Cardiopulmonary Emergencies

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Abstract

Children with malignancies are at risk for a number of cardiopulmonary complications. These are most frequently seen at the time of initial presentation but can also be seen in the setting of progressive disease or relapse. When severe, these complications require prompt evaluation and may require emergency intervention. This chapter reviews the pathophysiology, clinical presentation, diagnosis and treatment of the most common cardiopulmonary emergencies seen in the pediatric oncology population: superior vena cava and superior mediastinal syndromes, pericardial effusion and tamponade, pleural effusion, hypertensive emergencies, and pulmonary leukostasis. Recommendations for management are included and graded based on a review of the existing available evidence.

4.1 Introduction

Children with malignancies are at risk for a number of cardiopulmonary complications. These are most frequently seen at the time of initial presentation but can also be seen in the setting of progressive disease or relapse. When severe, these complications require prompt evaluation and may require emergency intervention. This chapter reviews the pathophysiology, clinical presentation, diagnosis and treatment of

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Table 4.1 Summary of recommendations for management of cardiopulmonary emergencies

Clinical scenario	Recommendations	Level of evidence[a]
SVCS/SMS	Elevate head of the bed	1C
	Place all IV lines in lower extremities	2C
	Consider use of loop diuretics	2C
	Remove indwelling catheter if associated with thrombosis	1C
	Avoid sedation with general anesthesia if possible	1B
	Consider use of pre-biopsy steroids to shrink tumor	2C
	Consider pre-biopsy radiation therapy to shrink tumor	2C
Malignancy-associated pericardial effusions	Close observation only if patient is asymptomatic	1C
	Emergent pericardiocentesis under echocardiographic guidance if patient is symptomatic	1C
	Consider pigtail drainage catheter for prolonged drainage	2C
	Surgical management if not controlled by above methods	1C
	Volume resuscitation to elevate intracardiac pressures	2C
	Avoid mechanical ventilation with positive airway pressure	2C
Malignancy-associated pleural effusions	Close observation only if patient is asymptomatic	1B
	Thoracentesis if patient is symptomatic (send fluid for evaluation, including cytology)	1B
	Consider indwelling catheter for prolonged drainage	2C
	Intrapleural fibrinolysis for loculated effusion	1A
	VATS for early organizing empyema	1C
	Thoracotomy with decortication for advanced organizing empyema	1C
	Consider pleurodesis for refractory and recurrent effusion	2C
Hypertensive emergencies	Immediate intravenous therapy for severe hypertension Rapid bolus of phentolamine Continuous infusion of phentolamine or sodium nitroprusside Avoid β-blocking agents initially	1C
	Oral therapy for less severe hypertension α-blocking agent (i.e., doxazosin) Calcium channel blocker Consider addition of β-blocker after α-adrenoreceptor blockade	1C
	Prevention of hypertensive crisis if marked catecholamine release anticipated α-adrenoreceptor blockade with phenoxybenzamine Subsequent addition of β-blockade to prevent reflex tachycardia	1C

SVCS superior vena cava syndrome, *SMS* superior mediastinal syndrome, *IV* intravenous, *VATS* video-assisted thoracoscopic surgery

[a]Per Guyatt et al. (2006); see Preface

the most common cardiopulmonary emergencies seen in the pediatric oncology population: superior vena cava and superior mediastinal syndromes, pericardial effusion and tamponade, pleural effusion, hypertensive emergencies, and pulmonary leukostasis. Recommendations for management are included and graded based on a review of the existing available evidence (Table 4.1).

4.2 Superior Vena Cava and Superior Mediastinal Syndromes

Superior vena cava syndrome (SVCS) occurs when the superior vena cava is obstructed, thereby restricting blood return to the heart. Superior mediastinal syndrome (SMS) is the term used when SVCS coexists with obstruction

of the trachea. The terms are sometimes used interchangeably in children, in whom mediastinal pathology frequently involves compression of both the SVC and the trachea. Malignancies are the most common cause of this condition. The most common pediatric malignancy associated with SVCS is lymphoma, but it can also be seen in other solid tumors such as germ cell tumors, neuroblastoma, Ewing sarcoma, and soft tissue sarcoma, as well as leukemia (Ingram et al. 1990; Halfdanarson et al. 2006).

4.2.1 Pathophysiology

The superior vena cava carries blood from the head, arms and upper torso to the heart. This thin-walled vessel is easily compressed by tumors or other pathology in the mediastinum leading to impedance in venous return. If the occlusion occurs gradually, collaterals may form thereby mitigating the symptoms. Airway compromise results from both direct compression of the tracheobronchial tree and edema of these airways due to venous engorgement.

4.2.2 Clinical Presentation and Diagnosis

4.2.2.1 History and Physical Exam

SVCS/SMS should be suspected in a patient with engorgement of the veins in the head, face and neck. The most common presenting signs and symptoms are facial swelling and plethora, distended neck and chest wall veins, and upper extremity edema. Respiratory symptoms include dyspnea and cough. Less frequently seen are central nervous system (CNS) symptoms caused by impeded venous return and subsequent cerebral edema. These can include headache, dizziness, confusion, syncope and even obtundation (Wilson et al. 2007a). The onset of symptoms is usually insidious but may occur rapidly especially when the underlying cause is a rapidly growing tumor.

4.2.2.2 Imaging Studies

The diagnosis of SVCS/SMS is often made on the basis of clinical signs and symptoms but imaging studies are helpful in determining the underlying etiology. A chest radiograph is easy to obtain and can confirm the presence of a mediastinal mass. A computed tomography (CT) scan of the chest is typically the most useful imaging study and should be obtained after the administration of intravenous (IV) contrast to best evaluate the SVC. CT can provide information regarding the exact size and location of the mass (which can provide clues regarding its etiology), as well as infiltration into surrounding structures and vascularity. It is important to keep in mind that patients with SMS are at high risk for adverse cardiorespiratory events if sedated. Ultrasonography can be performed when sedation is not possible or if the patient cannot lie supine. Echocardiography may be required if there is suspicion of infiltration by the mass into the pericardial cavity or pericardial effusion, based on physical exam or CT scan findings.

4.2.2.3 Other Studies

Tissue is required to make a definitive diagnosis and should be obtained by the least invasive procedure possible to reduce the possibility of an adverse cardiorespiratory event. If there is an associated pleural or pericardial effusion, thoracentesis or pericardiocentesis respectively may be not only therapeutic but also diagnostic in approximately 50 % of cases (Rice et al. 2006). An enlarged palpable lymph node may be more easily biopsied than a mediastinal mass. Mediastinoscopy is more invasive but has the highest diagnostic yield, and some studies have reported low complication rates even in the presence of SMS (Dosios et al. 2005).

4.2.3 Treatment

SVCS/SMS is not typically considered to be a true medical emergency unless airway compromise or neurologic symptoms are present (Yellin et al. 1990). However, tumors with rapid

growth can lead to a rapid progression of symptoms. Management consists of both relief of the obstructive symptoms and treatment of the underlying malignancy (Table 4.1). Most data regarding management of SVCS come from case series as there have not been many randomized controlled trials; such studies comparing management options for patients with SVCS/SMS have had difficulty accruing patients (Wilson et al. 2007b). Elevation of the head of the bed can assist in venous drainage and decreasing edema (Cheng 2009). All IV lines should be placed in the lower extremities, so as to prevent further raised hydrostatic pressure in the SVC. Loop diuretics are sometimes used, although it is unclear whether these agents have a significant effect on the rate of clinical improvement (Schraufnagel et al. 1981). In patients with SVC obstruction resulting from intravascular thrombosis associated with an indwelling catheter, removal of the catheter should be strongly considered.

Sedation should be avoided as much as possible, as sedative medications result in reduced respiratory drive and relaxation of bronchial muscles. When a biopsy is required, obtaining tissue under local anesthesia should be the goal. The indicators of risk for general anesthesia in such patients are controversial. Large retrospective reviews have not identified any single clinical sign or test that can accurately predict which patients with a mediastinal mass will experience complications under general anesthesia (Hack et al. 2008). Patients with stridor, orthopnea, wheezing, SVC obstruction, CNS symptoms, pericardial effusion, tracheal or bronchial compression >50–70 %, pulmonary artery outflow obstruction, or peak expiratory flow rate (PEFR) of <50 % are considered to be at higher anesthetic risk (Hack et al. 2008). Others have suggested that PEFR and tracheal cross-sectional area seem to be the most reliable criteria in identifying children at greatest risk for anesthetic complications, and that if both the PEFR and the tracheal cross-sectional area are >50 % of predicted values general anesthesia can be administered safely (Ricketts 2001). If general anesthesia is considered necessary, spontaneous ventilation should be maintained if possible.

As lymphoma and leukemia are among the most common causes of a mediastinal mass and resultant SVCS in children, many centers recommend delaying diagnostic biopsy in symptomatic patients for 24–48 h while emergent corticosteroids or radiation are given in an effort to shrink the tumor size. However, there is concern that such pretreatment can distort cellular morphology and thereby adversely affect the ability to make a histologic diagnosis (Ferrari and Bedford 1990). Retrospective reviews have found that pre-biopsy steroid or radiation treatment caused delay or failure of definitive diagnosis or staging in a minority of children; fortunately many of these patients who were empirically treated did well and have remained disease-free at last follow-up (Loeffler et al. 1986; Borenstein et al. 2000). In an effort to preserve tumor histology for diagnostic purposes, radiation oncologists should attempt to spare radiation to a limited portion of the tumor, with the later goal of obtaining untreated biopsy tissue from that region. This limited "postage stamp" approach to the radiation field is also used to safely treat various types of tumors (Slotman et al. 1996; Hayakawa et al. 1999). Alternate tissue sources from which to make the diagnosis should be considered when possible, including pleural or pericardial effusions and enlarged palpable lymph nodes (see Sect. 4.2.2.3). Ultimately, the decision to treat such a patient prior to obtaining tissue for biopsy should depend on the patient's clinical status and severity of cardiorespiratory symptoms.

4.3 Pericardial Effusion and Cardiac Tamponade

Pericardial effusions are common in adult malignancy, with some series reporting this condition in up to one-third of patients with cancer (Wilkes et al. 1995; McCurdy and Shanholtz 2012). Such effusion can be caused by direct tumor invasion into the pericardium or, rarely, by metastases from other locations. While frequently asymptomatic, severe cases can lead to compression of the heart chambers and cardiac tamponade (Medary et al. 1996).

4.3.1 Pathophysiology

The pericardium is composed of a serous layer of mesothelial cells adherent to the surface of the heart and a fibrous parietal layer formed by the pericardium and reflecting back on itself. The space between these two layers contains up to 50 mL of fluid which serves as a lubricant. Excess fluid can accumulate in this space without affecting the pericardial pressure until it reaches the volume that begins to distend the pericardium, termed the pericardial reserve volume. Once this reserve volume is reached, pressure begins to rise sharply due to the relative inextensibility of the pericardium. The heart is then forced to compete with the increased pericardial contents for the fixed intrapericardial volume which in turn leads to an impaired filling of the cardiac chambers and hemodynamic compromise. This compression of the heart due to the pericardial accumulation of fluid is termed cardiac tamponade and can be life threatening (Spodick 2003).

4.3.2 Clinical Presentation and Diagnosis

4.3.2.1 History and Physical Exam

Small pericardial effusions are frequently asymptomatic (Maher et al. 1996). The amount of pericardial fluid that causes tamponade is related to the rate of fluid accumulation. Rapidly accumulating effusions can cause symptoms with as little as 200 mL of fluid, whereas if fluid accumulates over weeks to months, the pericardial tissue can stretch and may hold >2 L or more before tamponade develops (Karam et al. 2001). In the case of malignancy, the onset is more often insidious.

The most common presenting symptom is exertional dyspnea (Wilkes et al. 1995). Other symptoms include cough, chest pain, dysphagia, hoarseness and hiccups (Karam et al. 2001). The most common sign is pulsus paradoxus, which is defined as a decrease in systolic blood pressure of more than 10 mmHg during inspiration. Tachycardia is frequently seen. The classic description of cardiac tamponade is Beck's triad: hypotension, increased jugular venous pressure and quiet heart sounds. However, this is seen mostly in rapidly forming effusions and acute tamponade, and only infrequently in patients with chronic pericardial effusion (Tseng et al. 1999).

4.3.2.2 Imaging and Other Studies

The presence of a pericardial effusion can be suspected based on chest radiograph findings which classically show an enlarged cardiac silhouette. The classic appearance of a "water bottle heart" that is globular in appearance is a sensitive but nonspecific finding (Fig. 4.1). An electrocardiogram may reveal low-voltage waveforms and less frequently electrical alternans, a condition where consecutive QRS complexes alternate in height between beats (Karam et al. 2001). Echocardiography, however, has become the preferred diagnostic test for assessing pericardial effusion and cardiac tamponade. It should be ordered when there is a significant pericardial effusion suspected, as it can not only define the size and location of an effusion but also assess the hemodynamic significance and help guide pericardiocentesis (Tseng et al. 1999).

4.3.3 Treatment

The timing and type of treatment for pericardial effusion depend on the severity of symptoms

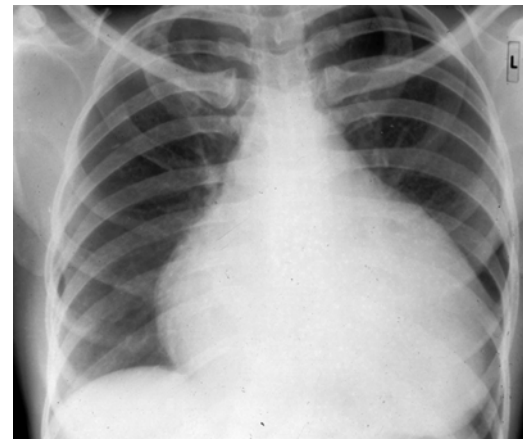

Fig. 4.1 Enlarged ("water bottle") silhouette of the heart on chest radiograph in a patient with pericardial effusion

(Table 4.1). If the effusion is asymptomatic, continued close observation for hemodynamic complications is required but the effusion generally resolves with treatment of the underlying malignancy (Bashir et al. 2007). In the case of tamponade or if the pericardial effusion is otherwise hemodynamically significant, the fluid should be drained emergently. Pericardiocentesis under echocardiographic guidance is the therapy of choice and has been shown to be a safe and effective treatment for pediatric oncology patients with symptomatic pericardial effusion or tamponade (Medary et al. 1996). In addition to relieving symptoms related to the effusion, this procedure can be used to determine the etiology of a malignant effusion. As the recurrence rate of pericardial effusions after initial drainage can be as high as 50 %, consideration should be given to introducing an indwelling pigtail drainage catheter at the time of pericardiocentesis to allow for prolonged drainage (Tsang et al. 1999). Surgical management of malignant pericardial effusion should be reserved for the rare case that cannot be controlled by this method (Maher et al. 1996). In the case of acute cardiac tamponade, the patient should receive volume resuscitation to elevate intracardiac pressures to greater than pericardial pressures. Mechanical ventilation with positive airway pressure should be avoided in these patients because it can further decrease cardiac output (Spodick 2003).

4.4 Pleural Effusion

A pleural effusion is a collection of fluid that accumulates between the visceral and parietal pleurae. Excessive amounts of such fluid can impair breathing by limiting lung expansion during ventilation. In the pediatric population, the most common cause of a pleural effusion is an underlying pneumonia, followed by congenital heart disease and less commonly malignancy (Beers and Abramo 2007). Severe cases can lead to significant respiratory compromise and may require emergent management.

4.4.1 Pathophysiology

The pleural space is bordered by the parietal pleura which covers the inner surface of the thoracic cavity and the visceral pleura which covers the lung surfaces. Like the pericardial space, there is normally a small amount of lubricating fluid between these two layers, but this fluid can increase secondary to underlying pathology. Pleural effusions are classified as either transudates or exudates. Exudates are typically of infectious etiology and result from inflammation on the pleural surface. Transudates, on the other hand, are generally of noninfectious etiology and result from an imbalance between the rate of pleural fluid formation and its reabsorption as the distribution of hydrostatic and oncotic pressure across the pleura is altered.

Malignancy can cause pleural effusion in a number of different ways. A malignant pleural effusion is defined by the presence of cancer cells in the pleural space. This can result from direct extension of tumor cells from an adjacent cancer (such as cancers of the chest wall, lung or breast), hematogenous metastases to the parietal pleura, or invasion of the pulmonary vessels with embolization of tumor cells to the visceral pleural. Tumor deposits spread along the pleural membranes and obstruct lymphatic stomata (small openings of lymphatic capillaries on the free surface of the mesothelium), thereby impairing the drainage of intrapleural fluid. In addition, pleural tumor deposits stimulate the release of cytokines that lead to increased vascular and pleural membrane permeability (Das 2006). Malignancy can also cause pleural effusions indirectly. Such effusions can result from mediastinal lymph node tumor infiltration, superior vena cava syndrome, bronchial obstruction, or decreased oncotic pressure and are termed paraneoplastic or paramalignant effusions (Rice et al. 2006; Heffner and Klein 2008). Paraneoplastic pleural effusions are seen in up to 30 % of adult patients with lymphoma. Most effusions seen with Hodgkin disease are paraneoplastic and result from thoracic duct obstruction, while most effusions seen with non-Hodgkin lymphoma develop as a direct

result of pleural infiltration with tumor cells (Das 2006). Pleural effusions can be the initial presentation of a malignancy, a delayed complication in a patient with a known malignancy or the first sign of tumor recurrence following therapy (Heffner and Klein 2008).

4.4.2 Clinical Presentation and Diagnosis

4.4.2.1 History and Physical Exam

Many patients with small pleural effusions are asymptomatic. Larger effusions can cause respiratory signs and symptoms such as tachypnea, cough, dyspnea, orthopnea and retractions. Fever may also be present. Patients can develop pleuritic chest pain which is often described as sharp and worse with deep inspiration. Physical examination often reveals decreased or absent breath sounds on the side of the effusion, dullness on chest percussion and egophony. It should be noted that these physical findings are not always seen in infants (Beers and Abramo 2007).

4.4.2.2 Imaging Studies

When a pleural effusion is suspected, a chest radiograph is the first study to obtain. In the adult, about 200 mL of fluid must be present to be visible on a PA view, while just 50 mL will cause costophrenic blunting on the lateral view (Blackmore et al. 1996). A lateral decubitus chest radiograph can help establish whether the effusion is free flowing or loculated; free-flowing fluid will layer out in a dependent fashion when the affected side is placed down. Ultrasonography is useful to distinguish solid versus liquid lesions and to evaluate for the presence of loculations. CT is helpful in visualizing the underlying lung parenchyma and can also help visualize loculations although not with the same degree of certainty as ultrasound (Cassina et al. 1999). Magnetic resonance imaging (MRI) provides better imaging of soft tissues than chest CT and can detect tumor invasion into the chest wall and diaphragm (Lorigan and Libshitz 1989).

4.4.3 Treatment

Treatment of a pleural effusion depends on the size of the effusion and patient symptoms; not all effusions require drainage (Table 4.1). If the patient is symptomatic, pleural aspiration (thoracentesis) can be both diagnostic and therapeutic. When done under ultrasound guidance, this procedure is associated with a low complication rate (Jones et al. 2003). Once obtained, the fluid should be analyzed to determine whether it is a transudate or exudate. Transudates are generally pale yellow and serous in appearance and have lower protein and lactate dehydrogenase (LDH) concentrations compared with the serum. Exudates are more often cloudy or frankly purulent and contain protein and LDH concentrations that are greater than 50 % and 60 % of the serum concentrations respectively. A milky color to the fluid suggests a chylothorax, and triglyceride and cholesterol levels should be measured in these cases. When malignancy is suspected, the fluid should be sent for cytology as diagnosis has been shown possible in up to 65 % of cases in adults (Ong et al. 2000). The fluid can also be used to look for tumor markers such as α-fetoprotein (AFP), β-human chorionic gonadotropin (β-HCG) and others, depending on the type of tumor suspected. Flow cytometry and cytogenetics can also be performed on the pleural fluid (Das 2006).

Care must be taken when performing thoracentesis as the removal of large volumes of pleural fluid can lead to reexpansion pulmonary edema (RPE). RPE occurs when atelectatic lung regions are rapidly expanded beyond their capacity to reinflate, thus causing alveolar capillary injury. It has been suggested that intrapleural pressure be monitored during thoracentesis and the procedure discontinued when a certain threshold pressure has been reached or 1 L of fluid has been removed, but this is controversial. Others suggest that patients' symptoms during the procedure correlate with intrapleural pressure and that RPE can be avoided if thoracentesis is discontinued when patients experience nonspecific chest discomfort (Jones et al. 2003;

Feller-Kopman et al. 2006). Patients with malignancy-related pleural effusions and recalcitrant tumors may experience reaccumulation of fluid and recurrence of symptoms within 30 days following thoracentesis; therefore, the placement of an indwelling catheter should be considered to allow for prolonged drainage and longer-term relief of symptoms in such cases. Once the diagnosis of a new or recurrent malignancy is made, tumor-specific therapy should be initiated, as possible.

If the pleural effusion is complicated or has evolved to an empyema (an effusion that becomes infected), further intervention may be warranted. Fibrinolytic agents have been shown to be effective therapy in loculated pleural effusions in the pediatric population (Thomson et al. 2002; Cochran et al. 2003). These work by decreasing fibrinous strands and reopening pleural pores blocked by fibrinous debris, thereby increasing the reabsorption of pleural fluid. Intrapleural streptokinase and urokinase have been used in the past but carry a risk of hypersensitivity reactions. Many centers are now administering intrapleural tissue plasminogen activator (tPA) to assist with drainage of loculated pleural effusions in pediatric patients (Feola et al. 2003). When chest tube drainage and fibrinolytics have failed to alleviate a complicated effusion, more invasive surgical intervention is required. Video-assisted thoracoscopic surgery (VATS) is generally considered the procedure of choice for early organizing empyemas as it is less invasive than thoracotomy and has been shown to have significant success. For more advanced organizing empyemas, thoracotomy with decortication remains the treatment of choice (Cassina et al. 1999).

In select patients with refractory and severe recurrent effusions, pleurodesis may be considered. In pleurodesis the pleural space is artificially obliterated by injecting an irritant (such as talc) into the pleural space thus creating inflammation that then tacks the two pleura together. This permanently obliterates the pleural space and prevents reaccumulation of fluid. Pleurodesis is most often used in adults with advanced-stage cancer but has been shown beneficial in pediatric oncology patients with intractable effusions as part of palliative end of life care (Hoffer et al. 2007).

4.5 Hypertensive Emergencies

Severe hypertension has been noted in pediatric oncology patients with neuroblastoma, renal tumors including Wilms tumor and rhabdoid tumor, and, rarely, non-Hodgkin lymphoma involving the kidney, pheochromocytoma, and paraganglioma (Manger and Gifford 2002; Madre et al. 2006). Hypertension can be secondary to catecholamine release in neuroblastoma, pheochromocytoma or paraganglioma, from renal parenchymal tumor involvement, from compression of the renal arteries, or from renal vein thrombosis (Madre et al. 2006). Hypertensive emergency is generally seen secondary to catecholamine release and is a rare finding in neuroblastoma (Manger and Gifford 2002, Seefelder et al. 2005). Pheochromocytoma and paraganglioma are rare catecholamine-producing tumors of chromaffin cells that produce catecholamines which cause some degree of hypertension in most cases (Manger and Gifford 2002). When there is a rapid and marked release of catecholamines, a hypertensive crisis can be precipitated which can be life threatening if not treated emergently.

4.5.1 Pathophysiology

Tumor secretion of catecholamines is responsible for the majority of signs and symptoms associated with pheochromocytoma. These tumors usually secrete predominantly norepinephrine, but in some cases epinephrine and rarely dopamine are secreted. Patients with neuroblastoma and severe hypertension have been similarly noted to have release of norepinephrine and dopamine (Seefelder et al. 2005). Some pheochromocytomas secrete catecholamines intermittently and cause paroxysmal hypertension, while others constantly secrete catecholamines and cause sustained hypertension. Physiologically, norepinephrine increases peripheral vascular resistance with a consequent increase in both systolic and diastolic blood

pressure. Epinephrine increases cardiac output and systolic blood pressure but has no major effect on diastolic blood pressure (Prejbisz et al. 2011).

Hypovolemia also occurs in the majority of patients, primarily those with sustained hypertension. In addition, many peptide substances have been identified in these tumors, including vasoactive intestinal peptide (a potent vasodilator), neuropeptide Y (a potent vasoconstrictor), calcitonin, serotonin and others.

4.5.2 Clinical Presentation and Diagnosis

4.5.2.1 History and Physical Exam

Patients with pheochromocytoma typically have "attacks" precipitated by hypercatecholaminemia, and these can occur as often as several times daily. Attacks tend to occur abruptly and subside slowly and are often precipitated by palpation of the tumor, postural changes, exertion, anxiety, pain, or ingestion of certain drugs or foods containing tyramine.

During paroxysmal hypertension, headaches are common and are usually severe and throbbing. They are often accompanied by nausea and vomiting. Palpitations with tachycardia occur frequently as does generalized sweating. Many patients experience acute anxiety with fear of impending death. Other symptoms include tremulousness, pain in the chest, abdomen, lower back or groin, weakness, fatigue, severe weight loss, and heat intolerance (Manger and Gifford 2002).

4.5.2.2 Laboratory Studies

The diagnosis of pheochromocytoma is best made by measuring plasma free metanephrines or catecholamines and 24 h urine fractionated metanephrines. Urinary catecholamines, total metanephrines and vanillylmandelic acid (VMA) measurements are less reliable in pheochromocytoma as compared to neuroblastoma. Rarely patients with essential or neurogenic hypertension will have moderate elevations of plasma catecholamines. In these cases the clonidine suppression test is used to differentiate etiologies of hypertension. Clonidine suppresses sympathetic nerve activity and plasma norepinephrine by >50 % in patients with neurogenic hypertension, but not in patients with pheochromocytoma. This is because the catecholamine release from pheochromocytoma is believed to be "autonomous" and not responsive to the normal physiological suppressive effect of clonidine (Karlberg et al. 1986).

4.5.2.3 Imaging Studies

When the clinical presentation and laboratory studies are suggestive of pheochromocytoma, imaging is necessary to establish the tumor location. CT identifies 95 % of adrenal pheochromocytomas that are ≥1 cm and about 90 % of extra-adrenal abdominal locations ≥2 cm. However, MRI is more sensitive and specific than CT for detecting these tumors. MIBG (I-metaiodobenzylguanidine) scanning is highly specific for diagnosis and localization as this radiopharmaceutical agent concentrates in approximately 85 % of pheochromocytomas. It can be especially helpful in detecting metastases, very small tumors or those in unusual extra-adrenal locations. Additionally, bone scanning with technitium-99m may demonstrate metastatic lesions missed by MIBG (Manger and Gifford 2002).

4.5.3 Treatment

In the case of very severe hypertension, immediate and proper antihypertensive therapy is needed (Table 4.1). There are no official guidelines, but consensus recommends phentolamine as a rapid IV bolus. Phentolamine is a nonselective α-adrenergic antagonist and works primarily by causing vasodilation by α_1 blockade. It has a short half-life so may need to be repeated at 5 min intervals until hypertension is adequately controlled. It can also be given as a continuous infusion, with the infusion rate adjusted for the patient's blood pressure. Alternatively, sodium nitroprusside can be given by continuous infusion. This agent is broken down to release nitric oxide in the circulation which initiates a cascade of reactions resulting in vascular smooth muscle relaxation and vasodilation. β-blocking agents should not be used initially as this can result in unopposed stim-

ulation of α-adrenoreceptors thereby leading to a rise in blood pressure (Boutros et al. 1990; Manger and Gifford 2002; Darr et al. 2012).

If hypertension is less severe, treatment should include an α-blocking agent that can be given orally, such as doxazosin. Calcium channel blockers have also been used successfully in these patients, although diltiazem fails to prevent uncontrolled blood pressure during surgery for pheochromocytoma, and verapamil has been associated with the development of pulmonary edema in the postsurgical period. If tachycardia or arrhythmias are present, β-blockers such as propranolol or atenolol are indicated after appropriate α-adrenoreceptor blockade (Brouwers et al. 2003; Seefelder et al. 2005).

When marked catecholamine release is anticipated (such as with direct manipulation of tumor during surgery), caution must be taken to prevent hypertensive crises. The patient must be prepared using pharmacological blockade of α-adrenoreceptors, ideally with phenoxybenzamine (Seefelder et al. 2005). Phenoxybenzamine is usually given at a starting dose of 10 mg twice a day (or 0.2 mg per kg per day in pediatric patients), and then gradually increased up to 0.4–1.2 mg per kg per day, divided into 3–4 separate doses. With this regimen adequate α-receptor blockade is generally achieved within 14 days. Once α-blockade is achieved, β-blockade is added to prevent reflex tachycardia. Atenolol is frequently used in this scenario (Witteles et al. 2000; Brouwers et al. 2003).

4.6 Pulmonary Leukostasis

Hyperleukocytosis is defined as a white blood cell (WBC) count $>100 \times 10^9$/L and is associated with increased morbidity and mortality in patients with acute myelogenous leukemia. Hyperleukocytosis can cause pulmonary leukostasis which may lead to severe respiratory compromise and even death. Pulmonary leukostasis can present with hypoxia, dyspnea and tachypnea. Chest radiography and CT scan often reveal bilateral parenchymal infiltrates as well as diffuse ground glass opacities (Piro et al. 2011). Other organs can be involved as well, such as the CNS. Please refer to Chap. 6 for a discussion of the pathophysiology and management of hyperleukocytosis.

4.7 Summary

Cardiopulmonary emergencies compromise many etiologies in the broader category of oncologic emergencies and often present at initial oncologic diagnosis. The practitioner must be aware of potential tumor pathology that can lead to such emergent situations and how best to manage such patients during the acute period. The evidence basis for management in these circumstances is often based on best practice and consensus statements rather than controlled trials as it is difficult to conduct interventional trials in such emergency situations.

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