Cardiac Myxoma with Cerebral Metastases and Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: A Case Report and Review

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Abstract

Background  Cardiac myxomas, the most common primary cardiac tumors, are generally benign neoplasms. Primary cardiac lymphoma is a rare cardiac malignancy with a very poor prognosis. Here we present a case of a cardiac myxoma with cerebral metastases and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) arising within the cerebral metastases.

Case description  A 62-year-old man, who presented with symptoms of multiple transient ischemic attacks, was found to have a left atrial myxoma. Twelve months after excision of the myxoma, the patient experienced a recurrence of neurologic symptoms. Brain magnetic resonance imaging revealed multiple hemorrhagic masses. Craniotomy was performed to resect the lesions. Histopathologic examination confirmed cardiac myxoma metastases and a small lymphocytic infiltrate within the tumor consistent with CLL/SLL.

Conclusion  Including the present case, there are 27 cases of cardiac myxoma cerebral metastases and 22 cases of lymphomas arising within myxomas. The present case is the first known instance of both entities in the same patient. There is no standard management for either cardiac myxoma metastases or lymphoma within a myxoma. For both diseases, surgical excision is the primary treatment modality, but postoperative chemotherapy and/or radiation have been attempted. Myxomas may create a chronic inflammatory state that could lead to the development of CLL/SLL.

Keywords  ► cardiac myxoma  ► atrial myxoma  ► cerebral metastases  ► lymphoma  ► CLL/SLL

Introduction

Primary cardiac tumors are rare, occurring in 0.02 to 2.8% of autopsy series; a plurality of these cases are cardiac myxomas, which account for 30 to 50% of primary cardiac tumors in pathologic series.1 The vast majority of cardiac myxomas (~83% of cases) occur in the left atrium, while 13% occur in the right atrium.1 Demographically, patients are diagnosed at a mean age of 50 with nearly a 2:1 female predominance.1 Myxomas are generally benign tumors1 that are thought to be derived from endocardial multipotent mesenchymal cells.2,3 However, they have a higher risk of recurrence in the setting of incomplete resection, multiple foci, and tumor embolism.2
While the most common clinical presentation of cardiac myxomas is dyspnea secondary to congestive heart failure,4 as many as 50% of the reported cases of atrial myxomas present with complications due to embolization, and up to half of these cases present with neurologic manifestations.5 Among these neurologic manifestations, atrial myxomas can cause infarction, aneurysm, or rarely metastasis.5 To date, only 27 cases of cardiac myxoma metastasis to the brain have been reported, including the present case.

Primary cardiac lymphoma is also particularly rare, amounting to less than 2% of all primary cardiac tumors.3 The most common histological subtype of primary cardiac lymphoma is large B cell lymphoma.6 Most cases of primary cardiac lymphoma occur in immunocompromised patients.5 The outlook for these patients is generally poor—the median survival is 7 months after initial diagnosis.5 Primary cardiac lymphoma arising within cardiac myxoma is exceedingly rare with only 22 reported cases since 2009, including the present case.3,7

The present case is the first known case of myxoma metastases and lymphoma arising within myxoma occurring in the same patient. Additionally, it is the first known instance of a lymphoma arising within cardiac myxoma metastases rather than within the cardiac primary tumor.

Case Report

A 62-year-old male patient with a past medical history of hypertension, hypertrophic cardiomyopathy, and an episode of left arm numbness in April 2016 initially presented to the hospital with mild chest discomfort, left arm numbness, visual changes, and gait instability in June 2016. The patient underwent stroke workup including a magnetic resonance imaging (MRI) of the brain, which demonstrated hemorrhagic lesions to the brain and transesophageal echocardiography, which revealed a 4.2 × 2.4 cm (centimeters) mass in the left atrium. Gross total resection of the cardiac lesion was performed under cardiopulmonary bypass through a right thoracotomy approach in July of 2016. The patient had an uneventful postoperative course. Echocardiography showed no evidence of residual tumor. Histopathologic examination confirmed a diagnosis of left atrial myxoma. In December 2016, the patient presented to the hospital with painful fingertip nodules. Following resection of these lesions, histopathologic evaluation proved that these lesions were myxomatous.

The patient returned to the hospital in June 2017. 12 months after his initial presentation, complaining of 2 weeks of weakness and clumsiness of the left upper extremity and episodes of blurred vision lasting 30 to 40 minutes several times a week. Repeat transesophageal echocardiogram showed no evidence of intracardiac recurrence. Brain MRI performed with and without contrast demonstrated enlarged heterogeneously enhancing hemorrhagic masses in the right posterior occipital–parietal region with increased vasogenic edema and mild mass-effect on the posterior horn of the right lateral ventricle (► Fig. 1). The dominant enlarging hemorrhagic lesion measured 36 × 36 × 37 mm (millimeter) and a second measured 18 × 14 × 12 mm. Three other lesions from previous scans in the posterior frontal and parieto-occipital regions were decreasing or resolved. Image-guided right parieto-occipital craniotomy with neuromonitoring for resection of the dominant and three other lesions was performed. Four tan hemorrhagic soft tissue specimens were submitted for histopathologic evaluation, which demonstrated metastatic atrial myxoma and a small lymphocytic lymphoma/chronic lymphocytic leukemia arising (SLL/CLL) from within the metastatic atrial myxoma (► Fig. 1). These immunohistochemical results, together with the morphologic features, are consistent with CLL/SLL. There was no evidence of lymphoma outside the myxoma. Neither chemotherapy nor radiotherapy was administered.

Following the procedure, the patient recovered well. Postoperative MRI showed postoperative changes and no evidence of residual tumor. The patient was placed on levetiracetam prophylactically for 5 days. He initially reported worsening visual fields on postoperative day 1, which partially resolved by postoperative day 2. There were no other signs or symptoms. The patient was discharged on postoperative day 2 for close outpatient follow-up. As of a 48-month follow-up visit, the patient was doing well with continuous visual field improvement and no evidence of disease.

Discussion

There are 27 cases—including the present case—of a cardiac myxoma metastasizing to the brain reported in the literature (► Table 1).2 The authors are aware of only one other case of histopathologically proven CLL/SLL within a cardiac myxoma8 and only 21 other cases of lymphomas within a cardiac myxoma (► Table 2).3,7 The present case also represents the first known instance of a lymphoma arising within a myxomatous cerebral metastasis.

As this is the first reported case of both cardiac myxoma metastases and lymphoma within a cardiac myxoma in the same patient, it is unclear if the presence of lymphoma is related to the metastatic potential of an otherwise usually benign tumor. Cardiac myxomas are thought to metastasize secondary to embolism prior to or during surgical handling.2 Despite this, embolic manifestations can be delayed months or even years.2,13,14 This patient’s additional presentation with myxomatous involvement of the extremities 6 months after his initial presentation supports the theory of arterial embolization. Additionally, cardiac myxomas are known to secrete several inflammatory cytokines such as endothelin-1, interleukin-6, cysteine X cysteine cytokines, interleukin-8, and growth-related oncogene α.46 It is also known that chronic inflammation in several inflammatory conditions is associated with the development of lymphoma.47 Therefore, a more parsimonious hypothesis is that the CLL/SLL arose within the cardiac myxoma metastases because of the chronic inflammatory state created by the
myxoma. Given the present case’s neurologic manifestations prior to diagnosis of his cardiac myxoma, it is possible that the cerebral metastases were present several months before they were formerly diagnosed; if so, this longstanding inflammation would potentially allow for malignant transformation. Laird-Fick et al hypothesize that a shared genetic defect could be the link between myxoma and CLL/SLL, noting that abnormalities on chromosomes 12 and 17 as well as in the protein kinase-A pathway (including Carney complex gene mutations) have been associated with both tumors. A recent study showed that myxomas express elevated oncogenes and malignancy-related proteins such as c-MYC, p53, vimentin, and hypoxia-inducible factor 1-α compared with normal heart tissue. This suggests that even though myxomas often clinically behave as benign tumors, they possess latent oncogenic and metastatic potential.

It is also notable that lymphomas arising within cardiac myxomas do not behave like primary cardiac lymphomas. While most cases of primary cardiac lymphoma occur in immunocompromised patients, all 22 reported cases of lymphoma within myxoma occurred in immunocompetent patients. The prognosis for lymphoma arising within myxoma also seems to be better than the 7-month median survival associated with primary cardiac lymphoma. However, the sample size and follow-up data are limited so caution should be used when interpreting these data.

Because cardiac myxomas with cerebral metastases are extremely rare, there is no established gold standard treatment. Surgical excision seems to be the primary approach for diagnostic purposes, treatment of one to two isolated brain metastases, or treatment when one of several lesions is life-threatening. Radiation therapy can be used as a possible alternative treatment in patients with multiple metastases or as a supplementary treatment for patients who do not experience resolution with surgery alone. Most often, radiotherapy consisted of palliative whole brain radiation at 25 to 30 Gy (Gray) but doses as high as 40.8 and 50 Gy have been attempted with positive results. Postoperative chemoradiotherapy using ifosfamide and doxorubicin and postoperative chemotherapy using doxorubicin alone have been attempted in two cases with positive and equivocal results, respectively.
Additionally, the standard management of lymphomas arising within cardiac myxomas has not yet been determined because the cases occur so infrequently. While 7 out of the 22 cases have been treated with postoperative chemotherapy, it is not clear if chemotherapy is needed in the setting of disease confined within the myxoma status post total resection. One out of the 22 cases died as a result of chemotherapy-induced neutropenic fever and opportunistic pneumonia and three other cases that did not receive postoperative chemotherapy had no evidence of disease recurrence at a six-, ten-, and eleven-year follow-up. Furthermore, it is possible that the lymphoma remains localized completely within the myxoma, and if so, it may be prudent to withhold postsurgical chemotherapy until the patient develops a recurrence. As of now, the patient presented in this report has been treated with surgery alone.

Further characterization of cardiac myxomas through molecular markers might allow for a better understanding of the pathogenesis of cardiac myxoma and myxomatous metastases as well as more rapid diagnosis of this rare disease. Future studies examining the potential for a related pathogenesis between cardiac myxoma and CLL/SLL might also improve the generalizable knowledge surrounding these two diseases. Additional case reports and follow-up may elucidate the most appropriate treatments for cardiac myxoma.

### Table 1

Reported cases of histopathologically proven cardiac myxoma metastasizing to the brain

| Case | Report (reference) | Year | Age | Interval to recurrence (months) | Other recurrent sites | Surgery for brain lesions | RT | CT | Outcome follow-up (months) |
|------|--------------------|------|-----|--------------------------------|----------------------|--------------------------|----|----|---------------------------|
| 1    | Maas [our case]    | 2019 | 62  | 12                              | Fingertips           | Yes                      | No | No | NED48                     |
| 2    | Rose et al case 1   | 2016 | 44  | 5                               | No                   | Yes                      | No | No | DOD17                     |
| 3    | Rose et al case 2   | 2016 | 52  | 0                               | No                   | No                       | Yes | No | AWD63                     |
| 4    | Badrisyah et al9    | 2012 | 15  | 36                              | No                   | Yes                      | No | No | NED72                     |
| 5    | Radoi et al10       | 2012 | 45  | 18                              | No                   | Yes                      | No | No | AWD12                     |
| 6    | Kumar et al11       | 2011 | 30  | 24                              | No                   | Yes                      | No | No | ?                         |
| 7    | Suzuki et al12      | 2008 | 68  | 6                               | No                   | Yes                      | No | No | ?                         |
| 8    | Moiyadi et al13     | 2007 | 35  | 48                              | No                   | Yes                      | Yes | No | AWD6                      |
| 9    | Altundag et al14    | 2005 | 41  | 15                              | No                   | Yes                      | Yes | No | AWD63                     |
| 10   | Acikel et al15      | 2004 | 58  | 0                               | No                   | No                       | No | No | ?                         |
| 11   | Hirundayaraj et al16| 2004 | 50  | -1                              | No                   | Yes                      | No | No | ?                         |
| 12   | Hou et al17         | 2001 | 37  | 10                              | Bone                 | No                       | No | No | DOD12                     |
| 13   | Bernet et al18      | 1998 | 31  | 2                               | Muscle, lung         | Yes                      | Yes | Yes | NED120                    |
| 14   | Scarpelli et al19   | 1997 | 64  | 144                             | No                   | Yes                      | No | No | ?                         |
| 15   | Samaratunga et al20 | 1994 | 60  | -7                              | No                   | Yes                      | No | No | NED21                     |
| 16   | Kanda et al21       | 1994 | 70  | -7                              | No                   | Yes                      | No | No | NED9                      |
| 17   | Chozick et al22     | 1992 | 61  | 8                               | No                   | Yes                      | No | No | NED72                     |
| 18   | Todo et al23        | 1992 | 32  | 10                              | Jejunum              | No                       | No | No | DOD10                     |
| 19   | Kotani et al24      | 1991 | 48  | 3                               | Soft tissue, aorta   | Yes                      | No | No | DOD53                     |
| 20   | Ng et al25          | 1990 | 54  | 6                               | No                   | Yes                      | No | No | AWD18                     |
| 21   | de Morais et al26   | 1988 | 73  | 0                               | Kidney, pancreas, stomach | No                      | No | No | DOD1                      |
| 22   | Bazin et al27       | 1987 | 56  | 48                              | No                   | Yes                      | No | No | ?                         |
| 23   | Kadota et al28      | 1987 | 44  | 3                               | Skin                 | Yes                      | No | No | ?                         |
| 24   | Markel et al29      | 1986 | 18  | 30                              | Bone                 | No                       | No | No | AWD39                     |
| 25   | Seo et al30         | 1980 | 36  | 96                              | Bone                 | Yes                      | No | No | AWD120                    |
| 26   | Budzilovich et al31 | 1979 | 52  | 0                               | No                   | No                       | No | No | DOD1                      |
| 27   | Rankin and De Sousa32 | 1978 | 44  | 96                              | No                   | Yes                      | No | No | AWD120                    |

Abbreviations: AWD, alive with disease; CT, chemotherapy; DOD, died of disease; NED, no evidence of disease; RT, radiotherapy.

Note: “?” refers to unknown outcome.
Table 2  Reported cases of histopathologically proven lymphoma within cardiac myxoma

| Case | Report (Reference) | Year | Age | Sex | Location | Phenotype | Immune status | Chemotherapy | Outcome follow-up (months) |
|------|-------------------|------|-----|-----|----------|-----------|---------------|--------------|--------------------------|
| 1    | Maas (our case)   | 2019 | 62  | M   | Intracranial met from left atrium | CLL       | IP            | None         | NED48                    |
| 2    | Garces and Sriganeshan | 2019 | 50  | M   | Left atrium | FA-DLBCL  | IP            | None         | NED65                    |
| 3    | Park et al        | 2018 | 44  | M   | Left atrium, Right CFA embolus   | nGG-DLBCL | IP            | R-CHOP x 6   | None                     |
| 4    | Yan et al case 1  | 2017 | 46  | M   | Left atrium | nGG-DLBCL | IP            | None         | NED120                   |
| 5    | Yan et al case 2  | 2017 | 61  | F   | Left atrium | GC-DLBCL  | IP            | None         | NED84                    |
| 6    | Yan et al case 3  | 2017 | 54  | M   | Left atrium | nGG-DLBCL | IP            | None         | NED7                     |
| 7    | Yan et al case 4  | 2017 | 46  | F   | Left atrium | nGG-DLBCL | IP            | None         | NED3                     |
| 8    | Jiang et al       | 2017 | 63  | M   | Left atrium | nGG-DLBCL | IP            | None         | NED7                     |
| 9    | Boyer et al case 1| 2017 | 54  | M   | Left atrium | nGG-DLBCL | IP            | NA           | NED130                   |
| 10   | Boyer et al case 2| 2017 | 55  | F   | Left atrium | nGG-DLBCL | IP            | None         | DOC2                     |
| 11   | Boyer et al case 3| 2017 | 54  | M   | Left atrium | nGG-DLBCL | IP            | None         | DOD26                    |
| 12   | Pineda et al      | 2015 | 50  | M   | Left atrium | HGBCL     | IP            | None         | None                     |
| 13   | Aguilar et al     | 2015 | 52  | M   | Left atrium | nGG-DLBCL | IP            | None         | NED42                    |
| 14   | Liu et al         | 2015 | 52  | M   | Left atrium | nGG-DLBCL | IP            | None         | NED3                     |
| 15   | Tapan et al       | 2015 | 49  | M   | Left atrium | nGG-DLBCL | IP            | CHOP x 6     | NED12                    |
| 16   | Laird-Fick et al  | 2014 | 56  | F   | Left atrium | CLL       | IP            | FCR x NA     | AWD18*                   |
| 17   | Bartolini et al   | 2013 | 55  | F   | Left atrium | ALBP      | IP            | None         | NED72                    |
| 18   | Svec et al        | 2012 | 60  | F   | Left atrium | nGG-DLBCL | IP            | CHOP x 6     | NED7                     |
| 19   | Loong et al       | 2010 | 70  | F   | Left atrium | nGG-DLBCL | IP            | CEOP x 4     | DOC5*                    |
| 20   | Dimitrova et al   | 2010 | 51  | M   | Left atrium | GC-DLBCL  | IP            | CHOP x 6     | None                     |
| 21   | White et al       | 2010 | 75  | F   | Left atrium | PLL       | IP            | NA           | None                     |
| 22   | Bagwan et al      | 2009 | 81  | F   | Left atrium | GC-DLBCL  | IP            | R-CHOP x NA  | None                     |

Abbreviations: ALBP, atypical lymphoid B-cell proliferation; AWD, alive with disease; CFA, common femoral artery; CLL, chronic lymphocytic leukemia; DOD, died of other cause; DOC, died of disease; FA-DLBCL, fibrin associated diffuse large B-cell lymphoma; FCR, fludarabine, cyclophosphamide, and rituximab; HGBCL, high grade B-cell lymphoma; IP, immunocompetent patient; NA, not available. R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; NED, no evidence of lymphoma recurrence or dissemination; nGG-DLBCL, nongerminal center diffuse large B-cell lymphoma; PL, plasmacytic lymphoma; R-CEOP, rituximab, cyclophosphamide, epirubicin, vincristine, and prednisone.

aAdapted from Yan et al 2017 and Liu et al 2015; added Maas et al (our case), Jiang et al, Pineda et al, Garces et al, and Park et al.
bCardiomegaly, myocardial infarction.
cComplications of chemotherapy.

dLocal recurrence at 18 months after no chemotherapy; began FCR chemotherapy, with clinical remission.

Conflicts of Interest
The authors declare that there are no conflicts of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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