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Thromboembolic Events in Patients with Testicular Germ Cell Tumours Are Predominantly Triggered by Advanced Disease and by Central Venous Access Systems

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Keywords
Testicular germ cell tumour · Thrombosis · Pulmonary embolism · Cisplatin · Chemotherapy · Central venous access system

Abstract
Background: Thromboembolic events (TEEs) may significantly complicate the clinical management of patients with testicular germ cell tumours (GCTs). We analysed a cohort of GCT patients for the occurrence of TEEs and looked to possible pathogenetic factors. ***Patients, Methods:*** TEEs occurring within 6 months after diagnosis were retrospectively analysed in 317 consecutive patients with testicular GCT (median age 37 years, 198 seminoma, 119 nonseminoma). The following factors were analysed for association with TEE: histology, age, clinical stage (CS), chemotherapy, use of a central venous access device (CVA). Data analysis involved descriptive statistical methods with multivariable analysis to identify independent risk factors. ***Results:*** Twenty-three TEEs (7.3%) were observed, 18 deep vein thromboses, 4 pulmonary embolisms, and 1 myocardial infarction. Univariable risk calculation yielded the following odds ratios (ORs) : >CS1 OR = 43.7 (95% confidence intervals [CIs] 9.9–191.6); chemotherapy OR = 7.8 (95% CI 2.3–26.6); CVA OR = 30.5 (95% CI 11.0–84.3). Multivariable analysis identified only CS > 1 (OR = 16.9; 95% CI 3.5–82.4) and CVA (OR = 9.0; 95% CI 2.9–27.5) as independent risk factors. ***Conclusions:*** Patients with CSs >CS1 are at significantly increased risk of TEEs even without chemotherapy. Particular high risk is associated with the use of CVA devices for chemotherapy. Caregivers of GCT patients must be aware of the particular risk of TEEs.

Introduction

Testicular germ cell tumour (GCT) represents a paradigm of a curable malignancy, and treatment-related complications are increasingly becoming a therapeutic challenge [1]. Although the hypercoagulable state of cancer patients is well-established knowledge since Trousseau's pioneering work in 1865 [2], thromboembolic events (TEEs) in GCT patients had not been considered a major problem [3], until 1987 when 3 cases of pulmonary embolisms (PEs) in GCT patients undergoing cisplatin-based chemotherapy were reported [4]. The events were considered to result from vascular damage caused

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by the drugs. Thrombosis triggered by the disease itself had been first suggested in 1988 [5]. Bulky lymphadenopathy with pelvic vein compression and consecutive reduction of intravenous blood flow was considered to be 1 important pathogenetic mechanism for thrombosis. Today, there is consensus that 3 factors contribute to TEEs in GCT patients: (1) cancer itself as a prothrombotic state, (2) compression of abdomino-pelvic veins by metastases, and (3) cisplatin-based chemotherapy may cause intravasal damage and may, thus, trigger intravasal and even intra-arterial coagulation [6–8]. Additional factors may further activate the cascade of intravasal coagulation such as older age, surgery, bed rest, corticosteroid application [6], genetic predisposition (e.g., Factor V Leiden mutation) [9], and possibly, venous access systems [10]. Currently, only little information regarding the overall frequency of TEEs in GCT patients is available since most of the recent reports had exclusively looked to patients receiving chemotherapy [11–22]. Particularly, the role of central venous access systems (CVAs) and the utility of anticoagulant therapy for prevention of TEEs are unresolved problems [10, 15, 19, 20]. The aims of this study are to evaluate the incidence and clinical features of TEEs in a cohort of testicular GCT patients of all stages, to look to possible clinical risk factors, and to compare the findings with previous reports.

Methods

Patients

All patients treated for testicular GCT at the Asklepios Klinik Altona, Hamburg, during January 2010–June 2020 were retrospectively analysed for TEEs occurring at diagnosis or within 6 months after completion of treatment. TEE was defined as a partial or complete occlusion of veins or arterial vessels by thrombosis as documented with imaging techniques. Superficial thrombophlebitis was not included. We registered time and location of TEE occurrence as well as clinical management. To look for risk factors, we noted histology (seminoma, nonseminoma), age (categories ≤40, 40–50, >50 years), Lugano clinical stage (CS), treatment (no chemotherapy, adjuvant carboplatin chemotherapy, cisplatin-based chemotherapy 1–2 cycles, >2 cycles of cisplatin-based chemotherapy), and employment of CVA devices (yes/no). Upon surgical procedures, all patients had been given prophylactic low-molecular weight heparin treatment. Patients undergoing cisplatin-based chemotherapy received anticoagulant treatment during hospital stay since 2017. CVA systems for the administration of cisplatin-based chemotherapy had been used during 2010–2017.

Ethical approval was given by Ärztekammer Hamburg on June 2, 2020 (PV7288). All study activities had been conducted according to the Declaration of Helsinki of the World Medical Association.

Table 1. Patients characteristics

Patients subgroup	Eligible, *n*	(%)	Age median, years	Age IQR, range, years
All GCT	317		37	31–47; 16–78
Seminoma	198	62.5	39.5	34–48; 18–78
Nonseminoma	119	37.5	31	26–38; 16–69
CS 1	239	75.4	37	31–44; 16–78
CS 2a,b	40	12.6	36.5	29.5–47.5; 18–60
CS 2c	18	5.7	47.5	43–53; 32–63
CS 3	20	6.3	32	23–45; 18–69

GCT, germ cell tumour; IQR, interquartile range; CS, clinical stage.

Literature Survey

The literature was searched for reports on TEEs in GCT patients by using the PubMed data base and additional hand search. Only cases series published since 2000 were included. The results were tabulated and analysed descriptively.

Statistical Analysis

Statistical analysis was performed with SAS software package version 9.4 (SAS Institute, Cary, NC, USA) on windows platform and involved calculation of median ages with interquartile ranges and calculation of relative proportions with exact Clopper-Pearson 95% confidence intervals (CIs). For comparison of relative proportions, the χ^2 test was employed. Odds ratios (ORs) with 95% Wald CIs were calculated using logistic regression to estimate the relative risk of TEE regarding various factors. In subgroups without TEEs exact conditional analyses with median unbiased estimates and exact 95% confidence limits were provided. For testing the significance of ORs, Wald χ^2 tests were employed considering $p < 0.05$ as significant. To look for independent risk factors, we employed logistic regression modelling using a stepwise procedure to identify parameters independently influencing the rate of TEEs.

Results

A total of 317 consecutive patients with GCT were included, clinical characteristics are summarized in Table 1. Twenty-three TEEs (7.3%; 95% CI 4.65–10.69) were recorded, and clinical details of individual patients are listed in online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000512055. Seven of the 23 patients developed TEE before the start of cisplatin-based chemotherapy. Eight TEEs occurred despite anticoagulant therapy. Seventeen of the TEE patients had CVAs, and the event was mostly located in the vein where the CVA was placed. TEE was located in the lower limbs in 6 cases, in the abdominal/pelvic veins in 3, and in port

Table 2. Frequencies of TEEs in subgroups

Variable	Eligible (*n*)	Frequency of TEEs, *n*	%	95% CIs	*p* value*
Histology					
Seminoma	198	12	6.1	3.17–10.35	0.29
Nonseminoma	119	11	9.24	4.71–15.94	
CS					
CS 1	239	2	0.8	0.1–2.99	<0.001
CS 2a,b	40	11	27.5	14.6–43.89	
CS 2c	18	4	22.2	6.41–47.64	
CS 3	20	6	30.0	11.89–54.28	
CVA					
CVA (no)	275	6	2.2	0.8–4.69	<0.001
CVA (yes)	42	17	40.5	25.63–56.72	
Type of chemotherapy					
No chemotherapy	161	3	1.9	3.9–5.35	<0.001
Carboplatin mono	52	0	0	0	
≤2 cycles cisplatin	33	1	3.0	0.08–15.76	
>2 cycles cisplatin	71	19	26.8	16.94–38.59	
Age-groups					
≤40 years	201	15	7.5	4.24–12.01	0.958
41–50 years	68	5	7.4	2.4–16.3	
>50 years	48	3	6.3	1.31–17.2	

CI, confidence interval; CS, clinical stage; CVA, central venous access; TEE, thromboembolic events. * χ^2 test.

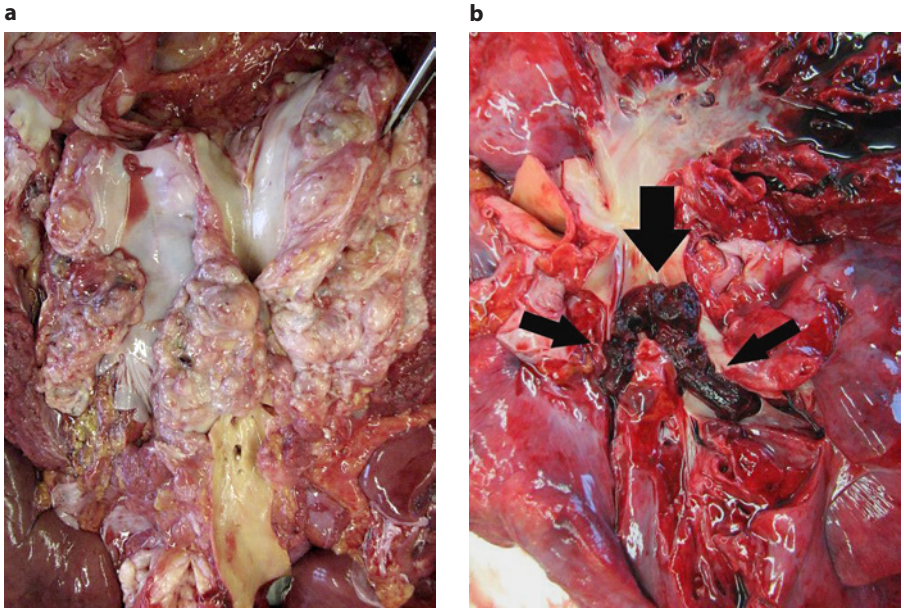

Fig. 1. a Autopsy finding of a 19-year-old patient who deceased subsequent to PE. Pelvic veins are surrounded and compressed by teratomatous metastatic tissue. PE, pulmonary embolism. **b** Autopsy finding, same patient: pulmonary arteries are obstructed by large blood clots. Clinical diagnosis: fatal PE. PE, pulmonary embolism.

system or upper limbs in 11. PE was noted in 4 patients, 2 of whom had no other venous thrombosis. One patient succumbed to PE 3 days after orchiectomy. Autopsy revealed huge intra-abdominal lymph node metastases compressing the pelvic veins and large thromboembolic deposits in the pulmonary arteries (Fig. 1). One patient developing myocardial infarction had been reported previously [23].

The relative frequencies of TEEs in various subgroups are listed in Table 2. By far, the highest frequency of 40.5%

Table 3. Calculated TEE risk ratios according to clinical factors

Reference group	TEE, %	Comparison group	TEE, %	OR	95% CI	*p* value
Seminoma	6.1	Nonseminoma	9.24	1.579	0.674–3.700	0.293
CS1	0.84	>CS 1	26.9	43.657	9.949–191.58	<0.001
CS1 + CS2a,b	4.7	CS2c + CS3	26.3	7.308	2.936–18.186	<0.001
No chemotherapy	1.9	Any chemotherapy	12.8	7.745	2.253–26.627	0.001
No chemotherapy	1.9	Carboplatin mono	0	0.799*	0–5.328*	0.859*
Carboplatin mono	0	Any cisplatin chemotherapy	19.2	17.177	3.637–inf*	<0.001*
Carboplatin mono	0	>2 cycles cisplatin chemotherapy	26.8	26.091*	5.473–inf*	<0.001*
Age ≤40 years	7.5	Age >40 years	6.9	0.919	0.377–2.237	0.852
CVA no	2.2	CVA yes	40.5	30.487	11.027–84.286	<0.001

OR, odds ratio; CS, clinical stage; CVA, central venous access; CI, confidence interval; TEE, thromboembolic events. * Exact conditional analysis with unbiased estimate and exact 95% CIs.

was found in patients with CVA. A rate of 19.2% was observed in patients with cisplatin chemotherapy compared to no TEE in those receiving adjuvant carboplatin. CS >1, any chemotherapy, chemotherapy with cisplatin, and the use of CVA represent statistically significant risk factors by univariable calculation (Table 3). However, multivariable analysis revealed that only CS > 1 (OR = 16.95) and the use of CVA (OR = 9.0) were independent risk factors (online suppl. Table 2). If only patients receiving cisplatin-based chemotherapy (n = 104) are considered, CVA involves a 14.17 fold increased risk of developing TEE ($p < 0.001$; online suppl. Table 3). The literature search yielded 15 studies on TEEs in GCT patients (Table 4) thereof only one reporting on all GCT patients (i.e., including those without chemotherapy) [24].

Discussion

The central result of our study is that TEEs represent a clinically relevant problem in patients with testicular GCT in spite of their young age. The risk of TEE is significantly increased in patients with CS >1 and in those with CVA systems.

Previous studies documented frequencies of 8.1–26% in GCT patients receiving cisplatin-based chemotherapy, and the 19.2% rate found in our patients undergoing chemotherapy is well in line with these results. No events were recorded after adjuvant carboplatin therapy. However, this observation does probably not relate to a possibly less thrombogenic effect of carboplatin compared to cisplatin since none of these patients had any particular risk factors except for the diagnosis of cancer.

Of note, 7 patients (30%) developed events without chemotherapy, and obviously, this observation provides more evidence for the contribution of disease-related factors for the development of TEEs. The significance of large volume metastases compressing abdominal or pelvic veins with consecutive activation of the intravasal coagulation cascade was clearly defined in the seminal report of Cantwell et al. [5] and later confirmed by others [7, 8, 15, 19, 21]. In our evaluation, we did not employ the Khorana score [25] for risk assessment because that score was developed in a general population of cancer patients that is substantially dissimilar to a typical population of GCT patients.

In our analysis of risk factors, cisplatin chemotherapy involved a significantly elevated risk of TEE in univariable analysis, and even a clear dose-relationship was found. This result is consistent with the existing evidence for acute vascular damage from cisplatin therapy in both the arterial and venous system [26, 27].

However, upon multivariable analysis, cisplatin chemotherapy lost significance and only CS >CS1 and CVA remained significantly associated with TEE. This result is probably explained by the fact that most of the patients receiving chemotherapy are characterized by advanced disease. The inferior role of cisplatin-based chemotherapy compared to advanced disease stage as found in our study is at variance with many of the previous reports on TEE in GCT patients.

However, except for 1 report [24], all of the investigations on TEE in GCT patients had only looked to patients undergoing chemotherapy and were, thus, inappropriately designed to analyse independent disease-related factors precipitating TEEs. Yet, many of the previous reports

Table 4. Frequencies of thromboembolic events in previous series

First author	Year	Country	Sample size, *n*	TEE, %	Risk factors identified	Remarks
Series of patients with cisplatin-based chemotherapy						
Weijl et al. [6]	2000	NL	179	8.4	>80 mg dexamethasone(cycle, liver mets)	Arterial events included
De Haas et al. [11]	2010	NL	324	8.1		Arterial events excluded
Honecker et al. [15]	2013	Germany	193	11	CVA; CS >1	80% of events occurred before start of chemotherapy
Srikanthan et al. [18]	2015	Canada	216	10	Large lymphadenopathy, high Khorana score, IGCCCG intermediate and poor prognosis	
Gizzi et al. [13]	2016	France	279	14	Increased LDH; nonseminom histology; large lymphadenopathy	Superficial thromboses were included; low dose heparin reduced risk by 50%
Solari et al. [17]	2016	Germany	93	23.7		Arterial events included; prophylactic heparin treatment not efficacious
Worst et al. [20]	2016	Germany	109	9.2		CVA same frequency of TEE but more serious complications
Lubberts et al. [12]	2016	NL	73	11		Four arterial events included
Gonzalez-Billalabeitia et al. [8]	2017	Spain	416	9		25% of all events occurred before start of treatment; TEE impaired survival rate
Heidegger et al. [14]	2017	Germany	153	26	CS ≥2c	50% of patients with TEE had heparin prophylactic treatment
Bezan et al. [24]	2017	Austria	286	10.5	CS >1, large lymphadenopathy	TEE before treatment were excluded
Tran et al. [19]	2019	International	1,135	13.2	Large lymphadenopathy; IGCCCG intermediate/poor; increased LDH; Khorana >3; CVA	
Nitta et al. [21]	2020	Japan	121	21.5	Large lymphadenopathy; increased LDH	50% of TEE occurred before start of treatment
Paffenholz et al. [16]	2019	Germany	255	19	CS ≥2c; increased LDH; CVA; febrile neutropenia	Impaired survival of patients with TEE
Thorsen et al. [22]	2020	Norway	17	18	High-intensity training	
Present series	2020	Germany	104	19.2		
Series with all GCT patients (all stages, all treatment modalities)						
Bezan et al. [24]	2017	Austria	657	5.2		
Bezan et al. [24]	2017	Switzerland	349	5.2		
Present series	2020	Germany	317	7.3		

CS, clinical stage; CVA, central venous access device; TEE, thromboembolic event.

had noted TEEs occurring before the start of chemotherapy [8, 15, 21] and that observation clearly points to the pathogenetic relevance of disease-related factors such as advanced disease and vein compression by bulky metastases. Instead, arterial occlusive events observed during chemotherapy [23, 28] are obviously triggered by the known endothelial damage caused by cisplatin [27] rather than by disease-related factors. In aggregate, our results suggest that the pathogenesis of TEE in GCT patients is predominantly associated with advanced stage of the disease and to a lesser degree with cisplatin-based chemotherapy.

Apart from advanced disease, only the use of CVA was shown to be an independent predisposing factor for TEE involving a 14-fold increased risk of TEE in patients receiving cisplatin-based chemotherapy. Accordingly, thrombosis was always located close to the site of the CVA in these cases. The use of CVAs has always been a matter of dispute in GCT patients. Although low TEE rates of 6.3% [20] and 8.1% [29] had been reported, some authors strongly cautioned the use of CVAs [15, 16, 19]. Recent reviews encompassing patients of a wide oncological spectrum revealed that the incidence of TEEs in CVAs varies among patient populations, underlying disease, catheter types, and vein cannulated [30, 31].

One reason for the strikingly high rate of TEEs in patients with CVA in our series (40%) may relate to the omission of thrombo-prophylactic therapy in the majority of cases. But noteworthy, 2 patients with CVA developed TEE despite anticoagulant therapy. Accordingly, the efficacy of anticoagulant therapy to prevent CVA-associated thrombosis is controversial [16, 17, 30, 32]. The majority of investigations, however, found at least a reduction of TEE rates of 40–50% through anticoagulant therapy in patients with CVA [13, 24, 33]. In summary, there is clear evidence for the high risk of TEE imparted by CVA devices. Thrombo-prophylactic therapy with low-molecular-weight heparin does not prevent such events but significantly reduces the risk.

Limitations of the present study involve the retrospective character of the survey. As only chart reviews were performed, some TEEs might have been missed. A detailed analysis of other risk factors such as BMI, smoking habits, and serum levels of lactate dehydrogenase was not possible because these data were not always available. Our patient cohort is not homogeneous with respect to standards of care, since CVAs had only been used during 2010–2017, and routine anticoagulant therapy is given only since 2017. One strength of our evaluation could be the fact that the analysis was not restricted to patients undergoing chemotherapy but that all GCT patients were included.

Conclusion

We noted a TEE rate of 7.3% in the entire population of GCT patients, and the incidence was 26.3% in advanced stages. TEEs are a relevant problem that may complicate the clinical management of GCT patients. CS >CS1, and the use of CVA systems were identified as independent risk factors. Practically, the use of CVA systems should be avoided in GCT patients whenever possible. Prophylactic anticoagulant therapy is advised in all patients undergoing cisplatin-based chemotherapy, but TEEs cannot be prevented in all cases.

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Statement of Ethics

Ethical approval was provided by Ärztekammer Hamburg (PV7288, June 2, 2020). All study activities had been conducted according to the Declaration of Helsinki of the World Medical Association (as amended by the 64th General Assembly, 2013).

Conflict of Interest Statement

All authors declare no conflicts of interest.

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Author Contributions

Study concept: K.P.D. and C.W.; ascertainment of clinical data: D.M., C.W., and K.P.D.; statistical analysis: U.P.; interpretation of data: K.P.D., U.P., D.M., and C.W.; manuscript writing: K.P.D. and U.P. All authors critically reviewed and finally approved the manuscript.

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