

Diagnostic challenge in primary cardiac lymphoma: a case report

Chonthicha Tanking^{1*} and Supawat Ratanapo ²

¹Chulabhorn Hospital, 906 Kamphaeng Phet 6 Rd, Talat Bang Khen, Lak Si, Bangkok 10210, Thailand; and ²Phramongklutkiao College of Medicine & Phramongklutkiao Hospital, 315 Ratchawithi Rd, Thung Phaya Thai, Ratchathewi, Bangkok 10400, Thailand

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Background

Primary cardiac lymphoma is an extra-nodal non-Hodgkin's lymphoma, which usually responds well to chemotherapy. The disease has high mortality rate unless it is recognized and treated in time. Tissue pathology is crucially the diagnosis gold standard for treatment plan. This is a case report of an elderly female who presented with a huge right-sided cardiac tumour obstructing tricuspid flow.

Case summary

An 81-year-old Asian female presented with clinical right-sided heart failure. Echocardiogram showed a large mass compressing and obliterating the right atrium. Trans-jugular tissue biopsy was performed. Initial pathology report was consistent with an angiosarcoma, based on an expression of Fli-1 (Friend leukaemia virus integration 1) from immunohistochemical staining. She died shortly after refusal to surgery. Autopsy was performed with diagnosis change to a diffuse large B-cell lymphoma (DLBCL) after tissue pathology.

Discussion

Primary cardiac lymphoma is extremely rare. Adequate tissue and proper immunohistochemical staining are mandatory for treatment plan. Besides an angiosarcoma, DLBCL should be considered in the differential diagnosis of Fli-1 positive tissue cardiac mass.

Keywords

Primary cardiac lymphoma • Heart failure • Trans-jugular cardiac biopsy • Friend leukaemia virus integration 1 • Case report

Learning points

- Primary cardiac lymphoma is a rare condition and may present with an isolated cardiac mass.
- The application of most appropriate immunohistochemical staining is crucial for diagnosis accuracy of malignancy type. Diffuse large B cell lymphoma should be considered in the differential diagnosis of Fli-1 (Friend leukaemia virus integration 1) positive tissues.
- In case of inconsistent results, the pathological review or repeated biopsy may change the course of this patient due to higher chemotherapy response rate of primary cardiac lymphoma.

*Corresponding author. Tel: +66 819855882, Email: chonthicha.t@gmail.com

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Introduction

Primary cardiac tumours are extremely rare clinical entities, with incidence ranging from 0.001% to 0.03% on collected series.¹ Among these unusual primary cardiac malignancies, angiosarcoma is the most common. Primary cardiac lymphoma is even more scarce with prevalence varying from 1% to 2% of primary cardiac tumours, in which diffuse large B cell lymphoma (DLBCL) accounts for most.² Tissue histopathology is a crucial step for diagnosis and treatment plan. In this case report, we presented the pitfall in tissue diagnosis of a patient with a large mass infiltrating right atrium and protruding intracavitary causing right ventricular inflow obstruction.

Timeline

Day 1	An 81-year-old woman presented with 1 week predominantly right-sided heart failure.
Day 3	Echocardiography revealed a large mobile homogenous mass obliterating the right atrium cavity and protruding into the right ventricular inflow, with another large non-vascular extracardiac mass compressing right-sided heart.
Day 5	Chest computed tomography showed a 8.4 × 8.9 × 9.1 cm ill-defined enhancing soft tissue mass, extending from the pericardial cavity into the right atrium and right ventricle, with several lobulated enhancing soft-tissue masses at epicardial fat and some abutting the left ventricle.
Day 7	Trans-jugular cardiac biopsy was performed.
Day 14	Histopathology showed spindle to round neoplastic cells with positive Friend leukaemia virus integration 1 stain, suggestive of angiosarcoma.
Day 15	Surgical removal and chemotherapy were suggested by multidisciplinary team, but patient refused. Palliative care was planned.
Day 29	The patient died from kidney failure. Autopsy was done with reinvestigated cardiac mass tissue. Final diagnosis was primary cardiac diffuse large B cell lymphoma.

Case presentation

An 81-year-old Asian female, with no known past medical history, presented with progressive shortness of breath and bilateral legs swelling for a week.

On examination, she had tachycardia of regular rhythm at rate of 130 b.p.m. and tachypnoea at rate of 24 breaths/min with normal blood pressure (127/92 mmHg). Her SpO₂ was 92% at room air and 97% on 3 L/min of oxygen delivered via nasal cannula. Her neck veins were engorged. Cardiac auscultation was normal. Bilateral crackles with decreased breath sounds in the right lower lung were revealed from lung auscultation. Abdominal examination was normal. Grade III

pitting oedema was found at both lower extremities. No lymphadenopathy was noted.

An intravenous diuretic was administered with positive clinical response. Chest radiography revealed bilateral pleural effusion (Figure 1B). Her lactate dehydrogenase (LDH) was 1228 U/L (100–250 U/L). The remaining laboratory results were within normal range. Transthoracic echocardiography (TTE) demonstrated a large mobile homogenous mass obliterating the right atrium cavity and protruding into the right ventricular inflow, with another large non-vascular extracardiac mass compressing right heart (Figure 2). Computed tomography (CT) of chest with abdomen showed a large ill-defined enhancing soft tissue mass extending from the pericardial cavity into the right atrium and right ventricle. Several lobulated enhancing soft-tissue masses were demonstrated at epicardial fat with some abut left ventricle (Figure 3A and B). Right pleural effusion and enlarged lymph nodes in the bilateral lower para-tracheal areas and the right hilar region were illustrated with neither hepatosplenomegaly nor abdominal lymphadenopathy. Cytology analysis of her pleural effusion was negative for malignancy. After multiple attempts of trans-jugular cardiac biopsy under fluoroscopic and TTE guidance, the limited amount of tissue was obtained. Initial histopathology illustrated spindle to round neoplastic cells. Immunohistochemical staining showed expression of ERG (ETS-related gene) and Fli-1 (Friend leukaemia virus integration 1), as a marker of angiosarcoma. Further immunohistochemical staining for AE1/AE3 (Anti-Cytokeratin), EMA (epithelial membrane antigen), CD31, and CD34 were all negative.

Primary cardiac angiosarcoma was diagnosed. Surgical excision with additional chemotherapy was offered to the patient. Due to complicated procedure and patient's high operative risk, the surgical plan was rejected by the patient. Although chemotherapy could be a chance in prolonging her life, the patient decided to make her last term of life smooth and peaceful. The patient died 2 weeks later due to kidney failure. Autopsy was performed due to some concerns regarding the diagnosis, and cardiac mass tissue was re-investigated (Figure 4). Multiple lymphocytes were noted in the mass. The immunohistochemical staining yielded positive CD20, High Ki67, and negative in CD3, AE1/AE3 (Figure 5). The final diagnosis was changed to primary cardiac diffuse large B cell lymphoma.

Discussion

We reported a case of female patient with primary cardiac lymphoma and cardiac mass infiltrating right heart, who was misdiagnosed of angiosarcoma due to the pitfall in choosing and interpreting tissue immunohistochemical staining. Selecting type of immunohistochemical staining is important for diagnosis, especially with limited amount of obtained tissues. In this case, a certain panel of immunohistochemical staining without CD20 was done and the positive of Fli-1 immunohistochemical staining turned out to be a misleading. Since Fli-1 was 100% positive and extremely sensitive and specific for vascular tumour diagnosis from a previous report of common vascular markers for endothelial angiosarcoma,^{3,4} angiosarcoma became the suggested diagnosis from the pathology perspective. Other suggestive markers of sarcoma included BNH9 (72% positive and negative for all other soft tissue sarcomas, except angiosarcoma), CD 31 (90% positive), CD 34 (50–74% positive), vimentin, and von Willebrand

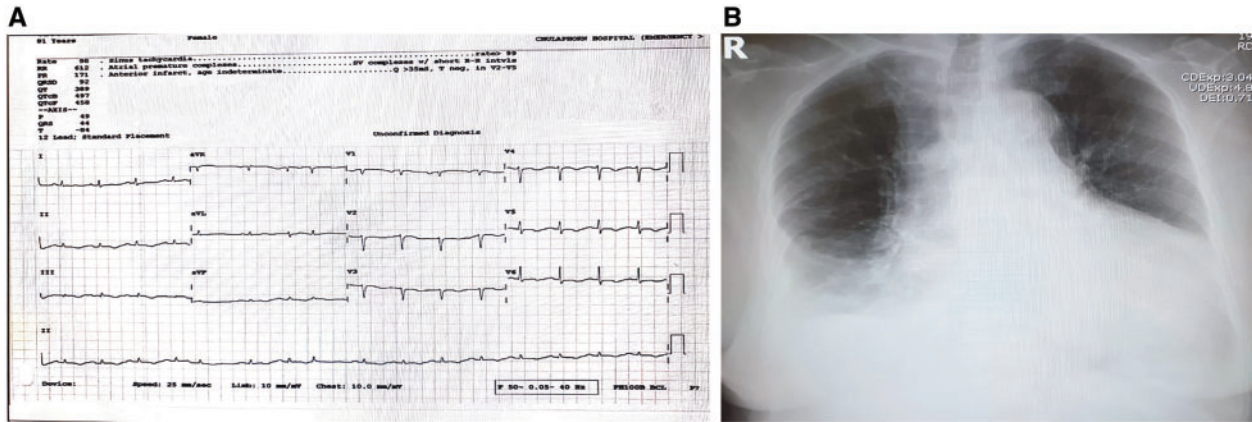


Figure 1 (A) Electrocardiogram with sinus rhythm rate of 98 b.p.m. with poor voltage in chest leads. (B) Chest X-ray with increased computed tomography ratio and bilateral pleural effusion.

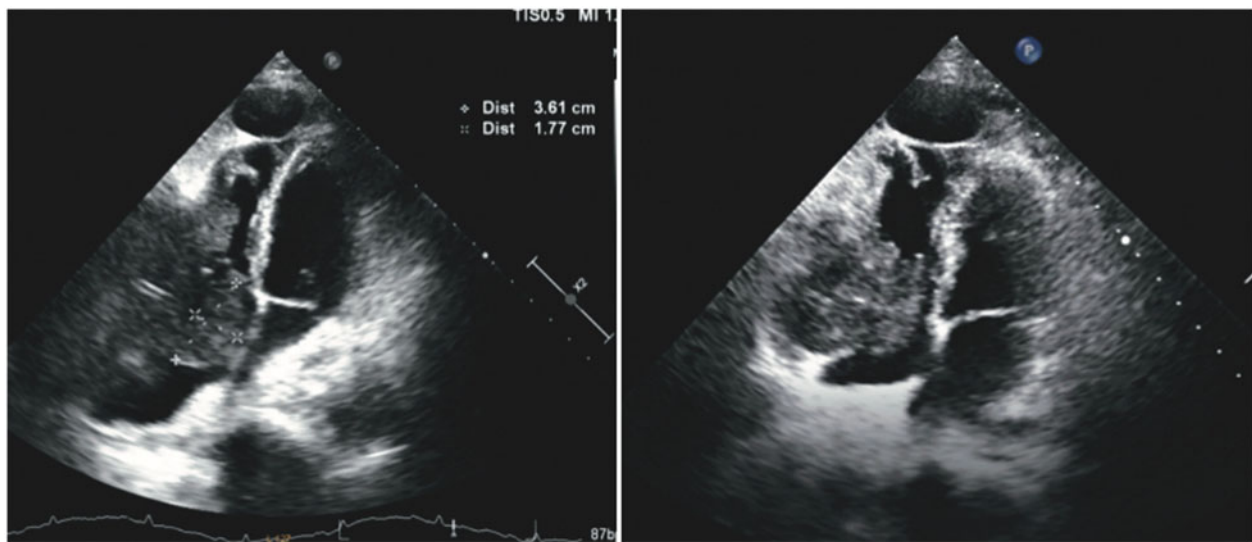


Figure 2 A large mobile homogenous mass in the right atrial protruding into the right ventricle during diastole, with mean pressure gradient of 12 mmHg across the right ventricular inflow and another large non-vascular extracardiac mass compressing right side heart.

factor.^{3,4} However, Fli-1 (a marker expressed in endothelial and haematopoietic cells which consistent with a role as a transcription factor) could also be positive in DLBCL cases. A study from Ufuk in 2013 reported the unexpectedly frequent expressions of Fli-1 in DLBCL (16.7%), with a statistically significant positive correlation between Ki67 index and Fli-1 ($P = 0.046$).⁵ Whilst, biological and clinical

significance of using Fli-1 in DLBCL had yet to be clarified. Interpretation of these cases with immunoreactivities of Fli-1 should be made cautiously to avoid misdiagnosis.

The primary cardiac lymphoma and cardiac angiosarcoma may be difficult to distinguish from one perspective. Clinical integration, imaging and histopathology could be crucial. In our case, diagnosis was

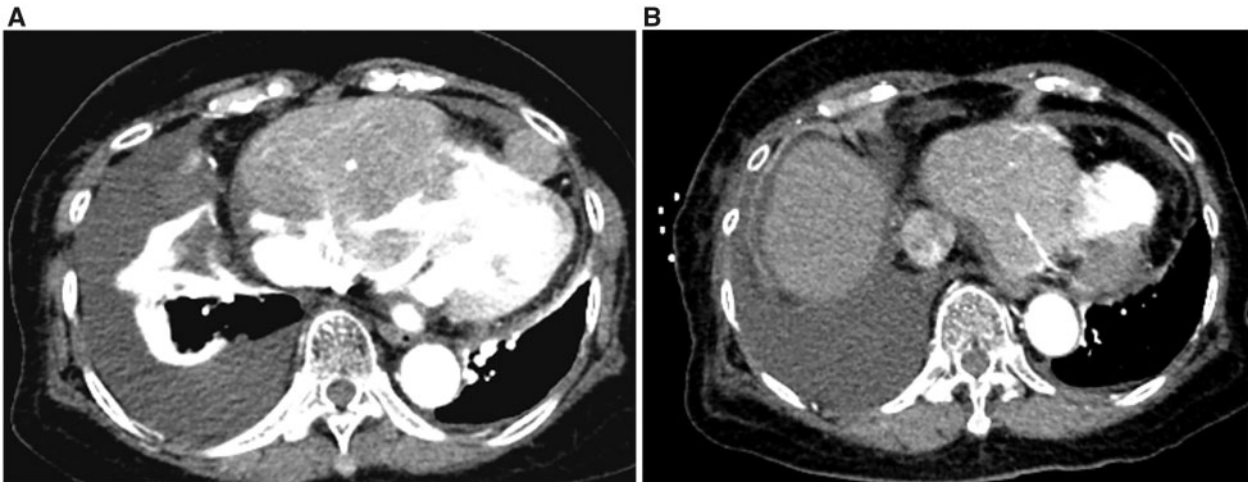


Figure 3 (A) A 8.4 × 8.9 × 9.1-cm ill-defined soft tissue mass in pericardial cavity extending into the right atrium and right ventricle. (B) The mass encircling a right coronary artery.



Figure 4 Gross pathology: coronal view (green arrow) Infiltrative tumour at right ventricular wall. (Red arrow) satellite nodule. (Blue arrow) Left ventricular chamber.

made based on immunohistopathology despite the rising LDH. The absence of coronary invasion from CT gave a hint of lymphoma. With inconsistency, the pathology review or repeated biopsy might have changed the course of this patient due to higher chemotherapy

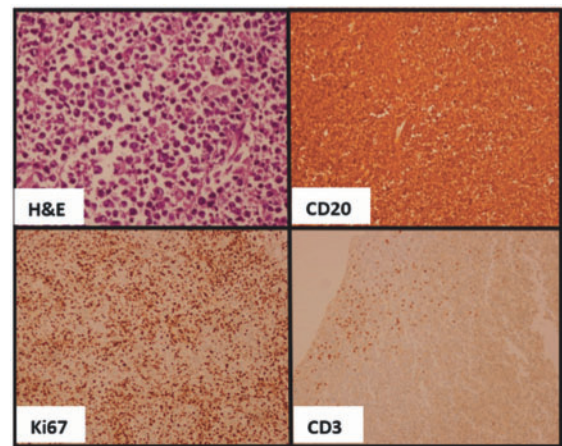


Figure 5 Pathology from protruded mass: haematoxylin and eosin 40× showed medium to large malignant cells. Immunostaining showed positive CD20 with high Ki67.

response rate of primary cardiac lymphoma. In a study by Carras *et al.*,⁶ the overall response rate was as high as 85%, with 62% complete response.⁶ Table 1 shows characteristic of primary cardiac lymphoma compared with primary cardiac angiosarcoma.

In conclusion, primary cardiac lymphoma is a rare entity. Adequate tissue sampling and proper immunohistochemical staining can be crucial for diagnosis. Diffuse large B-cell lymphoma should be considered in the differential diagnosis of FLI-1 (Friend leukaemia virus integration 1) with positive tissue.

Table 1 Characteristic of primary cardiac lymphoma compared with primary cardiac angiosarcoma^{3,7}

	Primary cardiac lymphoma	Primary cardiac angiosarcoma
Incidence in primary cardiac tumour	1–2%	30–35%
Mean age	60s	40s
Sex	Male > female (2:1)	1:1
Location	Right side (right atrium)	Any ^a
Coronary invasion	Spare	Invasion is reported
Presenting symptoms	Constitutional symptoms (17%) ⁷ Congestive heart failure, pericardial effusion, dyspnoea, syncope, facial oedema	Dyspnoea, congestive heart failure, usually asymptomatic until mass develops pressure effect
Pathology	<ul style="list-style-type: none"> • Medium to large size malignant lymphoid cell infiltrated in diffuse pattern 	<ul style="list-style-type: none"> • Anastomosing vascular channels • Solid spindle cell areas • Foci of endothelial tufting • Lack of calcification
Immunohistochemical staining	Positive CD20, Ki67 high Negative CD3	Positive CD31, CD34, Fli-1, and von Willebrand factor
Treatment	Chemotherapy (CHOP) and palliative resection	Surgical excision and additional chemotherapy (doxorubicin, ifosfamide)/radiotherapy
Mean survival	7 months after treatment	6 months

^aSome report predominantly in right side, Fli-1 = Friend leukaemia virus integration 1, CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone).

Lead author biography



Miss Chonthicha Tanking is a current CMR fellow at Royal Brompton Hospital in London. She previously worked as cardiology consultant at Chulabhorn Hospital in Bangkok. Born in Bangkok on 24 June 1987. She received medical degree from King Chulalongkorn university in July 2011. She also finished internal medicine training from faculty of medicine, Khonkaen university in 2015 and cardiology fellowship training from Phramongklutklao hospital in July 2017.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text was obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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