Cardiovascular Oncologic Emergencies

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Abstract

Oncologic emergencies can present either as a progression of a known cancer or as the initial presentation of a previously undiagnosed cancer. In most of these situations, a very high degree of suspicion is required to allow prompt assessment, diagnosis, and treatment. In this article, we review the presentation and management of cardiovascular oncologic emergencies from primary and metastatic tumors of the heart and complications such as pericardial tamponade, superior vena cava syndrome, and hyperviscosity syndrome. We have included the cardiovascular complications from radiation therapy, chemotherapeutic agents, and biologic agents used in modern cancer treatment.

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Primary and Metastatic Tumors of the Heart

Primary malignancy of the heart is rare and poses a diagnostic challenge to clinicians. The autopsy prevalence of these tumors is 0.001–0.03% [1]. The majority

of the primary tumors, about 90%, are benign. Myxomas constitute the majority of benign tumors, while sarcomas are the most common primary malignant tumors [2, 3].

Metastatic malignant tumors to the heart and pericardium are more common than primary cardiac tumors. Cardiac involvement is as high as 20% in patients with diagnosed cancer [4].

Primary Benign Cardiac Tumors Cardiac Myxomas

Cardiac myxomas most commonly arise in the left atrium of the heart. They are more common in women and peak between the third and fifth decade of life. The pattern of occurrence is sporadic, but there is a familial inheritance pattern as well, inherited as an autosomal dominant disorder with occurrence earlier in life and at atypical locations. They may have a polypoid, villous or papillary appearance. The villous or papillary myxomas are more likely to embolize. Symptoms depend on the size, location, and mobility of the tumor. Patients may present with symptoms of embolism, constitutional symptoms or dyspnea on exertion.

Echocardiography is useful for defining the features of myxomas and hemodynamic consequence. CT and MRI may be useful if echocardiography images are limited.

Surgical resection is the treatment of choice. Recurrence has been reported following resection and a surveillance echocardiography every 6 months is recommended.

Papillary Fibroelastomas

Papillary fibroelastomas are the second most common benign primary cardiac tumors. They predominantly affect the cardiac valves [5]. These tumors are often asymptomatic and are incidentally detected on routine echocardiography as a small, mobile, pedunculated valvular mass. The diagnostic imaging modality of choice is a transthoracic echocardiography. CT and MRI are limited by their temporal and spatial resolution to detect and define these small tumors.

Other less common primary cardiac benign tumors include cardiac lipomas, rhabdomyoma, and cardiac fibromas.

Primary Malignant Cardiac Tumors

Sarcomas represent about 95% of primary malignant cardiac tumors. The remaining 5% constitute cardiac lymphomas and mesotheliomas [4]. Sarcomas have a rapidly progressive clinical course with local infiltration, metastasis, and intracavitary obstruction. The signs and symptoms are nonspecific and may depend on the location of the tumor. Echocardiography may be useful to delineate the tumor. Arterial phase enhancement may be seen on CT and MRI. Management is primarily surgical resection in symptomatic patients. The role of radiation, chemotherapy or cardiac transplantation is controversial. Overall prognosis is poor with survival after diagnosis of about 6 months [4].

Clinical Presentation

Cardiac tumors have a diverse clinical presentation with clinical features relating to embolization, obstruction, and arrhythmias.

Embolization may be related to the tumor or a thrombus adherent to the tumor. Smaller left-sided emboli may mimic endocarditis or vasculitis, whereas larger emboli may lead to a cerebrovascular accident. Right-sided emboli may result in pleurisy or right-sided heart failure [6].

Obstruction of the atrioventricular valve due to tumors arising from the atria, such as myxomas, may present with symptoms of dyspnea on exertion. Obstruction of the ventricular outflow tract may present with chest pain, syncope or shortness of breath [6].

Arrhythmias can be triggered by either direct infiltration of the conduction system or through irritation to the myocardium. Ventricular tachycardia and atrioventricular

block have been seen at risk of sudden cardiac death [6].

Secondary Cardiac Tumors

Cardiac metastasis is seen either by direct extension of the tumor, venous, lymphatic or arterial spread. Metastasis occurs most commonly from tumors of the lung, breast, esophagus, and stomach, renal tumors, lymphoma, leukemia, and melanomas [4].

Lung and breast carcinoma may spread via local infiltration through the pericardium and may result in pericardial effusion. Renal cell carcinomas may invade the inferior vena cava and embolize the right atrium.

Metastasis to the heart is asymptomatic in 90% of cases [6]. The onset of arrhythmias, cardiomegaly or heart failure and tachycardia in a patient with a history of carcinoma should raise the suspicion for cardiac metastasis. Isolated pericardial effusion or cardiac tamponade may sometimes be an initial presentation of malignancy [6].

Pericardial Disease: Pericardial Constriction and Pericardial Tamponade

Pericardial syndromes in malignancies can present as pericarditis, pericardial effusion, pericardial tamponade (PT), or pericardial constriction [7]. PT and constriction can result in hemodynamic collapse and can present as an emergency in patients with malignancies.

Malignancies are the most common cause of pericardial effusion in the developed nations [8]. A prospective observational study that included all patients with PT showed malignancies as the most common cause with 32% of all cases for PT [9]. A 10-year prospective study of 114 patients with PT demonstrated malignant disease in 74 patients (65%) [10]. In autopsy series, the pericardium was involved in about two-thirds of patients with cancers. In addition to malignant causes, nonmalignant causes such as radiation pericarditis and infections can cause pericardial diseases. Pericardial effusion can be the presenting feature in certain malignancies, with nearly 20% of large undiagnosed symptomatic pericardial effusions turning out to be malignant [7].

Pathophysiology

Malignant pericardial effusions can occur either by direct invasion of cancer or by metastatic invasion via the lymphatics or by hematogenous spread. Chemotherapy, radiation and opportunistic infections are other causes of pericardial effusions in malignancies. PT develops when

the increased intrapericardial pressure compresses the cardiac chambers. A rapid increase in the pericardial fluid volume by 150–200 mL can sufficiently raise the intrapericardial pressure and cause tamponade. However, in subacute to chronic accumulation, the pericardial sac can accommodate as much as 2 L without significantly increasing the intrapericardial pressure [11]. As the pericardial sac distends, the intrapericardial pressure compresses the ventricles and reduces diastolic compliance.

Pericardial constriction, on the other hand, is secondary to pericardial scarring and loss of elasticity which impairs ventricular filling.

Clinical Manifestations

The insidious nature and the nonspecific symptoms of the malignant pericardial effusion create a diagnostic challenge. The symptoms can be secondary to the stretching of the pericardium and either have a mechanical effect on neighboring structures such as the esophagus and the lungs or direct pressure effects on the cardiac chambers. The symptoms can be mild to severe depending on the size of the effusion. Patients usually present with cough (46.6%), chest pain (27.3%), and dyspnea on exertion (78.8%). As the disease progresses, symptoms include dyspnea at rest with other symptoms of heart failure such as peripheral edema (34.9%) and orthopnea (26.3%) [12]. On occasions, patients might present with altered mental status, making the diagnosis difficult.

Beck's triad, which consists of increased jugular venous distention, muffled heart sounds, and hypotension, was noted in a small subset of patients presenting with trauma and is less likely to be appreciated in malignant PT [13]. Pulsus paradoxus, defined as a drop in systolic blood pressure by 10 mm Hg during normal inspiration, is seen in about 30% of patients with malignant PT [14, 15]. Patients with pericardial constriction usually present with symptoms of diastolic heart failure such as dyspnea on exertion, ascites, and peripheral edema.

Diagnosis

Doppler echocardiography is the most useful test when the clinical suspicion for PT is high. Pericardial fluid accumulation with the diastolic collapse of the right atrium (Fig. 1) and ventricle is very concerning for tamponade physiology. Right ventricular collapse is considered a very specific finding, whereas right atrial collapse is more sensitive for PT. Left atrial and ventricular collapse is less common in PT of malignancy.

In PT, the right ventricle cannot expand to accommodate blood flow during inspiration, and the interventricu-

Fig. 1. Apical 4-chamber view showing large pericardial effusion in the anterior aspect with tamponade physiology.

lar septum pushes into the left ventricle. Reciprocal changes occur during expiration. These respiratory variations can be prominent on Doppler and are concerning for decreased cardiac output. In most cases of PT, the inferior vena cava is dilated and noncollapsible [11].

Chest radiographs in patients with malignancies presenting with PT usually demonstrate an enlarged cardiac silhouette. Cross-sectional imaging with contrast-enhanced helical CT or MRI, although not required to make the diagnosis, is very sensitive to demonstrate cardiac metastasis and pericardial thickening [16]. Cardiac MR images have become increasingly popular to study the structural and functional aspects of the myopericardium. Cardiac MRI with T1 and T2 images and gradient-recalled echo cine sequences could provide superior images of pericardial effusions and masses [17]. Cardiac MRI can also detect associated myopericarditis [18]. CT scan, on the other hand, is a better modality to evaluate exudative effusions, pericardial calcifications, and hemorrhage [17]. Recent advances in technology have permitted better image reconstructions with reduced imaging artifacts. Invasive procedures such as right heart catheterization can reveal equalization of pressures in the right atrium and right ventricle as well as the pulmonary capillary wedge pressure [16].

Table 1. Management of pericardial tamponade

Assess for hemodynamic stability
– Airway: patients with pericardial tamponade are preload dependent; reserve intubation for impending respiratory failure
– Circulation: assess for hypovolemia and intravenous hydration if hypovolemic
– Inotropes: can be used as part of supportive care; however, its utility is controversial [16]
Definitive management
– Pericardiocentesis and surgical drainage are effective; urgent pericardiocentesis is recommended if tamponade physiology is noted [71]
Prevention of recurrences
– Intrapericardial instillation of sclerosing and cytotoxic agents (cisplatin for lung cancer and thiotepa for breast cancer with pericardial metastases)
– Radiation and chemotherapy for lymphomas and leukemias
– Pericardiectomy with surgical pericardial drain or pericardial window
– Echocardiography-guided pericardiocentesis with catheter drainage [71–73]
– Percutaneous balloon pericardiectomy: advanced procedure, requires cardiac catheterization and special balloon catheters; can reduce relapse up to 62% [74]
– Surgical pleuropericardiectomy: surgical drainage of the pericardial fluid into the pleura; high complications and no noted benefits over pericardiocentesis and drainage [71]

Management (Table 1)

Patients with hypotension and hemodynamic instability will invariably require attention to the basics of airway, breathing, and circulation. Intravenous hydration is appropriate in patients who appear hypovolemic [19]. Intubation for airway protection should be reserved for patients with impending respiratory collapse. However, tracheal intubation and the anesthetic agents used during the procedure can drop both preload and afterload, which can be detrimental in patients with PT [15].

Pericardiocentesis is the definitive intervention for PT. In most cases, pericardiocentesis can be planned as an elective procedure; only hemodynamically unstable patients with known malignant pericardial effusion would require emergent pericardiocentesis [11, 16]. Pericardial effusions secondary to malignancies reaccumulate in as many as 60% of the cases [9]. Placement of a drain should be considered in most cases at the time of initial pericardiocentesis in neoplastic pericardial effusions. Some patients with neoplastic PT might require a surgical procedure, such as a pericardial window, for long-term symptomatic relief [19]. A prospective study by Celik et al. [20]

showed that systemic chemotherapy plus pericardial window was more effective than either chemotherapy alone or chemotherapy plus pericardial drain placement in patients with malignant effusions. Considering the nonmalignant causes of pericardial effusion in malignancy culture, cell count, and cytology of the pericardial fluid would be necessary. Cytology of the pericardial fluid can reveal malignant cells and is usually diagnostic [11].

Mortality

Despite adequate treatment, patients with malignant pericardial involvement have a poor prognosis [8]. The development of tamponade physiology in patients with malignant pericardial effusion was the immediate cause of death in up to 85% of the cases [7]. Patients with malignant pericardial effusions in lung cancer have an overall worse prognosis than individuals with breast or hematological malignancies. A 10-year survey of patients with PT showed that patients with malignant pericardial effusion carried a high in-hospital mortality with a median survival of 150 days and a 1-year mortality of almost 77% [10]. Considering recurrence is a major issue in malignant pericardial effusion, balloon pericardiectomy or surgical drainage is effective in symptomatic management. A recent systematic review suggested the superiority of surgical drainage for symptom relief and reduction of morbidity in malignant PT [21]. Surgical approaches such as pericardial window and pericardioperitoneal shunt creation currently offer success rates of 87–100% and symptom-free survival of at least 2 months [21, 22]. Due to recent improvements in instruments and techniques, the complication rates with these surgical interventions is relatively low (4.7%) [21]. There are no randomized controlled trials or consensus statements on optimal management of the cancer-related pericardial disease.

Superior Vena Cava Syndrome

Superior vena cava syndrome (SVCS) results from a mechanical obstruction of the SVC, either external from a tumor or lymph node compressing the SVC or internal from an intraluminal obstruction by a venous thrombosis. The incidence of SVCS secondary to untreated infections such as syphilis is declining [23]. Malignancies account for about 60–90% of the cases of SVCS [23, 24]. Additionally, with the increasing use of indwelling venous catheters and a higher predilection to form venous thrombosis in patients with malignancies, the incidence of thrombosis-associated SVCS is increasing.

Table 2. Proposed grading system for superior vena cava syndrome by Yu et al. [27]

Grade	Category	Estimated incidence, %	Definition ¹
0	Asymptomatic	10	Radiographic superior vena cava obstruction in the absence of symptoms
1	Mild	25	Edema in head or neck (vascular distention), cyanosis, plethora
2	Moderate	50	Edema in head or neck with functional impairment (mild dysphagia, cough, mild or moderate impairment of head, jaw or eyelid movements, visual disturbances caused by ocular edema)
3	Severe	10	Mild or moderate cerebral edema (headache, dizziness) or mild/moderate laryngeal edema or diminished cardiac reserve (syncope after bending)
4	Life-threatening	5	Significant cerebral edema (confusion, obtundation) or significant laryngeal edema (stridor) or significant hemodynamic compromise (syncope without precipitating factors, hypotension, renal insufficiency)
5	Fatal	<1	Death

¹ Each sign or symptom must be thought to be due to superior vena cava obstruction and the effects of cerebral or laryngeal edema or effects on cardiac function. Symptoms caused by other factors (e.g., vocal cord paralysis, compromise of the tracheobronchial tree or heart as a result of mass effect) should not be considered as they are due to mass effect on other organs and not superior vena cava obstruction. Reproduced with permission from Yu et al. [27].

Pathophysiology

Masses in the anterior or middle mediastinum can cause extrinsic compression of the SVC. Enlarged paratracheal lymph nodes, lymphomas, and thymomas are notorious for causing SVCS; however, bronchogenic carcinoma has the highest association with the development of SVCS [25, 26]. Insidious progression of SVC obstruction leads to the development of collaterals between the SVC and the inferior vena cava or the azygous vein, resulting in dilated veins and swelling of the upper extremities [25].

Clinical Presentation

Patients with SVCS are rarely asymptomatic. The wide range of nonspecific symptoms in SVCS arises from the venous obstruction and subsequent increased venous pressure in the upper body. Patients with SVCS usually present with cough (54%), dyspnea (54%), hoarseness (17%), and stridor (4%) secondary to edema of the larynx and pharynx [23, 25–27]. The severity of symptoms depends on the degree of obstruction and the rapidity with which it occurs [27]. Patients with acute SVCS may present with altered mentation (2%) or headaches (9%) from the cerebral edema which results from the increased venous pressure. In many cases, SVCS may be the presenting symptom of an undiagnosed primary lung cancer. Yu

et al. [27] have proposed a grading system based on symptomatology (Table 2).

Physical examination can reveal facial plethora (20%), distended neck veins (46%), or distended chest veins (56%), the latter especially if sufficient time has passed for the development of venous collaterals [27].

Diagnosis

A strong clinical suspicion and a detailed physical examination are required to make the clinical diagnosis of SVCS. CT of the chest with contrast to evaluate the SVC is the most useful diagnostic test for SVCS [23]. MRI of the chest is equally sensitive in patients who cannot tolerate administration of iodinated contrast agents [28].

The clinical presentation and medical imaging studies are usually sufficient not only to make the diagnosis but also to differentiate between thrombosis and external compression as the cause of the SVCS. Other diagnostic studies such as venography may be performed on a case-by-case basis, especially if surgery or stent placement is planned [28].

In patients who present with SVCS and an unknown primary malignancy, a tissue biopsy is needed to confirm the diagnosis and plan the subsequent treatment strategy. As lung cancers are the most common neoplastic cause of SVCS, cytology of the sputum, bronchoscopy, and lymph

Table 3. Management of superior vena cava syndrome

Initial assessment and management of SVCS
– Assess for hemodynamic stability: SVCS rarely manifests with life-threatening symptoms (5% incidence) [27]; altered mental status, laryngeal edema, or hemodynamic instability such as hypotension require urgent intervention
– Emergent stent placement: stents can be placed before tissue diagnosis; high success rate with prompt symptom relief [32, 33]
– Thrombolytic therapy or mechanical thrombectomy: high rate of complications like gastrointestinal bleeding [33, 75]
– Emergent radiation therapy is no longer needed: can obscure the diagnosis
Supportive care ¹
– Glucocorticoids
– Diuretics
Long-term management directed at the SVCS
– Anticoagulation: when SVCS happens in the setting of a thrombus
– Chemotherapy for the underlying malignancies: small cell lung cancer [30, 76], lymphoma [77]; non-small cell lung cancer has a relatively poorer response to chemotherapy
– Radiation: provides symptom relief by reducing the tumor burden [30]
– Endovascular stenting: prompt relief of symptoms with low relative periprocedural complications; can be palliative for patients with non-small cell lung cancers
– Surgical venous bypass: less commonly used these days with the improvements in the minimally invasive procedures

SVCS, superior vena cava syndrome. ¹ There is no evidence to support the benefit of supportive care in patients with SVCS. Steroids can provide symptom relief by reducing the edema around the tumor as well as improve the laryngeal edema.

node biopsies can be useful investigations before proceeding with invasive approaches such as mediastinoscopy [29].

Management (Table 3)

Treatment for SVCS in large part hinges on the management of the underlying cause. Many factors contribute to the decisions for overall management, including the prognosis, the staging, and extent of the underlying disease, the patient's performance status, and – most importantly – the severity of symptoms. Patients who develop SVCS as a result of a germ cell tumor, lymphoma or small-cell lung cancer usually have a better response when their primary malignancy is treated with chemotherapy. Patients with underlying non-small cell lung cancer, unfortunately, do not have as good a response as the former group [26].

Supportive care may include corticosteroids, elevation of the head of the bed, and diuretics (for symptomatic relief of edema). However, there is no evidence-based validation for any of these approaches. Arguably, steroids may cause tumor shrinkage and provide relief, especially in lymphoid malignancies.

A systematic review by Rowell and Gleeson [30] concluded that in patients with SVCS caused by lung cancer, there was no difference in outcomes among groups treated with radiation therapy, radiation plus chemotherapy, or chemotherapy alone. In contrast, stent insertion provided symptom relief in more patients (95%) and more rapid improvement in symptoms.

Placement of intravascular stents can provide an immediate symptomatic improvement in patients with SVCS and can be performed before biopsy and confirmation of underlying diagnosis [31]. Stenting can be especially useful in patients with acute or severe symptoms and in those whose SVCS is caused by venous thrombosis [32]. Reported complications of SVC stent procedures range from 0 to 19% [33]. Although there are no randomized controlled trials, several case studies report the utility of stenting in the management of SVCS.

SVCS secondary to an intravascular thrombus is treated with anticoagulation. If the thrombus is associated with a central venous catheter, that device should preferably be discontinued. However, acute symptoms can be managed with thrombolysis. The success rate is highest if treatment is commenced within 5 days when the thrombus is soft [32]. Catheter-guided thrombolysis with newer techniques has shown encouraging results and is fast gaining clinical utility.

Prognosis and Mortality

Contrary to popular belief, SVCS is not always an actual medical emergency. In most cases, there is sufficient time to stabilize the patient and to treat and relieve symptoms, unless there is a concern for concomitant laryngeal or cerebral edema [26].

The prognosis and management of SVCS in patients with malignancies are individualized, and depending on the underlying malignancy, a curative or palliative approach is undertaken. The median reported survival is anywhere between 1.5 and 9.5 months [26].

Hyperviscosity Syndrome

Hyperviscosity syndrome (HS) results from increased serum viscosity and erythrocyte aggregation. HS is classi-

cally associated with Waldenström macroglobulinemia (lymphoplasmacytic lymphoma) and can be the initial presentation of the disease [34]. Multiple myeloma, cryoglobulinemia, amyloidosis, acute leukemia, and polycythemia vera are some other common causes of HS [35]. The increase in the viscosity can be secondary to excess circulating proteins as in the monoclonal gammopathies and cellular components in conditions such as leukemia and myeloproliferative disorders. Leukostasis is often a term associated with HS secondary to excessive circulating white cells [36].

Pathophysiology

Excess circulating proteins or high levels of red blood cells, leukemic blasts, or platelets result in impaired blood flow, which in turn causes relative hypoperfusion to the end organs with ischemia in severe cases. The viscosity of blood is measured in centipoise (cp) and is referenced to water, which has a viscosity of 1 cp at room temperature. The normal viscosity of blood is 1.4–1.8 cp. Symptoms of HS usually develop when the serum viscosity approaches 4–5 cp [37]. In a study of patients with monoclonal gammopathies, Crawford et al. [38] showed that the serum gamma globulin concentration correlated well with plasma viscosity; no patients with a viscosity less than 3 cp developed HS.

The abnormal circulating paraproteins can result in red blood cell aggregation, commonly demonstrated on the peripheral blood smear as “rouleaux formation.” These aggregations can be large and cause occlusion in blood vessels with symptoms ranging from that of hypoperfusion to frank ischemia [39].

Clinical Presentation

Symptoms of HS range from a mild headache, dizziness, and vertigo to severe manifestations such as altered mentation and deafness. Retinal venous congestion is common in HS, and visual changes such as blurring of vision are often reported. In severe cases, patients may present with blindness due to severe retinal ischemia or retinal vein thrombosis [40].

Thromboembolic events in both the arteries and veins can complicate the clinical diagnosis of HS and may be associated with clinical presentations mimicking those of ischemic stroke, transient ischemic attack, myocardial ischemia, and thrombosis in unusual sites such as the hepatic veins (Budd-Chiari syndrome) [34]. Of note, concomitant symptoms in patients with plasma cell dyscrasias may include neuropathy secondary to the deposition of the paraproteins on the myelin sheath of the periph-

eral nerves and bleeding manifestations due to the impairment of the hemostatic function by circulating monoclonal paraproteins [41].

Diagnosis

A high degree of clinical suspicion is necessary to make the clinical diagnosis of HS. The clinical presentation of a combination of mucosal or skin bleeding, visual abnormalities and focal neurological defects in a patient with a plasma cell dyscrasia are highly suggestive of HS [37]. On physical examination, fundoscopy can reveal retinal venous engorgement (“string of sausages” appearance [40]), hemorrhages, and possibly retinal vein occlusion, especially in patients with visual symptoms [42]. Prompt measurement of serum viscosity is warranted and levels greater than 4 cp suggest the diagnosis of HS. However, individual patients can have different viscosity thresholds above which symptoms appear [37].

The erythrocyte sedimentation rate is usually elevated in HS. Serum and urine protein electrophoresis studies are useful to detect the elevated levels of monoclonal proteins; immunofixation can further determine the specific immunoglobulin type and specific light chain of the plasma cell dyscrasia. HS is usually seen in monoclonal gammopathies of IgG, IgA, and IgM.

Management (Table 4)

Management of HS involves prompt diagnosis and early initiation of plasmapheresis or plasma exchange to remove the excess circulating paraproteins [43]. Using an apheresis apparatus, blood is centrifuged, and plasma is separated from the cellular components. The excess proteins removed from the plasma are replaced with normal saline or 5% albumin. Plasmapheresis can successfully remove large molecules such as IgA and the IgM multimer. A single exchange cycle can remove as much as 65% of the proteins and can reduce the serum viscosity by about 20% [34]. There are no randomized controlled trials to support plasmapheresis; however, several observational and case studies have consistently shown the efficacy of plasmapheresis in the treatment of HS [44]. Plasmapheresis is safe and well tolerated [34, 37]. Most patients respond well to this treatment approach with a relatively low complication rate. The goal of the treatment of HS is to bring about symptom resolution and not to merely normalize the serum viscosity. Daily plasmapheresis and periodic monitoring of the serum viscosity can be continued until adequate symptom resolution. In cases of HS associated with hyperleukocytosis, as in acute leukemias, an apheresis apparatus can be used to remove leukocytes

Table 4. Management of hyperviscosity syndrome

Short-term approach of reduction of the serum viscosity

- Plasmapheresis with albumin or fresh frozen plasma; usually, 2–3 cycles are required and is continued till symptomatic relief is observed
- Cascade filtration: selective removal of macromolecules [78]

Long-term management: targeted therapy at the underlying cause

- Monoclonal gammopathies: multiple myelomas, Waldenström macroglobulinemia, amyloid light chain amyloidosis
- Myeloproliferative disorders like polycythemia vera
- Hyperleukocytosis secondary to acute myeloid leukemia and acute lymphoblastic leukemia
- Polyclonal gammopathies: autoimmune conditions like rheumatoid arthritis and Sjögren syndrome

(leukocytapheresis), often with the administration of hydroxyurea for cytoreduction.

HS is occasionally noted after initiation of rituximab therapy in Waldenström macroglobulinemia due to the transient increase in the clonal IgM proteins resulting from lysis of malignant cells [45]. If the serum viscosity is greater than 3.5 cp, then prophylactic plasmapheresis before initiation of rituximab can be considered [46].

Mortality and Morbidity

Several retrospective cohort studies have shown lower 3-week mortality with therapeutic apheresis in patients with acute myeloid leukemia and hyperleukocytosis. However, this initial benefit did not translate into a long-term survival benefit [44]. Plasmapheresis does not treat the underlying disease process, and concurrent chemotherapy is warranted. Overall prognosis depends on the underlying disease process with patients needing plasmapheresis in spaced intervals to keep them asymptomatic [34, 35]. One-year and 5-year survival data in patients with HS in a Latin American 30 years' retrospective study were 84 and 58%, respectively. All deaths were secondary to infections associated with the underlying disease [47].

Emergencies Secondary to the Use of Chemotherapeutic Agents

Cardiovascular complications secondary to chemotherapeutic agents and biological agents can develop in an acute, subacute or chronic fashion. In most cases, the side effects are dose-dependent and increase with the ad-

ministration of a concomitant cardiotoxic agent. Complications such as acute mesenteric ischemia due to the occlusion of mesenteric arteries have been observed with chemotherapeutic agents such as cisplatin and 5-fluorouracil [48]. Similarly, coronary vasospasm and sudden cardiac death have been noted with the use of 5-fluorouracil [49]. Hemorrhagic myocarditis is a rare complication of the use of high-dose cyclophosphamide [50].

The use of biologic agents in the setting of cancers previously treated with chemotherapeutic agents significantly increases the risk of cardiotoxicity. Trastuzumab-induced cardiomyopathy has an incidence range of 3 to 7% when administered as monotherapy; however, in combination with anthracyclines and cyclophosphamide, the risk increases to as high as 27% [51]. Hypertensive crisis and uncontrolled hypertension are noted in patients treated with VEGF target agents such as bevacizumab, the risk being dose dependent with the relative risk as high as 7.5 times greater for patients receiving the high-dose regimen [52, 53].

Table 5 shows a summary of cardiovascular complications secondary to the use of older and newer agents in the treatment of cancer.

Effect of Radiation Therapy to the Heart

Multiple studies have shown patients treated with radiation therapy for the management of thoracic malignancy to be at increased risk for coronary artery disease, congestive heart failure, valvular heart disease, pericardial disease, and sudden cardiac death [54]. Radiation treatment causes direct damage to the blood vessels resulting in endothelial damage. Endothelial dysfunction is believed to precipitate the cardiac sequela [55].

Pericardial Disease

Acute radiation pericarditis typically manifests few weeks after radiation therapy. Acute pericarditis usually follows a self-limited course. About 10–20% of patients develop chronic or constrictive pericarditis 5–10 years following treatment [56]. Some patients may develop effusive pericardial effusion progressing to a tamponade physiology due to collection of a tense effusion between fibrotic and thickened layers of the pericardium [57]. Pericardiocentesis or pericardiectomy may be needed.

Coronary Artery Disease

Radiation-induced endothelial dysfunction is believed to be the basis of the development of cardiovascular se-

Table 5. Cardiovascular complications from commonly used chemotherapeutic and biologic agents

Type of emergency	Chemotherapeutic agent
Ventricular tachycardia/fibrillation	Alkylating agents (cisplatin, cyclophosphamide) Antimetabolites (5-fluorouracil, capecitabine) ¹ Anthracyclines (daunorubicin, doxorubicin) Monoclonal antibodies (rituximab, trastuzumab) Arsenic compounds used in treatment of relapsed acute leukemias
Hemorrhagic myopericarditis	Alkylating agents (cyclophosphamide)
Myocardial ischemia by coronary vasospasm	Fluoropyrimidines (5-fluorouracil) Vinca alkaloids Cisplatin Biologic agents (trastuzumab) Etoposide Aromatase inhibitors Taxanes Proteasome inhibitors – bortezomib (Takamatsu)
Thromboembolism	Tamoxifen Cisplatin VEGF-targeted agents – bevacizumab Immunomodulatory agents – lenalidomide, thalidomide (Senkus) and pomalidomide
Pericardial effusion	Anthracyclines (daunorubicin, doxorubicin)
Congestive heart failure	Anthracyclines (daunorubicin, doxorubicin) ² Biologic agents – trastuzumab ³ VEGF-targeted agents – bevacizumab ³
Hypertensive crisis	VEGF-targeted agents – bevacizumab, sunitinib, sorafenib

¹ Potential to induce ischemia, QTc prolongation and torsades de pointes. ² Usually within a year of therapy. ³ In conjunction with anthracyclines and alkylating agents.

quel in coronary artery disease. Radiation-associated coronary artery disease is more common in women and is characterized by a high incidence of left main and right ostial coronary disease [58]. Patients may present with chest pain or acute myocardial infarction.

Myocardium

Radiation-induced capillary wall injury causes microvascular insufficiency and ischemia resulting in diffuse interstitial fibrosis [59]. These fibrotic changes lead to altered cardiac compliance with systolic and diastolic dysfunction. The presence of diastolic dysfunction has been shown to be associated with stress-induced ischemia and a poorer prognosis [60].

Valve Dysfunction

Radiotherapy may cause valve retraction, valvular fibrotic thickening, and late calcification. Valve retraction

with resultant regurgitation may be the earliest sign of radiation-induced valvular damage. Aortic and mitral valves are more affected than the pulmonic or tricuspid valves [61].

Conduction System

Abnormality of the conduction system, including increased frequency of QT prolongation, sick sinus syndrome, atrioventricular block, supraventricular tachycardias and ventricular tachycardias have been reported following radiation therapy [62]. Symptoms relating to the conduction system are uncommon but could result in syncope, palpitations, and sudden death. Patients with mediastinal radiotherapy may also have a decreased perception of angina pain secondary to autonomic system dysfunction [63].

Other Emergencies

Hemorrhagic and septic shock is common in cancers. All intraluminal tumors are prone to bleeding, and often acute anemia, secondary to frank bleeding, can be the presenting symptom. The role of anticoagulation in patients with atrial fibrillation and cancers is gaining importance considering that cancer creates a thromboembolic state, while the nature of the tumor and metastasis inherently increase the risk of bleeding. No clear practice guidelines have been formulated for this population, and all the clinical trials on the novel oral anticoagulants have excluded cancer patients [64]. Hence, initiation of anticoagulants to prevent thromboembolic events in patients with atrial fibrillation has to be individualized, weighing in the risk-benefit profile. Hemoptysis is a common symptom in bronchogenic cancers. However, massive hemoptysis has been defined with several different criteria ranging from 100 to 1,000 mL of acute blood loss at a rapid rate in 24 h [65]. Approximately 10% of patients with lung cancers, usually the centrally located lung cancers such as squamous cell cancers, can present with massive hemoptysis [66]. A prompt diagnosis with angiomultidetector CT scans, bronchoscopy, and a multidisciplinary team approach is warranted. Definitive treatment is usually with successful embolization of the involved vessels [67]. Death usually results from asphyxiation over true hypovolemia [68]. Tumors of the hepatic system, splenic system, and ovaries are prone to rupture or cause internal bleeding resulting in severe anemia. Hepatic adenomas, splenic hemangiosarcomas, and ovarian stromal tumors

[69] are a few examples. The mechanisms for cancer-triggered disseminated intravascular coagulation are unclear; however, it can be seen in solid cancers and hematologic malignancies such as acute promyelocytic leukemia [70]. Severe infections, electrolyte disturbances, and their sequelae are common in malignancies; infections can rapidly progress to sepsis, acute respiratory distress syndrome, and septic shock in malignancies. Details and management of shock are beyond the scope of this literature.

Conclusion

Internists should become familiar with the diagnosis and initial management of common oncologic urgencies and emergencies. Prompt recognition of these conditions can reduce morbidity. The long-term outcome, however, is largely dependent on the underlying malignant process. The practitioner should review treatment, prognosis, and both short- and long-term goals with the patient at their initial encounter.

Conflict of Interest

None of the authors who contributed to this article have any conflict of interest to disclose.

All authors have made substantial contributions to drafting the article or revising it critically for important intellectual content and have approved it for submission.

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