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ORIGINAL SCIENTIFIC REPORT

Hypercoagulability After Resection of Thoracic Malignancy: A Prospective Evaluation

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Abstract

Background Rates of venous thromboembolism are increased in thoracic malignancy; however, coagulation patterns are not established. We hypothesize that patients with esophageal and lung malignancy have similar hypercoagulable pre- and postoperative profiles as defined by rotational thromboelastometry (ROTEM).

Methods Prospective study was conducted in 47 patients with esophageal and lung cancer undergoing surgical resection. ROTEM evaluated pre/postoperative coagulation status.

Results Patients with thoracic malignancy were hypercoagulable by ROTEM, but not by conventional coagulation tests. Preoperative hypercoagulability was higher in lung versus esophageal cancer (64 vs. 16%, $p = 0.001$). Lung cancer patients that were hypercoagulable preoperatively demonstrated decreased maximum clot firmness (MCF) ($p = 0.044$) and increased clot time ($p = 0.049$) after surgical resection, suggesting reversal of hypercoagulability. Resection of esophageal cancer increased hypercoagulability (16 vs. 56%, $p = 0.002$) via elevated MCF (reflecting platelet activity). Hypercoagulability remained at follow-up clinic for both lung and esophageal cancer patients.

Conclusions Hypercoagulability in patients with lung malignancies reversed following complete surgical resection, whereas hypercoagulability occurred only postoperatively in those with esophageal malignancies. In both, hypercoagulability was associated with fibrin and platelet function.

Introduction

Lung and esophageal malignancies are associated with elevated risk of venous thromboembolism (VTE) [1–3] which increase complications and cost [4]. Deep vein thrombosis (DVT) and pulmonary embolism (PE) increase mortality fivefold after cancer operations [5]. Coagulation changes in these patients are related to patient comorbidities, tissue factor displayed by tumor, and effects of chemotherapy and surgical resection [6–9].

Rotational thromboelastometry (ROTEM) is a viscoelastic test and represents a global assessment of coagulation. Previous studies in trauma patients [10–14] and in select populations of cancer patients [15–17] diagnosed coagulopathy using ROTEM.

We previously reported ROTEM distinguishes preoperative hypercoagulability in those with abdominal malignancy [18]; hypercoagulability increases after resection, persists for at least 1 month postoperatively, and returns to baseline at 6–12 months [19, 20]. Previous studies in thoracic surgery have evaluated coagulation profiles, but did not identify preoperative hypercoagulability or obtain samples after hospital discharge [21–23]. We hypothesize

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that patients with esophageal and lung malignancies have similar pre- and postoperative coagulation profiles.

Materials and methods

We conducted a prospective observational study with informed consent and IRB approval at Jackson Memorial Hospital and Sylvester Comprehensive Cancer Center at the University of Miami from 2/2011 to 8/2015. A total of 119 patients underwent lung or esophageal resection with nonconsecutive enrollment of 51, 4 of whom were excluded because the disease was benign or unresectable. Of 56 esophageal cancer patients, 25 were enrolled from February 2011 to November 2012 in the clinic of one surgical oncologist (ASL). Of 63 lung cancer patients, 22 were enrolled from March 2013 to August 2015 in the clinic of one thoracic surgeon (DMN), with an 11-month period without lung cancer patient enrollment.

Peripheral blood was obtained preoperatively, postoperatively (postoperative day 1), and after hospital discharge in outpatient clinic (approximately 2 weeks), as previously described [19]. Cases without follow-up clinic samples were secondary to unsuccessful venipuncture or patient refusal of venipuncture at that visit.

As previously described, samples were analyzed within 2 h with ROTEM® (Durham, NC). Citrated blood was mixed with calcium chloride for recalcification (20 µL of 0.2 mol/L star-TEM reagent). ROTEM was analyzed using INTEM, EXTEM, and FIBTEM pathways. INTEM analyzes the contact activation or intrinsic pathway, and represents a comprehensive overview of coagulation. INTEM analyzes coagulation factors I, II, V, VIII–XII, contribution of platelets, fibrinogen, and effect of heparin. EXTEM analyzes the tissue factor or extrinsic pathway, and also represents an overview of coagulation factors I, II, V, VII, X, contribution of platelets, and fibrinogen/fibrinolysis. However, the effect of heparin is not measured in EXTEM. The clinical utility of the INTEM and EXTEM assays is to help discriminate which factor or blood product requires replenishment. FIBTEM eliminates the effect of platelets and analyzes only fibrin contribution to coagulation, thereby detecting fibrinogen deficiencies or fibrin polymerization disorders [19].

We analyzed ROTEM parameters with published reference values. The time to initial clot aggregation is clot time (CT). The time measured in seconds between initial clot formation and clot strength of 20 mm is clot formation time (CFT). Alpha represents the quickness of clotting. Maximum clot firmness (MCF) analyzes the largest size of clot and reflects clot quality. Hypercoagulable changes are represented with reduced CT and/or CFT and elevated MCF and/or alpha. Patients having at least one of the nine ROTEM variables outside reference values (CT, CFT, MCF, Alpha in EXTEM; CT, CFT, MCF, Alpha in INTEM; MCF in FIBTEM) were defined as hypercoagulable.

Conventional coagulation markers prothrombin time (PT), international normalized ratio (INR), and partial thromboplastin time (PTT) were ordered at the discretion of the surgical team. INR below normal reference range (0.8–1.2) was considered hypercoagulable. Staging is reported with the American Joint Committee on Cancer (AJCC) criteria.

SPSS Ver. 21.0 (IBM Corporation, Armonk, NY) was used for statistical analysis. Univariate analysis was performing using Student's t test or paired t test, as appropriate. Qualitative variables were compared using χ^2 test or Fisher's exact test. McNemar test was used for paired (non-independent data). For comparisons with greater than two groups, repeated measures analysis of variance (ANOVA) was performed. Bonferroni correction was also used. Data are presented as mean ± standard deviation. $p < 0.05$ was considered statistically significant.

Results

Forty-seven patients were included (68% male) aged 66 ± 10 years: 25 with esophageal (53%) and 22 with lung cancer (47%). Body mass index (BMI) was 26 ± 5 kg/m^2, and 77% had history of cigarette smoking. The mortality rate was 9% ($n = 4$)—12% ($n = 3$) for esophageal and 5% ($n = 1$) for lung cancer.

Clinic blood samples were obtained from 24 esophageal (96%) and 14 lung patients on an average of 13 days postoperatively (64%; Fig. 1). Conventional coagulation markers were ordered preoperatively in 33 patients. No patients were hypercoagulable based on preoperative INR; however, 33% were hypercoagulable based on preoperative ROTEM values (0 vs. 33%, $p = 0.0004$).

Three patients (6.4%) developed VTE; VTE rates were similar between esophageal and lung cancer patients (8 vs. 4.5%, $p = 1$). Two DVTs were diagnosed in patients with esophageal cancer: one 4 months postoperatively and one preoperatively. One PE occurred 11 days postoperatively after lung resection. The VTE and no VTE group had similar demographics and cancer staging. There were no significant differences in ROTEM values between groups.

Demographics and pathologic features of lung and esophageal cancer patients are reported in Table 1. There were no intraoperative complications during lung resection. During esophagectomy, three patients required blood transfusion and one required reoperation for bleeding. The most common stage was stage 1 (59%, $n = 13$) for lung cancer and stage 2 (32%, $n = 8$) for esophageal cancer.

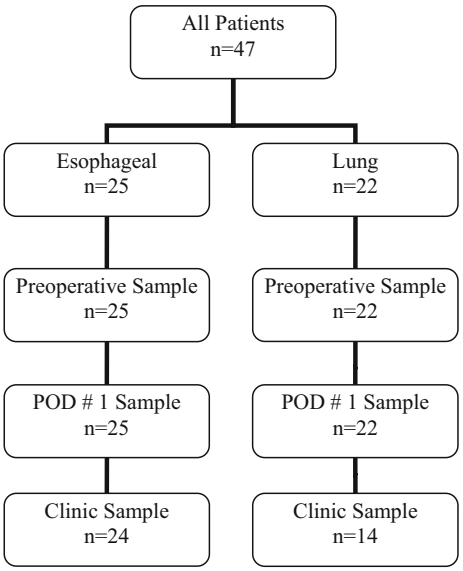

Fig. 1 Blood sample schedule. *POD* postoperative day

Table 1 Demographics and pathologic stage of lung and esophageal cancer

(n = 47)	Esophageal (n = 25)	Lung (n = 22)
Age, years	66 ± 11	66 ± 10
Gender, % male	92%	41%
Open surgery	92%	31%
Estimated blood loss, mL	300 (200)	50 (30)
Intraoperative time, min	252 ± 66	317 ± 59
BMI	27 ± 6	25 ± 4
Diabetes	24%	23%
Hypertension	40%	41%
Hyperlipidemia	44%	18%
Coronary artery disease	32%	32%
Smoking history	76%	77%
History of VTE	4%	0%
Aspirin/clopidogrel	12%	27%
Adenocarcinoma	88%	81%
pCR	16%	5%
Stage 1	20%	59%
Stage 2	32%	27%
Stage 3	24%	9%
Stage 4	8%	0%
Neoadjuvant chemo	72%	5%
Hypercoag pre-op	16%	64%
Hypercoag post-op	56%	46%
Hypercoag clinic	83%	71%
Mortality	12%	5%
VTE	8%	5%

Seventy-two percent (n = 18) of esophageal cancer patients received neoadjuvant treatment. For esophageal patients, preoperative hypercoagulability rates were not significantly different between those that received neoadjuvant treatment and those that did not (16.7 vs. 14.2%, p = 1). Only 1 lung cancer patient received neoadjuvant therapy, so analysis was not performed. Lung cancer patients were also more hypercoagulable preoperatively compared to esophageal cancer patients (64 vs. 16%, p = 0.001).

In lung cancer patients (n = 22), significant differences between preoperative and postoperative ROTEM values were not identified (Table 2). Hypercoagulability rates were unchanged after lung resection (64% preoperative vs. 46% postoperative, p = 0.219). Of 22 lung cancer patients, 14 had blood samples at follow-up clinic visit, and hypercoagulability rates persisted (50% postoperative vs. 71% clinic, p = 0.375).

In the subset of lung cancer patients who were hypercoagulable preoperatively (n = 14), postoperative ROTEM values tended to be reversed. Postoperative MCF (FIBTEM pathway) was significantly decreased (28.2 ± 8.6 vs. 24.0 ± 8.0, p = 0.044), and CT (EXTEM pathway) was significantly increased (55.4 ± 17.7 vs. 68.7 ± 20.9, p = 0.049). These changes reflect reversal of hypercoagulable status after lung resection. However, the apparent reduction in hypercoagulability rates did not reach statistical significance (100% preoperative vs. 64% postoperative, p = 0.063).

Of 14 patients, 8 had samples at all three time points (pre, post, clinic). For these eight patients, hypercoagulability rates were 100% pre-op, 62.5% post-op (n = 5), and 87.5% (n = 7) clinic. For pre-op versus clinic, INTEM MCF was significantly decreased (p = 0.019), and EXTEM CFT, alpha, and MCF were all significantly decreased (p = 0.033, 0.037, 0.02, respectively).

Lung cancer patients with stage 2 or stage 3 were hypercoagulable compared to stage 1 (Fig. 2); with decreased CFT (p = 0.032) and increased MCF (p = 0.002) and Alpha (p = 0.028) in the EXTEM pathway. Similar changes were seen in the INTEM pathway with decreased CFT (96.4 ± 54.4 vs. 51.5 ± 12.9, p = 0.027), increased MCF (59.6 ± 5.7 vs. 69.5 ± 6.3, p = 0.001), and increased Alpha (71.5 ± 8.3 vs. 79.4 ± 2.5, p = 0.012). Because the FIBTEM MCF and the INTEM MCF were both increased, the hypercoagulability depends on both the function of platelets and fibrin.

Esophageal cancer patients became hypercoagulable postoperatively (Table 3). MCF in the EXTEM (63.8 ± 4.3 vs. 65.8 ± 5.4, p = 0.047) and FIBTEM pathway (17.4 ± 3.8 vs. 21.7 ± 5.7, $p < 0.001$) were increased, which suggests that the hypercoagulability depends on both platelets and fibrin. Hypercoagulability

Table 2 Pre- versus postoperative ROTEM values in lung cancer

(*n* = 22)	Reference values	Pre-op	Post-op	*p*
INTEM				
CT	122–208 s	183.7 ± 44.3	185.1 ± 68.3	0.916
CFT	45–110 s	80.0 ± 48.7	106.6 ± 146.4	0.434
MCF	51–72 mm	63.2 ± 7.5	62.9 ± 9.7	0.881
Alpha	70–81°	74.4 ± 7.7	74.4 ± 5.0	0.972
EXTEM				
CT	43–82 s	59.7 ± 18.4	66.7 ± 17.2	0.146
CFT	48–127 s	82.9 ± 38.4	104.0 ± 107.8	0.401
MCF	52–70 mm	65.5 ± 7.5	64.2 ± 9.9	0.560
Alpha	65–80°	74.3 ± 6.7	73.9 ± 4.7	0.713
FIBTEM				
MCF	7–24 mm	23.2 ± 10.1	22.3 ± 8.5	0.444

s seconds, *mm* millimeter

rates significantly increased after esophagectomy (16% preoperative vs. 56% postoperative, $p = 0.002$) and remained hypercoagulable at follow-up clinic visit (56% postoperative vs. 83% clinic, $p = 0.109$). Stratifying ROTEM values based on esophageal cancer stage demonstrated significant differences in EXTEM CT ($p = 0.031$). There were no significant differences in CT in the INTEM pathway, and no differences in MCF or Alpha (Table 4).

Discussion

This study provides new data on VTE risk stratification, optimal VTE thromboprophylaxis regimens, and duration of thromboprophylaxis in patients with lung and esophageal malignancies. We also confirm that ROTEM identified a hypercoagulable state that was not detected by conventional coagulation markers, which is consistent with several other studies [15, 24–27].

Lung cancer patients have higher preoperative rates of hypercoagulability than esophageal cancer patients. Preoperative hypercoagulability did not change with advanced esophageal stage. However, hypercoagulable changes were more pronounced with advanced lung cancer stage, although this subgroup analysis was limited by the small sample size. Hypercoagulability tends to be reversed after surgical resection in lung cancer patients who were hypercoagulable preoperatively. Postoperative hypercoagulability persisted at least 1–2 weeks after surgery in both esophageal and lung cancer patients. The response to surgery was different between lung and esophageal cancer patients, and the postoperative hypercoagulability is most likely related to higher rates of open surgery for esophagectomy.

Hypercoagulability in lung and esophageal cancer patients was related to increased MCF. The INTEM MCF is primarily influenced by platelets with a lesser contribution of fibrin. FIBTEM eliminates the effect of platelets and analyzes only fibrin contribution to coagulation. Because INTEM, EXTEM, and FIBTEM MCF were all increased for lung cancer, and EXTEM and FIBTEM MCF were increased for esophageal cancer, the hypercoagulability is associated with both platelets and fibrin. We speculate that antiplatelet agents may reduce the VTE rate in patients with thoracic malignancies. Platelets have been implicated in the hypercoagulability of cancer [20] and trauma patients [28]. Prospective studies are ongoing in trauma patients to evaluate the effectiveness of adding antiplatelet agents to standard VTE prophylaxis regimens. Future research is necessary to evaluate whether adding

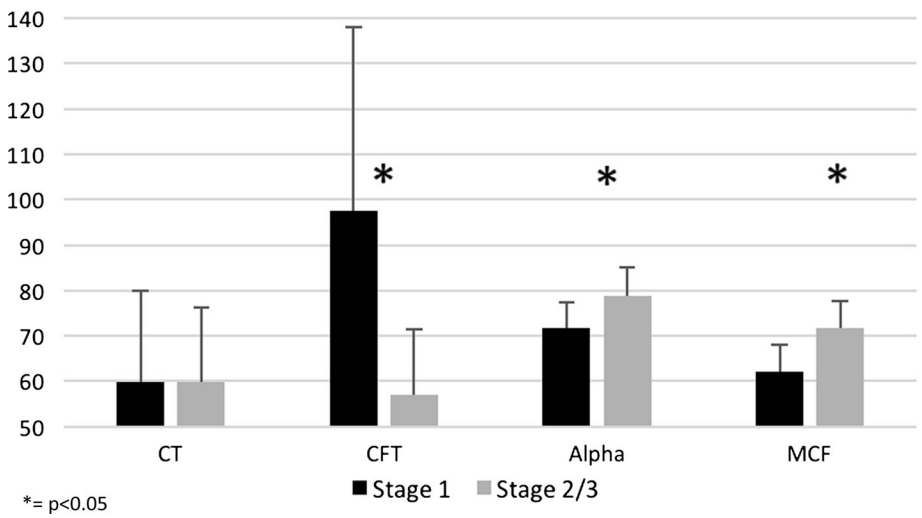

Fig. 2 ROTEM (EXTEM) values—lung cancer by stage

Table 3 Pre- versus postoperative in esophageal cancer

(n = 25)	Pre-op	Post-op	p
INTEM			
CT	166.6 ± 24.2	172.3 ± 26.2	0.463
CFT	82.0 ± 41.6	76.6 ± 21.9	0.550
MCF	60.2 ± 3.7	61.2 ± 5.4	0.282
Alpha	74.8 ± 6.6	75.3 ± 3.7	0.755
EXTEM			
CT	57.5 ± 14.6	61.7 ± 14.1	0.248
CFT	84.2 ± 24.8	79.0 ± 22.8	0.358
MCF	63.8 ± 4.3	65.8 ± 5.4	0.047
Alpha	74.6 ± 4.6	75.5 ± 4.5	0.388
FIBTEM			
MCF	17.4 ± 3.8	21.7 ± 5.7	<0.001

antiplatelet agents to thromboprophylaxis regimens can decrease VTE rates in those with thoracic malignancy.

VTE rates after esophagectomy and lung resection range from 7 to 14% [1, 2], and may in part be due to variation in thromboprophylaxis regimens. As many as 30% of thoracic surgeons may use sub-optimal dosing after esophagectomy [29]. Even standard thromboprophylaxis dosing may not be adequate for thoracic surgery patients. A recent prospective evaluation of Anti-Factor Xa levels with standard prophylaxis dosing of enoxaparin 40 mg daily in thoracic surgery patients found that 67% had inadequate Anti-Factor Xa levels [30]. Alternatively, esophageal cancer patients had more advanced disease at diagnosis compared to lung cancer patients, thus perhaps explaining the differences in the persistence of hypercoagulability after surgery.

CHEST guidelines recommend extended duration chemical thromboprophylaxis regimens (4 weeks) for postoperative patients with abdominal/pelvic malignancy [31]. However, there are no recommendations for patients with thoracic malignancy. Recently, the Society for Translational Medicine published guidelines for the prevention of VTE after lung cancer resection [32]. However, these guidelines are limited due to their reliance on patients from general surgery rather than thoracic surgery [33]. The National Surgical Quality Improvement Program (NSQIP) database was recently reviewed for all anatomic lung resections. The VTE rate was 1.6%; 44% of VTE was diagnosed in the outpatient setting [34]. Since we observed hypercoagulability for at least 2 weeks after surgical resection, our data support extended duration thromboprophylaxis regimens.

Risk assessment models such as the Caprini score identify patients undergoing esophagectomy and lung resection who are at increased risk of VTE [1, 2]. Sterbling et al. implemented Caprini scoring for patients undergoing anatomic lung and esophagectomy. Those deemed moderate/high risk were discharged home on extended thromboprophylaxis regimens. They found a trend toward decreased VTE rates in the Caprini score/extended duration cohort compared to historical controls (7.3 vs. 3.1%, p = 0.28) [35, 36]. ROTEM provides a viscoelastic measurement of a patient's coagulation status, which is not taken into account by the Caprini score. Incorporation into risk assessment models could result in better identification of high-risk patients.

Our study demonstrates that ROTEM can detect hypercoagulability in thoracic malignancy. ROTEM and TEG (Haemonetics, Braintree, MA) are viscoelastic assays

Table 4 Esophageal cancer by stage—preoperative samples

	pCR (n = 4)	Stage 1 (n = 5)	Stage 2 (n = 8)	Stage 3 (n = 6)	Stage 4 (n = 2)	p
INTEM						
CT	156.3 ± 17.1	152.6 ± 16.0	173.4 ± 20.6	184.5 ± 28.8	142.0 ± 8.5	0.060
CFT	73.5 ± 10.3	73.6 ± 17.9	80.9 ± 17.2	95.3 ± 84.7	84.0 ± 26.9	0.926
MCF	60.0 ± 1.8	60.0 ± 2.9	59.9 ± 3.7	62.2 ± 4.7	57.0 ± 5.7	0.545
Alpha	76.3 ± 2.1	76.8 ± 2.7	74.6 ± 3.1	72.3 ± 13.0	75.5 ± 3.5	0.846
EXTEM						
CT	52.5 ± 16.1	49.6 ± 11.8	53.9 ± 6.6	73.3 ± 15.6	54.0 ± 15.6	0.031
CFT	80.0 ± 15.8	82.2 ± 14.1	86.9 ± 21.3	82.5 ± 42.0	91.5 ± 30.4	0.983
MCF	63.8 ± 2.2	63.4 ± 2.8	63.5 ± 4.4	65.7 ± 6.3	61.0 ± 5.7	0.759
Alpha	76.5 ± 1.7	74.8 ± 2.6	74.3 ± 3.6	73.8 ± 7.8	73.5 ± 7.8	0.924
FIBTEM						
MCF	18.8 ± 2.2	16.4 ± 3.5	17.9 ± 4.4	17.0 ± 4.9	17.0 ± 4.2	0.920

pCR complete pathologic response

reporting a global examination of coagulation. Both identify patients at risk of VTE who are hypercoagulable [28, 37, 38]. They share similar viscoelastic principles and in general report the same parameters (with different names). In our experience, both provide reliable results, and either can be incorporated into routine clinical care. There is no consensus for what values are hypercoagulable; however, previous studies have used our definition of ROTEM, i.e., values outside of the established reference range [39].

There are several practical implications of our study. ROTEM has higher sensitivity for detecting hypercoagulability than conventional coagulation markers and is a 'point of care' test with faster results than conventional and advanced coagulation markers. There are potential therapeutic interventions based on ROTEM findings. Elevated MCF is related to increased platelet activity and can be treated with antiplatelet therapy such as aspirin. Decreased CT/CFT is related to activity of plasmatic coagulation system and can be treated with increasing dosing of subcutaneous heparin. Cost-effectiveness has been demonstrated for identifying coagulopathy and decreasing blood product transfusions in cardiac surgery and liver transplants [40]. However, cost-effectiveness has not been studied for guiding VTE thromboprophylaxis in thoracic surgery patients.

Our study has several limitations. ROTEM results were not used for clinical decisions in this study. Patients were not enrolled consecutively introducing the potential for selection bias. Additionally, this case series at a single institution may not be representative of the general population. Sample size is another major limitation of our study, especially when performing subgroup analysis. However, a sample size analysis based on detecting differences between pre- and postoperative ROTEM values using paired analysis, an estimated effect size of 0.625, power of 0.8 and significance level of 0.05, estimated a necessary sample size of 22, precisely the size used in our study. ROTEM did not identify patients who developed VTE, which may be a type II error due to the small sample size and low rate of VTE. There were no patients with benign disease that served as a control group. Rather, each patient had repeated samples and served as their own control. VTE screening protocol with venous duplex ultrasound was not performed. ROTEM results were not compared to an advanced panel of hemostasis markers [such as protein C, prothrombin fragment $1 + 2$ antigen, coagulation factor VIII, antithrombin III, and plasminogen activator inhibitor-1 (PAI-1)] as our previous work found these hemostatic markers to be poor predictors of VTE at a significant additional cost [20]. Nevertheless, not including a panel of hemostatic markers for comparison is a limitation. Blood samples were not obtained in all patients at follow-up visits because venipuncture was unsuccessful, or patient refused venipuncture.

In conclusion, ROTEM identified a hypercoagulable state that was not detected by conventional coagulation markers. Future studies are needed to determine whether VTE rates can be decreased by utilizing ROTEM to optimize VTE risk stratification and thromboprophylaxis agents and duration. We cannot make conclusions about treatment regimens per se, but it seems that ROTEM is a promising diagnostic modality for detecting hypercoagulability in patients with thoracic malignancy.

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Compliance with ethical standards

Conflict of interest No conflicts of interest to declare.

Informed consent Institutional review board approval and informed consented was established.

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