Late Vascular Occlusion of Central Lines in Pediatric Malignancies

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ABSTRACT. *Objective.* **To determine whether thrombi or vascular occlusion represent a late complication persisting several years after removal of central venous lines (CVLs) in children and adolescents treated for childhood cancer.**

Methods. **Children whose treatment for malignancy included placement of a CVL that had been removed at least 2 months previously were studied during scheduled follow-up that included contrast-enhanced computed tomography. Spiral volume acquisition was used to obtain 3-mm images from the chest apices through the right hilum, and three-dimensional reconstruction of angiograms was performed. Thrombosis/occlusion was defined as narrowing, obstruction, or filling defect of the deep venous system, with or without the formation of collateral veins. Charts were reviewed to document patient characteristics, previous CVL complications, administration of hyperalimentation, use of urokinase, and family history of venous thrombosis.**

Results. **Twenty-three patients treated for solid tumors and 2 treated for B-cell acute lymphocytic leukemia or lymphoma were studied. Lines had been in place from 0.2 to 36 months (median, 7.4) and were removed at 2.3 to 121.8 months (median, 32.5) before study. Nine patients received hyperalimentation for periods ranging from 2 to 38 weeks (median, 12). Four patients had required urokinase instillations, and one developed superior vena cava syndrome; 4 had a CVL-related infection (two superficial and two *Candida* line infections). Occlusion was seen on computed tomography angiograms in 3 of the 25 patients (12%; 95% confidence interval: 4.5–31%). One of the patients with occlusion had superior vena cava syndrome; none had a family history of thrombosis, use of a double lumen CVL, or multiple instillations of urokinase.**

Conclusions. **Persistent asymptomatic vascular occlusion does occur as a late complication of CVL placement for treatment of childhood malignancies, although the frequency appears low among patients treated primarily for solid tumors. Prospective studies of large numbers of patients with a broader spectrum of diagnoses are necessary to define the incidence of and risk factors for this complication and to assess the need for prevention with anticoagulation or other therapy. Pediatricians caring for patients with a history of cancer and CVLs should be aware that these patients may have persistent vascular occlusion that could predispose them to recurrent thrombosis or postphlebitic syndrome. *Pediatrics* 1998; 101(2). URL: http://www.pediatrics.org/cgi/content/full/101/2/e7; *thrombosis, central venous lines, late effects, malignancies.***

ABBREVIATIONS. CVL, central venous line; DVT, deep-vein thrombosis; CT, computed tomography; TPN, total parenteral nutrition.

Central venous lines (CVLs) are used routinely to facilitate the administration of chemotherapy, blood products, antibiotics, and parenteral nutrition in children and adolescents requiring prolonged venous access for the treatment of cancer and other illnesses. These devices simplify treatment delivery and enhance patients' quality of life during therapy, but they are not without risks. The most common and potentially severe acute sequelae are infection and thrombosis.[1] Of interest, a registry study designed to determine the incidence and characteristics of deep-vein thrombosis (DVT) among children in the general population identified the use of CVLs as the single most important predisposing factor for DVT.[2]

Acute thrombosis of CVLs usually becomes evident by the inability to draw blood from or infuse products into the line, although there are reports of emergency presentations with pulmonary embolus, congestive heart failure, or superior vena cava syndrome. Among pediatric cancer patients, the reported frequency of clinically evident CVL-related thrombus during treatment ranges from 8% to 25%.[3,4] Late effects of thrombosis have been described and include the development of superficial collateral veins, postphlebitic syndrome (pain, swelling, discoloration, and ulceration), and superior vena cava syndrome.[2] Little is known, however, about the persistence and late effects of CVL-related thrombi or occlusion in the growing population of childhood cancer survivors.

There are several potential explanations for this lack of data. It is possible that persistent thrombi/occlusion are extremely rare among childhood cancer survivors or occur only or primarily in those with specific predisposing features. Alternatively, follow-up experience in these patients may be inadequate for such complications to have become clinically evident. In an initial attempt to address these issues, we obtained computed tomography (CT)-based angiograms of the subclavian veins during routine follow-up imaging of patients who had CVLs placed during treatment for childhood malignancy and removed months to years before study.

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METHODS

Patients

Children and adolescents treated for a malignancy at St Jude Children's Research Hospital were eligible for the study if they had completed therapy that included placement of a CVL, had not had a CVL in place for at least 2 months, and were scheduled for a routine follow-up CT scan requiring administration of intravenous contrast material. This study was approved by the hospital's Institutional Review Board, and signed informed consent was obtained from patients, parents, or guardians, as appropriate. Patients scheduled for follow-up visits over a 5-month period were asked to consider participation in this study. All of the patients and families we approached agreed to participate. Patient charts were reviewed to identify CVL-related complications and document the incidence of administration of hyperalimentation and urokinase. Parents were interviewed regarding family history of venous thrombosis or pulmonary emboli.

Imaging Studies

CT scans were obtained using a Siemens Somatom 400 Plus Scanner (Siemens, Iselin, NJ) after intravenous administration of nonionic contrast material. Contrast was administered via a peripheral vein in the arm ipsilateral to the site of the previous CVL (for patients who had bilateral CVLs, the side of contrast injection was chosen arbitrarily). Intravenous contrast was administered via a power injector at a dose of 2 mL/kg (maximum, 150 mL). Spiral volume acquisition was used to obtain 3-mm contiguous axial images from the chest apices through the right hilum. Images were filmed with mediastinal windows (window = 804; center = 204) in the axial plane. Using the angiography software program, three-dimensional reconstruction then was performed, with manual postprocessing by a pediatric radiologist (S.C.K.), and images chosen were filmed (window = 3000, center = 1120). The routine CT for follow-up of the primary malignancy followed immediately.

Outcome Measures

The primary measure was thrombosis/occlusion, defined as narrowing, obstruction, or filling defect involving the deep venous system, with or without the development of collateral veins. We used a group sequential design, as proposed by Fleming,[5] to evaluate the incidence of thrombosis. This design incorporated rules to terminate the study when there was evidence that the true incidence of thrombosis/occlusion in this sample was <10% or >30%. Modification or discontinuation of the study was considered appropriate if the risk was extremely small; alternative approaches and prospective studies were planned if the probable incidence exceeded 30%.

RESULTS

We studied a total of 25 patients seen in the outpatient clinic for follow-up care between June 1996 and November 1996. Characteristics of these patients are summarized in Table 1. All but two of these patients were treated for solid tumors, the malignancies for which routine follow-up contrast-enhanced CT is most likely to be scheduled. These patients had received a variety of disease-specific protocol-based treatments. Chemotherapeutic agents used most often, in varying combinations, were vincristine, actinomycin-D, Adriamycin, cyclophosphamide, ifosfamide, cisplatin or carboplatin, etoposide, and 5-fluorouracil. None of the patients had received L-asparaginase. Only two patients had any family history of venous thromboses.

CVLs had been placed by the same group of surgeons at our center in 22 cases and by surgeons at other centers in the 3 remaining patients. Seven patients had more than one line placed (total = 17 lines in this subgroup). Of the total 35 lines inserted, 30 were on the side of the CT angiogram. Data summarized here relate to these 30 CVLs. Table 2 summarizes the use of CVLs in these patients. The lines were in place for periods ranging from 0.2 to 36 months (median, 7.4), and had been removed a median of 32.5 months previously (range, 2.3 to 121.8). Seventeen lines were placed in the right subclavian/cephalic vein and the rest in the left. All lines had been used for the delivery of chemotherapy and blood sampling. In addition, 9 patients had received hyperalimentation via CVL for periods ranging from 2 to 38 weeks (median, 12 weeks).

Four patients had required instillation of urokinase, 5 to 10 000 U for 2 to 4 hours, into the line (two patients on one occasion, one on two occasions, and one on three occasions). Another patient received urokinase and heparin therapy when she developed superior vena cava syndrome. Four patients had a history of CVL-related infection (two at the insertion site and two *Candida* line infections). Lines were removed in both patients with *Candida* infections. There were no other significant complications.

Thrombosis/occlusion involving the deep venous system was identified on CT angiograms in only 3 of the 25 patients studied (12%; 95% confidence interval, 4.5%–31%). Characteristics of these patients and pertinent CT findings are detailed in Table 3. In case 2, the positive findings are not surprising in retrospect. This patient developed superior vena cava

TABLE 1. Patient Characteristics

	Number
Primary diagnosis	
Neuroblastoma/ganglioneuroblastoma	5
Ewing's family of tumors	5
Rhabdomyosarcoma	4
Germ cell tumors	4
Hepatoblastoma	3
Lymphoma/B-cell acute lymphocytic leukemia	2
Malignant nerve sheath tumor	1
Cellular blue nevus	1
Sex	
Male	18
Female	7
Race	
White	22
Black	2
Hispanic	1
Age at insertion of CVL (years)	
Median	4.1
Range	0.1–20.4

TABLE 2. CVL Characteristics

Duration of CVL placement (months)	
Median	7.4
Range	0.2–36
Time from catheter removal to CT angiography (months)	
Median	32.5
Range	2.3–121.8
Complications	
Infection	4
Urokinase instillations	4
TPN	
Number of patients	9
Duration (weeks)	
Median	12
Range	2–38

TABLE 3. Characteristics of Long-term Thrombi After CVL Removal

Patient	Diagnosis	Age Inserted*	Duration Line	Duration Removal to CT	Urokinase	Infection	CT
1	Hepatoblastoma	11 months	7 months	25 months	No	Cellulitis insertion site	Focal occlusion left subclavian at junction with left axillary
2	Permeative neuroectodermal tumor	20 years, 5 months	1 month	10 months	No, superior vena cava syndrome	No	Obstruction left subclavian, multiple collaterals
3	Cellular blue nevus	13 years, 5 months	15 months	30 months	1	No	Occlusion medial left subclavian, extensive collaterals to vertebral plexus and left shoulder

* All patients had left cephalic insertion sites.

syndrome 11 months previously, necessitating removal of her CVL. The CT angiogram, shown in Fig 1, illustrates obstruction of the left subclavian vein, with significant collateral development through recruitment of the azygous, left internal mammary veins, and venous collaterals around the left shoulder. The other two patients with occlusion also had evidence of collateral formation, although not as striking as in case 2. Figure 2 illustrates the CT angiogram of patient 3 and Fig 3 provides a normal angiogram for comparison.

We did not attempt statistical analysis of potential predisposing or interacting factors because of the small number of positive findings. Of interest, however, none of the patients with occlusion had a family history of thrombosis, previous placement of a double-lumen Hickman catheter, or multiple instillations of urokinase. The patient with the superior vena cava syndrome received treatment with anticoagulants. She had normal testing for antithrombin III, proteins C and S, and factor V Leiden. Because the two other patients were asymptomatic 21 and 30 months after catheter removal, no intervention was suggested.

DISCUSSION

We found a 12% incidence of persistent deep venous occlusion as a late complication of childhood cancer therapy that included the use of CVLs. Among 25 patients who had central lines removed 2.3 to 121 months previously, 3 had evidence of venous obstruction and collateral formation on CT-based angiography. There are few comparable studies of late effects of central venous access devices in cancer patients of any age, although one study of adult patients showed persistent obstruction after previous subclavian catheter placement that prevented subsequent venous access in 14% of cases.[6] Given this finding, and the frequency of reported thrombotic complications while CVLs are in place (from 8.7% to 42% in children and adults treated for malignancy),[3,7] we were not surprised to find that 3 of our sample of 25 childhood cancer survivors had evidence of persistent obstruction and collateral formation after catheter removal. We chose specifically to study patients months to years after catheter removal, because these patients with persistent abnormalities would appear to be at greatest risk of clinical complications.

Although there are no systematic studies of late effects of catheter-related thrombosis/occlusion, scattered reports are available. Korones and associates described a residual small right atrial thrombus in a child treated for acute lymphocytic leukemia, whose catheter had been removed 2 years previously.[8] Petäjä and co-workers found that 2 of 10 children with central venous thrombosis after cardiac surgery had residual thrombi when studied at 5 to 108 months after surgery.[9]

We used unilateral CT-based angiography, as reported previously by Tello et al[10] and Baldt et al,[11] to

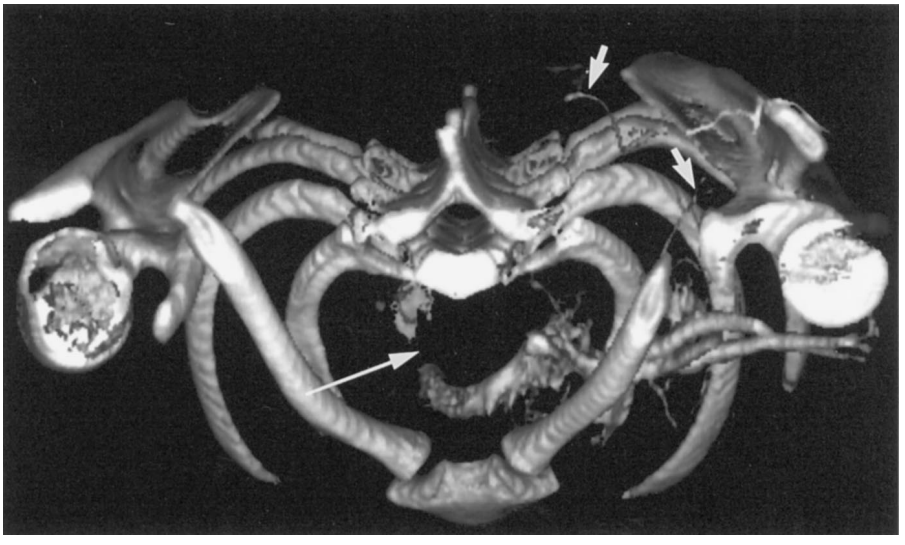

Fig 1. Three-dimensional reconstruction of a spiral CT angiogram through the left upper extremity (oriented in a cranial–caudal projection with the spine at the top of the image and the manubrium at the bottom) reveals obstruction of the superior vena cava (arrow) with venous collaterals around the left shoulder (arrowheads). The enlarged azygous vein is located posteriorly along the right side of the spine adjacent to the obstructed portion of the superior vena cava.

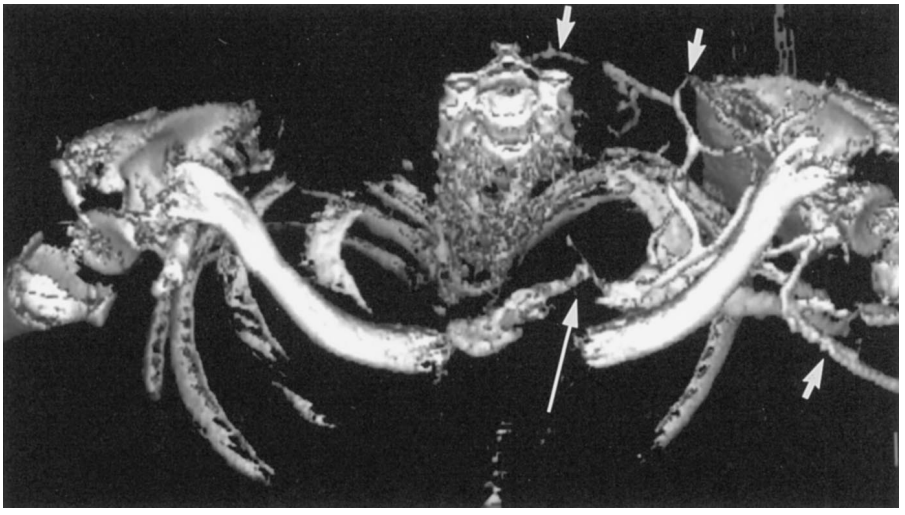

Fig 2. CT angiogram of the deep venous system of the left upper extremity. The image is oriented in the anteroposterior projection with mild caudal rotation. There is marked irregular narrowing of the left subclavian vein (arrow) with numerous venous collaterals around the left shoulder and to the vertebral plexus (arrowheads).

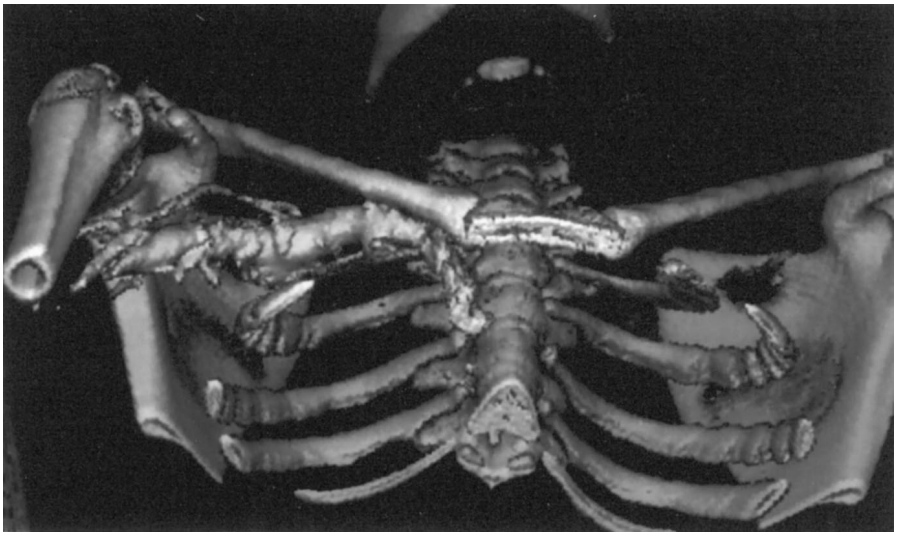

Fig 3. Normal CT angiogram of the right upper extremity depicted in the anteroposterior projection shows a smooth contour of the right subclavian and innominate veins with homogenous opacification.

detect thrombosis and related anomalies. With this approach, we were able to study vascular anatomy during routine contrast-enhanced follow-up CT studies. Thus, patients were not exposed to additional risks in this preliminary screening study. Although fluoroscopic venography has long been considered the standard of venous imaging, there are studies validating CT angiography in the lower extremity. Baldt and associates compared conventional extremity venograms with CT venography in 52 patients and found that the sensitivity of CT venograms was 100%; specificity, 96%; positive predictive value, 91%; and negative predictive value 100%.[11] Our studies in the subclavian area are more difficult to image because of bony structures that obstruct some image data. However, there are advantages to the use of CT-based angiography. These include fewer cases of incomplete venous filling, the construction of three-dimensional images that provide multiplanar visualization, the ability to record and salvage studies that might have been lost in a fluoroscopic study, standardized technique leading to less operator-dependent parameters, and higher resolution. Potential disadvantages of CT venograms include inflow phenomena, which can mimic intraluminal filling defects and suggest false-positive readings of DVT in certain situations. The amount of x-ray exposure with the two techniques is approximately equal. It should be noted that we used only unilateral injections, and additional thrombi might have been detected by bilateral injections and angiography for the 5 patients who had had bilateral CVLs. However, we did not feel we could justify an invasive procedure in asymptomatic children without additional baseline data.

Factors that predispose children to thrombosis include inherited prethrombotic disorders such as deficiencies of proteins C and S, or antithrombin III, and the factor V Leiden mutation; the lupus anticoagulant; infection; and trauma.[2,12,13] Specific factors that predispose patients to the development of CVL-related thrombus have not been defined clearly. However, two studies of children[14] or adults[15] receiving long-term total parenteral nutrition (TPN) via CVL revealed a very high frequency of thrombosis on venograms. Most of these patients had gastrointestinal disorders and multiple line placements. All of the children studied required multiple instillations of urokinase. The adult study from l978 is of interest in that catheters had been removed 0 to 453 days

before phlebography, which showed thrombosis without recanalization in 7 of 27 patients. These studies, combined with reports mentioned previously and clinical observation, suggest that patients requiring long-term TPN should be monitored for acute and late thrombotic complications. In our sample, only 9 patients had received TPN, for periods of 2 to 36 weeks. Notably, none of the 3 patients who had persistent thrombi received hyperalimentation. Other studies suggest that risk factors for thrombotic complications include the diagnosis of acute lymphocytic leukemia,[8] (which represented only 8% of our sample), treatment with asparaginase,[16] malposition of the catheter,[17] or large catheter diameter.[18]

Prospective studies of large numbers of patients are necessary to determine the true incidence of both acute and, particularly, late complications of CVL-related thrombosis, predisposing conditions, and the potential role of prevention with anticoagulation or other therapies. Pediatricians caring for patients with a history of cancer and CVLs should be aware that these patients may have persistent occluded sites that could predispose them to recurrent thromboses or postphlebitic syndrome.

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