Role of Anticoagulation in the Management of Tumor Thrombus: A 10 year single center experience

Shreya Agarwal[1], Dolores Mullikin[2], Valeria Smith[2], Michael Scheurer[1], Bindi Naik-Mathuria[1], Paul Guillerman[1], Jennifer Foster[1], Rosa Diaz[1], and Sarah Sartain[2]

[1]Texas Children's Hospital
[2]Baylor College of Medicine

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Abstract

Background: Children with cancer diagnosis are overall at a higher risk of thrombosis. For a newly diagnosed bland thrombus, patients are commonly started on anticoagulants to prevent further extension and embolization of the clot. In the rare instance that a pediatric patient has a tumor thrombus, the role of anticoagulation is less clear. Procedure/Methods: Patients under 21 years of age with a finding of tumor thrombus on imaging from 2010-2020 at Texas Children's Hospital were identified and their medical records were reviewed. Results: A total of 50 patients were identified. Most thrombi were incidental findings at diagnosis; however, there were two patients who presented with pulmonary embolism (PE). Inferior Vena Cava extension was noted in 36% of the patients and 24% patients had an intracardiac tumor thrombus. Hepatoblastoma (26%) was the most common malignancy associated with tumor thrombus. Anticoagulation was initiated in 10 patients (20%). Only 2 of these 10 patients showed response to anticoagulation. However, 40% (4/10) patients in the anticoagulation cohort were noted to have bleeding complications ($p < .05$). Conclusion: Children with intravascular extension of solid tumors were not commonly started on anticoagulation at the time of diagnosis, irrespective of the extent of tumor thrombus. Furthermore, we observed a significant trend toward higher incidence of bleeding complications after initiation of anticoagulation. There is inadequate evidence at this time to support routine initiation of anticoagulation in pediatric patients with intravascular extension of solid tumors.

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Shreya Agarwal, MD[1], Dolores Mullikin, MD[1], Michael E. Scheurer, PhD, MPH[1,2] , Valeria Smith, MD[1], Bindi Naik-Mathuria, MD MPH[3], Robert P. Guillerman, MD[4], Jennifer H. Foster, MD[1], Rosa Diaz, MD[1], Sarah E. Sartain, MD[1]

[1] Texas Children's Cancer and Hematology Center, Baylor College of Medicine, Houston Tx

[2] Center for Epidemiology and Population Health, Texas Children's Hospital, Baylor College of Medicine, Houston Tx

[3] Department of Surgery, Texas Children's Hospital, Baylor College of Medicine, Houston Tx

[4] Department of Radiology, Texas Children's Hospital, Baylor College of Medicine, Houston Tx

Corresponding Author: Shreya Agarwal, MD

Texas Children's Hospital

Hematology and Cancer Center

6701 Fannin Suite 1510

Houston, Texas

sa9@bcm.edu

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Abstract:

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Procedure/Methods : Patients under 21 years of age with a finding of tumor thrombus on imaging from 2010-2020 at Texas Children's Hospital were identified and their medical records were reviewed.

Results: A total of 50 patients were identified. Most thrombi were incidental findings at diagnosis; however, there were two patients who presented with pulmonary embolism (PE). Inferior Vena Cava extension was noted in 36% of the patients and 24% patients had an intracardiac tumor thrombus. Hepatoblastoma (26%) was the most common malignancy associated with tumor thrombus. Anticoagulation was initiated in 10 patients (20%). Only 2 of these 10 patients showed response to anticoagulation. However, 40% (4/10) patients in the anticoagulation cohort were noted to have bleeding complications ($p < .05$).

Conclusion: Children with intravascular extension of solid tumors were not commonly started on anticoagulation at the time of diagnosis, irrespective of the extent of tumor thrombus. Furthermore, we observed a significant trend toward higher incidence of bleeding complications after initiation of anticoagulation. There is inadequate evidence at this time to support routine initiation of anticoagulation in pediatric patients with intravascular extension of solid tumors.

INTRODUCTION:

Children with cancer are at increased risk for venous thrombosis (VT) or venous thromboembolism (VTE). This complication can manifest as bland thrombus or tumor thrombus[1,2]. Tumor thrombus is defined as the extension of the tumor into the vessel lumen, typically a vein. Incidence of tumor thrombus varies depending upon the type of cancer[3]. In children, it is most widely reported to be associated with Wilms tumor[4,5]. Although pathologic exam is the reference standard, imaging is very reliable and helps in early detection of tumor thrombus, without the use of any invasive technique[6].

Bland thrombus on the other hand, is a fibrin clot without neoplastic cells which may occur in patients with or without an underlying malignancy. Bland thrombus is thought to result from the interaction of various factors such as cancer type, presence of central venous catheters, chemotherapy and acquired or inherited prothrombotic defects, among others[1]. Cancer can also contribute to the development of bland thrombus by mechanical effects on the venous flow, as in those with solid tumors[2]. It is unknown if intravascular extension or tumor thrombus increase the risk for bland thrombus formation. Anticoagulation is sometimes administered in conjunction with cancer-directed therapy to this group of patients.

Available literature describing the treatment characteristics and outcomes of pediatric patients with solid tumor-associated tumor thrombus is limited, and there are no evidence-based studies to guide management.

The purpose of this study is to describe the role of anticoagulation in patients with tumor thrombus. We performed a retrospective review at a large pediatric tertiary care center to evaluate the clinical and treatment characteristics of patients with tumor thrombus, indications for starting anticoagulation, and rate of bland tumor formation and bleeding events for those treated with and without anticoagulation.

METHODS:

Ethics approval, including waiver of consent, was obtained from the BCM Institutional Review Board prior to data collection. We conducted a retrospective review of consecutive patients with tumor thrombus between January 2010 to May 2020 at Texas Children's Hospital (TCH)/Baylor College of Medicine (BCM).

Data collection:

Imaging studies, including computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography (US) and echocardiography, for all patients who were seen at TCH Cancer Center during the study period were pulled from the electronic medical record using the keywords "TUMOR" and "THROMBUS" in the final impression. Epic Clarity reporting database, based on the Oracle relational database management system, was used. Pulled data was written in the Oracle SQL Developer tool. Exclusion criteria included patients with age above 21 years or no finding of tumor thrombus on imaging. For patients meeting the criteria, the electronic medical records were comprehensively reviewed and following data collected: patient demographics, tumor type, imaging findings, treatment including chemotherapy, surgery, radiation, anticoagulation- dose, duration, rationale, and complications.

Definitions:

Therapeutic anticoagulation was defined as low molecular weight heparin (LMWH) dosed as 1 mg/kg subcutaneously (SQ) every 12 hours to attain anti-FXa levels between 0.5 to 1, or unfractionated heparin (UFH) administered intravenously to attain anti-FXa levels of 0.3 to 0.7 and/or PTT of 70 to 110 seconds. Prophylactic anticoagulation was defined as LMWH 0.5 mg/kg SQ every 12 hours to attain anti-FXa level between 0.2 to 0.4 or adult dose of 40 mg SQ daily.

Bleeding was defined per International Society on Thrombosis and Hemostasis (ISTH) guidelines. Non major or minor bleeding was defined as overt bleeding requiring blood product transfusion (not directly attributable to the patient's underlying condition), bleeding requiring medical or surgical intervention to restore hemostasis other than in the operating room, other bleeding for which medical attention has been sought and/or any overt macroscopic evidence of bleeding not fulfilling above criteria for major bleeding[7]. Major bleeding defined as fatal bleeding, symptomatic bleeding in a critical area or organ (like intracranial, intraocular, pericardial), and/or bleeding causing a fall in hemoglobin by 2 g/dL or more requiring transfusion of 2 or more units of while blood or red blood cells[8].

Outcomes:

Our primary outcomes were the percent of patients with tumor thrombus who received anticoagulation in combination with cancer-directed therapies and the rate of bland tumor formation in patients treated with or without anticoagulation.

Our secondary outcomes were all-cause mortalities; and the rate of clinically relevant, non-major or minor bleeding, and/or major bleeding.

Statistics:

Descriptive statistics were used to compare demographic and clinical characteristics between patients who did and did not experience a bleeding event at the end of our follow up period. The Chi squared test or Fisher's exact test, if less than 5 patients were in any given cell of the contingency table, was used to compare categorical variables. A two-sided p-value of 0.05 was used for statistical significance.

RESULTS:

On initial search of the medical records, 100 patients were identified. Of these, only 50 met the study criteria. A total of 50 patients were included in the final analyses. The remaining patients either did not meet the age criteria (below 21 years) or on further detailed review of the imaging, did not have a tumor thrombus. Patient characteristics are summarized in Table 1. Most patients (n=13, 26%) had hepatoblastoma, followed by osteosarcoma (n=7, 14%) (Figure 1). Eighteen patients (36%) had tumor thrombus confined to the inferior vena cava (IVC) and 12 patients (24%) had tumor thrombus extending beyond the IVC to the heart. For the remaining patients, tumor thrombus was limited to the invasion of local draining vessels. The diagnostic imaging modalities most frequently identifying tumor thrombus were CT (48%) and MRI (40%). Echocardiogram was performed for all patients who had an IVC or intracardiac tumor thrombus. Seventy percent (35/50) of tumor thrombus cases on imaging were confirmed by pathological examination. 31 of these 35 patients underwent surgical resection, and for the remaining patients, tissue for pathology was obtained on tumor biopsy (n=3) or during thrombectomy (n=1).

Overall, 5 patients received upfront surgery and 6 did not receive any cancer-directed therapy due to relapsed terminal disease. All others received pre-operative chemotherapy (n=39, 78%). Cardiac bypass was required in 5 of the 12 patients with intracardiac tumor thrombus at the time of surgical resection of the primary tumor and tumor thrombus.

OVERALL OUTCOMES

Anticoagulation use and rate of bland thrombus

A total of 10 (20%) patients with tumor thrombus received anticoagulation in combination with cancer-directed therapies. Patient and tumor thrombus characteristics are summarized in Table 2. Six patients received therapeutic doses of anticoagulation and 4 received prophylactic doses of anticoagulation. The rationale for starting anticoagulation was symptomatic tumor thrombus in 4 patients: pulmonary embolism (PE, n=2), renal vein thrombus (RVT, n=1) and lower extremity pain and swelling (n=1) concomitant to tumor thrombus diagnosis. Patient 6 was a teenager who relapsed with a right atrial thrombus identified on routine surveillance imaging after completing therapy and achieving complete remission of osteosarcoma. Despite therapeutic anticoagulation, she developed a symptomatic PE 1 week later which required urgent mechanical thrombectomy. Tissue specimen confirmed relapsed osteosarcoma and the anticoagulant was discontinued. She subsequently died of another PE. Patient 7 had newly diagnosed Ewing sarcoma treated with upfront radical nephrectomy and IVC tumor thrombectomy, which was confirmed by pathology. Routine scans obtained 2 weeks later, showed possible residual tumor thrombus in IVC surgical site and pulmonary infarcts with confirmation of PE via CT angiography. She was started on chemotherapy following the surgery. The finding of thrombus on repeat imaging was concerning for tumor thrombus vs a component of bland thrombus that might have developed post thrombectomy. Hence, she was started therapeutic anticoagulation in addition to chemotherapy for Ewings sarcoma. After 6 months of therapeutic anticoagulation and chemotherapy, repeat imaging studies showed complete resolution of IVC thrombus and PE. She ultimately died due to relapsed disease. Patient 8 had clear cell sarcoma with extensive tumor thrombus extending from IVC to common iliac and femoral veins. Chemotherapy was initiated soon after diagnosis, but anticoagulation was not started at that time. However, he presented a few weeks later with left lower leg pain and swelling. Repeat imaging showed the same extensive tumor thrombus and a new separate small occlusive thrombus in the superficial femoral vein which could be tumor thrombus vs bland thrombus. Given the patient was symptomatic, he was started on therapeutic anticoagulation. Leg pain and swelling resolved after 4 days and anticoagulation was discontinued at that point. Patient underwent surgical resection and IVC thrombectomy later and pathology confirmed the finding of tumor thrombus. Finally, patient 10 was started on therapeutic anticoagulation for occlusive renal vein tumor thrombus causing elevated creatinine, concerning for acute kidney injury. He received three months of therapeutic anticoagulation along with chemotherapy for metastatic embryonal carcinoma and repeat imaging at the end of three months showed improved blood flow through the renal vein. The other six patients had an asymptomatic tumor thrombus. Rationale for initiating anticoagulation in these patients was to prevent further progression and possible embolism of the bland thrombus component of the tumor from high risk locations (IVC and/or right atrium).

The follow up period for the cohort was a median of 13.5 months (range 1 month to 7 years). Of the patients with or without anticoagulation, none developed a subsequent bland thrombus and/or embolization secondary to tumor thrombus, although there was uncertainty about one patient: Patient 7 developed another thrombus post-surgical resection, but without pathologic exam, it was unknown if this was bland thrombus or a remnant of the previous tumor thrombus. A single patient developed a clearly catheter-associated deep vein thrombus not related to tumor thrombus 1 month after his cancer diagnosis.

Mortality and bleeding events

The all-cause mortality was 38% (19/50). The mortality rate for the anticoagulation and no anticoagulation groups was 30% (n=3) and 40% (n=16), respectively, and this was not statistically significant (p =.7222). These deaths were mostly related to cancer progression and one patient died of pulmonary embolism (patient 6).

A larger percentage of patients on anticoagulation had bleeding complications than patients who did not receive anticoagulation (p <.05) (Anticoagulation cohort: n=4, 40%; no anticoagulation cohort: n=2, 5%). Of the 4 anticoagulated patients who bled, 3 had gastrointestinal bleeding. One with massive post-op intra-abdominal bleeding requiring exploratory laparotomy, two with bloody stool with no notable drop in hemoglobin. One patient had mild epistaxis and gingival bleeding. Two of the 40 patients who did not receive anticoagulation had bleeding complications, including one with intra-operative hemorrhagic shock due to intra-tumoral bleeding. No statistical difference was noted for bleeding events based on gender, ethnicity, or the type of tumor.

DISCUSSION:

The major focus of this study was to review the role of anticoagulation in the treatment of tumor thrombus. Our study showed that a minority (20%) of patients with tumor thrombus at a large tertiary center received anticoagulation with the purpose of preventing bland thrombus formation and/or embolization. Furthermore, there was no significant difference in the rate of bland thrombus formation and/or embolization or in overall survival in pediatric patients with intravascular extension of a solid tumor or tumor thrombus treated with or without anticoagulation. Patients who received anticoagulation experienced a statistically significant increase in bleeding events.

Tumor thrombus is overall an uncommon clinical entity. However, its presence can complicate the management plan. Hence, early and accurate detection is helpful in surgical planning and in some cases, tumor staging [9,10]. Imaging is critical for early detection and differentiation from bland thrombus [11]. In adults, renal cell carcinoma, hepatocellular carcinoma, and adrenocortical carcinoma are the malignancies most frequently associated with tumor thrombus[12]; while in children, Wilms tumor has a tendency for vascular invasion [3,13]. In Wilms tumor, 20-35% patients have renal vein involvement, while extension into the IVC is reported in 4-10% of patients [4,13]. There are isolated case reports reporting vascular invasion and tumor thrombus in patients with Ewing sarcoma, osteosarcoma, neuroblastoma, and hepatoblastoma [14–17]. In our study, the most common malignancy associated with tumor thrombus was hepatoblastoma, followed by osteosarcoma and Wilms tumor.

Most of the patients were asymptomatic and tumor thrombus was detected on routine imaging, similar to the observation in previous studies[5,13]. However, two of our patients presented with PE and one with lower extremity pain and swelling. PE has been previously reported as a presenting sign of primary or relapsed osteosarcoma associated with tumor thrombus [18,19]. Yeduluri et al speculated that this could be attributable to the predilection of metastatic spread by vascular invasion in osteosarcoma[20]. Our patient with Ewing sarcoma had tumor thrombus-related PE, similar to a report by Dotson et al describing a patient with Ewing sarcoma who developed systemic emboli and myocardial infarction from tumor thrombus located in the left atrium[21].

Although chemotherapy, surgery, and/or radiation form the backbone of management of primary tumor and potentially, tumor thrombus, there is a risk of tumor rupture or spread with potential complications

such as PE or systemic emboli of bland thrombus components. This risk is particularly high in cases where tumor thrombus is located in the IVC or extending to the heart. Hence considering anticoagulation, either by prophylactic or therapeutic dosing, is not unreasonable. However, the use of anticoagulation for patients with tumor thrombus is inconsistent. While all Wilms tumor patients with intracardiac extension of the tumor received anticoagulation post-resection for a minimum of 3 months in a study by Cox et al [22], anticoagulation was not attempted in some other similar studies [4,13,23] and the results were comparable in terms of survival and response to treatment. In a review assessing OS patients with cardiovascular involvement, the authors reported one patient was on anticoagulation before the diagnosis of tumor thrombus was correctly established, but otherwise almost all patients received chemotherapy and/or surgery with no adjuvant anticoagulation with good outcomes [20]. In a study of patients with renal cell carcinoma, the most common tumor associated with tumor thrombus in adults, presenting with PE, 5 of the 7 patients received anticoagulation with either unfractionated heparin or enoxaparin; anticoagulation was held in the remaining two patients due to bleeding [24]. The authors' rationale was that patients with malignancy are already at a high risk for thrombosis and in the presence of an IVC tumor thrombus, there is additional disturbance of flow through the IVC, further increasing their risk of bland thrombosis or thromboembolism. In our patient cohort, we noted a similar approach by the providers in that most of patients did not receive anticoagulation, but it was initiated in 20% of the patients for management of signs or symptoms and/or to prevent further complications from progression of bland components of the tumor thrombus or thromboembolism. However, we want to emphasize that although anticoagulation could be helpful, the backbone of treatment of tumor thrombus is surgical with or without chemotherapy and radiation (when indicated) for the underlying malignancy [3]. This is supported by findings in our patient cohort. Our patient with relapsed osteosarcoma continued to have worsening tumor thrombus despite therapeutic anticoagulation until thrombectomy was performed, and despite initial improvement, had another episode of PE in the absence of cancer-directed therapy. In contrast, our patient with Ewing sarcoma received anticoagulation in conjunction with chemotherapy and surgery and had a complete resolution of the tumor thrombus. The underlying characteristics of tumor thrombus are different than bland thrombus making it more likely to resolve with chemotherapy and respond minimally to anticoagulation.

The benefits of anticoagulation must be weighed against the risks of bleeding. Malignancy itself places patients at a high risk of bleeding and thrombosis. In our dataset, 40% patients on anticoagulation developed bleeding, while this percentage was only 5% for the group not on anticoagulation. This difference in bleeding was statistically significant, which is not surprising given the use of anticoagulation in one group, but further underscores the importance of considering anticoagulation on a case-by-case basis.

There are some limitations of this study. The design is retrospective with subjects being identified by reported imaging findings. It is possible that some patients may not have been included if tumor thrombus was diagnosed intra-operatively but not appreciated on imaging, leading to underreporting of the finding in our study. This could possibly explain why there was a lower proportion of Wilms tumor thrombus in our study compared to other pediatric reports. Pathological confirmation was not made for all the suspected tumor thrombus cases, raising the possibility that some tumor thrombi may have a component of bland thrombus and hence, may have responded in part to anticoagulation. As a single center study, our sample size is small, limiting the statistical power to draw conclusions. Hence, further larger multi-center studies are to needed to confirm these findings.

In conclusion, this study reports the largest case series of pediatric tumor thrombus treated with or without anticoagulation in combination with cancer-directed therapy. An important advantage of our study over previous reports is that we focused on the role of anticoagulation in lessening the potential risk of bland thrombus formation and/or embolization in this cohort of patients since data is limited on this subject. We found no difference in rate of bland thrombus formation and/or embolization or survival in patients who did or did not receive anticoagulation. However, we did find a significantly higher rate of bleeding events in the anticoagulation group. Our study provides some practical information and guidance for clinicians considering the use of anticoagulation in these complicated patients both at risk for bleeding and clotting. While we found no clear evidence that anticoagulation administered in conjunction with cancer-directed

therapies improves outcomes in pediatric patients with tumor thrombus, further studies are indicated to identify subgroups that may benefit from thromboprophylaxis.

Conflict of Interest: Authors have no conflict of interest to disclose.

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Figure 1: Distribution of solid tumor malignancies with tumor thrombus in our patient cohort.

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