Pericardial Involvement in Cancer

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Despite the monumental advances in the diagnoses and therapeutics of malignancy, several cancer patients have presented with pericardial involvement, including acute pericarditis, constrictive pericarditis, and pericardial effusion.
Multiple factors can contribute to acute pericarditis, including direct metastasis to the heart, pericardial hemorrhage, infections due to immunosuppression, and cancer therapies that include chemotherapy, immunotherapy, and radiation. Pericardial effusion, either due to cancer invasion or cancer treatment, is one of the most common incidental findings in cancer patients, which significantly worsens morbidity and mortality. If left untreated, pericardial effusion is known to cause complications such as pericardial tamponade. Constrictive pericarditis can be due to radiation exposure, chemotherapy, or is a sequela of a previous episode of acute pericarditis. In conclusion, early detection, prompt treatment, and understanding of pericardial diseases are necessary to help improve the quality of life of cancer patients, and we aim to summarize the knowledge of pericardial involvement in patients with cancer. **(Am J Cardiol 2021;145:151−159)**

The most common primary tumors metastasizing to the heart are lung, breast, and esophageal cancers and lymphomas. Most pericardial involvement in cancer patients is due to their malignancy.[1,2] The pericardium might be directly affected by the tumor (primary or secondary) or indirectly due to chemotherapy, immunotherapy, or radiation toxicities. Infectious pericarditis can also occur in the setting of chemotherapy-induced immunosuppression. This article reviews the current knowledge of pericardial involvement in cancer patients. Figure 1 summarizes the types of involvement and their various etiologies, and Table 1 demonstrates the distribution of pericardial manifestations depending on cancer type.

Acute Pericarditis and Cancer

Epidemiology

Recently, there has been an increased interest in the concurrence of pericarditis and systemic diseases, particularly cancer.[64,65] A study conducted in Denmark demonstrated that 1,550 patients out of 13,759 patients (around 11%) with pericarditis had new cancer diagnoses during the median follow-up period of 6.4 years.[3] On the other hand, pericarditis has been associated with high-dose chemotherapy.[4] The occurrence of pericarditis postradiotherapy varies from months to up to a decade,[5,6] and can also affect other cardiac structures. The risk of pericarditis increases from 5% to more than 50% with an increase in the total dose from 40 to 50 Gray.[7] Radiation-induced pericarditis also depends on the amount of radiation the heart is exposed to, with a higher incidence of pericarditis if more than 30% of the heart area receives 50 Gray (historical doses).[8] Recently, pericarditis has been attributed to immune checkpoint inhibitors.[9] Myopericarditis has been seen in cancer patients undergoing treatment with chemotherapy and radiation therapy.[10] Chemotherapeutic agents that were reported to cause myopericarditis were capecitabine and ivosidenib.[11,12] In both cases, there was an improvement upon discontinuation of the inciting agent and administration of steroid therapy. Ventilatory support and diuresis might also be required.[12]

Pathophysiology

The mechanisms of malignancy-associated pericarditis depend on the cause. Those include direct infiltration by malignant cells from nearby structures, pericardial hemorrhage, or hematogenous spread of cancer cells.[13] Radiotherapy is thought to generate reactive oxygen species and makes the pericardium porous resulting in neutrophilic infiltration and exudate collection.[14,15] These secondary inflammatory changes can result in fibrosis.[14] Chemotherapy may also increase the chances of opportunistic bacterial or viral infection of the pericardium.[16] In the case of immune checkpoint inhibitors, an enhanced affinity of T cells to antigens shared by the tumor and heart tissue may lead to pericarditis.[17]

Clinical features

The typical presentation of pericarditis is central chest pain, which is pleuritic and positional (improves on leaning forward).[18] Fever and pericardial rub might be present.[15,19] Patients with malignant pericarditis were found to have a higher incidence of tachycardia and a low amplitude QRS complex.[20]

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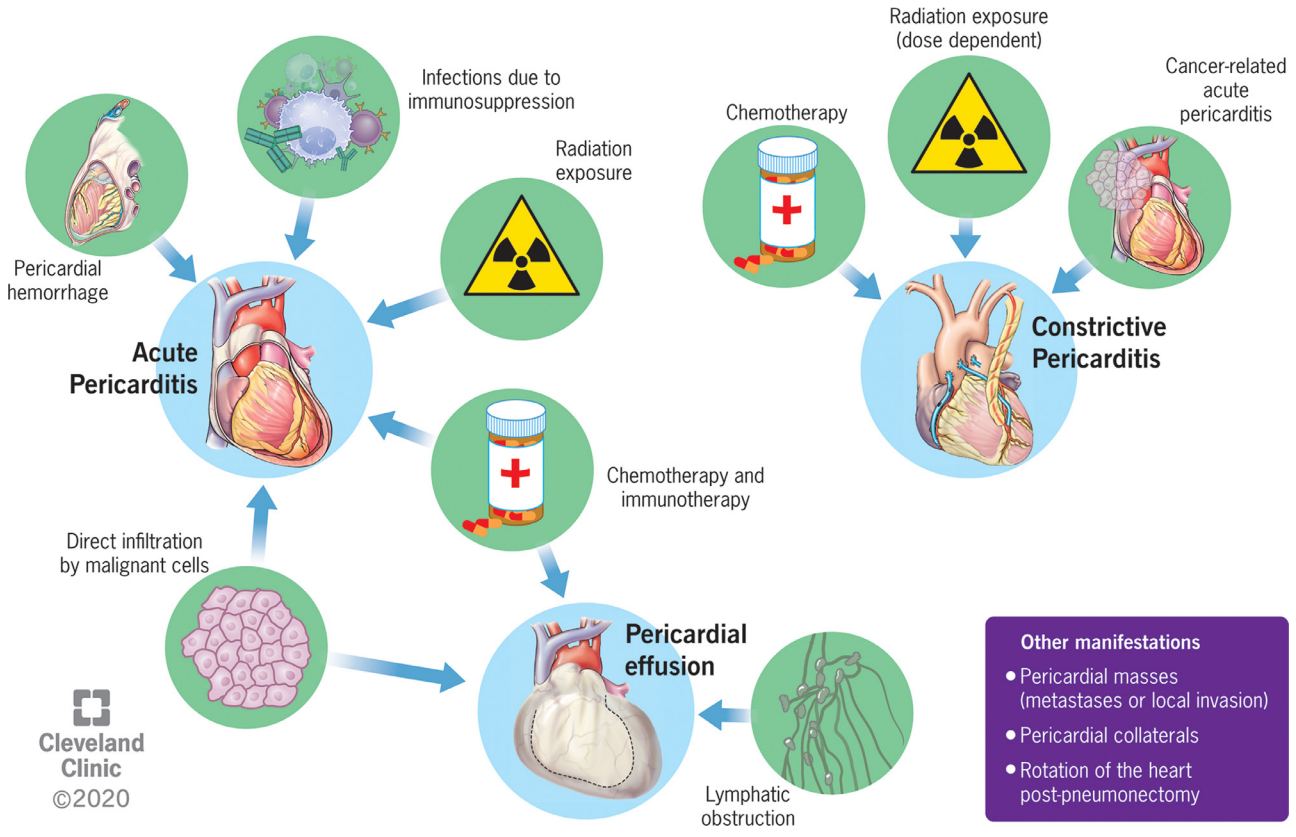

Figure 1. **(Central Illustration).** Pathophysiology of pericardial involvement in cancer patients.

Diagnosis and management

It is recommended to assess inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), renal and liver function, creatinine kinase, troponin, chest X-ray, and echocardiogram.[18] An electrocardiogram (EKG) can show saddle-shaped ST-segment elevation in a noncoronary distribution and PR segment depression.[21] In high-risk patients, imaging modalities such as cardiac computed tomography (CT) and cardiovascular magnetic resonance (CMR) are indicated.[22] CMR might show moderate to severe pericardial delayed enhancement with fat-suppression and pericardial edema on T2 short-tau inversion recovery weighted imaging (**Figure 2**). There is a significant correlation between the presence of pericardial thickening or late gadolinium enhancement on CMR and clinical diagnosis of acute pericarditis.[23] CMR is the gold standard test for assessing pericardial inflammation as it does not involve ionizing radiation. For those who have a contraindication to CMR, an alternative imaging modality is fluorodeoxyglucose positron emission tomography (FDG PET)/CT for diagnosis, risk stratification, and therapy monitoring in patients with pericarditis.[24] A "ring of fire" sign around the heart can highlight increased metabolic activity indicative of acute pericarditis.[25] Imaging, along with specific tumor markers, can also help to determine possible malignant causes for pericarditis.[26] It has been reported that higher levels of carcinoembryonic antigen (more than 5 ng/mL) and cytokeratin fragment-19 (CYFRA 21-1) (more than 50 ng/mL) in the pericardial fluid in patients are associated with malignant pericarditis.[20]

Treatment

Treatment predominantly involves nonsteroidal anti-inflammatory drugs (NSAIDs) and a 2- to 4-week taper after symptoms have resolved, and inflammatory markers (CRP and ESR) have normalized (**Figure 3**). In our institution, we repeat those markers every 2 to 4 weeks until they normalize or if there is recurrent typical chest pain. To reduce the risk of recurrent pericarditis, a 3-month course of colchicine is recommended.[27] Corticosteroids are only reserved for cases where NSAIDs cannot be used, where standard therapy fails multiple times, or in the case of immune-checkpoint inhibitors-induced toxicity.[27,28] However, due to abnormalities in cell counts and coagulation, NSAIDs are used with greater caution in pericarditis associated with malignancy since the patients can have a higher predisposition for bleeding. Anti-interleukin 1 therapy, such as anakinra and rilonacept, has been beneficial in refractory cases.[27] New techniques such as 3D radiotherapy[15] and delivering radiation in breath-hold[29] have shown to reduce the chances of developing pericarditis. Pericardial fenestration has also been found to be helpful.[30]

Constrictive Pericarditis and Cancer

Epidemiology

Even though the epidemiology of constrictive pericarditis (CP) vastly varies by geography and referral bias, it is

Table 1
Pericardial manifestations depending on cancer types

Primary cancer site	Overall standardized incidence ratio for acute pericarditis[3]	Other pericardial manifestations[13,33,60–62]	Common causative factors[3,5,63–66]
Heart and thoracic cavity	19.7	-Pericardial effusion	-Primary tumor -Direct spread
Lung, bronchi and trachea	3.3	-Pericardial effusion -Constrictive pericarditis	-Metastasis -Direct spread -Chemotherapy -Radiation therapy
Myeloid leukemia	3.1	-Pericardial effusion	-Metastasis -Chemotherapy -Paraneoplastic syndrome
Hodgkin's lymphoma	2.8	-Pericardial effusion -Constrictive pericarditis	-Metastasis -Chemotherapy -Radiation therapy
Non-Hodgkin Malignant Lymphoma	2.3	-Pericardial effusion -Exudative pericarditis	-Metastasis -Chemotherapy -Radiation therapy
Oral cavity	2.2		-Metastasis
Ovary	1.7		-Metastasis -Chemotherapy
Kidney	1.7	-Pericardial effusion	-Metastasis
Colon	1.4		-Metastasis -Chemotherapy
Esophagus	1.1	-Pericardial effusion	-Metastasis -Radiation therapy -Chemotherapy
Breast	0.9	-Pericardial effusion -Constrictive pericarditis	-Metastasis -Chemotherapy -Radiation therapy

one of the most common complications of an unresolved pericardial effusion in cancer patients.[31] The development of pericarditis significantly increases morbidity and mortality in cancer patients and may be one of the first clinical manifestations of occult cancer.[3] With lung cancer being the most common type of cancer complicated by pericarditis, other cancers like breast, ovary, prostate, lymphoma, leukemia, and malignant melanoma, are also frequently associated with pericarditis.[3,20,32–37]

Pathophysiology

The etiologies of CP are numerous, including previous cardiac surgery, postradiotherapy, paraneoplastic tumor, sarcoidosis, connective tissue disease-related, postinfectious, or idiopathic.[38] CP can complicate cancer-related acute pericarditis, with or without associated inflammation (transient constriction). Patients receiving radiotherapy may present with CP or effusive-constrictive pericarditis

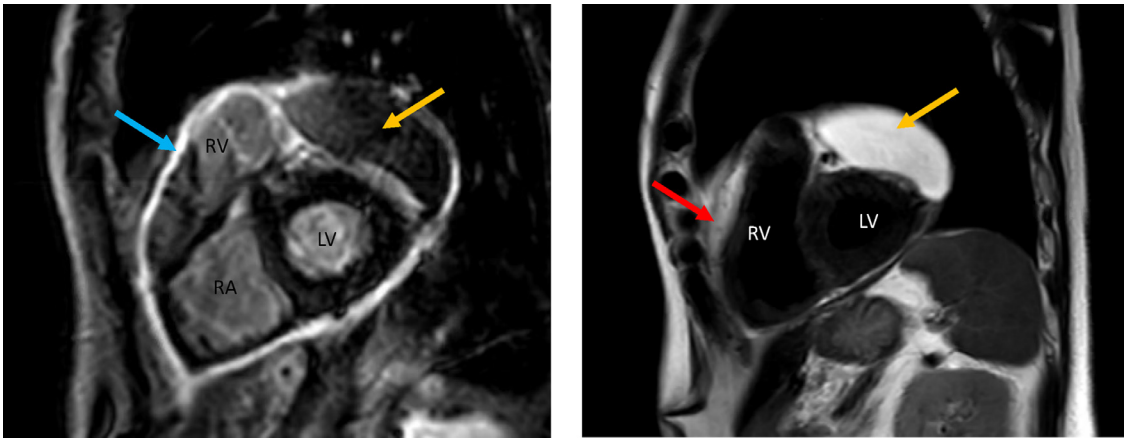

Figure 2. Cardiac magnetic resonance imaging showing a pericardial mass (orange arrow) associated with signs of pericardial inflammation as demonstrated on short-axis views by severe delayed enhancement (blue arrow) and pericardial edema on T2 short-tau inversion recovery weighted imaging (red arrow). LV = left ventricle; RA = right atrium; RV = right ventricle.

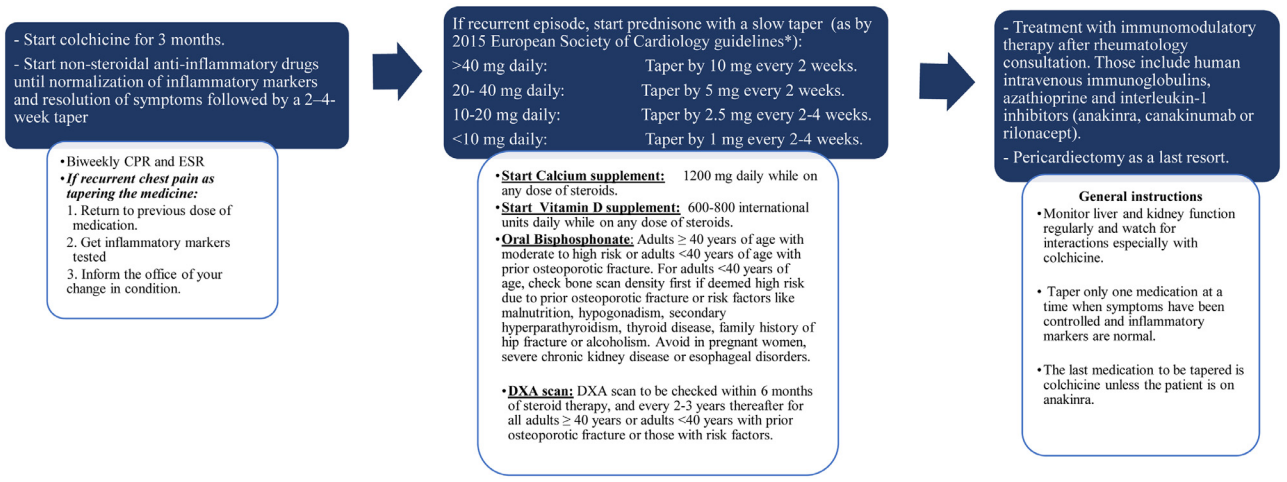

Figure 3. Flow chart showing the management of acute and recurrent pericarditis.
DXA = dual-energy X-ray absorptiometry.
*Adapted from Adler Y, Charron P, Imazio M, Badano L, Barón-Esquivias G, Bogaert J, Brucato A, Gueret P, Klingel K, Lioni C, Maisch B, Mayosi B, Pavie A, Ristić AD, Tenas MS, Seferovic P, Swedberg K, Tomkowski W. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC) Endorsed by: The European Association for Cardio-T. Eur Heart J. 2015;36:2921−2964.

several years later.[39−41] Exposure to radiation leads to T cell-mediated injury.[42] However, these complications are thought to depend on the dosage of the radiotherapy that patients are exposed to. Cancer medications and treatments may also worsen pre-existing pericardial effusions, a late manifestation of which is CP. In fact, cardiovascular disease is the leading nonmalignant cause of death in cancer patients.[43]

Clinical features

Patients with CP usually present with a constellation of symptoms relating to fluid overload or with decreased cardiac output on exertion. Physical examination may show Kussmaul's sign (lack of jugular venous pressure decrease with inspiration), pericardial rub, pericardial knock (early diastolic sound indicative of early ventricular filling), jugular venous distension, pedal edema, and pulsus paradoxus (decrease of blood pressure of more than 10 mm Hg during inspiration). As many as 93% of surgically confirmed cases of CP have been noted to have a raised jugular venous pressure.[31]

Diagnosis and management

Hemodynamically, CP is characterized by dissociation of intrathoracic and intracardiac pressures and greater ventricular interdependence.[44] Respiration-related ventricular septal shift, preserved or increased medial mitral annular e' velocity, and increased hepatic vein expiratory diastolic flow reversals are noted using echo-Doppler evaluation.[66] Tissue Doppler imaging may also demonstrate the characteristic mitral annular lateral e′ to medial e′ ratio less than 1, or annulus reversus, highlighting pericardial tethering of the lateral ventricular wall. Myocardial strain imaging by 2D speckle tracking may also help demonstrate a lower magnitude of negative peak systolic strain in free walls when compared with septal peak systolic strain.[44] CMR may also be a useful tool in identifying constrictive physiology, showing septal bounce, pericardial tethering, ventricular interdependence, and dilated inferior vena cava.[44,45] CMR can also detect pericardial thickening, pericardial edema, and active inflammation in cases of transient constriction. Definitive diagnosis is made by right heart catheterization showing square root sign in the right and left ventricular waveforms, significant x and y descents in atrial tracings, and identical diastolic pressures of less than 5 mm Hg. Cytology of pericardial fluid may help in establishing the malignant etiology.[46] Cardiac CT is the gold standard for imaging pericardial calcification and may also be a useful tool in preoperative planning for pericardiectomy (in particular for those patients who have had previous heart surgery).

Treatment

Pericardial pathologies from radiotherapy may be prevented or attenuated with reduced cardiac radiation dose secondary to the implementation of advanced radiation technology techniques, specific dosimetry as well as targeted precautions, and careful patient selection.[10] Once it develops, the definitive treatment for chronic constrictive pericarditis remains pericardiectomy performed in experienced centers.

Pericardial Effusion and Cancer

Epidemiology

The morbidity and mortality of cancer patients significantly worsen once pericardial effusion (PEEF) occurs due to cancer invasion or to nonmalignant causes like radiation, other therapies, or infections.[26,35,46] The development of PEEF in cancer patients represents an advanced stage of the disease, and the mean survival time of these patients seldom exceeds 12 months.[47−49] About one-third of cancer patients with PEEF develop pericardial tamponade.[35,49,50] Thus, early identification of PEEF and its prompt treatment are necessary.

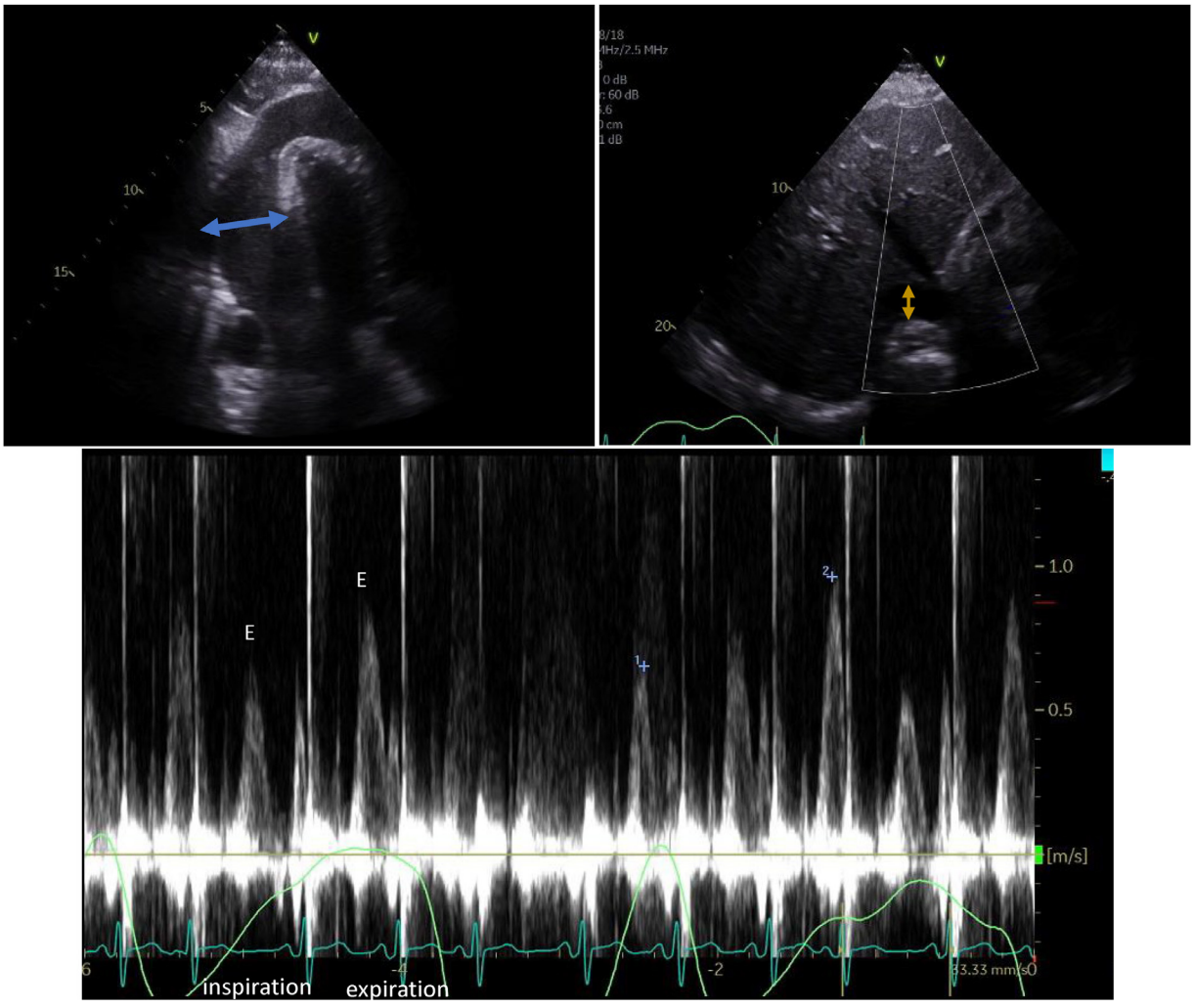

Figure 4. Large circumferential pericardial effusion adjacent to the left ventricle (blue double arrow) measuring 2.9 cm on echocardiography three-chamber view in a patient with metastatic nonsmall cell lung cancer. There is dilation of the inferior vena cava of 2.5 cm (double orange arrow). On Doppler, there is a 32% change in mitral valve peak E-wave inflow (E) velocity with respiration. This patient underwent pericardiocentesis for cardiac tamponade due to a hemorrhagic pericardial effusion.

Pathophysiology

PEEF in cancer patients may arise through one of several mechanisms. First, primary tumors of the breast, esophagus, and lungs may themselves metastasize to the heart or cause mediastinal lymphatic drainage obstruction.[49–52] However, in about two-thirds of cancer patients, PEEF develops due to nonmalignant causes.[53] A potential side-effect of cancer drugs is the derangement of liver function, kidney function, or cardiac function, which could also lead to PEEF. Anthracyclines, cyclophosphamide, busulfan, cytarabine, interferon tyrosine kinase inhibitors, arsenic trioxide, all-trans retinoic acid, methotrexate, 5-fluorouracil, and docetaxel may also lead to cardiac injury by the formation of reactive oxygen species.[53–55] Immune checkpoint inhibitors (like ipilimumab, nivolumab, and pembrolizumab) are associated with PEEF.[9]

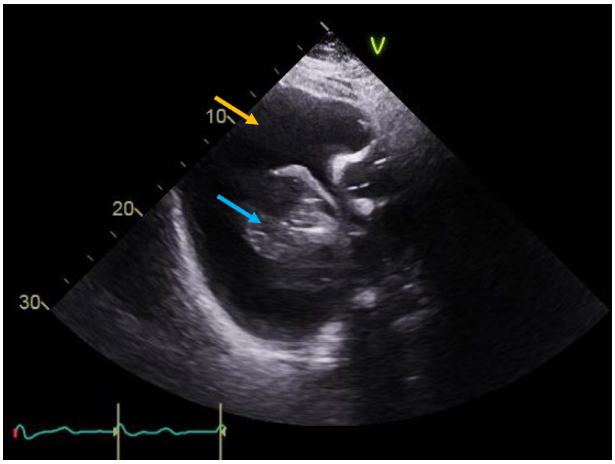

Figure 5. Large pericardial effusion (orange arrow) in a patient with a history of radiation for thyroid cancer with associated lung atelectasis (blue arrow).

Clinical features

Patients with PEEF typically are asymptomatic but may present with symptoms related to the underlying cause of

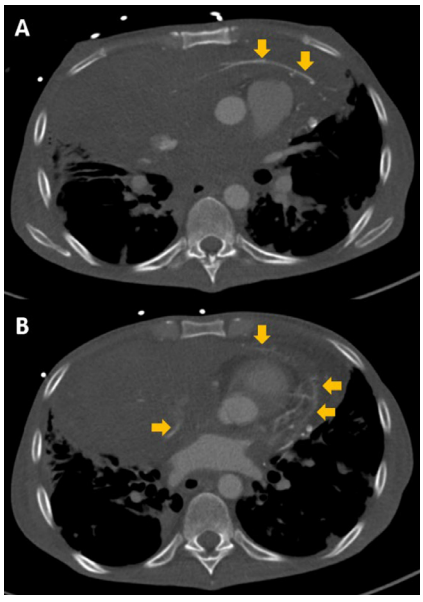

Figure 6. Pericardial collaterals (orange arrows) seen in chest computed tomography surrounding a large pericardial effusion of more than 3 cm, making pericardiocentesis nonfeasible in a patient with refractory Hodgkin lymphoma.

the effusion. Other nonspecific features may be chest pain and fever in the setting of pericarditis or symptoms and signs of cardiac tamponade-like fatigue, dyspnea, raised jugular venous pressure, edema, and hypotension.

Diagnosis and management

Once suspected, the diagnostic work-up should revolve around identifying the cause of the PEEF. A low QRS voltage and electrical alternans on EKG might be present. Transthoracic echocardiography is the gold-standard test and is helpful in guiding pericardiocentesis. Signs of cardiac tamponade are found on echocardiography in more than half of patients with malignant pericardial effusion and include diastolic right heart collapse, increased respiratory variations of tricuspid and mitral flow velocities, and engorgement of the inferior vena cava (**Figures 4–5**).[50,56,57] Cardiac CT and MRI images may show enlargement of the inferior vena cava and hepatic veins, compression of the cardiac chambers, bowing of the interventricular septum, and reflux of contrast into the azygous vein or inferior vena cava.[26] A definitive diagnosis of malignant PEEF can only be made through cytological fluid analysis. The size of the effusion needs to be monitored through regular echocardiography. Echocardiography should be repeated within 1 month in those with small effusions, 2 weeks in moderate effusions, and within a week in those with large effusions. It is important to review previous imaging (including CMR and CT) to assess true chronicity. Patients should present to the emergency room for any symptoms that might indicate tamponade physiology. Even if asymptomatic, drainage of large pericardial effusions might be considered in selected cases (if massive, on anticoagulation or for those living remotely from acute care hospitals).

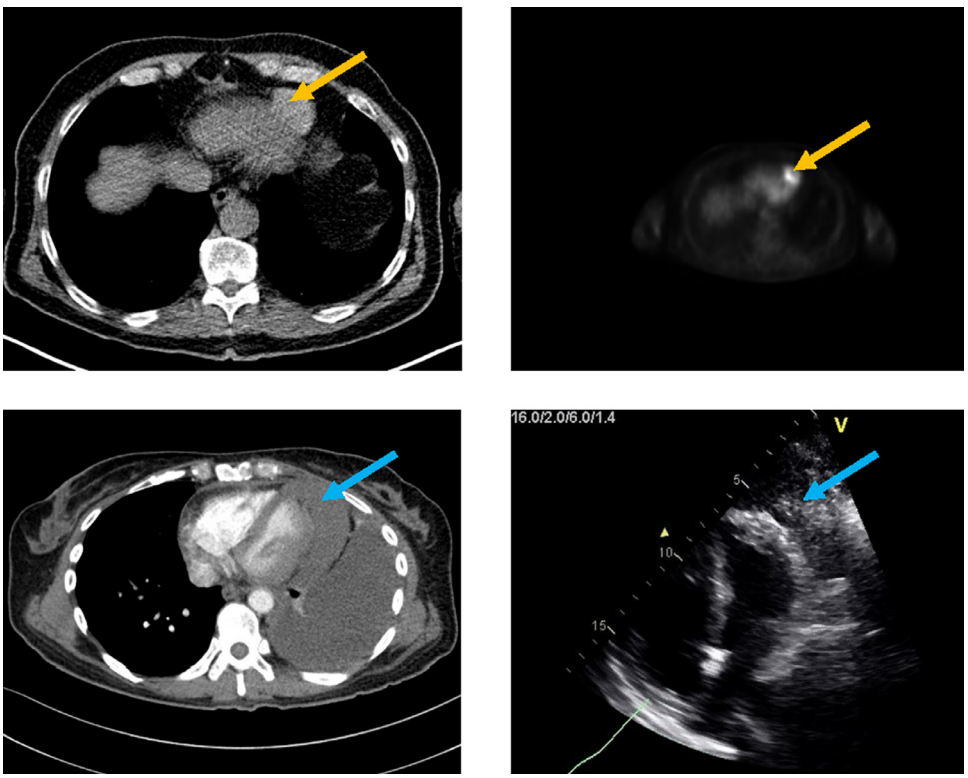

Figure 7. Positron emission tomography - computed tomography (PET/CT) (1A) showing a pericardial mass with increased uptake (orange arrow). In another patient (1B), computed tomography and echocardiography four-chamber view depicting a large pericardial mass (blue arrow).

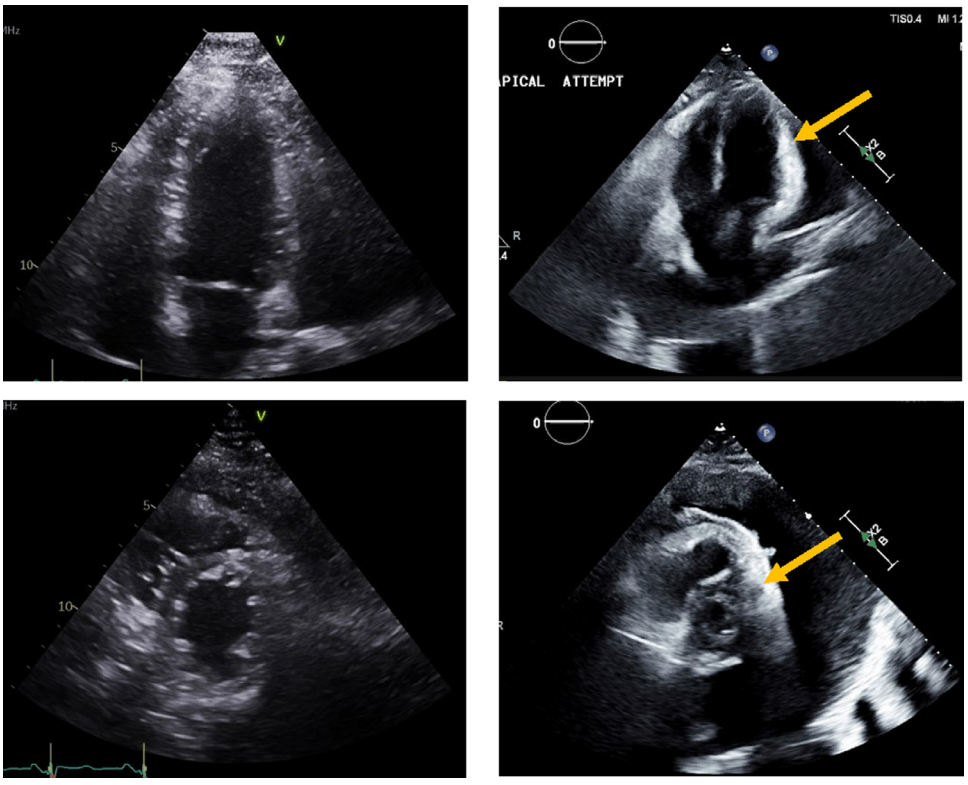

Figure 8. Echocardiography four-chamber views (upper images) and parasternal short axis (lower images) showing off-axis cardiac images and mediastinal fluid after pneumonectomy (images on the right, arrows), compared with prepneumonectomy (images on the left).

Treatment

Treatment strategies for patients with PEEF revolve around improving the quality of life, relieving the symptoms, and preventing recurrence. Doses of cancer drugs may be reduced or withheld in chemotherapy-related PEEF based on the prognosis of cancer.[53] Pericardial effusion due to neoplastic involvement of pericardium is a definitive indication for pericardiocentesis.[22] Other treatment options include pericardial instillation of bleomycin for malignant pericardial effusion, drainage via percutaneous or surgical approach for a large effusion, and placement of a pleuropericardial or pleuroperitoneal window for preventing recurrences.[22,52]

Other Types of Pericardial Involvement

These include pericardial masses due to local invasion or metastases and pericardial collaterals (which can complicate a possible need for pericardiocentesis) (**Figures 6 to 7**). Benign tumors of the pericardium include lipoma, hemangioma, teratoma, fibroma, and pericardial cysts, among others. Lipomas are slow-growing encapsulated tumors consisting of adipose cells and are fairly asymptomatic. Hemangiomas of the pericardium are mostly cavernous in nature and arise from the visceral pericardium.[58] Pericardial cysts are congenital growths arising from the pericardium, unilocular, and lined by mesothelial cells.[59] They are commonly located in the cardiophrenic angles, more commonly right-sided. The majority of the cysts are found incidentally on imaging. Surgical resection of these benign growths is reserved for symptomatic individuals or if complications occur. On the other hand, malposition of the heart after pneumonectomy can affect echocardiographic imaging of the pericardium (**Figure 8**).

Conclusion

Pericardial involvement in cancer patients can take multiple forms and be due to cancer itself or to the treatment given. Early recognition of pericardial toxicity due to cancer therapies is vital in preventing complications like cardiac tamponade and pericardial constriction.

Disclosure

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