Short commentary

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Cardiac recurrence in diffuse large B-cell lymphoma

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Abstract

Non-Hodgkin Lymphoma (NHL) ranks first among all hematological malignancies. Diffuse Large B Cell Lymphoma (DLBCL) is a heterogeneous tumor group consisting of large and transformed B cells that make up 30-40% of all NHL. Unlike Hodgkin lymphoma, NHL tends to frequently spread hematogenically, so systemic involvement is more common. Despite preferred current treatments, approximately 30% of patients experience recurrence. Heart tumors are rarely seen as primary tumors, but they are sometimes observed as the spread of a tumor from surrounding tissues and sometimes as the metastasis of a distant tumor. Primary Cardiac Lymphoma (PCL) constitutes a small proportion of non-Hodgkin lymphomas and may progress with involvement of the heart and pericardium. It is seen in less than 0.01% of all cardiac tumors. Secondary cardiac and pericardial involvement of lymphomas is extremely rare, accounting for 0.5% of cardiac involvement and 1% of extranodal NHL. It is known that the most common lymphoma subtype is DLBCL. In a case report we published in 2020, we are presenting a 45-year-old female patient diagnosed with DLBCL with cardiac relapse after treatment. A female patient who was diagnosed as nodular sclerosing HL by being examined with lymphadenopathy reached remission after chemotherapy and radiotherapy. In the 11th year follow-up exam, newly developed multiple lymphadenopathies were diagnosed with a pathology result of diffuse large B-cell lymphoma. The patient was diagnosed with non-germinal center type DLBCL by cervical lymph node biopsy. In addition to 8 cycles of R-CHOP treatment, she received central nervous system prophylaxis with 2 cycles of high dose methotrexate. 3 months after the last PET/CT control, she was admitted to our outpatient clinic because of chest pain and B symptoms. A hypermetabolic mass was observed isolated in the widest place in contact with the pericardium at the left pre-cardial distance 2.9 * 2.2 cm (suv-max: 34.8), even if there was no sign of recurrence in interim or end of treatment PET/CT scanning. Pericardial biopsy was found to be compatible DLBCL recurrence. Isolated cardiac relapse is a very rare entity in DLBCL and our case report makes a valuable contribution to the literature in this respect. In addition to difficulties in diagnosis and accessing pathological samples, important problems are also encountered in treatment. In this context, the highlighted points in terms of methods to be used and treatment preferences should be considered.

Keywords: Cardiac involvement; Diffuse large b cell lymphoma; Prognosis; Recurrence

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Abbreviations

NHL: Non-Hodgkin lymphoma

DLBCL: Diffuse large B cell lymphoma

LDH: Lactate dehydrogenase

IPI: International prognostic index

R-IPI: Revised- International prognostic index

CR: Complete remission

PCL: Primary cardiac lymphoma

SLL: Small lymphocytic lymphoma

PEL: Primary effusional lymphoma

HL: Hodgkin lymphoma

AST: Aspartate aminotransferase

ALT: Alanine aminotransferase

CRP: C- reactive protein

PET/CT: Positron emission tomography/ computed tomography

FDG: Fluorodeoxyglucose

BCL: B-cell lymphoma

MUM-1: Multiple myeloma oncogene 1

FISH: Fluorescence in situ hybridization

R-CHOP: Rituximab-Cyclophosphamide-Adriamycin-Vincristine-Prednol

CNS-IPI: Central nervous system international prognostic index

EZN: Ehrlich ZiehlNeelsen

LJ: Löwenstein Jensen

SVC: Superior vena cava

TTE: Transthoracic echocardiography

TEE: Transesophageal echocardiography

ICE: Intracardiac echocardiography

Introduction

Non-Hodgkin Lymphoma (NHL) ranks first among all hematological malignancies. Diffuse Large B Cell Lymphoma (DLBCL) is a heterogeneous tumor group consisting of large and transformed B cells that make up 30-40% of all NHL [1]. Its incidence increases with age and median age at diagnosis is 64. It is more common in men and 55% of the patients are male [2,3]. It can occur de novo or histologically transformed from indolent lymphomas. The disease typically presents as a rapidly growing nodal or extranodal mass associated with systemic symptoms [4].

Clinical parameters such as age, gender, presence of B symptoms, nodal and extranodal involvement areas, clinical stage and serum Lactate Dehydrogenase (LDH) level in DLBCL have been frequently studied. As these variables can affect survival rate independently from each other, the most frequently used in predicting the prognosis calculated by evaluating several parameters; it is the "International Prognostic Index (IPI)" [5-7]. Clinically, the IPI or Revised IPI (R-IPI) scoring system is used to determine the prognosis. These clinical parameters and IPI score are not always enough to determine prognosis [8].

DLBCL and recurrence

Lymphomas originate from lymph node and extranodal lymphatic tissues; it can spread to all areas where lymphatic fluid reaches. Unlike Hodgkin lymphoma, NHL tends to frequently spread hematogenically, so systemic involvement is more common [9]. Despite preferred current treatments, approximately 30% of patients experience recurrence [10]. Relapsed DLBCL is defined as the emergence of any new lesions after a Complete Response (CR) is achieved. Refractory disease is defined as the condition in which less than 50% of the tumoral tissue disappears after treatment [11]. The standard approach in this patient group is to consolidate chemo-sensitive patients with stem cell transplantation after the rescue regimen.

Considering the literature data, it is possible to say that the disease has recurred, specifically from previous involvement areas. Especially the presence of tumoral residues, whether these areas are targeted with radiotherapy or they are not seen as other clues for recurrence. The relationship of recurrence areas with prognosis can also be considered as another controversial issue.

Only a small portion of patients with DLBCL present as stage I or stage II non-bulky disease [12]. After the standard chemotherapy regimen, localized radiotherapy is the standard approach in this patient group; however, it is not possible to plan consolidative radiotherapy due to the majority of patients occuring at more advanced stages [12]. Consolidative radiotherapy contributes to the prognosis, specifically in the presence of a bulky target mass. Despite all treatment planning, 30% of the patients cannot be cured and the prognosis is poor [10].

Cardiac involvement and recurrence

Heart tumors are rarely seen as primary tumors, but they are sometimes observed as the spread of a tumor from surrounding tissues and sometimes as the metastasis of a distant tumor. They are the most common myxomas among primary benign heart tumors. Secondary heart tumors are mainly originated in the lung and breast or occur during hematological malignancies [13].

Primary Cardiac Lymphoma (PCL) constitutes a small proportion of non-Hodgkin lymphomas and may progress with involvement of the heart and pericardium. It is seen in less than 0.01% of all cardiac tumors. The degree and location of invasion determine presentation of patients. Secondary cardiac and pericardial involvement of lymphomas is extremely rare, accounting for 0.5% of cardiac involvement and 1% of extranodal NHL [14]. It is known that the most common lymphoma subtype is DLBCL, but Burkitt lymphoma, T-cell lymphomas, Small Lymphocytic Lymphoma (SLL) and plasmablastic lymphoma may also be seen. Cardiac involvement of lymphoma may present as heart failure, arrhythmia, syncope or pericardial effusion [15].

The formation of a pericardial effusion or mass can occur with hematogenous spread as well as the direct spread of lymphoma. Massive pericardial effusion is particularly seen in two rare NHL subtypes: PCL and Primary Effusional Lymphoma (PEL). PEL is an NHL subtype that occurs also in HIV-infected patients, specifically in the body cavities without a mass form [16].

In the literature, we see that data related to lymphoma, especially DLBCL and cardiac involvement are based on case reports. In a case report we published in 2020 [17], we are talking about a 45-year-old female patient diagnosed with DLBCL with cardiac relapse after treatment.

A rare case presentation: DLBCL and isolated cardiac recurrence

A female patient who was diagnosed as nodular sclerosing HL by being examined with lymphadenopathy reached remission after chemotherapy and radiotherapy. In the 11thyear follow-up exam and at the age of 45, newly developed multiple lymphadenopathies were diagnosed with a pathology result of diffuse large B-cell lymphoma in her advanced examination. Laboratory tests of the patient: Hemoglobin 8.8 g/dl, white blood cell 11,620/mm^3, neutrophil 8,540/mm^3, platelet 456,000/mm^3, urea 22mg/dl, creatinine 0.64 mg/dl, uric acid 7.1 mg/dl, aspartate transaminase (AST) 25 U/L, Alanine Transaminase (ALT) 13 U/L, Lactate Dehydrogenase (LDH) 848 U/L, total protein 6.4 g/dl, albumin 3.2 g/dl and C-Reactive Protein (CRP) 68 mg/dl . Positron Emission Tomography/Computed Tomography (PET/CT) showed hypermetabolic Fluorodeoxyglucose (FDG) involvement in the bilateral jugular chain in the neck (standardized uptake value-max (suv-max): 14.8), spleen sizes in the abdominopelvic sections (270 mm), hypermetabolic FDG in places of heterogeneous character in this cystic lesion area, the largest of which reaches a diameter of 70 mm (suv-max: 30.7), hypermetabolic FDG involvement (suv-max: 14.0) in the paraaortocaval region, hepatogastric area, bilateral inguinal fossa at the portal hilus level and sclerotic lesion in the midline in the sacrum (suv-max: 15.8). The patient was diagnosed with DLBCL (Immunohistochemistry of pathology: KI-67: %80, CD20 (+), BCL2 (+), BCL6 (+), MUM1 (+), C-MYC (-), non-germinal center type DLBCL and Fluorescence in Situ Hybridization (FISH) negative for c-myc) by cervical lymph node biopsy. In addition to 8 cycles of R-CHOP (Rituximab-Cyclophosphamide-Adriamycin-Vincristine-Prednol) treatment, she received central nervous system prophylaxis with 2 cycles of high dose methotrexate because of the high Central Nervous System International Prognostic Index (CNS-IPI) score (a total score of 5, high risk). Doxorubicin was also removed from protocol after reaching the cumulative dose of 450 mg/m^2. The pathology of splenectomy specimen did not include tumoral invasion; only cystic necrotic area was observed. At the end of her

treatment, a PET/CT was performed 1 month after the surgery and was compatible with complete remission.

3 months after the last PET/CT control, she was admitted to our outpatient clinic because of chest pain and B symptoms. A hypermetabolic mass, which was evaluated in favor of the involvement of primary disease, was observed isolated in the widest place in contact with the pericardium at the left pre-cardial distance 2.9*2.2 cm (suvmax: 34.8), even if there was no sign of recurrence in interim or end of treatment PET/CT scanning. A pericardial biopsy was performed for possible secondary malignancy due to the absence of involvement in another area of the whole body and it was found to be compatible with CD20 (+), BCL2 (+), BCL6 (+), C-MYC(-) immune reactivity non-germinal center type DLBCL recurrence. Ehrlich ZiehlNeelsen (EZN) staining and Löwenstein Jensen (LJ) cultures were negative for tuberculosis.

Discussion

DLBCL is associated with cardiac recurrence or cardiac involvement with a poor prognosis, although PCL appears with CR rates of up to 60% after treatment. Early surgical intervention may seem necessary depending on the localization of the disease; it may become a necessity especially in cases where hemodynamics is impaired. The goal of surgical interventions should be to gain time, especially until chemo-immunotherapy, in addition to obtaining samples for pathological examination [18].

Most cardiac lymphomas (primary or secondary) are in the B cell group and DLBCL is the most common of these lymphomas [18]. While PCL usually affects the right heart, lymphomatous infiltrates in disseminated lymphoma are typically common and affect the epicardium (61%) and myocardium diffusely [19]. Involvement of the heart is usually a late sign of disseminated lymphoma. In case of relapse, it can be predicted that the diagnosis will be made later than normal. Among the mediastinal tumors; we can say that invasion develops through directly, hematogenous and retrograde lymphatic spread. Direct lymphoma spread leads to predominantly pericardial disease, infiltration of the pericardial space and tamponade clinic. Sometimes tumor infiltration follows the course of the epicardial coronary arteries and sometimes causes compression. There is no pericardial pressure and myocardial involvement may be mild or absent. There is no priority for the diffuse interstitial-perivascular pattern, the epicardial or endocardial aspects of the heart [18, 19].

Cardiac involvement of lymphoma recurrence has been rarely shown in the literature. In this context, the contribution of our case to the literature is highly important. Detection of cardiac involvement in DLBCL follow-up constitutes a very difficult clinical picture. Lymphoma spread is most often asymptomatic; when there are symptoms, the findings may not be specific. When present, symptoms include heart failure (34%), chest pain (12%), superior vena cava (SVC) syndrome and arrhythmia [18, 20]. Radiological methods cannot show enough efficiency in detecting the presence of a cardiac tumor.

In a retrospective study, Transthoracic Echocardiography (TTE) had 60% sensitivity in detecting cardiac involvement. The most common site involved was pericardium (41.1%), followed by right heart cavity invasion (34.8%). The least affected cardiac area was the heart valves [21]. In another conducted study; Transesophageal Echocardiography (TEE) has been found to be more sensitive in PCL patients compared to TTE [22]. Tomography represents an important point in diagnosis with its high sensitivity and resolution. Cardiac MR is another important imaging method and provides superiority in terms of anatomical resolution. The use of PET alone for the diagnosis of cardiac lymphoma is difficult due to its low anatomical resolution and physiological accumulation of radiotractors within myocytes[23]. The PET/CT combination provides both anatomical and functional imaging in the same position and is superior to any modality alone [23]. It offers superior anatomical resolution compared to PET alone and higher accuracy in lymphoma overall staging compared to CT [23,24]. PET/CT is useful in distinguishing DLBCL from other types of cardiac tumors [23,24].

On the way to diagnosis, it is recommended to evaluate the location of the recurrence. In pericardial involvement, although cytological examination of the pericardial sample is very important in terms of diagnosis, its sensitivity is described as 67% in the literature [25]. Therefore, if the results are negative, further diagnostic approaches such as endomyocardial biopsy with or without TTE or ultrasound guidance or biopsy via mediastinoscopy or thoracotomy are required. Endomyocardial biopsy has been proposed as a standard procedure for the diagnosis of cardiac tumors, guidance with TEE is recommended whenever possible [25]. Although TEE-guided transvenousendomyocardial biopsy usually requires local pharyngeal or general anesthesia, it is useful, simple, and safe [25]. The transvenous biopsy procedure, which has recently been introduced via Intracardiac Echocardiography (ICE)-guided cardiac catheterization, does not require anesthesia and may facilitate assessment of the cardiac structure [25].

Treatment strategies constitute another highly complicated and controversial issue. There is a combination of many modalities such as chemotherapy, radiotherapy, surgery, and stem cell transplantation. Chemotherapy is the mainstay of treatment in relapse, as in DLBCL. There is no evidence that surgery improves prognosis; tumor shrinkage can be considered as a palliative or life-saving measure in cases with significant or life-threatening obstructive symptoms [26].

Literature data also reveals that the management of lymphoma with cardiac involvement is quite difficult. Close clinical follow-up of the patient is required due to serious complications such as myocardial rupture, specifically during treatment. In a case report of 2019 [18], we see that an 18-year-old male patient with SVC syndrome was mentioned. The treatment of the patient diagnosed with DLBCL was started with standard chemotherapy at reduced doses and the dose was increased by close cardiac imaging. In this context, it is necessary to draw attention to the complications that may occur especially during treatment. Similarly, we see that the treatment of patients diagnosed with DLBCL was modified and applied in a series of 3 patients from 2017 [27]. It was aimed to achieve gradual tumor reduction with steroid and vincristine before applying the standard treatment regimen (R-CHOP). Similarly, it has been reported that the monoclonal antibody and steroid combination (Rituximab 375 mg / m2 and methylprednisolone 40 mg / day) is used primarily and after the safe cardiac function has been confirmed, the transition to standard chemotherapy regimens is gradually increased [28].

Conclusion

As a conclusion, isolated cardiac relapse is a very rare entity in DLBCL and our case report makes a valuable contribution to the literature in this respect. In addition to difficulties in diagnosis and accessing pathological samples, important problems are also encountered in treatment. In this context, the highlighted points in terms of methods to be used and treatment preferences should be considered.

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Declarations

Conflict of Interest

None to declare.

Authors' Contributions

All authors contributed to the editing of the manuscript.

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We respectfully remember all the colleagues we lost in the COVID-19 fight.

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