Case Report

A Case of Non-Compacted Left Ventricle and Lung Squamous Cell Carcinoma With Multiple Left Ventricular Clots

Azin Alizadehasl[1], MD; Niloufar Akbari Parsa[2*], MD; Seied Asadollah Mousavi[3], MD; Hosein Kamranzadeh Fumani[3], MD

ABSTRACT

Left ventricular (LV) non-compaction is a genetic disease which might result in heart failure, arrhythmias, and thromboembolic events. Nonetheless, other diseases and drugs or toxins like chemotherapy agents can also simulate or exacerbate this phenotype and accelerate systolic dysfunction. Moreover, cancer and receiving chemotherapy agents are procoagulant states leading to venous, arterial, and intracardiac thromboses.

Case: A 62-year-old man with a history of lung squamous cell carcinoma from 4 months earlier and non-compacted LV presented with dyspnea, severe LV systolic dysfunction, and multiple large LV clots.

Discussion: Non-compacted LV can be a risk factor to exacerbate the cardiotoxicity of cancer therapeutics and lead to severe LV systolic failure. Additionally, severe LV systolic dysfunction, advanced stages of the lung cancer, the hypercoagulable state of cancer, and chemotherapy drugs like platinum agents could result in the formation of multiple large clots in the LV. ***(Iranian Heart Journal 2023; 24(2): 94-99)***

KEYWORDS: Non-compacted LV, Lung SCC, LV clots

[1] Cardio-Oncology Department and Research Center, Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Science, Tehran, IR Iran.
[2] Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Science, Tehran, IR Iran.
[3] Hematology, Oncology and Stem Cell Transplantation Research Center, Tehran University of Medical Sciences, Tehran, IR Iran.

*** Corresponding Author:** Niloufar Akbari Parsa, MD; Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Science, Tehran, IR Iran.
Email: dr.niloufar.parsa@gmail.com **Tel:** +989113359748

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As the survival rates of patients with cancer increase, concerns regarding chemotherapy and radiotherapy-related cardiac dysfunction have become a major problem, although the timing and clinical manifestation vary widely. Left ventricular non-compaction (LVNC) is a cardiomyopathy characterized by prominent trabeculations, intertrabecular recesses, and LV meshwork with compacted and non-compacted myocardial layers. The present study revealed not only does LVNC have a high prevalence in hematological diseases, but also patients with LVNC are at high risk of significant deterioration in cardiac function after chemotherapy compared with patients without LVNC. [1]

Additionally, patients with cancer present a procoagulant state that increases the risk of thrombosis, mainly of the deep venous

system and pulmonary circulation. [2] Nevertheless, cancer-associated arterial thrombotic events (ATEs) are increasingly recognized in specific malignancies and in association with cancer therapies. [3] One of the rare patterns of ATEs is LV thrombosis, which represents an infrequent site of thrombotic complications in these patients. [2] We herein describe a patient with LVNC and metastatic lung squamous cell carcinoma (SCC) referred with deterioration in the LV function and multiple LV clots.

Case Presentation

A 62-year-old man presented to our clinic with shortness of breath. The patient had a history of grade I systemic hypertension and controlled blood pressure with losartan (25 mg twice daily). He did not smoke.

The patient had been diagnosed with lung SCC 4 years earlier. Six months prior to his presentation to our clinic, he underwent chemotherapy and radiotherapy when widespread spine metastases were found. His previous lung computed tomography (CT) scan had demonstrated a large (5×3 cm) lobulated soft tissue mass in the right lung hila and multiple bilateral large malignant lymphadenopathies, indicative of lung SCC (based on pathology and previous history) (Fig. 1).

In the patient's baseline cardiac examination before the initiation of cancer therapy, he had LVNC with a preserved left ventricular ejection fraction (LVEF) and no other abnormalities.

Upon presentation to our clinic, the patient was in a semi-sitting position and complained of severe dyspnea at rest and orthopnea. He had a blood pressure of 85/45 mm Hg, a heart rate of 122 beats per minute, a respiratory rate of 31 per minute, and an O_2 saturation level of 85% in ambient air. He had a distended jugular vein, fine crackles in the lungs, and absent breath sounds in the lower half of the lungs. Cardiac auscultation revealed S3 and systolic murmurs (III/VI) at the apex. He had cold limbs, thready pulses, 2+ peripheral edema, and right upper quadrant tenderness, probably due to liver congestion.

Electrocardiography showed left bundle branch block and sinus tachycardia.

Laboratory data showed a white blood cell count of 2500/dL, a hemoglobin level of 8.9 mg/dL, a platelet count of 65000, an international normalized ratio (INR) of 3.8, a creatinine level of 2.5, an aspartate transferase level of 256, an alanine transaminase level of 278, and elevated inflammatory markers and cardiac troponin I.

Chest-X ray showed a large irregular mass in the right lung hila, bilateral lymphadenopathy, lung congestion, and bilateral pleural effusion, most prominent on the right side.

Transthoracic echocardiography demonstrated a spherical and dilated LV with a non-compacted pattern, an LVEF of 25%, and grade II LV diastolic dysfunction. Moreover, multiple large fixed hyper echo masses were attached to different sites of the LV walls, suggestive of large clots. Other findings were mild right ventricular dilation with moderate systolic dysfunction, mild left atrial enlargement, moderate mitral regurgitation, and a systolic pulmonary artery pressure of 45 mm Hg (Fig. 2).

Oxygen, a diuretic (furosemide), and an inotropic agent infusion were initiated, but the patient's situation deteriorated into a shock state, necessitating tracheal intubation due to significant hypoxia. Due to the patient's low platelet count and elevated INR, creatinine, and liver transaminases levels, anticoagulant therapy was a challenge. Unfortunately, he passed away 2 days after admission.

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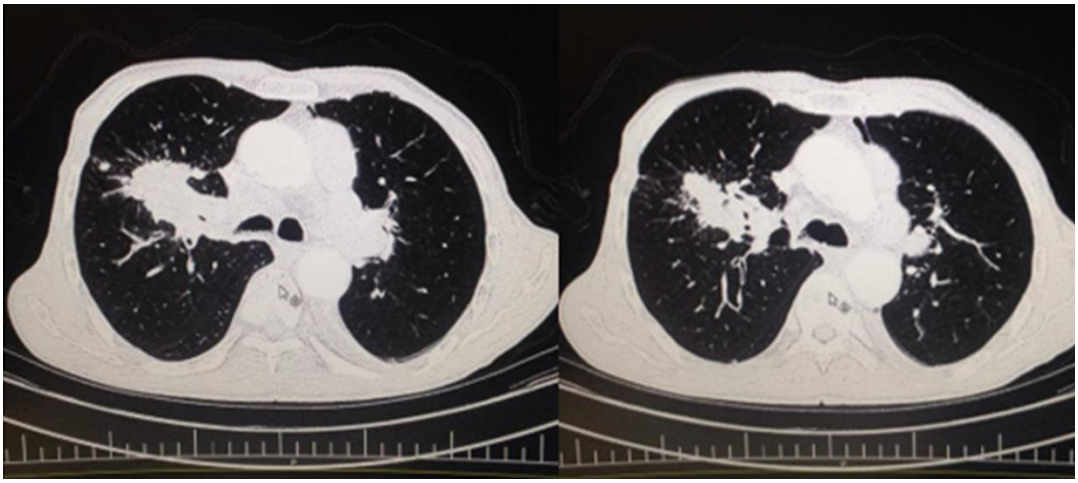

Figure 1: The lung computed tomography scan demonstrates a large (5×3 cm) lobulated soft tissue mass in the right lung hila and multiple bilateral large malignant lymphadenopathies, indicative of lung squamous cell carcinoma (based on pathology).

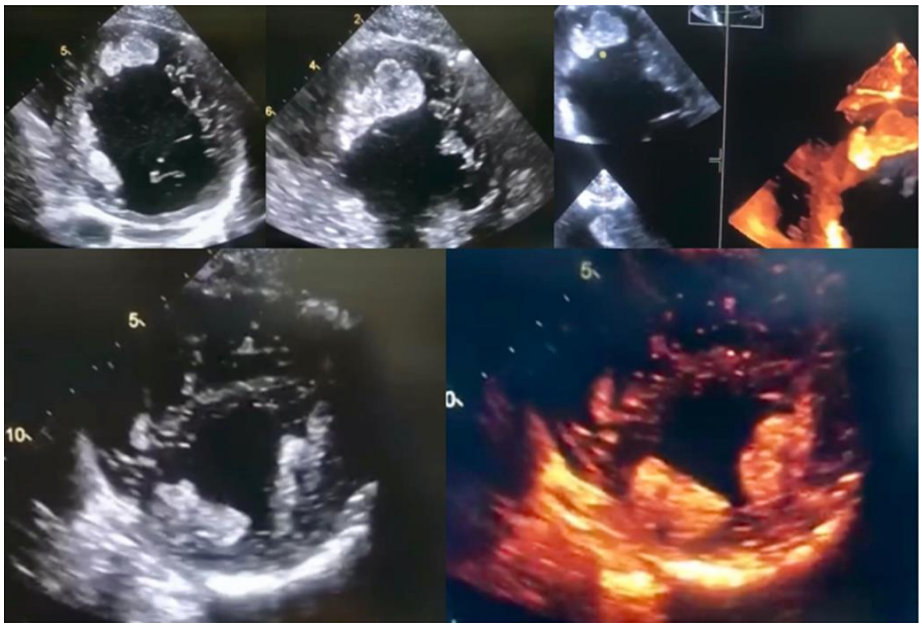

Figure 2: Transthoracic echocardiography shows a spherical and dilated left ventricle with a non-compacted pattern and an ejection fraction of 25%. There are multiple large fixed hyper echo masses attached to different sites of the left ventricular walls, suggestive of large clots.

DISCUSSION

LVNC is characterized by trabeculated myocardium with adjacent deep intertrabecular recesses communicating with the LV cavity. [4] The reported prevalence of LVNC varies widely, from 0.26% to 1.3% in the general population to 3.0% to 3.7% in patients with heart failure. Although most patients with LVNC are asymptomatic, the presence of LVNC in some cases can be associated with the deterioration of secondary cardiac complications, lethal arrhythmias, thromboembolic events, and poor survival outcomes. [1] In the more advanced stages of LVNC, heart failure is present in more than 50% of patients. LV

systolic dysfunction is the most common finding in both pediatric and adult populations (as many as two-thirds of patients) and usually depends on the extent of non-compacted cardiac segments. [4]

LVNC is a genetic disorder, and several gene mutations linked to LVNC have already been identified. Further, some mutual genetic and chromosomal aberrations have been reported in both LVNC and hematological diseases, but little is known about the relationship between LVNC and hematological diseases. To the best of our knowledge, LVNC prevalence is known to be high in some hematological diseases like β-thalassemia and myeloproliferative disorders.

Chemotherapy induces severe anemia due to myelosuppression, requiring frequent transfusions. The persistence of anemia and repeated transfusions during the treatment process can induce hypoxic stress and frequent changes in LV loading conditions. This stress and these conditions may have induced, to some extent, the acquired phenotypic prominence of LVNC.

Patients with LVNC are at high risk of significant deterioration in the cardiac function after chemotherapy compared with patients without LVNC. Because the structural feature of an abnormal non-compacted LV layer is a sponge-like form with prominent trabeculations, the leading cause of the greater deterioration in LVEF might be the greater vulnerability of this abnormal myocardial layer to anemia, hypoxia, and cardiotoxicity following chemotherapy. These novel findings suggest that LVNC has a marked effect on patients' long-term outcomes and is one of the major risk factors for chemotherapy and radiotherapy-related cardiac dysfunction. [1, 5, 6]

Moreover, it is well known that thrombosis is a common complication of malignancy and represents the second most frequent cause of mortality in patients with cancer. [7]

Though the association between cancer and thrombosis has been known for over 150 years, the mechanisms of cancer-associated thrombosis (CAT), much like cancer itself, are multifactorial and incompletely understood. Cancer type, stage, tumor-derived factors, and genetics all affect CAT risk. The presence of metastasis increases the risk of CAT multifold. Furthermore, cancer therapies themselves can increase the risk for CAT. The administration of chemotherapy or hormone therapy, the immobilization associated with surgical interventions, and the placement of indwelling central venous catheters elevate thrombosis risk. [8]

There are considerably more data on venous thromboembolism (VTE) than on arterial or intracardiac thromboses in cancer. Nevertheless, cancer-associated ATEs are increasingly recognized in specific malignancies and in association with cancer therapies. [3]

The risk is greatest during the first month following the cancer diagnosis. Pulmonary, gastric, pancreatic, and colorectal cancers carry the greatest risk of arterial or intracardiac thrombosis. The incidence and relative hazard of arterial thrombosis increases directly with cancer stage and negatively impacts survival rates. Pulmonary and colorectal cancers carry the greatest risk, with nearly 40% of patients having either stage III or IV cancer at the time. [9]

Chemotherapy itself causes endothelial damage, activates coagulation pathways by decreasing coagulation inhibitors (proteins C and S as well as antithrombin III), impairs the synthesis of natural anticoagulants, causes the release of cell-free DNA, induces aberrant cytokine release, and stimulates platelet aggregation. Notable high-risk chemotherapies include L asparagine, thalidomide, and lenalidomide. Other procoagulant chemotherapies include gemcitabine, platinum-based therapies,

monoclonal antibodies, and anti-hormonal therapies. Some non-chemotherapy intravenous treatments used in cancer may also be prothrombotic, including glucocorticoids, antibiotics, red cell growth factors, and blood transfusions. Several novel cancer therapies, in particular antiangiogenic agents such as bevacizumab, are associated with an increased risk of arterial and venous thromboses. The use of erythropoiesis-stimulating agents, epoetin-α and darbepoetin-α, as well as blood transfusions, has also been associated with an increased risk of VTE. [8]

One of the most frequently used chemotherapy drugs in lung SCC is platinum-based therapy like cisplatin and carboplatin, which were also prescribed for our patient. Life-threatening ATEs in unusual locations have been described after the administration of this drug, including the development of thrombi in the thoracic aorta or the LV. The pathophysiology of cisplatin-induced ATEs is believed to be endothelial cell damage and subsequent endothelial dysfunction. [3]

We herein described a 62-year-old man with a history of LVNC and widespread metastatic lung SCC referred to our clinic with progressive dyspnea. We diagnosed the patient with severe LV systolic dysfunction and multiple LV clots.

We believe that the presence of non-compaction is a risk factor for the exacerbation of the cardiotoxicity of cancer therapeutics and that it can lead to severe LV failure. In addition, severe LV systolic dysfunction, the advanced stage of the disease, the hypercoagulable state of cancer, and chemotherapy drugs like platinum agents resulted in the formation of multiple large clots in the LV.

The management of LV thrombosis in the setting of malignancy is always under discussion. Warfarin has well-known inferior efficacy in this setting compared with heparin compounds. More conveniently, prospective data now support the use of direct-acting oral anticoagulants (DOACs), such as edoxaban, rivaroxaban, and apixaban, in the setting of malignancy. Justifiably, the recent 2019 American Society of Clinical Oncology guidelines strongly recommend low molecular weight heparin and even certain DOACs over warfarin in patients with cancer.

Thus, in the dilemma of LV thrombi in malignancies, the information supporting warfarin for LV thrombi is poor in comparison with the robust data on the inferiority of warfarin for cancer-related thromboses. Prospective data on DOACs and LV thrombi are needed, and until such data are available, DOACs in this particular setting may be a more prudent option than warfarin. [8]

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