracoscopic wedge resection plus lymphadenectomy ($n = 1$). With focus on overall survival, no relevant difference was found between all tested subgroups ($P = 0.265$; logrank test).

Conclusions: In GCT patients, the coexistence of noncaseating granulomatous disease is common. Minimal invasive bronchoscopic techniques can serve for the cytopathologic exclusion of malignant thoracic manifestations. In our monocenter patient group the coexistence of SLL did not have any prognostic impact on overall survival.

Keywords: Noncaseating; Granulomatous diseases; Germ cell cancer

1. Introduction

In young men between 15 and 35 years, testicular Germ Cell Tumor (GCT) is one of the most common malignant diseases [1]. With regard to the histologic subtype, recently

*Corresponding author. Tel.: +49 (0)251-8344825; fax: +49 (0)251-8347680
E-mail address: larshenning.schmidt@ukmuenster.de (L.H. Schmidt).
[1]Shared senior co-authorship.

https://doi.org/10.1016/j.urolonc.2019.03.010
1078-1439/

a relative increase of Seminoma in comparison to nonseminomatous GCT was reported [2]. Even though prognosis of GCT patients is good with a worldwide relative 5-year survival rate above 92% [1], there are still patients with inferior prognosis. In Germany for instance, the annual (age adjusted) death rate for GCT is 0.3 per 100.000 [3]. Poor outcome is often due to tumor relapse and/or metastatic spread. With respect to localization of relapse, typical primary sites for tumor relapse are retroperitoneal lymph nodes and thoracic manifestations (i.e., lung infiltrations or hilar/mediastinal lymph node metastasis [4]). To reduce GCT mortality, careful follow-up care is crucial. In the past, computed tomography (CT) scanning was an integral part of tumor follow-up for all GCT patients. Recently, the recommendations for radiologic tumor surveillance were modified with regard to radiation induced carcinogenesis due to CT scanning [5]. Depending on the individual risk profile, tumor surveillance encompasses tumor markers, physical examination, and either chest CT or chest X-rays, respectively [6].

Apart from malignant thoracic manifestations, benign causes of mediastinal or hilar lymphadenopathy exist. Upon histological examination, often reactive lymphadenitis and noncaseating granulomatous diseases such as Sarcoid-likeike Lesions (SLL) or Sarcoidosis are important differential diagnoses [7]. By definition, Sarcoidosis is a multisystem disorder of unknown cause with histologically confirmed noncaseating epithelioid cell granulomas, with other causes of granulomatous disease excluded. Typically, it affects the lung and the lymphatic system [8]. If noncaseating epithelioid cell granuloma lesions are detected, but accompanying systemic symptoms are missing, the term SLL is applied [9–11]. In clinical practice, definitive diagnosis of either SLL or sarcoidosis is often difficult to establish. As a result, both for the exclusion of malignancy and for the final diagnosis, tissue sampling and histopathological differentiation are mandatory especially for patients with suspicious thoracic findings or previous malignant disease. With regard to epidemiology, the annual incidence rate of SLL/sarcoidosis is unclear. Depending on the ethnic group, incidence rate for Sarcoidosis varies between 10.9 to 35.5 per 100.000 [12].

Technically, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS TBNA) and thoracic surgery are useful tools for tissue sampling [13–21]. Without doubt, surgical procedures yield superior diagnostic probes. However, there are more associated risks and higher costs in comparison to less invasive techniques such as EBUS-TBNA [17].

With respect to pathogenesis, the development of SLL/sarcoidosis is complex. On the molecular level, there are distinct interactions between various antigens, human leukocyte antigen class II molecules, and T-cell receptors [22]. As a result of this interaction, granulomatous reactions with epithelioid histiocytes, and multinucleated giant cells with CD41 positive T lymphocytes arise [23]. In this context, SLL is often observed in association with malignant growth either adjacent to the primary tumor location or to local draining lymph nodes. Against this background, an immunological reaction to antigenic tumor products is postulated [7]. Here distant SLL reaction could reflect a reaction to soluble circulating tumor antigens [24]. There are various reports on a generally increased association between SLL/sarcoidosis with various tumor entities [9,25–27]. In particular for GCT patients, the coexistence of sarcoidosis and/or SLL is common [28–33]. One study even reported a cumulative incidence of granulomatous diseases in GCT patients of 168.7 per 100.000. This ratio corresponds well with a 10-fold increase compared to the general population [34]. In clinical practice, the majority of GCT patients with coexisting noncaseating granulomatous diseases are often identified during tumor surveillance [9,25,26].

Whether SLL/sarcoidosis have an impact on both, the clinical course of tumor diseases or prognosis, still remains unclear [9,26,27,33,35,36]. Our report investigated the influence of SLL/sarcoidosis in GCT patients with focus on clinical parameters, radiologic examinations and overall survival. Next, results were compared between GCT patients with confirmed tumor relapse and GCT patients free of relapse and SLL/sarcoidosis.

2. Material and methods

2.1. Study population

Following the approval of the Ethical committees of Muenster (Az. 2015-038-f-S) data from 636 GCT patients were analyzed retrospectively. Due to the retrospective study character, no exclusion criterion was established prior patient selection. Inclusion criteria included both confirmed diagnosis of GCT and treatment at University Hospital Muenster between 2007 and 2014. A flow diagram demonstrates the selection of the tested study groups (Fig. 1). Regular follow-up visits were offered to the GCT patients including tumor markers (i.e., alpha-fetoprotein, human chorionic gonadotropin), physical examination and radiologic examination (i.e., thorax CT or chest X-ray). Median follow-up in the full study collective was 86 months. In case of suspected tumor relapse, further diagnostic work-up was determined in interdisciplinary tumor conferences. In case of suspicious hilar/mediastinal lymphadenopathy or pulmonary infiltrates, histological examination was performed either via interventional bronchoscopy (i.e., transbronchial needle aspiration, forceps biopsy, and cytobrush) or thoracic surgery (i.e., mediastinoscopy or wedge resection). Hence, the presented study collective encompasses only GCT patients with suspicious findings, whose further diagnostic follow-up was decided in interdisciplinary tumor conferences.

2.2. Tissue sampling with bronchoscopy and thoracic surgery

GCT patients with suspected relapse were referred for further histological examination. Endobronchial

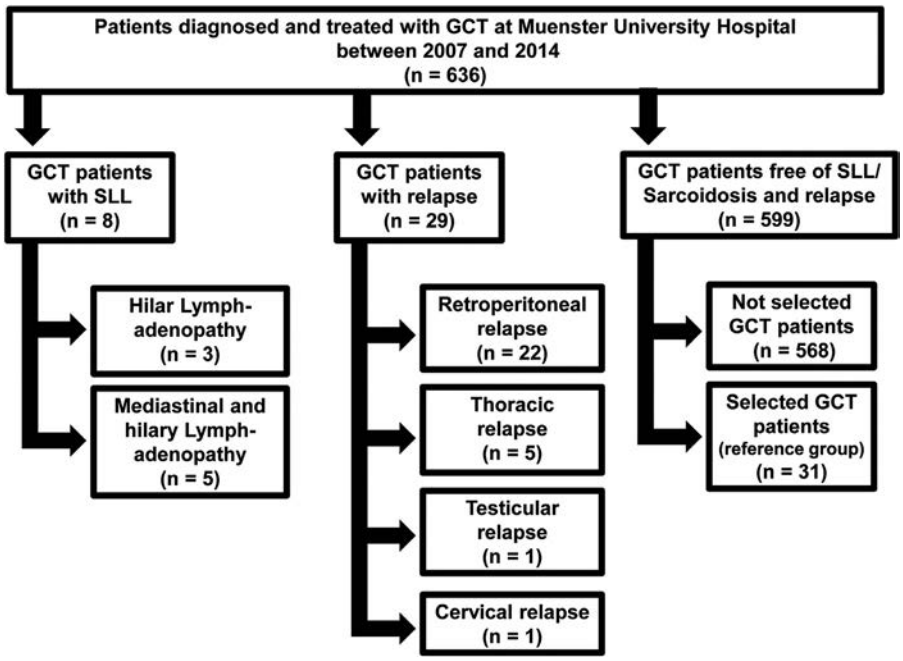

Fig. 1. Study collective and tested clinical subgroups. The flow diagram demonstrates the selection of the tested subgroups.

ultrasound-guided transbronchial needle aspiration (EBUS TBNA) was performed using a curvilinear scanning ultrasound bronchoscope (EB-1970K Bronchoscope, Pentax, Tokyo, Japan) connected to an ultrasound unit (HI VISION Avius, Hitachi Medical Systems GmbH, Tokyo, Japan). All procedures were performed under general anesthesia with an uncuffed endotracheal tube (Bronchoflex, Ruesch, Teleflex Medical GmbH, Fellbach, Germany).

Following biopsy, cell suspensions were collected in formaldehyde for carrying out Papanicolaou's staining and making paraffin cell blocks. Sarcoidosis or SLL was diagnosed in the presence of compatible clinical and radiographic manifestations, if other diseases (e.g., tuberculosis) were excluded and if noncaseating granulomas were detected upon histopathologic examination. Representative tissue samples for histopathologic examination of 2 GCT patients with coexisting noncaseating granulomatous disease are shown in Fig. 2. In case bronchoscopy was not diagnostic, the patient was referred to thoracic surgery. Primarily, mediastinoscopy was performed to explore mediastinal or hilar lymphadenopathy. Additionally, video-assisted thoracoscopy procedure or open thoracotomy was performed for parenchymal biopsy or lymphadenectomy if indicated.

2.3. Comparative analysis

Depending on the course of disease, 3 clinical subgroups were identified. One subgroup included all GCT patients with confirmed SLL ($n = 8$). As confirmed upon histological examination, a second subgroup included all GCT patients with any nonthoracic tumor relapse ($n = 24$) and a third subgroup consisted of all GCT patients with a detected thoracic tumor relapse ($n = 5$). These subgroups were compared to a study collective of $n = 31$ GCT patients who had a follow-up time of at least 60 months and who were free both of tumor relapse and SLL/sarcoidosis (i.e., GCT patients with no evidence of disease in the course of tumor surveillance). The subgroups were identified retrospectively. A further matching was not deemed necessary, since the main factors, age and stage, were comparable between the investigated subgroups. Baseline information of all study subgroups is summarized in Table 1.

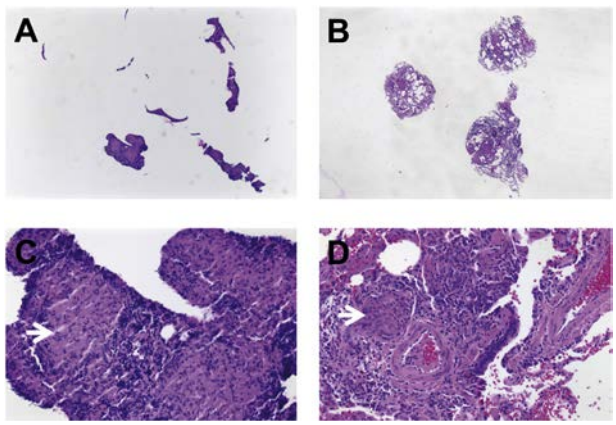

Fig. 2. Representative histological results of 2 (A, C and B, D) GCT patients with coexisting noncaseating granulomatous disease (images A and B at ×10, images C and D at ×40). In the presented examples endobronchial ultrasound-guided transbronchial needle aspiration (EBUS TBNA) yielded sufficient tissue samples for the final diagnosis of noncaseating granulomatous reaction. Arrows point at representative granulomas.

Table 1
Baseline characteristics of the investigated patient groups of GCT patients, who were either diagnosed with a relapse or noncaseating granulomatous disease or no evidence of disease (NED) during follow-up examination at University Hospital Muenster between January 2007 and December 2014

	GCT patients with SLL ($n = 8$)	GCT patients with nonthoracic relapse ($n = 24$)	GCT patients with thoracic relapse ($n = 5$)	GCT patients without relapse (NED) ($n = 31$)	P values
Parameter					
Age at initial diagnosis					0.488[d]
-Median (Q1[a], Q3[b]), years	32 (29;35)	36 (28;39)	33 (25;47)	30 (26;38)	
Tumor histology					0.585[e]
-Pure seminoma	2 (25%)	9 (38%)	3 (60%)	14 (45%)	
-Nonseminomatous germ cell tumor	6 (75%)	15 (63%)	2 (40%)	17 (55%)	
Initial risk score according to the International Germ Cell Classification Consensus (IGCCC)					0.017[e]
-Low risk	5 (63%)	19 (83%)	4 (80%)	29 (94%)	
-Intermediate risk	1 (13%)	4 (17%)	1 (20%)	2 (7%)	
-High risk	2 (25%)	0	0	0	
Initial clinical stage according to Lugano classification					0.610[e]
-Clinical Stage I (Lugano classification)	3 (38%)	9 (38%)	1 (20%)	15 (48%)	
-Clinical Stage II (Lugano classification)	5 (63%)	10 (42%)	3 (60%)	10 (32%)	
-Clinical Stage III (Lugano classification)	0	5 (21%)	1 (20%)	6 (19%)	
Initial therapy of GCT					0.238[e]
-Radical orchiectomy	0	6 (25%)	0	4 (13%)	
-Radical orchiectomy followed by adjuvant chemotherapy	5 (63%)	9 (38%)	1 (20%)	16 (52%)	
-Radical orchiectomy followed by adjuvant radiotherapy	0	3 (13%)	3 (60%)	6 (19%)	
-Radical orchiectomy followed by adjuvant chemotherapy and retroperitoneal lymphadenectomy afterwards	3 (38%)	5 (21%)	1 (20%)	5 (16%)	
-Radical orchiectomy followed by retroperitoneal lymphadenectomy and adjuvant chemotherapy afterwards	0	1 (4%)	0	0	
Overall Survival					0.114[d]
-Median (Q1[a], Q3[b]), days	2,575 (1653;4748)	2,049 (959;2,810)	2,268 (1,678;4,265)	2,653 (1,981;3,405)	
-Median (Q1[a], Q3[b]), months	84.6 (54.31;155.99)	67.32 (31.51;92.32)	74.51 (55.13;140.12)	87.16 (65.08;111.87)	
Latency between initial diagnosis and either relapse or SLL					0.850[d]
-Median (Q1[a], Q3[b]), days	536 (46;2182)	387 (235;840)	307 (160;1292)	n.e.[c]	
-Median (Q1[a], Q3[b]), months	17.61 (1.51;71.69)	12.71 (7.72;27.6)	10.09 (5.26;42.45)	n.e.[c]	

[a] Q1 = First quartile.
[b] Q3 = Third quartile.
[c] n.e. = not evaluable.
[d] P value according to Kruskal-Wallis test.
[e] P value according to Fisher's exact test.

2.4. Statistical analysis

The study population was described by standard descriptive statistical measures. For categorical variables, absolute, and relative frequencies are reported. For continuous variables median and interquartile range are reported, respectively. All statistical tests were performed as exploratory analyses on a local significance level of 0.05. Since multiplicity adjustment was not carried out, no distinct overall significance level was ascertained. Hence, our findings may be used to set up new hypotheses. For the evaluation of the association between thoracic findings on chest CT scan and clinical subgroup, Chi-square test was applied for categorical variables. Depending on the chest CT scan, thoracic lymphadenopathy was categorized (i.e., discrete lymphadenopathy, not suspicious; lymphadenopathy, typical for SLL/sarcoidosis; enlarged lymphadenopathy, still typical for SLL/sarcoidosis; lymphadenopathy, suspicious for malignancy). SPSS (SPSS Statistics, Version 25.0 released 2017, IBM Corp., Armonk, NY) was used for all statistical analyses.

3. Results

3.1. GCT patients with tumor relapse

Following the recommendation of interdisciplinary tumor boards, GCT patients with clinical or radiologic findings suspicious for tumor relapse were referred for further histological examination. In 29 GCT patients, tumor relapse was confirmed upon histological examination, which corresponds to 4.6% of the full patient group. Following histopathological examination in 22 patients a retroperitoneal relapse was found. Whereas 15 patients initially had suspicious thoracic findings (i.e. $n = 14$ hilar or mediastinal lymphadenopathy and $n = 1$ pulmonary parenchyma lesion), tumor relapse was confirmed in 5 patients upon open surgery. Of interest, initially in 2 GCT patients thoracic relapse was suspected, but not confirmed upon histologic examination (Table 2). In addition to retroperitoneal relapses, in 1 case a cervical tumor relapse and in another case a testicular relapse were observed. Approximately 80% of those GCT patients, who developed a relapse, initially had a low risk profile according to the International Germ Cell Classification Consensus [37]. Of interest, tumor histology (i.e., pure seminoma vs. nonseminomatous GCT) was not associated with the location of relapse. In total, 2 patients died due to retroperitoneal tumor relapse. Since 636 GCT patients were examined, this corresponds to a ratio of 0.3%, or 6.9% referring to the subgroup of 29 relapsed patients, respectively. Median overall survival for patients with thoracic tumor relapse was 2268 days, for those patients with non-thoracic tumor relapses it was 2049 days. Moreover, latency between initial diagnosis and relapse was analyzed. Median latency was 387 days for patients with nonthoracic tumor relapse and 307 days for patients with thoracic tumor relapse (Table 1).

Table 2
Correlation between chest CT and histology. Suspicious thoracic findings were found in 15 patients. Correlation between clinical subgroup and thoracic lymphadenopathy on chest CT is demonstrated ($P = 0.015$, Chi square test). Of interest, for this analysis radiologic examination was again performed retrospectively with focus on thoracic lymphadenopathy

	Histology			
Chest CT scan	GCT patients with detected SLL	GCT patients with thoracic relapses	GCT patients without relapses	GCT patients with suspicious thoracic findings
Discrete lymphadenopathy, not suspicious	0	3 (20%)	0	3 (20%)
Lymphadenopathy, typical for SLL/sarcoidosis	2 (13%)	0	1 (7%)	3 (20%)
Enlarged lymphadenopathy, still typical for SLL/sarcoidosis	6 (40%)	0	1 (7%)	7 (47%)
Lymphadenopathy, suspicious for malignancy	0	2 (13%)	0	2 (13%)
0	8 (53%)	5 (33%)	2 (13%)	15 (100%)

3.2. GCT patients with coexisting noncaseating granulomatous disease

In our patient group of 636 patients, 8 patients were identified with noncaseating granulomatous disease upon histological examination (1.3%). Of interest, 1 patient was diagnosed 55 days prior to the initial diagnosis of GCT. Median age of GCT patients with coexisting noncaseating granulomatous disease was 32 years. Among these 8 patients, 2 were classified as pure seminoma and 6 as nonseminomatous GCT. In all cases with confirmed noncaseating granulomatous diseases, no accompanying systemic symptoms of sarcoidosis were observed. Initially 5 patients had a low risk, 1 had intermediate risk, and 2 patients had a high risk profile according to the International Germ Cell Classification Consensus [IGCCC et al. 1997]. Initial clinical stage according to Lugano classification was as follows: Three had stage I and 5 patients had stage II. None of these patients had stage III (Table 1). Following the diagnosis of coexisting noncaseating granulomatous disease, only 1 patient required further immunosuppressive treatment with corticosteroids (data not shown). The other 7 patients were referred for further surveillance instead. With focus on overall survival all identified 8 patients are still alive at present. Median overall survival time of the study collective was 2575 days and median latency between initial diagnosis and SLL was 536 days (Table 1). Technically, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) was feasible without any complications such as severe bleeding, pneumothorax or hypoxia and diagnostic in 7 patients. In 1 case, thoracoscopic wedge resection plus lymphadenectomy led to the diagnosis of SLL.

3.3. GCT patients free of both SLL and tumor relapse

In total, 31 GCT patients free of both SLL and tumor relapse were identified. Patients in this subgroup had a similar profile with a median age of 30 years. Pure seminoma were diagnosed in 14 patients and 17 patients had nonseminomatous GCTs. The majority had a low risk profile (94%) and had clinical stage I according to Lugano classification (32%) at initial diagnosis. Median overall survival of this subgroup was 2653 days (Table 1).

3.4. Correlation between chest CT and histology

To investigate the correlation between chest CT and histology, chest scans of 15 patients were evaluated retrospectively with focus on thoracic lymphadenopathy. Here, hilar/mediastinal lymphadenopathy of GCT patients with SLL/sarcoidosis was considered as typical in all cases before histological examination was performed ($P = 0.015$, Chi square test; Table 2).

3.5. Prognostic impact of SLL and tumor relapse

To compare the prognostic impact of confirmed SLL or tumor relapse in comparison to no event such as SLL or tumor relapse, we investigated overall survival rates of GCT subgroups. Even though one patient died in the subgroup with identified tumor relapse, logrank test did not reveal any relevant difference for univariate overall survival for all tested subgroups ($P = 0.275$, logrank test; Fig. 3).

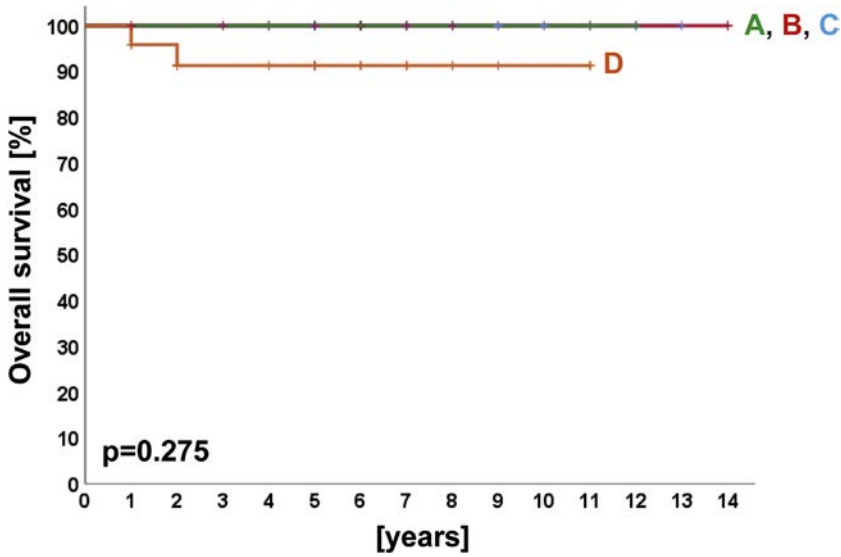

Fig. 3. Prognostic impact of SLL, thoracic relapse and nonthoracic tumor relapse in comparison to GCT patients both without SLL and any relapse. No relevant difference was found for overall survival for all tested subgroups ($P = 0.275$, logrank test). A letter in color refer to the overall survival curve of each subgroup (A: GCT patients with thoracic relapse; B: GCT patients free of both SLL and tumor relapse; C: GCT patients with coexisting SLL; D: GCT patients with nonthoracic relapses).

4. Discussion

Although overall survival rates of patients with GCT worldwide are high [1], the occurrence of metastasis has a strong prognostic impact. Besides retroperitoneal metastasis, thoracic manifestations such as hilar and/or mediastinal lymphadenopathy or pulmonary lesions can correspond to thoracic metastasis. Since both, tumor spread and inflammatory reactions (e.g., noncaseating granulomas) display increased 18F-fluorodeoxyglucose activity, positron emission tomography–CT serves for the identification of potential biopsy sites, but cannot differ between both [7,16]. Hence, tissue sampling is mandatory, to rule out malignancy.

Among benign reactions, which affect hilar and/or mediastinal lymph nodes or lung parenchyma, sarcoidosis, and SLL are typical differential diagnoses. The term sarcoidosis is used to describe a multisystem disorder of unknown origin with histologically confirmed noncaseating epithelioid cell granulomas [8]. In the absence of accompanying systemic symptoms, which are considered as typical for sarcoidosis, SLL reaction is diagnosed instead [9–11]. As demonstrated by various studies, in patients with hematologic malignancies and solid tumors there is an increased incidence of SLL in the tumor draining lymph nodes [9,25–27]. Especially for patients with testicular GCT increased coexistence of granulomatous diseases is reported [28–32,34]. Whether the development of SLL has a prognostic impact, still remains unclear [38].

As the first step in the diagnostic work-up of SLL/sarcoidosis, flexible bronchoscopy is recommended for the exploration of suspicious lymph nodes. This technique is considered as a readily available, safe, and well-tolerated procedure [8,39,40]. During bronchoscopy forceps biopsies for histological examination, bronchial washing for microbiological analysis and bronchoalveolar lavage for CD4/CD8 T-cell counting can be performed, too [41]. For the further histological differentiation of tumor spread from other diseases in case of hilar or mediastinal lymphadenopathy, both endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and thoracic surgery (e.g., mediastinoscopy) are feasible techniques [20].

To investigate the coexistence of noncaseating granulomatous diseases in testicular GCT patients and its impact, we performed this retrospective analysis. Among 636 GCT patients who were diagnosed and treated between 2007 and 2014, 29 patients developed tumor relapse in the course of disease. Whereas the majority of these patients suffered from retroperitoneal tumor relapse (69%), thoracic relapse was suspected in 15 patients, but was only confirmed in 5 patients. Besides, 8 patients were diagnosed with SLL instead and in 2 patients reactive lymphadenitis was detected. Since none of the investigated patients developed systemic symptoms of sarcoidosis, no further treatment was required, but regular follow-up controls were performed. With regard to the applied diagnostic methods, in 7 GCT patients SLL diagnosis was confirmed by EBUS-TBNA and in 1 patient upfront wedge resection yielded SLL diagnosis. With regard to complications, none of the investigated GCT patients with SLL suffered from any complications. Even though mediastinoscopy before video-assisted thoracoscopy or even open lung biopsy might have a superior yield, these techniques are costly and exhibit potential comorbidities if compared to EBUS-TBNA [17]. Overall, low mortality and adverse event rates following EBUS-TBNA are known [42]. Hence, EBUS-TBNA has become the gold standard for the further investigation of mediastinal and hilar lymphadenopathy [40]. Against this background, our analysis supports the use of EBUS-TBNA in daily practice as a safe tool for minimal invasive investigation of suspicious hilar and mediastinal lymph nodes in GCT patients. In this context, diagnostic sensitivity of EBUS-TBNA for sarcoidosis is reported to range between 52% and 81% [14,15,17,18,21,43].

Since suspicious thoracic findings in the course of tumor follow-up surveillance were seen on chest CT scans, we performed a retrospective analysis of these radiologic examinations. As demonstrated, in all cases with mediastinal/hilar lymphadenopathy with a typical pattern of SLL/sarcoidosis, no tumor infiltration was found upon histological examination. With regard to this analysis, minimal invasive techniques such as EBUS-TBNA can be used as the next diagnostic step for the further histological differentiation. In case of histologically confirmed noncaseating epithelioid cell granulomas, further thoracic surgical attempts must not be undertaken.

To evaluate the prognostic impact of SLL in GCT patients, we compared the overall survival rates of GCT patients with SLL to both, GCT patients with tumor relapse and to GCT patients free of relapse and free of SLL. With regard to stage and median age, the investigated subgroups had similar clinical profiles. In comparison to the other 2 study groups, only 35% of GCT patients with confirmed relapse had initial clinical stage I according to Lugano classification at first diagnosis. The majority of these patients had stage II and stage III disease. Of interest, we observed the highest rate of nonseminomatous germ cell tumor in GCT patients with SLL (75%) in contrast to the other two subgroups (i.e., 59% for GCT patients with relapses and 55% for GCT patients without any relapse). With regard to prognosis we observed a rather low death rate with only 2 deaths due to GCT tumor relapse in our complete patient group (0.3%). Even though GCT patients with confirmed nonthoracic tumor relapse had the lowest median overall survival, no relevant prognostic difference was found upon log rank analysis ($P > 0.05$, logrank test). Even though our study collective encompasses a large series of patients, there is a major limitation. Due to the retrospective study design, the evaluation of the clinical outcome is restricted to a descriptive and hypothesis-generating way. Moreover, the determination of statistical significance was not always feasible.

5. Conclusions

Whether both SLL and Sarcoidosis represent the result of complex immune reactions to various environmental triggers in genetically susceptible individuals under the influence of oxidative stress still remains unclear [7]. As demonstrated, there is an increased coexistence of SLL in GCT patients. However, this coexistence is not associated with any prognostic impact.

Considering the high accuracy of typical findings in identifying SLL, and since most patients with SLL did not require active treatment, follow-up imaging of suspicious lesions could be an option for those patients without any clinical symptoms such as weight loss or fever for instance. Hence, potential complications, which are associated with tissue sampling can be prevented. However, in the presence of clinical symptoms or elevated serum parameters (e.g., lactate dehydrogenase), we would recommend tissue biopsies. As demonstrated, minimal-invasive endobronchial ultrasound-guided transbronchial needle aspiration permits the safe exploration of mediastinal and hilar lymphadenopathy, and thus it can prevent the need for mediastinoscopy or even more invasive surgical attempts for GCT patients with suspicious thoracic findings [19].

Conflict of interest

The authors have no conflict of interest to declare.

Acknowledgments

We thank Inga Buchroth for her excellent technical assistance and helpful advice.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer Clin 2018;68:7–30. [PubMed: 29313949].
[2] Ruf CG, Isbarn H, Wagner W, et al. Changes in epidemiologic features of testicular germ cell cancer: age at diagnosis and relative frequency of seminoma are constantly and significantly increasing. Urol Oncol 2014;32:33. [PubMed: 23395239].
[3] Krebs in Deutschland für 2013/2014. 11. Ausgabe. Robert Koch-Institut (Hrsg) und die Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V. Berlin, 2017.
[4] American Joint Committee on Cancer Staging Manual. In: Fleming ID, Cooper JS, Henson DE, eds. American Joint Committee on Cancer Staging Manual, 5th, Philadelphia: Lippincott-Raven; 1997.
[5] Brenner DJ, Hall EJ. Computed tomography—an increasing source of radiation exposure. N Engl J Med 2007;357:2277. [PubMed: 18046031].
[6] Honecker F, Aparicio J, Berney D, et al. ESMO Consensus Conference on testicular germ cell cancer: diagnosis, treatment and follow-up. Ann Oncol 2018;29:1658. [PubMed: 30113631].
[7] Baughman RP, Culver DA, Judson MA. A concise review of pulmonary sarcoidosis. Am J Respir Crit Care Med 2011;183:573. [PubMed: 21037016].
[8] Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. Am. J. Respir. Crit. Care Med. 1999;160:736–55. [PubMed: 10430755].
[9] Cohen R, Kurzrock R. Sarcoidosis and malignancy. Clin Dermatol 2007;25:326. [PubMed: 17560310].
[10] Martella S, Lohsiriwat V, Barbalho DM, et al. Sarcoid-like reaction in breast cancer: a long-term follow-up series of eight patients. Surg Today 2012;42:259. [PubMed: 22160357].
[11] Tchernev G, Tana C, Schiavone C, et al. Sarcoidosis vs. Sarcoid-like reactions: the two sides of the same coin? Wien Med Wochenschr 2014;164:247. [PubMed: 24664574].
[12] Rybicki BA, Major M, Popovich J Jr, et al. Racial differences in sarcoidosis incidence: a 5-year study in a health maintenance organization. Am J Epidemiol 1997;145:234. [PubMed: 9012596].
[13] Annema JT, Veseliç M, Rabe KF. Endoscopic ultrasound-guided fine-needle aspiration for the diagnosis of sarcoidosis. Eur Respir J 2005;25:405. [PubMed: 15738281].
[14] Garwood S, Judson MA, Silvestri G, et al. Endobronchial ultrasound for the diagnosis of pulmonary sarcoidosis. Chest 2007;132:1298. [PubMed: 17890467].
[15] Wong M, Yasufuku K, Nakajima T, et al. Endobronchial ultrasound: new insight for the diagnosis of sarcoidosis. Eur Respir J 2007; 29:1182. [PubMed: 17331972].
[16] Costabel U, Bonella F, Ohshimo S, et al. Diagnostic modalities in sarcoidosis: BAL, EBUS, and PET. Semin Respir Crit Care Med 2010; 31:404. [PubMed: 20665390].
[17] Tournoy KG, Bolly A, Aerts JG, et al. The value of endoscopic ultrasound after bronchoscopy to diagnose thoracic sarcoidosis. Eur Respir J 2010;35:1329. [PubMed: 19897553].
[18] Agarwal R, Srinivasan A, Aggarwal AN, et al. Efficacy and safety of convex probe EBUS-TBNA in sarcoidosis: a systematic review and meta-analysis. Respir Med 2012;106:883. [PubMed: 22417738].
[19] Navani N, Lawrence DR, Kolvekar S, et al. Endobronchial ultrasound-guided transbronchial needle aspiration prevents mediastinoscopies in the diagnosis of isolated mediastinal lymphadenopathy: a prospective trial. Am J Respir Crit Care Med 2012;186:255. [PubMed: 22652031].
[20] Andrade RS, Podgaetz E, Rueth NM, et al. Endobronchial ultrasonography versus mediastinoscopy: a single-institution cost analysis and waste comparison. Ann Thorac Surg 2014;98:1003. [PubMed: 25038020].
[21] Zhu J, Zhang HP, Ni J, et al. Endobronchial ultrasound-guided transbronchial needle aspiration for diagnosing mediastinal lymphadenectasis: a cohort study from a single center. Clin Respir J 2017;11:159. [PubMed: 25918974].
[22] Moller DR, Chen ES. Genetic basis of remitting sarcoidosis: triumph of the trimolecular complex? Am J Respir Cell Mol Biol. 2002; 27:391. [PubMed: 12356571].
[23] Moller DR, Forman JD, Liu MC, et al. Enhanced expression of IL-12 associated with Th 1 cytokine profiles in active pulmonary sarcoidosis. J Immunol 1996;156:4952. [PubMed: 8648147].
[24] Tolaney SM, Colson YL, Gill RR, et al. Sarcoidosis mimicking metastatic breast cancer. Clin Breast Cancer 2007;7:804. [PubMed: 18021484].
[25] Brincker H. Coexistence of sarcoidosis and malignant disease: causality or coincidence? Sarcoidosis 1989;6:31. [PubMed: 2657921].
[26] Caras WE, Dillard T, Baker T, et al. Coexistence of sarcoidosis and malignancy. South Med J 2003;96:918. [PubMed: 14513992].
[27] Shigemitsu H. Is sarcoidosis frequent in patients with cancer? Curr Opin Pulm Med 2008;14:478. [PubMed: 18664979].
[28] Toner GC, Bosl GJ. Sarcoidosis, "sarcoid-like lymphadenopathy," and testicular germ cell tumors. Am J Med 1990;89:651. [PubMed: 2173404].
[29] Leatham EW, Eeles R, Sheppard M, et al. The association of germ cell tumours of the testis with sarcoid-like processes. Clin Oncol 1992;4:89. [PubMed: 1313282].

[30] Rayson D, Burch PA, Richardson RL. Sarcoidosis and testicular carcinoma. Cancer 1998;83:337. [PubMed: 9669817].
[31] Paparel P, Devonec M, Perrin P, et al. Association between sarcoidosis and testicular carcinoma: a diagnostic pitfall. Sarcoidosis Vasc Diffuse Lung Dis 2007;24:95. [PubMed: 18496978].
[32] Kaikani W, Boyle H, Chatte G, et al. Sarcoid-like granulomatosis and testicular germ cell tumor: the "great imitator". Oncology 2011; 81:319. [PubMed: 22179558].
[33] Ravaglia C, Gurioli C, Casoni GL, et al. Sarcoid-like lesion is a frequent benign cause of lymphadenopathy in neoplastic patients. Eur Respir J 2013;41:54. [PubMed: 23456935].
[34] Jeurkar N, Mamtani R, Vaughn DJ. Granulomatosis and testicular germ cell tumors. Urology 2012;80:1303. [PubMed: 23102438].
[35] Askling J, Grunewald J, Eklund A, et al. Increased risk for cancer following sarcoidosis. Am J Respir Crit Care Med 1999;160:1668. [PubMed: 10556138].
[36] Suen JS, Forse MS, Hyland RH, et al. The malignancy-sarcoidosis syndrome. Chest 1990;98:1300. [PubMed: 2225992].
[37] International Germ Cell Cancer Collaborative Group. International germ cell consensus classification: a prognostic factor-based staging system for metastatic germ cell cancers. J Clin Oncol 1997;15:594. [PubMed: 9053482].
[38] Spagnolo P, Luppi F, Roversi P, et al. Sarcoidosis: challenging diagnostic aspects of an old disease. Am J Med 2012;125:118. [PubMed: 22269612].
[39] Chapman JT, Mehta AC. Bronchoscopy in sarcoidosis: diagnostic and therapeutic interventions. Curr Opin Pulm Med 2003;9:402. [PubMed: 12904711].
[40] Costabel U, Ohshimo S, Guzman J. Diagnosis of sarcoidosis. Curr Opin Pulm Med 2008;14:455. [PubMed: 20665390].
[41] Kantrow SP, Meyer KC, Kidd P, et al. The CD4/CD8 ratio in BAL fluid is highly variable in sarcoidosis. Eur Respir J 1997;10:2716. [PubMed: 9493649].
[42] von Bartheld MB, van Breda A, Annema JT. Complication rate of endosonography (endobronchial and endoscopic ultrasound): a systematic review. Respiration 2014;87:343. [PubMed: 24434575].
[43] Madan K, Mohan A, Ayub, et al. II, et al. Initial experience with endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) from a tuberculosis endemic population. J Bronchology Interv Pulmonol 2014;21:208. [PubMed: 24992128].